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ORIGINAL ARTICLE

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Laser acupuncture induced specific cerebral cortical and subcortical activations in humans

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Abstract As recent studies demonstrated, acupuncture can elicit activity in specific brain areas. This study aims to explore further the central effect using laser acupuncture. We investigated the cerebral effects of laser acupuncture at both acupoints GB43 with functional magnetic resonance imaging (fMRI). As a control condition the laser was mounted at the same acupoints but without application of laser stimulation. The group results showed significant brain activations within the thalamus, nucleus subthalamicus, nucleus ruber, the brainstem, and the Brodmann areas 40 and 22 for the acupuncture condition. No significant brain activations were observed within the placebo condition. The activations we observed were laser acupuncture-specific and predominantly ipsilateral. This supports the assumption that acupuncture is mediated by meridians, since meridians do not cross to the other side. Furthermore, we could show that laser acupuncture allows one to design a pure placebo condition.

Keywords Laser acupuncture · Acupoint GB43 · Xiaxi · Functional magnetic resonance imaging (fMRI)

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Introduction

Acupuncture, one of the oldest and still most frequently employed treatments worldwide, induces beneficial effects such as the promotion of homeostasis and an improvement with regard to brain circulation and pain control in the central nervous system [1–4]. In the western countries, acupuncture has become increasingly popular within the last century and has aroused much interest in the scientific and medical communities [5, 6]. The National Institute of Health (USA), e.g., comments that acupuncture may be useful as an adjunct treatment or an acceptable alternative therapy with regard to indications like the treatment of acute and chronic pain, postoperative, and chemotherapy-induced nausea and vomiting, some forms of bronchial asthma, headache, stroke rehabilitation, migraine, and drug abuse [7]. Nevertheless, its mechanism remains quite elusive.

Functional magnetic resonance imaging (fMRI) is used to detect changes in neuronal cerebral activity during specific tasks [8]. Recent functional brain-imaging studies using fMRI or positron emission tomography (PET) have provided evidence that acupuncture at specific disease-implicated acupoints modulates the activity of the disease-related neuromatrix. It has been found that acupuncture on vision-related acupoints leads to activation in the visual cortex [1, 9–11] and acupuncture at analgesic acupoints modulates the hypothalamic-limbic system [12–17]. Furthermore, it was observed for the first time that the cerebral cortical activity induced by laser acupuncture was lateralized ipsilateral to the body side to which laser acupuncture was performed [11]. This finding supposes that acupuncture is not only based upon afferent somatosensory information processing and supports the classical hypothesis of traditional Chinese medicine that acupuncture is mediated by meridians.

It is rare, however, that laser acupuncture has been used for stimulation. Laser acupuncture as an alternative to manual acupuncture has considerable practical relevance because it permits the stimulation of acupoints in a precisely defined manner and offers the possibility of a pure placebo condition [11]. Furthermore, Whittaker emphasized in a review article of laser acupuncture that laser acupuncture is rapidly gaining in popularity, but he pointed out that an objective evaluation is also needed [18].

In the present study we investigated cerebral activation patterns induced by laser acupuncture at both acupoints GB43 in healthy volunteers using fMRI. Nevertheless, using a low-level hand laser within the fMRI environment has several constraints. Because of the static magnetic field of the MR-scanner we cannot investigate acupoints proximal to the foot. The metallic components of the laser will disturb the magnetic field of the MR-scanner and will produce susceptibility artifacts, which cannot be detected any more at the distance of the foot. Therefore, we can only operate with the laser at the foot.

The aim of our investigation with laser acupuncture was to compare our study with an investigation using needle acupuncture at the same acupoint. For the present study, we chose GB43 in accordance to a previous needle acupuncture study at this acupoint using fMRI [19]. Furthermore, GB43 has the advantage to be located on the foot.

Methods

Participants

Twenty-two healthy male volunteers (age range:20–35 years) took part in the study, who had no history of neurologic, psychiatric or internal disorders, and drug abuse. All subjects signed a form of written consent. The study protocol was approved by the local ethics committee.

Acupuncture

For acupuncture, we selected the left and right acupoint GB43, which is located proximal to the interdigital skin margin between the fourth and fifth toe. The traditional indications for GB43 are deafness, tinnitus, dizziness, ear diseases, headache, and migraine. The location of acupoint GB43 was identified with an acupoint detector (Silberbauer, Austria). The acupoint detector is a simple electrical device, which measured the electrical resistance of the skin. With the applied device, acupoints can be detected within the skin because the electrical resistance is reduced at the acupoints [20, 21]. At first, the acupoints were located by the acupuncturist at the best of his knowledge and afterwards, the acupoint was verified by using the acupoint detector. Acupuncture was performed with a commonly used low-power diode laser (Minilaser 2010F, Helbo-Medizintechnik, Gallspach, Austria) that operates with a continuous laser beam (10 mW power output, 670 nm wavelength).

Experimental design and procedure

We divided the 22 subjects into two groups of 11. One group was assigned the right acupoint, the other group was assigned the left acupoint. Subjects were instructed to lie relaxed with their hands on the abdomen, to keep their eyes closed, and not to engage in any specific mental activity. The light in the magnet room was dimmed and there was no acoustic stimulation apart from the scanner noise.

The experimental setup consisted of two fMRI runs for each volunteer, identical for the two groups. During the first fMRI run, placebo acupuncture (PA) at acupoint GB43 was performed by mounting the laser on the acupoint GB43 resulting in the same tactile stimulation as in the verum acupuncture (VA) onto the same acupoint. Throughout the fMRI measurement, the laser was held exactly in the same position without switching on the laser light. During the second fMRI run, VA to acupoint GB43 was applied and the fMRI measurement was conducted completely identical to PA, but with the laser light alternately switched on and off, in a block designed manner. A direct activation of the visual system through the laser light can be excluded because the laser was placed onto the foot of the subject outside the magnet and was hidden behind a black screen. To exclude conditioning and long-lasting effects of laser acupuncture, PA was always run before the verum trial.

Placebo acupuncture was used to control artificially induced brain activity caused by the setup of the experiment and to exclude effects of anticipation. The subjects were told that the placebo and laser stimulation would be presented in a random order. Subjects were not able to distinguish PA from VA because the verum stimulation and the dummy stimulation differed only by switching the laser light on or off.

A block design with two conditions (on: A/off: R) with each block lasting five scans (TR = 8 s) for 40 s was employed. A time series RARARARAR was acquired. In fMRI it is necessary to use a block design (or event-related design) to get acceptable and robust statistical results. For the verum condition the laser light was switched on only during the "on" epochs, whereas during the placebo condition the light was switched off throughout the whole measurement. Prior to the time series, five dummy images were collected and excluded from data analysis. Foam padding and a special helmet fixed to the head coil was used to restrict head motions during the measurement.

(Functional) magnetic resonance imaging

All experiments were performed on a 1.5 Tesla whole body scanner (Magnetom VISION, Siemens, Germany) with an echo-planar capable gradient system (gradient ramp time 77 T/s, gradient strength 23m T/m) and a circular polarized head coil (FoV = 250 mm). For fMRI, we employed T2*-weighted single shot echo-planar sequences (TR = 0.96 ms, TE = 66 ms, $\alpha = 90°$, matrix = 128×128, voxel dimension = 1.95×1.95×3.8 mm) [8, 11, 22–24]. We acquired 35 slices parallel to the bi-commissural plane.

Statistical analysis

Postprocessing of fMRI data was done offline on a computer workstation using Matlab (Version 6.1) and SPM99 (SPM99, The Welcome Department of Cognitive Neurology, University College London, UK; http://www.fil.ion.ucl.ac.uk/spm/software/spm99/) [25]. The 45-volume images were automatically motion corrected with regard to the first image of the time series. They were then normalized to the Montreal Neurological Institute (MNI) template, which corresponds to the Talairach space [24]. Spatial smoothing was done with a Gaussian kernel of full width at half maximum (FWHM) = 6×6×12 mm. For the elimination of high- and low-frequency artifacts unrelated to the experiment, high pass (cutoff: 0.001 Hz) and low pass (cutoff: 0.1 Hz) filtering was done. The design matrix was defined using a box-car function convolved with the canonical hemodynamic impulse response function. We defined contrasts comparing the activations observed during PA and VA. Activations are reported for clusters, which surpassed an initial threshold of $P < 0.001$ and had a corrected P-value of $P < 0.05$ on cluster level. [9, 11, 27–29]. The anatomical location of the clusters was determined using the atlas of Talairach and Tournoux [26, 30].

Results

In the left acupoint GB43 group, significant brain activation was observed within the left thalamus, the left nucleus subthalamicus, the left nucleus ruber, and the brainstem. No activation was observed within the right hemishere (Fig. 1, Table 1). In the right acupoint GB43 group, significant brain activation was observed centrally within the midbrain extending paramedially to the right side (Fig. 2a), corresponding to Brodmann areas 40 and 22 (Fig. 2b, Table 1). In the placebo group, no significant brain activations were observed, neither for the left nor for the right acupoint group.

Discussion

In this study, significant cerebral activations could be observed within Brodmann areas 40 and 22 on the right side that are involved in the processing of sound and language. The results indicate that laser acupuncture of acupoint GB43 leads to significant activations in anatomical brain areas that could be associated with tinnitus, dizziness and deafness, the major indications for this acupoint. Furthermore, activation foci within the

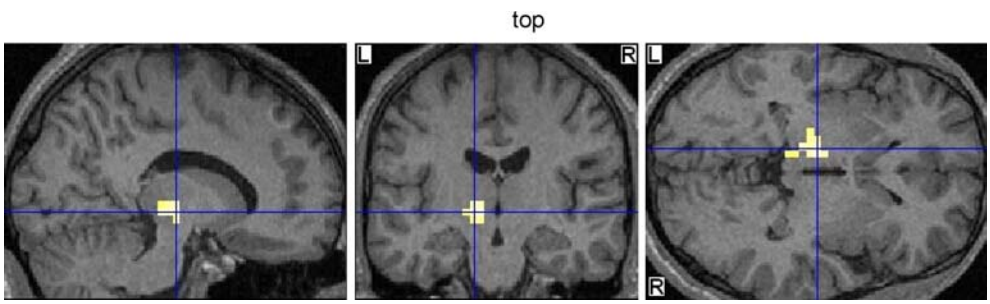

Fig. 1 The activation maps depicting the within-condition analysis for the laser stimulation on the left acupoint GB43. We found significant ipsilateral activation within the left brainstem, thalamus, nucleus subthalamicus and nucleus ruber

Table 1 Activation clusters detected for the contrasts of the images acquired during laser on and off condition. Activations are reported for clusters, which surpassed an initial threshold of $P < 0.001$ uncorrected and had a corrected P-value of $P < 0.05$ on cluster level. The same analysis of the dummy stimulation shows no significant cerebral activation cluster

	Location	P-value	Size	MNI-coordinates		
				X	Y	Z
GB43 right						
R	Midbrain, paramedian to the right side	0.049	7 voxel	4	−28	−12
R	Lobulus parietalis inferior(BA 40)	0.005	16 voxel	56	−36	32
	Gyrus temporalis superior(BA 22)			52	−48	12
GB43 left						
L	Brainstem, thalamus, nucleus subthalamicus, nucleus ruber	0.010	20 voxel	−12	−16	−4

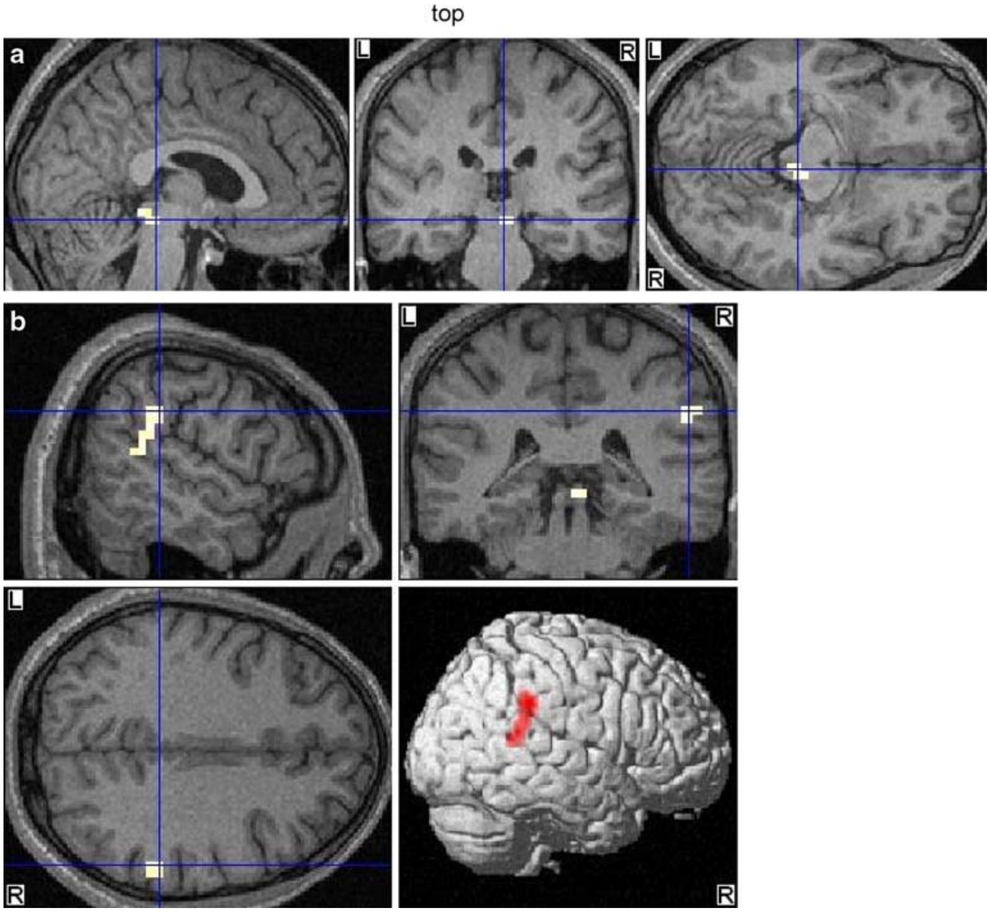

Fig. 2 a and b showed activation maps, while the within-condition analysis for the laser stimulation on the right acupoint GB43. Significant ipsilateral activation within the left midbrain Brodmann areas 40 and 22 could be detected

midbrain were observed. This finding corroborates the results of previous fMRI studies investigating hearing- and language-associated acupoints where a similar activation pattern was found [27, 31]. Especially an investigation on the same acupoint GB43 using needle acupuncture and fMRI could show activations in the auditory cortex too [19]. Thus, after a former investigation on acupoint BL67 [11] we were now able to demonstrate for the second time that laser acupuncture on a specific acupoint (GB43) leads to comparable cerebral activations like needle acupuncture at the same acupoint.

Most importantly, the present study shows that laser acupuncture induces cerebral activations predominantly in ipsilateral brain areas. These results indicate that the peripheral stimulation of acupoints does not primarily enter the brain by the afferent somatosensory pathways of the nervous system. Histological investigation of acupoints showed a large number of skin mechanoreceptors (e.g., Ruffini, Merkel, Meissner, Pacinian corpuscles) [32], which led to the assumption that the afferent nervous system is involved in the transmission of the acupuncture to the brain. We should therefore expect a contralateral cerebral response because of the crossing of the afferent long tracts at spinal and the lemniscal system at brainstem level.

However, we found brain activations ipsilateral to the body side to which acupuncture was applied. We therefore assume that the skin mechanoreceptors are not primarily involved in the underlying mechanism of acupuncture. These results support, however, the classical hypothesis of traditional Chinese medicine that acupuncture is mediated by meridians and medians do not cross to the other side like the afferent pathways.

Placebo acupuncture did not show any significant brain activations. This is in accordance with the findings of a previous fMRI study by Siedentopf et al. [11]. Important for the interpretation of the results is the fact that we were able to perform a "true" PA in this experiment, which is not possible in needle acupuncture studies [14]. In the present study, all subjects were asked after stimulation about their sensations with regard to "prolonged channel sensation" (PCS or *deqi*), a local mixture sensation including tingling, fullness, and heaviness, which is typical for needle acupuncture [33], and also about any visual perceptions. However, none of the subjects reported any sensation related to VA or PA. Therefore, low-level laser acupuncture did not provoke prolonged channel or other sensations. This is very different from needle acupuncture where these sensations are reported regularly. Therefore, in our experiment using laser acupuncture, VA was indistinguishable from the PA subjects. Thus, we were able to design a pure placebo condition.

We can also exclude that the tactile stimulus of the laser has any influence on the cortical activation pattern of the brain because it does not correlate with the periodicity of the time series of the applied block design during the fMRI runs. This has been proven with the placebo condition when the tactile stimulus was a constant afferent somatosensory input, which did not induce any detectable cerebral response [11].

This study demonstrated that laser acupuncture could induce a cerebral response within the human brain. Nevertheless, it is difficult to interpret the relevance of the brain activation pattern with regard to the therapeutic effect of acupuncture. Many other studies have to deal with this problem, too [1, 9–17, 19, 27, 31]. Acupuncture should modulate and promote homeostasis. A limiting factor to the interpretability of the results of the present and many other fMRI and PET studies is the use of only healthy volunteers. In healthy subjects the homeostasis differs from that of patients. Therefore, acupuncture might modulate homeostasis in a different way for healthy subjects than for patients.

This study at least shows that laser acupuncture has the potential to activate a network of cortical and brainstem structures in the human brain, and we hypothesize that this activation might lead to a modulation of the neuronal network of the involved brain structures. With regard to the predominantly ipsilateral brain activation, we conclude that this result confirms the assumption that acupuncture is not solely based upon afferent somatosensory information processing. Instead it might be mediated by other systems such as meridians, as it is assumed in traditional Chinese medicine.

Finally, we demonstrated that laser acupuncture not only resulted in cerebral activation comparable to needle acupuncture, but also made it possible to design a pure placebo condition, which is indistinguishable for the subject from the verum condition. This advantage is crucial with regard to the interpretation of the experimental results in acupuncture research.

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