Proceedings of the 28th IEEE
EMBS Annual International Conference
New York City, USA, Aug 30-Sept 3, 2006

The brain mapping on reinforcement acupuncture stimulation at ST36 (zusanli) evidenced by fMRI

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Abstract— **Purpose: To characterize the brain mapping on reinforcement acupuncture stimulation at ST36 (zusanli), and to discuss the mechanisms of acupuncture to treat diseases. Methods: fMRI was performed on 26 healthy Chinese student volunteers. Sixteen subjects were acupunctured at the acupoint ST36, while 10 others at sham-acupoint (lateral from ST36 about 3cm). The fMRI studies were performed using a gradient echo-EPI sequence. Brain mapping were generated using GE Functool program. Cerebral blood flow and correlation coefficient (CC) of ROI were analyzed. Results: Stimulation at the right ST36 elicited 13 brain functional areas, and 10 of these areas were the same with the sham-acupoint group. However, only the temporal gyrus was specificity while by using reinforcement manual acupuncture (MA) at ST36 (Fisher's Exact test, P=0.022), and the contralateral hemisphere activation was prominent (McNemer test, P=0.020). Conclusion: Our results support the theory of acupuncture about meridian distribution overlapping on the whole body. The special transmission channel of meridian may exists, and it may be consist of spinal nerve and autonomic nerve. However, our results may oppose the theory concerning on stomach meridian walking lateral.**

***Keyword*—functional MRI; brain; acupuncture**

I. INTRODUCTION

ACUPUNCTURE is a key component of traditional Chinese medicine and has practiced efficaciously against organic diseases and disorder for thousands of years in Asia, especially for chronic pain, headache, migraine, drug abuse and emesis developing after surgery or chemotherapy [1, 2, 3]. In the West, acupuncture has become generally known lately and accepted widely, however, the mechanism of acupuncture is mysterious and unclear. It still relies on ancient literature of practice, which is largely descriptive rather than quantitative or even factual. In acupuncture meridian theory, little effort has done to show the connection between the brain and various disorders and disease. However, the brain is defined as the central all of the organs by the Western medicine. The different theory between Oriental medicine and Western medicine prevents the development of Oriental medicine. Understanding the neurobiologic substrates and mechanisms underlying the effects of acupuncture will greatly promote the integration of this ancient healing art into the modern medical mainstream. With the development of medical imaging, a lot of methods can be chosen to study the response of brain to acupuncture, such as PET, SPECT, MEG, fMRI. Functional MRI (fMRI) is a powerful neuroimaging technique with capabilities of spatial and temporal resolution that make it an excellent modality to study the response of the brain to the acupuncture stimulation. The response of the brain to acupuncture has been studied using fMRI [4, 5, 6, 7]. Most of these studies demonstrated a broad neuromatrix response that involved the limbic system and limbic-related brain structures including the amygdala, hippocampus, hypothalamus, cingulated, prefrontal and insular cortices, basal ganglia, and cerebellum. A large amount of experimental data has already been obtained by fMRI to demonstrate the relationship among acupoint, brain, and organs. However, according to the acupuncture theory, the differential effects would come into being by used different manual stimulation techniques, such as reinforcement MA, purgation MA, normal therapy MA, rotating it after insertion, which is thought to change the effect of acupuncture, have not been studied. To our knowledge, the brain mapping on reinforcement acupuncture stimulation of ST36 has not been reported. We explored an important acupoint on the right leg, ST36, employing "reinforcement" technique manual acupuncture and compared the results to similar stimulations of a sham-acupoint. According to the theory of acupuncture, differences between sham and the real acupoint should be present. We performed fMRI on healthy volunteers and examined the brain modulated by the "reinforcement" technique-MA stimulation, compared the hemodynamic response in the brain to MA at acupoint (ST36) and sham-acupoint, in order to characterize the brain mapping on "reinforcement" acupuncture stimulation at ST36, and to discuss the mechanisms of acupuncture to treat diseases.

II. METHODOLOGY

Subjects: Twenty-six healthy Chinese student volunteers (9 females and 17 males, age range from 23 to 31 years old, with an average age of 24.54 years), all right-handed, were participated in this study after providing informed written consent. Subjects had no history of head trauma, neurological disease, substance abuse, or dependency. The

This study has been supported in part by the grants from SATCM, GATCM, NSFG, NSFC, and Li Ka Shing Foundation.
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subjects were first familiar with the experimental procedures and the environmental conditions to minimize anxiety and enhance task performance. Next, subjects lay supine on the scanning table and were fit with cotton in ears, designed to reduce noise. Elastic straps and tightly fitting foam pads were use to minimize head movement.

Experimental design and Imaging methods: The volunteers were randomly divided into two groups by single blind method: Group Ⅰ, 16 subjects, "reinforcement" MA stimulation at the right acupoint (ST36); Group Ⅱ, 10 subjects, the similar stimulation at the sham-acupoint. A 1.5T MRI scanner (GE-Signa) with standard head coil was used. The fMRI studies were performed using a gradient echo-EPI sequence with following parameters: TR 2000msec, TE 50msec, thickness 7mm, gap 1.5mm, FOV 240mm×240mm, Matrix 64×64, NEX 1, scan time 4:16. Anatomical images were acquired using T_1WI-flair before the fMRI sequence acquisition. The block design of RSRS was employed for mapping the brain activation during the manual acupuncture paradigm with R representing rest and S representing the acupuncture stimulation of either sham- or real acupoint task. Each period lasted 20sec. During "reinforcement" MA stimulation at the acupoint or sham-acupoint, 12 contiguous axial slices of 7mm in thickness were acquired to cover the whole brain; Images were acquired repeatedly during alternating rest and stimulation periods for six times, resulting in a total of 128 time points recorded with the beginning of R1=16s. For acupuncture, we used a stainless nonmagnetic needle, with a diameter of 0.25 mm and a length of 25 mm. The needle was inserted perpendicular to the surface of the skin, to a depth of 10mm. Using the "reinforcement" technique, the needle was rotated manually clockwise and anticlockwise at 2 Hz. All stimulation tasks were performed by one experienced acupuncturist. After each acupoint or sham-acupoint was stimulated, we enquired the subjects about the "De-Qi" effect, a characteristic effect of needle-manipulation sensation, manifest as numbness, heaviness, distention and soreness, with spreading sensation, and about pain, anxiety and unpleasantness. A score of 0 meant no somatosensory sensation, 3 the emerging De-Qi sensation, and 5 the subject's maximal tolerable De-Qi [8, 9, 10].

Image postprocessing and Data-analysis: Post-processing of fMRI data was performed using the Functool program (GE-ADW4.0). Correlation coefficients of ROIs were detected and functional activation images were generated (confidence level 0.001). Voxels with correlation coefficient exceeded 0.33(P<0.01) was reserved and clustered at the threshold of 4 voxels. Afterwards, functional images were registered with the anatomical MR images. The localization of the activated brain regions was confirmed by an experienced neuro-radiologist. The statistical analysis was performed using the SPSS13.0 for windows with Fisher's Exact test. Paired sample was used McNemer test, and the population rate confidence limit was used binomial distribution estimate, statistical significance level was defined as α=0.05.

III. RESULTS

All volunteers s cooperated well and good quality of MR images was obtained expect one subject 's head (group Ⅰ) moved significantly, so he was excluded from the statistical processing. Now, the real acupoint group remained 15 subject, the sham-acupoint group remained 10 subjects. The characteristic De-Qi sensation at ST36 was felt by 15 of 15 subjects, and at the sham point by 4 of the 10 subjects. This sensation increased when the needle was rotated. The remaining subjects' data analysis shows the following. Stimulation at the right ST36 elicited 13 brain functional areas, 10 are same in non-acupoint group. The activated brain functional areas were located in bilateral precentral gyrus, postcentral gyrus, temporal gyrus, PAVN, insula, occipital cortex, parietal lobe, cingulategyrus, pons, hypothalamus, thalamus, supramarginal gyrus and cerebellum. However, only the temporal gyrus was special in acu-point group (Fisher's Exact test, P=0.022). Contralateral hemisphere activation was prominent (McNemer test，P=0.020). The results of the multi-subject analysis are summarized in Table 1 and Table 2. Table 1 lists the results of acupoint acupuncture compared to non-acupoint acupuncture. Table 2 lists the results of the temporal gyrus in acu-point group.

There was remarkable overlap between the cortical activation of the real and sham acupoints. No significant difference in the most majority of brain activation with stimulation of real and sham-acupoint was, therefore, observed.

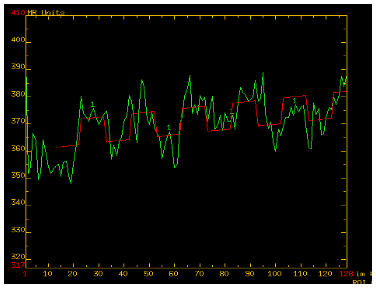

Fig. 1. Time waves showing ROI in one volunteer's temporal lobe

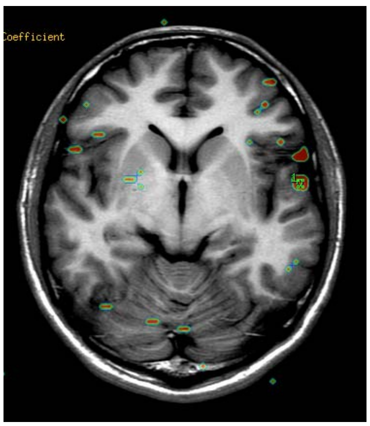

Fig.2. The contralateral temporal lobe activation was prominent in one volunteer

Table 1. Regions of activation for group analysis of MA stimulation at acupoint and sham-acupoint

Regions	Sham-acupoint (10)	acupoint (15)	P
frontal lobe	4	9	0.284
precentral gyrus	3	9	0.144
postcentral - gyrus	4	7	0.185
PAVN	1	7	0.065
temporal lobe	4	13	0.022
insula	1	2	0.654
cerebellum	3	9	0.144
parietal lobe	2	4	0.545
occipital lobe	2	1	0.346
cingulategyrus	1	6	0.118
thalamus	0	3	0.198
pons	0	3	0.198
supramarginal gyrus	0	2	0.350

Table 2. Results of the temporal gyrus in acupoit group

		Right TG*		Total	
		A	N-A		
Left TG	A	4	8	12	P=0.020
	N-A	1	2	3	(McNenar Test)
Total		5	10	15	

*TG: temporal gyrus; A: Activation; N-A: Non-Activation

IV. DISCUSSION

Human and animal studies suggest that acupuncture acts as a neuromodulating input into the central nervous system (CNS), which can activate multiple systems and stimulate modulation systems to release neurotransmitters such as dopamine. During stimulation of the real acupoints, several cortical and sub-cortical areas were identified, according with previous studies of manual acupuncture at ST36, which were locating at thalamus, insula, cingulategyrus , temporal gryus and cerebellum [11,12,13,14,15]. However, there are some different activated areas, such as basal ganglia, PAVN. Our results confirm these previous studies. However, since there was a remarkable overlap in activation areas during stimulation of the real and sham acupoints, the significance of this activation in the known "digestive system network" is not clear. It has been suggested that the activation might constitute a correlate of the known effect of acupuncture. On the other hand, it might be argued that the acupuncture sensation following insertion of a needle activates the modulation system regardless of whether it arises at sham or real acupoints. It is difficult to design controlled experiments for acupuncture studies and few have satisfied Western scientific standards [16,17] because of the difficulty of finding a true "sham point". An ideal "sham point" would be an area of skin some distance from any known acupoint or trigger point. But some physiological effects of acupuncture, such as De-Qi, have been observed when such supposed "sham points" were stimulated [20]; and sham acupuncture has also been found to have certain therapeutic effects and cannot therefore constitute a valid control. Acupuncture at sham points works in a third to a half of patients with chronic pain, while real points work in 55–85% [20]. We elicited acupuncture-related sensations from the sham point in 4 subjects (4/10), which differs from previous studies using placebo or minimal acupuncture devised to elicit no De-Qi in controls [16,17,18]. This may explain the overlap between the activation areas. We did find a significant difference between stimulation of the real and sham acupoints using "reinforcing" needling techniques. Acupuncture at the real acupoints elicited more significant activation of the areas noted above than the sham-acupoint, although the manipulation and parameters were identical. According to the theory of acupuncture, De-Qi is important for effective acupuncture treatment. Needling manipulation, also known as needling transmission, refers to various manipulations to induce this needling sensation; proper manipulation techniques can promote it [10]. The reason the "reinforcing" needling technique had the described effect on cerebral haemodynamics only at the real acupoints is not fully understood by the acupuncture theory of oriental medicine or the anatomi-physiology of western medicine. We can only presume that real acupoints are indeed more susceptible to needle manipulations and have special transmission channel of meridian. This would lead to the assumption of a differential effect of acupuncture in real and sham points and therefore, to the assumption of an effect of acupuncture that can be identified using functional neuroimaging studies, which in turn would warrant further research in this field.

V. CONCLUSION

Reinforcement technique MA stimulation at the acu-point and non-acupoint all can lead to broad neuromatrix response. This could be support the theory of acupuncture about meridian distribution overlapping on the whole body. Reinforcing technique manual stimulation at the acupoint ST36 can lead to the functional changes in specific brain areas, such as the temporal gyrus, and the contralateral hemisphere activation was prominent. This cannot be fully explained with the knowledge based on histomorphological central nervous system. Our study's results may suggest that the special transmission channel of meridian exists, and it may be consist of spinal nerve and autonomic nerve. However, our study's results may oppose the theory concerning meridian walking lateral.

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