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ORIGINAL ARTICLE

Study on the Regulatory Effect of Electro-acupuncture on Hegu Point (LI4) in Cerebral Response with Functional Magnetic Resonance Imaging*

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ABSTRACT **Objective:** To study, through blood oxygen level dependent functional magnetic resonance imaging (BOLD fMRI), the cerebral activated areas evoked by electro-acupuncturing (EA) the right Hegu point (LI4) or non-acupoint points on the face, and through comparing their similarities and differences, to speculate on the specific cerebral areas activated by stimulating LI4, for exploring the mechanism of its effect in potential clinical application. **Methods:** EA was applied at volunteers' right LI4 (of 9 subjects in the LI4 group) and facial non-acupoint points (of 5 subjects in the control group), and whole brain 3-dimensional T1 anatomical imaging of high resolution $1 \times 1 \times 1$ mm^3 used was performed with clustered stimulatory mode adopted by BOLD fMRI. Pretreatment and statistical *t*-test were conducted on the data by SPM2 software, then the statistical parameters were superimposed to the 3-dimensional anatomical imaging. **Results:** Data from 3 testees of the 9 subjects in the LI4 group were given up eventually because they were unfit to the demand due to different causes such as movement of patients' location or machinery factors. Statistical analysis showed that signal activation or deactivation was found in multiple cerebral areas in 6 subjects of LI4 group and 5 subjects of the control group (P<0.01). In the LI4 group, the areas which showed signal activation were: midline nuclear group of thalamus, left supra marginal gyrus, left supra temporal gyrus, right precuneous lobe, bilateral temporal pole, left precentral gyrus and left cerebellum; those which showed signal deactivation were: bilateral hippocampus, parahippocampal gyrus, amygdala body area, rostral side/audal side of cingulate gyrus, prefrontal lobe and occipital lobe as well as left infratemporal gyrus. In the control group, areas which showed signal activation were: bilateral frontal lobe, postcentral gyrus, Reil's island lobe, primary somato-sensory cortex, cingulate gyrus, superior temporal gyrus, occipital cuneiform gyrus and/or precuneus gyrus and right brainstem; and the area that showed deactivation was left median frontal lobe. **Conclusion:** The effects of EA LI4 in regulating cerebral activities could be displayed and recorded through BOLD fMRI, the distribution of signally deactivated area evoked by EA LI4 was similar to the known distribution of anatomical orientation of pain in brain, and closely related to the anatomic structure of limbic system, which areas are possibly the acupuncture analgesic effect's cerebral regulating area. Furthermore, activated portion of left central anterior gyrus, which represent the movement of oral facial muscles, and the activated portion of cerebellum are possibly related with the effect of using EA LI4 in treating facial palsy and facial muscle spasm. As for the mechanism of signal deactivation of cerebral activities exhibited in the present study that is unable to be elucidated, it awaits for further research.

KEY WORDS Hegu acupoint (LI4), nuclear magnetic resonance, acupuncture, brain, meridian

Traditional Chinese medicine (TCM) acupuncture is a marvelous treasure of the Chinese nation being used for treating many kinds of diseases. Until the middle of the 1970's, thanks to the progress made in acupunctural anesthesia researches, TCM acupuncture, as

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an alternative medicine, was introduced into the Occident[1,2]. The mechanism of acupuncture anesthesia was excellently explained from the physiological and anatomical aspects, and it is suggested by human and animal experimental studies that the stimulation of acupuncture is possibly some kind of input into the central nervous system through regulating nerves, activating multiple anodyne systems and evoking pain regulating system to release such transmitters as endorphin, and thus to achieve the analgesic effect of acupuncture[1-3]. Although the potential neuro-physiological mechanism of acupuncture is not so clear or definite, the relationship between "de-qi" (得气, getting needling sensation) and effect of acupuncture has been widely accepted. So, if the corresponding relation between the acupuncture effect and its orientation in central nerve system (CNS) as well as its correspondent data could be understood under "de-qi" status, it would undoubtedly provide more information and data for exploring the mechanism of anesthetic and non-anesthetic effect of acupuncture. Owing to the fact that blood oxygen level dependent functional magnetic resonance imaging (BOLD fMRI) is very sensitive to local change of blood oxygen level, it could be used to monitor the neurological activity[4]. On the assumption that effect of acupuncture is expressed through regulating the cerebral activity, its location and quality must be detectable by fMRI, we probed into the needling effect on Hegu point (LI4) and its corresponding response location in the brain. LI4 is the acupoint often used in experimental study on effect of acupuncture anesthesia, also one of the original points frequently used in clinical practice, mainly for treatment of headache, dizziness, toothache, swollen throat pain, facial palsy and hemiplegia, always showing efficacy in treating pain and facial palsy. Therefore, this study was designed to analyze and assess the cerebral activated location induced by acupuncture, through electro-acupunture (EA) on right LI4, with facial non-acupoint points used as control, and BOLD fMRI used to collect the signals in the whole brain, in combination with known function of cerebral construction and corresponding relationship between pain and various brain areas already reported to explore the specific brain activity induced by the regulation of EA on LI4 and its relativity with the potential efficacy in clinical application.

METHODS

General Data

Fourteen healthy volunteers, all college students, were randomly assigned to 2 groups: the 9 in the LI4 group were 6 males and 3 females, ages 22-27 years, mean age 24.6 years; the 5 in the control group were 3 males and 2 females, ages 22-27 years, mean age 23.5 years. All were without any neurological or psychological diseases, and during the experimental process, no discomfort, fear or feeling of seclusion was shown in them.

Preparation of Experiment

Several days before the experimental practice, the testees went through the experience of acupuncture themselves to relieve their scare and stress on acupuncture. Before they were scanned with MRI, it is also necessary for them to be familiar with the internal and external environment; they were asked to take a rest in the preparation room for 20 min; then use a self-made head device to fix their head to maximally reduce its movement; during scanning process, the light was turned off, their eyes closed and ears stuffed to reduce audio-visual stimulation; and the testees were asked to keep calm and avoid violent thinking activity.

Method of Needling

All the needles used were sterilized stainless steel needles 1.5 cun or 0.5 cun in length. Needling was performed by an acupuncturist rich in experience. To subjects in the LI4 group, needling was applied on acupoint LI4, which is located at the back of the hand between the first and second metacarpus, and corresponding to the radial side of middle point of second metacarpus. After the needle was inserted into the acupoint, it was gently twirled until the feeling of "de-qi" was obtained. On the line parallel to the Hand Yangming Meridian and 1 cm apart from LI4, another needle was inserted to construct an electric current circuit (care had to be taken to avoid contact of the 2 needles and form short circuit). Then the two needles were connected through 2 shielding electric line with the LH202 type Han's point stimulator outside the room. To subjects in the control group, instead of needling LI4, needling was applied in a non-acupoint point at face 1 cm apart from the right corner of the mouth to make stimulation but without "de-qi" feeling on the testees, and also another needle 1 cm beside it was applied to form electric circuit. All the rest of the process was done in the same way as in the LI4 group. The stimulation was applied at the frequency as 5 Hz random wave, 1-3 mA in strength, to give the testees "de-qi" yet no pain, making it tolerable to them; according to clustered design (Figure 1), the stimulatory mode was applied by alternatively putting one group at rest and stimulating the other. Data collection started from the group at rest, scanning was done at 28 time points for the first resting phase, and 20 time points afterward for stimulating phase, for totally 128 time points for 3 blocks (each block including the resting and stimulating phase, 3 times on the group at rest and 3 on that while stimulated), and altogether the process lasted for 8 min. The second time of scanning was repeated after an interval of 10 min. The data obtained from the first 8 time points were deleted during data analysis, not used for statistical analysis because they were obtained in the period when the machine was running from unstable state to balanced state.

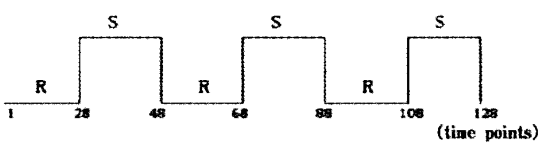


Figure 1. Experimental Design of Stimulatory Mode

Notes: R: resting phase, the time segment with no electric stimulation applied, including the 1st-28th, 49th-68th, and 89th-108th scanning; S: stimulating phase, the time segment in which electric stimulation was applied, including the 29th-48th, 69th-88th and 109th-128th time points

Technical Parameters of MRI

With Siemens 1.5 T MRI (Vision) and head array coil, BOLD fMRI with gradient echo-planar imaging sequence, employed parameters as follows: TR/TE 1.68 ms/64 ms, inverted angle 90°, field of view 230 mm, matrix 64 × 128, slice number 22, slice thickness 6 mm, interlayer distance 0 mm, tissue 1.8 mm × 1.8 mm × 6 mm, scanning time 2 s, signal-noise ratio 1.0, number of scanning 128 time points. The pictures of cross section were collected with scanning plane parallel to the anterior-posterior commissure line, and scanning range covering the whole brain. For the three-dimension anatomic T1 weighted sagittal imaging: TR/TE: 88 ms/4.76 ms, field of view 230 mm, signal-noise ratio 0.81, tissue 1 mm × 1 mm × 1 mm, acquisition time 5 min and 8 s. Anatomical structure imaging superimposed by the functional parameter was provided.

Data Reprocessing

Data were preprocessed and statistically analyzed with statistical parametric mapping (SPM2). Firstly the head movement correction, registering, spatial normalization and smoothening treatment were carried out, then data were deconvoluted, and linear regression and *t*-test analysis were conducted to obtain the parameter value of cerebral activated cluster expressed by pseudo-color, and superimposed to the 3-dimensional picture to form statistic parametric map, setting the cerebral activated threshold value as $P<0.01$.

RESULTS

Preprocession was conducted on data obtained from all the 14 testees, including 9 subjects in the LI4 group and 5 subjects in the control group, and those data with the corrected movement over 1 mm were deleted, not used for the further statistical analysis. Data of 3 subjects out of the 9 in the LI4 group were abandoned due to mechanical or machinery fault, so data from 11 subjects were analyzed finally. Statistical analysis showed that many different cerebral areas displayed activation or deactivation ($P<0.01$). In the LI4 group, the areas which showed the activation were: midline nuclear group of hippothalamus, left supra marginal gyrus, left supra temporal gyrus, right precuneous lobe, bilateral temporal pole, left precentral gyrus (Figure 2) and left cerebellum (Figure 3); those which showed the deactivation were: bilateral hippocampus, parahippocampal gyrus, amygdaloid body area, cingulatus gyrus rostral side/caudal side (Figure 4), frontal lobe and occipital lobe as well as left infra temporal gyrus (Table 1 and Table 2). In the control group, the activated areas were: bilateral frontal lobe, postcentral gyrus, Reil's island lobe, primary somato-sensory cortex, cingulative gyrus, temporal supra gyrus, occipital cuneiform gyrus and/or precuneus gyrus and right brainstem; and the deactivated area was left median frontal lobe.

Table 1. The Area and Parameters of Signal Activation in LI4 Group (*n*=6)

Area	Broadmann area	Talairach Coordinate (RAI mm) X R-L	Y A-P	Z I-S	T value (*P*<0.01)
Middle nuclear group of thalamus		0	16	0	3.16
Left supra marginal gyrus	40	51	42	41	3.86
Left supra temporall gyrus	22	50	17	-6	3.50
Right precuneus lobe	7	-16	66	6	3.13
Right temporal pole	38	-42	-12	-24	3.50
Left temporal pole	38	40	-12	-24	3.20
Left precentral gyrus	4/6	36	24	56	4.00
Left cerebellum		26	66	-44	3.50

Notes: RAI: right antero inferior; R-L: from right to left; A-P: from anterior to posterior; I-S: from infra to superior, the same as in Table 2

Table 2. The Area and Parameters of Signal Deactivation in LI4 Group (*n*=6)

Area	Broadmann area	Talairach (RAI mm) X R-L	Y A-P	Z I-S	T value (*P*<0.01)
Bilateral hippocampus		24.5	11.5	-22	3.13
		-32.5	-12.5	-20.5	3.13
Bilateral parahippocampal	28	-36	10	-23	4.00
gyrus	28	+36	10	-23	4.00
Bilateral amygdale body		23	5	-15	3.13
area		-23	4	-13	3.13
Rostral side of cingulated gyrus	24/32	-2	-34	6.5	4.00
Caudal side of cingulated gyrus	31	-1.5	56	24	4.00
Right prefrontal lobe	9/10	-24	-48	28	3.21
Left prefrontal lobe	8/9	24	-48	42	3.21
Left infra temporal gyrus	20	46	26	-18	5.84
Bilateral occipital lobe	19	-34	80	18	3.20
	19	36	84	22	4.00

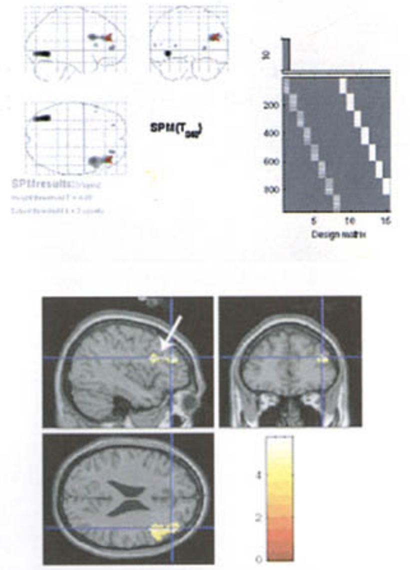


Figure 2. The Activated Cluster in Left Precentral Gyrus, and Its Matrix Chart of Experimental Design

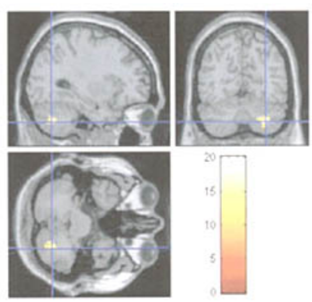
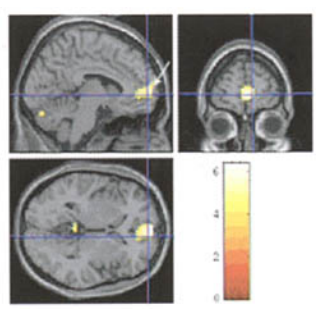


Figure 3. The Activated Cluster in Left Cerebellar Hemisphere



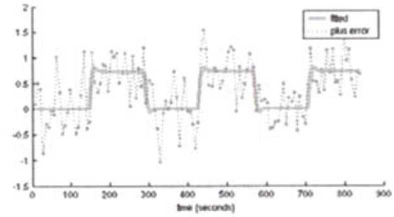


Figure 4. The Deactivated Cluster in Ventral Side of Precingulate Gyrus

Notes: showing an obvious relativity between the variation of time-signal intensity and the experimental designed mode

Comparison of the experimental results between the two groups was shown in Table 3, which showed that similar areas that displayed signal increasion mainly were: supra temporal gyrus, occipital lobe, brain stem; and the areas that displayed signal decreasion when LI4 was stimulated were different from those when facial non-acupoint points were stimulated, as these were mainly located at the limbic system and para-limbic system, while those that displayed signal decreasion were hippocampus, amygdalen nuclear area, cingulate gyrus and frontal lobar cortex.

Table 3. Comparison of Activated Areas between Two Groups

Group	Activating area	Deactivating area
LI4	Middle nuclear group of thalamus	Bilateral hippocampus
	Bilateral supra marginal gyrus	Bilateral amygdale body area
	Right precuneus Lobe	Bilateral parahippocampal gyrus
	Right temporal pole	Bilateral side of cingulated gyrus
	Left temporal pole	Bilateral prefrontal lobe
	Left precentral gyrus	Left infra temporal gyrus
	Left cerebellum	Bilateral occipital lobe
Control	Bilateral postcentral gyrus	Left median frontal lobe
	Bilateral Reil's island lobe	
	Bilateral primary somato-sensory cortex	
	Bilateral cingulated gyrus	
	Bilateral superior temporal gyrus	
	Bilateral occipital cuneiform gyrus/precuneus gyrus	
	Right brainstem	

DISCUSSION

Basis and Superiority of EA Application

EA is the product of traditional acupuncture, electronics and electronic technology. In the fifties of the 20th century, acupuncturist R-Vel in West Germany produced for the first time electronic needle. In China, this field of study began in 1959, and developed rapidly later on. For instance, HANS acupuncture therapeutic devices, which combines electroacupuncture, conical electrode, electrode plate, herbal medicine electrophoresis and multiple methods into one way, was widely used in clinical practice and researches.

Owing to the difficulty in controlling frequency and strength of stimulation and fixing it to a uniform degree by manual needle twirling in traditional manipulation, needle puncturing was quite affected by different individual performers, and hence objective evaluation on stimulation and statistical analysis was affected, too. Since quantitative manipulation of EA in stimulatory frequency, strength, wave form and other factors is quite simple, and thanks to the fact all its parameters are objective, its experiments are facilitated and easy to be repeated, results approved and turned to clinical application, EA stimulation has been chosen and used in the present study.

Feasibility of BOLD fMRI Application

It has been discovered in neuro-biologic researches that acupuncture effect is closely related to CNS[1-5]. Therefore how to record cerebral activity during acupuncture objectively in real time has already become a hot topic of modern imaging technology. Although during cerebral activities the mechanism of regulating blood vessels to change cerebral blood flow (CBF) and cerebral blood volume (CBV) is not clear, the fact that cerebral activity could obviously lead to changes of CBF and CBV has been confirmed[4,5]. Because of the changes of CBF and CBV induced by cerebral neuron activity could result in intravascular desoxy-haemoglobin change which could be sensitively detected by modern imaging technology such as BOLD fMRI, and through which cerebral neuron activity is positively likely to be indirectly orientated[4,5]. This method could be performed in living organism that is awake to observe holistically dynamically the functional activity of central nerve system, and has the characteristic of being noninvasive and repeatable. It is taken as, at present, the reliable and ideal method for studying acupuncture effect and cerebral activity orientation.

BOLD fMRI showed in the present study that EA could evoke cerebral activity in different areas, some of which displayed signal increase and some displayed signal decrease. It is held that the activation is caused by the increasing of local blood supply due to the enhanced neuron activity, but the potential mechanism of the deactivation is not clear so far. It is assumed that the lowering of local neuron activity leads to local blood flow decrease. Some scholars suggested the hypothesis concerning "stealing blood" and haemodynamic change independent to variation of local nervous activity, and so on[6,7]. In the present experiment, the activated or deactivated changes of cerebral area signal showed an obvious relativity with the time signal intensity curve, suggesting that both the activation and deactivation reflect local neuronal activity, not "stealing blood", or haemodynamic changes as mentioned above. But the mechanism about how EA induces the complicated network activity in brain and different responses of neuron activity like the deactivation, is still not to be completely elucidated, and awaits further design and study.

EA LI4 Induced Cerebral Activity, Its Orientation and Meaning

The known limbic lobar structure, including amygdala, hippocampus, medial septum, olfactory bulb, terminal strialine, nucleus accumbens septi, entorhinal cortex, infra-corpus callosum gyrus, cingulate gyrus, hippocampal gyrus and its deep structure, together with some cerebral structures under the limbic lobe and cortex, such as fornix, thalamus, mamillary body, tegment of midbrain, and so on, constitute the limbic system, which is also called "viscera of brain", the high regulatory controlling center of visceral functions and internal environment of organism as well as the emotional and sensational regulatory center. In present study, EA stimulation on LI4 evoked signal changes in multiple structures of limbic system, such as bilateral hippocampus, amygdala body area, para-hippocampal gyrus and cingulate gyrus, as well as those in the para-limbic system relative cortex, such as bilateral temporal pole and frontal lobe. This coincides with the hypothetical system of internal equilibrium in TCM, which recognizes that needling on superficial acupoint could regulate, through the center of brain, blood and qi of the whole body. Therefore in studies concerning acupuncture with brain response, limbic system is regarded as the most active area[7,8]. Besides, limbic system has a shuttle-like fiber connection with midbrain peripheral aquaduct grey substance, reticulo-structure, nuclei of median raphe and locus ceruleus, all of which jointly build up the pain sense regulating center. Therefore, it is postulated that the limbic system may play the role of the high neuro-regulation center for the analgesic effect produced by needling LI4.

Current studies showed that the anterior cingulate cortex (ACC) is related with multiple functions, such as orientation of integrative stimulation, strength encoding, pain recognizing, attentive response, kinetic response to pain sensation, and prediction of pain[9,10]. Results in our study showed that the signal in ACC got deactivated after EA LI4 (Figure 4), while an activation in cingulative gyrus was shown in the control group, suggesting that EA LI4 may play its role in analgesia and sedation through inhibiting neuronal activities in ventral region of anterior cingulate gyrus to suppress appearance of unpleasant sensation and visceral response.

Besides, another important application of needling LI4 is the treatment of facial palsy and facial muscle spasm. The present experimental results displayed that EA LI4 on the right hand could evoke cerebral activated cluster at the orofacial represent area located in the left precentral gyrus (Figure 2), also at the cerebellum hemisphere (Figure 3). These areas are the high center of somatic movement, closely related to its generation and regulation.

Thus, it is postulated that these areas possibly participate in the recovery of facial palsy and control of facial spasm.

Conclusion

EA LI4 regulation on cerebral activity can be displayed and recorded by BOLD fMRI. The distribution of areas where EA LI4 can induce cerebral deactivation is similar to that of the known cerebral anatomic orientation of pain and closely related with the anatomical structure of limbic system. These areas are possibly the acupunctural analgesia regulatory areas in the brain. Besides, the signal activation portion at the orofacial representative area in motor area of precentral gyrus as well as that at cerebellum are possibly related with the application of needling LI4 in treating facial palsy and facial muscular spasm. The mechanism of the deactivation induced in this study remains to be explained and awaits further study and research.

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