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ACUPUNCTURE RESEARCH

Effects of Electro-acupuncture at Tongli (HT 5) and Xuanzhong (GB 39) Acupoints from Functional Magnetic Resonance Imaging Evidence*

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ABSTRACT **Objective**: To explore the specificity of Tongli (HT 5) and Xuanzhong (GB 39) paired acupionts in aspects of Deqi sensation and brain activation patterns during electroacupuncture. **Methods**: In this study, 15 healthy subjects were enrolled. All participants suffered two kinds of functional magnetic resonance imaging (fMRI) examinations randomly: Examination A received electro-acupuncture (EA) at the bilateral Tongli (HT5) and Xuanzhong (GB 39) acupoints (ACU), and examination B received EA at bilateral non-acupoints (NAP). The subjects reported the feeling of Deqi at each examination later respectively. A multi-voxel pattern analysis method and Statistical Program for Social Sciences were used to analyze the data. **Results**: The ACU group (Exam A) reported fullness, heaviness, numbness, soreness and throbbing of significantly greater intensity than the NAP group (Exam B). In addition, there was no statistical significance between two groups in aching, tingling, deep pressure, sharp pain, dull pain, warmness and cold. Meanwhile, fMRI data revealed differences between two groups in discriminating accuracy of brain somatosensory cortex and language-related cortices. **Conclusion**: Needling HT 5 and GB 39 may modulate language function through a complex brain network, suggesting that it may be beneficial to the recovery of language function in patients with aphasia.

KEYWORDS electroacupuncture, Tongli (HT 5), Xuanzhong (GB 39), functional magnetic resonance imaging, brain network

Chinese medicine (CM) has evolved over thousands of years, through the accumulation of clinical experience. Acupuncture is an essential component of CM, and has been proven to be a beneficial complementary or alternative treatment for various diseases.(1-3) CM theory holds that the human body has acupoint (ACU) along the meridian that is closely linked to the brain. The hypothesis about ACU-brain relation supposes that needling certain ACU can induce specific changes in different brain areas or networks.(4,5) Previous studies have demonstrated the clinical effectiveness of acupuncture.(6,7) However, there is a lack of objective evidence for the effectiveness of acupuncture with advanced methodology.

Several new techniques have been introduced into clinical practice, including functional magnetic resonance imaging (fMRI), positron emission tomography, single photon emission computed tomography, electroencephalography and magneto-encephalography.(8)Compared with other methodologies, fMRI is perhaps the best technique to study cerebral function, as it has the advantages of high spatial resolution.(9) And fMRI has already been widely applied to the study of acupuncture.(10,11) Studies have demonstrated that stimulating a certain ACU can cause changes in the blood oxygen saturation of particular (corresponding) regions of the cerebral cortex, reflecting specific brain activity and networks.(12,13) Hence, fMRI technology is an effective method for analyzing brain activation patterns induced by acupuncture. However, selecting an appropriate analytical method to match the experimental purposes is a prerequisite for acquiring reliable results. Traditional fMRI analysis is

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voxel-based, assessing different levels of activity within single voxel. Voxel-based methods provide only limited information because they need more correction for multiple comparisons, and the signal-to-noise ratio is low.[14] Therefore, large sample size is required to attain sufficient statistical power based on traditional fMRI analysis.

In order to overcome the limitations of voxel-based approaches, this study used a new technique named searchlight analysis,[15] which was based on multi-voxel pattern analysis (MVPA),[16] which allowed us to examine the entire brain. MVPA applied powerful classification algorithms and discriminative pattern to probe local information concerning differences of the neural pattern under various conditions.[17] Some studies have successfully used MVPA to detect spatial distribution in the brain.[18,19] Whereas, few studies have used the MVPA technique to analyze the brain activation patterns detected by MRI, which is induced by acupuncture stimulation at language-related acupoints. Presently, combining the searchlight algorithm and principal component analysis (PCA), we adopted a modified MVPA method to classify the responses of needling in ACU and in non-acupoints (NAP). Therefore, we applied MVPA to identify differences of the neural responses, which induced by acupuncture stimulation between language-related ACU and NAP.

In addition, current studies have adopted a randomized controlled trial design with groups of subjects,[20] and few have used a single-object, multi-task, repeat-trial paradigm to investigate the specificity of ACU. The design of single-object could avoid individual differences between two different groups. Therefore, it may provide an objective evidence for the effectiveness of acupuncture ACU and a better guide for clinical practice.

METHODS

Subjects

Fifteen Chinese healthy college students participated in this study (8 males and 7 females; age, 25.7±1.4 years; all right-handed). All participants signed written informed consent. None of the participants had previous acupuncture experience; taken medicine within 1 month prior to the experiment; a history of major medical illness, including head trauma and neuropsychiatric disorders; had contraindications to exposure in the high magnetic field. Before entering the MRI chamber, each participant received a clear explanation about the feeling which they might experience during the electro-acupuncture (EA) experiment. All the experimental procedures were approved by the Ethics Committee of the Teaching Hospital of the Beijing University of Chinese Medicine (No. ECPJ-BDY-2011-06).

Experimental Procedures

In order to reduce inter-subject variability, the method of single-subject and multiple-test experimental pattern used in the field of psychology commonly was adopted. All subjects received two kinds of functional MRI examination randomly: EA at Tongli (HT 5) and Xuanzhong (GB 39) ACU, EA at nearby NAP. The interval time of the two examinations was 20 min. All subjects reported the feeling of Deqi at each examination later respectively. The fMRI experimental design was a classical resting/stimulation (R/S) block design that comprised a resting period of 30 s followed by a stimulation epoch of 30 s (Figure 1); such blocks were repeated for 6 cycles.

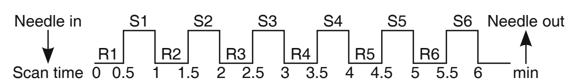

Figure 1. EA Stimulation Procedure (Block Design)
Notes: R: rest; S: stimulation

The locations of the ACU were selected according to the "Name and Location of Acupoints" (GB/T 12346-2006). These points were located simultaneously at both sides. HT 5 is located on the anteromedial aspect of the forearm, radial to the flexor carpi ulnaris tendon, 1.0 cun proximal to the palmar wrist crease, with an insertion depth of 0.5 cun. GB 39 was carried out 3 cun above the tip of the external malleolus, on the anterior border of the fibula, with an insertion depth of 1 cun. NAP was undertaken 0.5 cun to the ulnar side of HT 5, and 1 cun to the fibular side of GB 39 (Figure 2). Silver needles of size 35×40 mm were used (Huatuo; Suzhou Medical Supplies Co., Ltd., Suzhou, China). The location, depth and stimulation patterns were the same for all the subjects, and the needling was carried out by a qualified practitioner in CM. After inserted into the ACU, the needles were connected to an electrical stimulator (Han's Acupoint Nerve Stimulator; model LH-202H, Neuroscience Research Institute, Peking University, China) to deliver a dilatational wave of equal amplitude to the ACU and NAP with current strength of 2 mA, and stimulation frequency of 2 Hz.

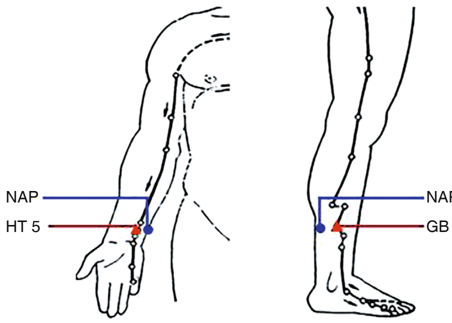

Figure 2. The Location of HT 5 and GB 39 (ACU) and NAP

At the beginning of the experimental procedure, each participant underwent baseline scanning to produce a 3-dimensional (3D) structural image, which lasted 8 min and 34 s. After each time of acupunture as well as the following scan, the participant reported his/her feelings of Deqi of ACU and NAP respectively, according to the Massachusetts General Hospital Acupuncture Sensation Scale.(21) The sensations assessed were: soreness, aching, deep pressure, heaviness, fullness, tingling , numbness, sharp pain, dull pain, warmness, cold and throbbing. The degree of the sensation was marked with numbers from 0 to 10 (0 = no sensation; 1–3 = mild; 4–6 = moderate; 7–8 = strong; 9 = severe; and 10 = unbearable).

Data Acquisition

The images were acquired on a 1.5-T MRI whole-body scanner (Siemens AG, Munich, Germany). In order to ensure a consistent baseline, a band and foam pillow were used to restrict head movement. The 3D structural scan employed T1-weighted sequence [repetition time (TR)/echo delay time (TE) = 2 s/3.93 ms, field of view (FOV)= 256 mm × 256 mm, slice thickness= 1 mm, the total scanning time = 8 min and 34 s)]. The functional images were collected in a sagittal orientation, parallel to the anterior commissure-posterior commissure plane, using a single shot gradient-recalled echo planar imaging sequence (TR = 3s; TE = 65 ms; flip angle = 90° ; FOV= 230 mm × 230 mm; 27-slice scanning; slice thickness = 5 mm. The total scanning time was 6 min and 6 s).

Analysis of Deqi Sensations

Comparisons of Deqi on the acupuncture of ACU and NAP were made with paired Student's *t*-test and Wilcoxon signed-rank test based on SPSS 17.0.

MRI Data Analysis

For each subject, the first 5 time-series and the last 10 ones of each run were removed to eliminate nonequilibrium effects of magnetization. Finally, 100 time-series scans (totally 300 s) were acquired in each run. Free-Surfer (https://surfer.nmr.mgh.harvard.edu/) was adopted to tackle the high-resolution T1-weighted image for cortical data preparation. A 'standard' cortical mesh model was used and analysis was undertaken with the analyses of functional neuroimages software package (http://afni.nimh.nih.gov/afni/). Simultaneously, the same preprocessing was applied to a Colin brain so that all the calculations and results could be related to the same standard brain (the cortical mesh model and the Colin brain had the same cortical top points). All scans were realigned to correct for head movement and standardized to the Montreal Neurological Institute (MNI) space. None of the subjects had head rotation movements that exceeded 3 mm. The fMRI data were preprocessed with Statistical Parametric Mapping 5 software (SPM5; http://www.fil.ion.ucl.ac.uk/spm).

Cortex-based MVPA

An enormous range of classification algorithms, referenced from previous machine learning-related studies, can be applied in MVPA studies. Cortex-based morphometry, together with a MVPA technique that combined a searchlight algorithm and PCA, was used to classify the brain activation patterns induced by EA at ACU and NAP. The "searchlight" for an appropriate set of vertices to define multivariate features as the input for the pattern classification analysis was applied. In detail, a cortex area with a 6-mm radius (the smallest unit of the pattern recognition) was defined as a multivariate "searchlight" centered on each area, and this "searchlight" was moved through the whole brain cortex. The "searchlight" standard template grid of the brain cortex was programmed using MATrix laboratory code. Therefore, we acquired a data matrix $X=T \times N$ where T was the number of time points (T=100) of each run and N was the number of the vertices in this cortex area. Using PCA for all vertices of the searchlight, the principal components represented the maximum variance (the data matrix $X=T \times 1$).

Then classification was performed using support vector machines (SVM) based on statistical learning theory. SVM is a powerful tool for statistical pattern recognition, and have been used successfully in fMRI studies; in particular, they show a much better performance when encountering large numbers of dimensions.[22] The Library for Support Vector Machines toolbox (http: //www. csie. ntu.edu.tw/wcjlin/ibsvm) was used to perform the classification. Then leave-one-out cross-validation to evaluate the SVM classier was applied. There were 15 subjects and every subject had two conditions (the ACU and NAP). Fourteen subject's ACU and NAP runs were chosen as training set to train this linear classifier, which was used to predict the label (ACU or NAP) of the two runs belong to the subject left. The procedures were repeated 15 times so each subject had the chance to be the test set. After both labels of the test runs were correctly predicted, the result of classifier defined by the authors was successful. And the accuracy was the percentage of the successful prediction over 15 folds. The chance of one good prediction is $1/2 \times 2 = 25\%$, while in 15 times of prediction, in 5%–95% confidence limits, the range of success time is between 1 and 7. As a result, if classifier gave 8 correct prediction corresponding 53.3% (P=0.0042) in one vertex, this vertex was considered as a discrimination point. So the discrimination accuracy (DA) was an indicator of distinguishing different neural responses induced by EA at ACU and NAP. Then the classification results of SVM were displayed on an inflated standard brain (threshold of the patch was 10 mm^2).

RESULTS

Results of the Psychophysics Analysis

Since both examinations A and B were performed on the same group of subjects, there were no differences between the two examinations in terms of participants' gender and age. The number and density of each sensation of Deqi reported by participants in response to acupuncture are presented in Figure 3. Figure 3A described the number of subjects in each group reporting the Deqi sensations. Numerically higher values were found for soreness, heaviness, fullness, numbness and throbbing in the ACU group. In Figure 3B, the Deqi sensations ranged from mild to moderate intensity in the ACU group. Yet the intensity of the NAP group remained in mild scope. In detail, the ACU group (Examination A) reported heaviness and soreness of significantly greater intensity (P<0.05) than the NAP group (Examination B). Meanwhile, fullness, numbness and throbbing showed significant higher intensity (P<0.05) in the ACU than NAP group. Nevertheless, there was no statistical significance between two groups in aching, tingling (P>0.05), deep pressure, sharp pain, dull pain, warmth and cold (P>0.05).

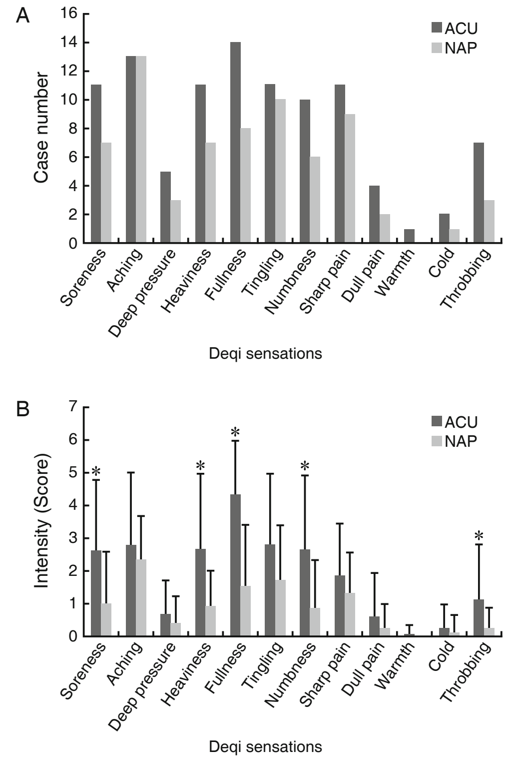

Figure 3. Comparison of Number (A) and Intensity (B) of the Deqi Sensations between ACU and NAP (n=15, $\bar{x} \pm s$)

Note: *P<0.05, compared with the NAP group

Results of the fMRI Data based on MVPA

Significant differences between the two examinations were found at the somatosensory cortex, frontal cortex, temporal cortex, parietal cortex, occipital cortex and limbic system (Table 1). The resulting spatial maps are shown in Figure 4.

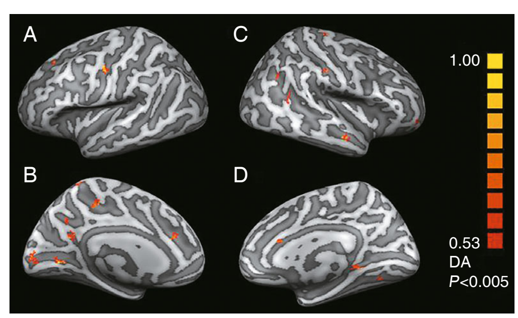

Figure 4. DA Showed in Inflated Standard Brain

Notes: The resulting spatial maps displayed the discriminating accuracies of neural response patterns between ACU and NAP conditions. 3D inflated brain were divided into two hemispheres by the middle sagittal plane, the left hemisphere and the right hemisphere. A: the outer side of the left hemisphere; B: the inner side of the left hemisphere; C: the outer side of the right hemisphere; D: the inner side of the right hemisphere; DA, P<0.005

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Table 1. Significant DA between ACU and NAP Derived from Pattern Classification

Region	Brodmann area	Hemisphere	MNI			DA	Cluster area (mm^2)
			X	Y	Z		
Somatosensory cortex							
Precentral gyrus	3,4,6	L	–44	–9	41	0.80	45.03
Precentral gyrus	6	R	30	–22	71	0.73	13.62
Postcentral gyrus	4	L	–32	–31	67	0.73	11.67
Frontal cortex							
Triangle inferior frontal	45	L	–54	26	20	0.73	12.04
Orbital middle frontal	46,47	R	37	54	–5	0.60	13.76
Superior frontal gyrus	32	L	–19	27	38	0.73	13.25
Orbital superior frontal	11	R	14	55	–17	0.67	19.51
Temporal cortex							
Middle temporal gyrus	21	R	52	–4	–20	0.80	27.99
Parietal cortex							
Angular gyrus	39	R	38	–58	30	0.60	10.08
Supramarginal gyrus	48	R	52	–18	26	0.73	21.21
Occipital cortex							
Inferior occipital gyrus	19,37	L	–51	–66	–14	0.80	14.73
Inferior occipital gyrus	18,19	R	38	–88	–1	0.73	11.05
Calcarine cortex	17,18	L	–3	–93	11	0.73	60.77
Calcarine cortex	17	R	7	–69	11	0.67	10.70
Lingual gyrus	17,18,19	L	–4	–66	6	0.87	80.33
Lingual gyrus	27	R	12	–39	0	0.80	25.40
Fusiform gyrus	19.37	R	26	–60	2	0.67	12.47
Limbic system							
Middle cingulum cortex	—	L	–16	–31	45	0.73	19.68
Posterior cingulum cortex	23	L	–6	–51	27	0.73	32.40
ParaHippocampal gyrus	27	R	12	–39	0	0.80	25.40
Insular cortex	48	L	–32	–21	12	0.67	12.24
Precuneus	—	L	–11	–58	41	0.60	11.40
Precuneus	—	R	12	–55	45	0.73	12.14

Note: L: left; R: right; The discriminating accuracies shown in this table were the highest values among all the cluster areas identified (with 0.53 as the threshold for the DA) for the specific brain areas. Cluster size > 10 mm^2, uncorrected (P<0.005)

DISCUSSION

Theoretical Origins of Language-related ACU in CM

The theory of CM holds that advanced cognition is closely related to the human brain, and it is stated in the *Compendium of Materia Medica* (Ben Cao Gang Mu), written by LI Shi-zhen, in the Ming Dynasty, that "Primordial spirit comes from the brain." In the Zangxiang theory of CM, the physiology and pathology of the brain are closely linked to the Xin (Heart), one of the five zang organs: "The Xin is the major organ among five zang and six fu organs and the residence of the spirits." Hence, advanced cognitive activity is closely related to the brain and the Xin. HT 5 is the Luo-connecting point of the Xin Meridian of Hand-Shaoyang. Through a collaterals path (named Luo-Mai in CM), HT 5 is closely linked to the tongue. Meanwhile, language is a part of cognitive activity and depends on a flexible tongue. Since CM holds "the Xin dominates the mind activity" and "the tongue body movement and language expression function depend on the Xin," HT 5 is closely related to language function. GB 39 is located on the Dan Meridian of Foot-Shaoyang. The Dan dominates judgment and decision in mental activity. Then GB

39 is in the influential point of the marrow: "Marrow aggregates in the brain." So needling in this point tonifies the Shen (Kidney), fills up the marrow, and benefits the recovery of language function. Integrating syndrome differentiation in Zangxiang theory and meridian theory, HT 5 and GB 39 have been selected for research into the underlying mechanisms of acupuncture efficacy on aphasia.

In a previous study, 30 cases of motor aphasia after cerebral infarction were divided into a control group and a treatment group, with the treatment group receiving acupuncture at HT 5.[23] The severity grade of aphasia were observed before and after treatment in two groups. It was shown that the improvement in aphasia severity in the treatment group was superior to that in the control group, with greater improvement in the speaking and reading scores of the aphasia scale in the treatment group. This indicated that HT 5 was an effective ACU for the treatment of motor aphasia after cerebral infarction. Chang, et al[24] observed the changes in the linguistic scale and the activation of brain function, before and after needling HT 5 and GB 39, in patients with sub-cortical aphasia. The results showed that there was activation of the linguistic brain area after EA at HT 5 and GB 39, as well as activation of the bilateral temporal cortex. Obvious improvements in linguistic scale and the language function of the patients provided objective evidence for the treatment of aphasia with acupuncture at HT 5 and GB 39. Current research on acupuncture specificity is based mainly on fMRI technology. Kong, et al[25] have demonstrated that the fMRI signal can accurately reflect the specificity of acupuncture in different individuals. This study may provide some evidence for specificity of HT 5 and GB 39.

Deqi Sensations and DA in the Brain Somatosensory Cortex

Many physicians and researchers approved that acupuncture can achieve clinical efficacy, and research on acupuncture mechanisms is merited. Deqi, known as Qizhi in ancient times, or needling sensation in modern times, refers to the response to stimulations such as the thrusting, lifting or rotating of the needle after its insertion into an acupoint. The degree and duration of Deqi are often closely related to acupuncture efficacy.[26] In our study, the needling sensation was fully recorded. Statistical analysis revealed significant differences between the ACU and NAP groups in heaviness, fullness, numbness, soreness and throbbing, but not in the other sensations. Acupuncture at NAPs produced only sharp surface sensations, with significantly lower intensities for heaviness, fullness and soreness. Needling the skin surface can activate the somatosensory motor cortex of the brain.[27] Therefore, we assumed that the neural response patterns in the somatosensory motor cortex differed between the ACU and NAP groups.

Previous fMRI data on ACU-brain specificity have commonly been analyzed with "ACU-brain activation-function" analysis. Restricted by the analytical methods, a few studies have studied differences between the neural activation patterns of ACU and NAP. Li, et al[27] studied the specificity of the vision-related ACU Guangming (GB 37) via voxel-based MVPA. They found high classification accuracies for sub-regions of the brain somatosensory area that can effectively identify between ACU and NAP Napadow's team proposed that needling ACU was able to modulate the brain somatosensory motor network (SMN) and default mode network (DMN).[28,29] We used cortex-based MVPA to investigate the brain activation patterns induced by EA between ACU and NAP. In the somatosensory motor cortex, the postcentral gyrus (also known as the primary somatosensory motor area, DA=0.73) and superior frontal gyrus (sensory systems area, DA=0.73) has presented large differences. Combined with the Deqi sensations, we have established that the neural response patterns in the somatosensory motor cortex that differ between ACU and NAP. The specificity of the effects induced by EA at HT 5 and GB 39 may provide evidence for the clinical efficacy of acupoints.

Acupuncture Modulates Language-related Brain Networks

CM meridian theory is the cornerstone of acupuncture theory, and also a hotspot in the field of acupuncture research. Shi, et al[30] reported that stimulating ACU led to corresponding body reactions distinguishable from the reactions to other non-meridian points, which is known as ACU specificity. Researchers generally believed that changes in functional brain represented strong evidence for the existence of ACU specificity. Generally, NAPs are located several millimeters or centimeters from ACU. Liu, et al[31] and Dong, et al[32] compared the brain areas activated by acupuncture of GB 37 and NAP, using generalized

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linear model and independent component analysis, respectively. Both found that GB37 activated the corresponding visual cortex, supporting the specificity of vision-related ACU. Fang, et al[33] investigated different ACU based on fMRI, and agreed that Deqi was significant in acupunture studies. They also found commonalities as well as differences between different points. The hypothesis was proposed that acupuncture could modulate limbic-paralimbic-neocortical networks, including the amygdala, hippocampus, septal nuclei, cingulate gyrus, precuneus and angular gyrus, and activate the SMN and a few paralimbic structures.[31-33]

Language is a uniquely human higher cognitive activity involving listening, speaking, reading, writing, comprehension, imagination and many other aspects. The process of language generation is complex. The brain is the coordinating center of all linguistic activity; it controls both the production of linguistic cognition and meaning, and the mechanics of speech production. We process language in many different locations in the human brain, but especially in Broca's and Wernicke's areas. There is no consensus as to the mechanism of language function. The present study identified significant differences between the effects of stimulating ACU and NAP in the frontal cortex, temporal cortex, parietal cortex, occipital cortex, limbic system and the DMN. Therefore, we presume that stimulating ACU influences language functions by mobilizing an extensive, complex network. In detail, the superior frontal gyrus is mainly concerned with the regulation of self-consciousness and sensory systems. The middle temporal gyrus focuses on reading comprehension tasks. Studies have shown that damage to the left middle temporal gyrus may lead to alexia and agraphia of characters.[34,35] The angular gyrus is involved in a number of processes related to language, number processing and spatial cognition, memory retrieval, attention. It is probably involved with language perception and processing, and lesions in it may cause receptive aphasia.[36] The fusiform gyrus plays a role in face recognition, word recognition and classification. Although belongs to the visual cortex, the lingual gyrus plays an important role in the identification and recognition of words (especially letters). These gyri may be involved in the processing and handling of language.

Raichle, et al[37,38] proposed the term DMN, a network of brain regions that are active when the individual is not focused on the outside world and the brain is at wakeful rest; this is also called the task-negative network. Its subsystems include part of the medial prefrontal cortex for theory of the mind, part of the medial temporal lobe for memory, and the posterior cingulate cortex for integration,[39] along with the adjacent ventral precuneus[40] and the inferior, medial, lateral and parietal cortex. Some scholars proposed that needling ACU can modulate the brain SMN and the DMN.[28,29,41] The research found that stimulation at Neiting (ST 44) selectively activated the bilateral posterior cingulate cortex, a sub-system of the DMN.[42] In the subsequent research, Wang, et al[43] investigated the neural correlates of individual components of Deqi during acupuncture at the right Taichong (LV 3). The neural activity of the DMN was found to respond to the different sensations of Deqi induced by acupuncture stimulations. The above studies suggested that acupuncture at acupoints can mobilize the reserved functions of the DMN.

Hence, we believed that EA at ACU (HT 5 and GB 39) influences language cognitive functions through mobilization of the frontal lobe, temporal lobe, parietal lobe and limbic system. EA at HT 5 and GB 39 may modulate language cognition through a complex network formed by an extensive brain cortex, suggesting that it may be beneficial to the recovery of language function in patients with aphasia. Furthermore, differences between stimulation at ACU and NAP in Deqi and the DA of brain cortex, may provide objective evidence for specific clinical effects of acupuncture.

The limitations for our study cannot be overlooked. We couldn't prevent the influence of the residual effects of acupuncture for ACU and NAP. Further studies with a large sample size are needed to determine the specificity of HT 5 and GB 39. It is possible that our findings may not relate directly to the clinical efficacy of acupuncture at ACU. Therefore, an fMRI study of acupuncture in patients with aphasia after stroke will be interesting.

Conflicts of Interest

The authors declare no conflicts of interest.

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REFERENCES

1. Ng SM, Yiu YM. Acupuncture for chronic fatigue syndrome: a randomized, sham-controlled trial with single-blinded design. Altern Ther Health Med 2013;19:21-26.
2. Lee JS, Kim SG, Jung TG, Jung WY, Kim SY. Effect of Zhubin (KI 9) acupuncture in reducing alcohol craving in patients with alcohol dependence: A randomized placebo-controlled trial. Chin J Integr Med 2014. [Epub ahead of print] DOI: 10.1007/s11655-014-1851-1.
3. Leung A, Zhao Y, Shukla S. The effect of acupuncture needle combination on central pain processing: an fMRI study. Mol Pain 2014;10:23.
4. Xing JJ, Zeng BY, Li J, Zhuang Y, Liang FR. Acupuncture point specificity. Int Rev Neurobiol 2013;111:49-65.
5. Rong PJ, Zhao JJ, Gao JH, Li X, Li SY, Ben H, et al. Progress of research on specificity of meridian acupoint efficacy. Chin J Integr Med 2013;19:889-893.
6. Yuan Y, Chen F, Yang JS. Forty-nine cases of Parkinson's disease treated by acupuncture adjunctive therapy. Chin Acupunct Moxibust (Chin) 2014;34:53-54.
7. Jin HP, Wu QY, Zhang W, Xie JJ, Chen JC. Post-stroke dysphagia in chronic stage treated with magnetic-ball sticking therapy at the auricular points: a randomized controlled trial. Chin Acupunct Moxibust (Chin) 2014;34:9-14.
8. Aguirre GK. Functional neuroimaging: technical, logical, and social perspectives. Hastings Cent Rep 2014;44:S8-S18.
9. Zhou YL, Duan YL, Su CG. Progress on application of fMRI in studies of meridians and acupoints. World J Acupunct Moxibust 2012;22:49-52.
10. Lan L, Wu F, Zeng F, Liang FR. Progress of fMRI research in central effect mechanism of acupuncture overseas. Chin Acupunct Moxibust (Chin) 2013;33:426-430.
11. Bai L, Lao L. Neurobiological foundations of acupuncture: the relevance and future prospect based on neuroimaging evidence. Evid Based Complement Altern Med 2013;2013:812568.
12. Zeng F, Qin W, Ma T, Sun J, Tang Y, Yuan K, et al. Influence of acupuncture treatment on cerebral activity in functional dyspepsia patients and its relationship with efficacy. Am J Gastroenterol 2012;107:1236-1247.
13. Jiang Y, Liu J, Liu J, Han J, Wang X, Cui C. Cerebral blood flow-based evidence for mechanisms of low- versus high-frequency transcutaneous electric acupoint stimulation analgesia: a perfusion fMRI study in humans. Neuroscience 2014;26:180-193.
14. Todd MT, Nystrom LE, Cohen JD. Confounds in multivariate pattern analysis: theory and rule representation case study. Neuroimage 2013;15:157-165.
15. Ecker C, Rocha-Rego V, Johnston P, Mourao-Miranda J, Marquand A, Daly EM, et al. Investigating the predictive value of whole-brain structural MR scans in autism: a pattern classification approach. Neuroimage 2010;49:44-56.
16. Allefeld C, Haynes JD. Searchlight-based multi-voxel pattern analysis of fMRI by cross-validated MANOVA. Neuroimage 2014;89:345-357.
17. Coutanche MN. Distinguishing multi-voxel patterns and mean activation: why, how, and what does it tell us? Cogn Affect Behav Neurosci 2013;13:667-673.
18. Kaplan JT, Meyer K. Multivariate pattern analysis reveals common neural patterns across individuals during touch observation. Neuroimage 2012;60:204-212.
19. Looser CE, Guntupalli JS, Wheatley T. Multivoxel patterns in face-sensitive temporal regions reveal an encoding schema based on detecting life in a face. Soc Cogn Affect Neurosci 2013;8:799-805.
20. Liu CZ, Xie JP, Wang LP, Liu YQ, Song JS, Chen YY, et al. A randomized controlled trial of single point acupuncture in primary dysmenorrhea. Pain Med 2014;15:910-920.
21. Kong J, Gollub R, Huang T, Polich G, Napadow V, Hui K, et al. Acupuncture Deqi, from qualitative history to quantitative measurement. J Altern Complement Med 2007;13:1059-1070.
22. Chen Y, Namburi P, Elliott LT, Heinzle J, Soon CS, Chee MW, et al. Cortical surface-based searchlight decoding. Neuroimage 2011;56:582-592.
23. Wu F, Yang WZ, Zhao N, Sheng YX, Xie BY, Liu XL. Impacts on motor aphasia after cerebral infarction treated with acupuncture at Tongli (HT 5) and speech rehabilitation training in the patients. Chin J Integr Med Cardio/Cerebrovasc Dis (Chin) 2010;3:290-292.
24. Chang JL, Gao Y. Linguistic evaluation and imaging exploration on post-stroke motor aphasia in one patient of the damage at left temporal and occipital junctional zone. J Beijing Univ Tradit Chin Med (Clin Med, Chin) 2012;4:1-5.
25. Kong J, Gollub RL, Webb JM, Kong JT, Vangel MG, Kwong K. Test-retest study of fMRI signal change evoked by electroacupuncture stimulation. Neuroimage 2007;34:1171-1181.
26. White P, Prescott P, Lewith G. Does needling sensation (deqi) affect treatment outcome in pain? Analysis of data from a larger single-blind randomized controlled trial. Acupunct Med 2010;28(3):120-125.
27. Li L, Qin W, Bai L, Tian J. Exploring vision-related acupuncture point specificity with multivoxel pattern analysis. Magn Reson Imaging 2010;28:380-387.
28. Dhond RP, Yeh C, Park K, Kettner N, Napadow V. Acupuncture modulates resting state connectivity in default and sensorimotor brain networks. Pain 2008;136:407-418.
29. Napadow V, Lee J, Kim J, Cina S, Maeda Y, Barbieri R, et al. Brain correlates of phasic autonomic response to

acupuncture stimulation: an event-related fMRI study. Hum Brain Mapp 2013;34:2592-2606.

30. Shi GX, Li QQ, Liu CZ, Zhu J, Wang LP, Wang J, et al. Effect of acupuncture on Deqi traits and pain intensity in primary dysmenorrhea: analysis of data from a larger randomized controlled trial. BMC Complement Altern Med 2014;14:69.
31. Liu J, Nan J, Xiong S, Li G, Qin W, Tian J. Additional evidence for the sustained effect of acupuncture at the vision-related acupuncture point, GB 37. Acupunct Med 2013;31:185-194.
32. Dong M, Qin W, Sun J, Liu P, Yuan K, Liu J, et al. Tempo-spatial analysis of vision-related acupoint specificity in the occipital lobe using fMRI: an ICA study. Brain Res 2012;1436:34-42.
33. Fang J, Wang X, Liu H, Wang Y, Zhou K, Hong Y, et al. The limbic-prefrontal network modulated by electroacupuncture at CV 4 and CV 12. Evid Based Complement Altern Med 2012;2012:515893.
34. Acheson DJ, Hagoort P. Stimulating the brain's language network: syntactic ambiguity resolution after TMS to the inferior frontal gyrus and middle temporal gyrus. J Cogn Neurosci 2013;25:1664-1677.
35. Sakurai Y, Mimura I, Mannen T. Agraphia for kanji resulting from a left posterior middle temporal gyrus lesion. Behav Neurol 2008;19(3):93-106.
36. Gazzaniga MS, Ivry RB, Mangun GR, eds. Cognitive neuroscience, the biology of the mind. 3rd. ed. New York: W. Norton and Company; 2009:395-401.
37. Raichle ME, MacLeod AM, Snyder AZ, Powers WJ, Gusnard DA, Shulman GL. A default mode of brain function. Proc Natl Acad Sci USA 2001;98:676-682.
38. Raichle ME. The brain's dark energy. Sci Am 2010;302(3):44-49.
39. Buckner RL, Andrews-Hanna JR, Schacter DL. The brain's default network: anatomy, function, and relevance to disease. Ann N Y Acad Sci 2008;1124:1-38.
40. Zhang S, Li CS. Functional connectivity mapping of the human precuneus by resting state fMRI. NeuroImage 2012;59:3548-3562.
41. Quah-Smith I, Williams MA, Lundeberg T, Suo C, Sachdev P, et al. Differential brain effects of laser and needle acupuncture at LR8 using functional MRI. Acupunct Med 2013;31:282-289.
42. Liu H, Xu JY, Li L, Shan BC, Nie BB, Xue JQ. FMRI evidence of acupoints specificity in two adjacent acupoints. Evid Based Complement Alternat Med 2013;2013:932581.
43. Wang L, Shen H, Tang F, Tang F, Zang Y, Hu D. Combined structural and resting-state functional MRI analysis of sexual dimorphism in the young adult human brain: an MVPA approach. Neuroimage 2012;61:931-940.

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