◆ Human Brain Mapping 18:233–238(2003) ◆

An fMRI Study Comparing Brain Activation Between Word Generation and Electrical Stimulation of Language-Implicated Acupoints

Geng Li,[1,3] Ho-Ling Liu,[2] Raymond T.F. Cheung,[3*] Yu-Chiang Hung,[2] Kelvin K.K. Wong,[1] Gary G.X. Shen,[1] Qi-Yuan Ma,[1] and Edward S. Yang[1]

[1]*The Jockey Club Magnetic Resonance Imaging Engineering Centre, The University of Hong Kong, Hong Kong*
[2]*Department of Medical Technology, Chang Gung University, and Diagnostic Radiology, Chang Gung Medical Center, Taoyuan, Taiwan*
[3]*Division of Neurology, University Department of Medicine, Faculty of Medicine, The University of Hong Kong, Hong Kong*

Abstract: We compared the brain activation on functional magnetic resonance imaging (MRI) during word generation with the activation during electrical stimulation of two language-implicated acupoints in 17 healthy, Mandarin-speaking, Chinese male volunteers (age 19–26 years). All subjects were strongly right handed according to a handedness inventory. Using a standard functional MRI procedure and a word-generation paradigm, significant activation was seen in the left and right inferior frontal gyri (BA 44, 45) as well as the left superior temporal gyrus (BA 22, 42). Stronger activation with a larger volume was seen in the left hemisphere. Electrical stimulation of either one of the two language-implicated acupoints, SJ 8 (11 subjects) and Du 15 (6 subjects), without the word-generation paradigm in the same cohort, produced significant activation in the right inferior frontal gyrus (BA 44, 46) and in the left and right superior temporal gyri (BA 22, 42), respectively. Nevertheless, no activation was seen in the left inferior frontal gyrus. In addition, electrical stimulation of the adjacent non-acupoints did not produce any significant brain activation. Although our results support the notion of acupoint–brain activation, applying acupuncture at SJ 8 or Du 15 does not activate the typical language areas in the left inferior frontal cortex. *Hum. Brain Mapping 18:233–238, 2003.* © 2003 Wiley-Liss, Inc.

Key words: fMRI; neuroimaging; language; Chinese reading; acupuncture

Contract grant sponsor: The Hong Kong Jockey Club Charities Trust; Contract grant sponsor: The Hong Kong University Foundation.

*Correspondence to: Dr. Raymond T. F. Cheung, University Department of Medicine, Faculty of Medicine, The University of Hong Kong, Queen Mary Hospital, Pokfulam Road, Hong Kong. E-mail: rtcheung@hkucc.hku.hk

Received 17 May 2002; Accepted 5 October 2002
DOI 10.1002/hbm.10098

© 2003 Wiley-Liss, Inc.

INTRODUCTION

Acupuncture is a key component of traditional Chinese medicine (TCM) and has been practiced for longer than two millennia [Kaptchuk, 2002]. As alternative medicine, acupuncture was not widely known to the West until the scientific basis of acupuncture-induced analgesia was explored in the mid-1970s. In recent years, acupuncture has become popular among patients and has aroused interest in the scientific community. There are reports on the physiological basis of TCM, for example, pulse diagnosis [Yoon et al., 1987], acupoints [Plummer, 1980], meridians [Zhu et al., 1986], and resonance theory [Wang et al., 1995]. Other studies have reported the therapeutic benefits of acupuncture in various medical disorders [Bullock et al., 2002; Hardware and Lacey, 2002; Johnstone et al., 2002; Kam et al., 2002; Leibing et al., 2002]. The National Institutes of Health Consensus Development Panel concluded that acupuncture is efficacious in some medical conditions and may be helpful in many other conditions [NIH Consensus Conference, 1998]. Nevertheless, its mechanisms remain elusive.

The investigation of neuronal correlates of acupuncture in human brain was hindered by the lack of a non-invasive method until the recent development of functional brain imaging. Studies using functional magnetic resonance imaging (fMRI) or positron emission tomography have provided evidence of acupoint–brain correlation: acupuncture at disease-implicated acupoints modulates the activity of the disease-related neuromatrix. Analgesic points such as gallbladder [GB] 34, large Intestine 4, and stomach 36 have been shown to modulate the activity of the hypothalamic–limbic system [Biella et al., 2001; Hsieh et al., 2001; Hui et al., 2000; Wu et al., 1997, 1999]. Activations of specific cerebral sites were reported for the vision-implicated acupoints (bladder [BL] 67, BL 66, BL 65, and BL 60) [Cho et al., 1998; Siedentofp et al., 2002] and the hearing-implicated acupoints (GB 43) [Cho et al., 2000]. In addition, activations over disease-irrelevant brain sites have also been noted when acupuncture was applied to GB 37 or GB 34 [Gareus et al., 2002; Wu et al., 2002]. Thus, examining cerebral activation due to acupuncture stimulation may clarify the central mechanism of the therapeutic benefit of acupuncture.

According to ancient Oriental literature, at least eight acupoints are relevant to language disorders: small Intestine 19, sanjiao [SJ] 8 of hand-shaoyang meridian, SJ 21, GB 2, du 15 of du meridian, extra point of head and neck (EX-HN) 12, EX-HN 13, and EX-HN 14 [Zmiewski, 1994]. The therapeutic mechanism of applying acupuncture to the language-implicated acupoints is unknown. Electro-acupuncture, an alternative of manual acupuncture, permits stimulation of acupoints in an objective manner [Wu et al., 2002]. To the best of our knowledge, functional neuroimaging has not been previously applied to study the neuronal correlates of electro-acupuncture over language-implicated acupoints. In this study, we compared the brain activation on fMRI between word generation and electrical stimulation of SJ 8 and Du 15. SJ 8 is located in the forearm at mid-position between the distal ulna and the distal radius and at 4 cm above the carpoulnar junction. Du 15 is located in the depression below the spinous process of the first cervical vertebra at 1.5 cm above the midpoint of the posterior hairline.

SUBJECTS AND METHODS

Subjects

The experimental protocol was approved by the Ethics Committee of the Chang Gung Medical Center, Taiwan. Eighteen healthy, Mandarin-speaking, Chinese male volunteers participated after providing informed written consent. All were strongly right handed with a score of more than 40 on a handedness inventory [Snyder and Harris, 1993], in which the highest score was 45. The subject was first familiarized with the experimental procedures and the environmental conditions to minimize anxiety and enhance task performance. Next, the subject lay supine on the scanning table and was supported by a body-length, vinyl-upholstered, dense foam pad. The subject was then fit with plastic ear-canal molds with the head immobilized by a tightly fitting, thermally molded plastic facial mask extending from the hairline to chin.

Imaging methods

All MRI studies were done in a 1.5 T Siemens Vision Whole-body MRI scanner at the MRI Center of Chang Gung Medical Center. A T_2*-weighted gradient-echo echo planar imaging (EPI) sequence was used for the fMRI scans, and in-plane resolution of 3 × 3 mm. The field of view was 192 × 192 mm, and the acquisition matrix was 64 × 64. During the word-generation paradigm, 17 contiguous axial slices of 7 mm in thickness were acquired to cover the whole brain; each slice was scanned 60 times in 120 sec with TR/TE/θ = 2,000 msec/60 msec/90 degrees. Following insertion of four acupuncture needles in each subject (two inserted over SJ 8 and two over the non-acupoints at 1 cm lateral to SJ 8 in 12 subjects; two inserted over du 15 and two over the non-acupoints at 1 cm lateral to du 15 in the remaining subjects), the language paradigm was repeated without electrical stimulation of the acupoints and non-acupoints. During electrical stimulation of the acupoints or non-acupoints, 40 contiguous axial slices of 3 mm in thickness were acquired to cover the whole brain; 108 images were acquired for each slice in 540 sec with TR/TE/θ = 5,000 msec/60 msec/90 degrees. Anatomical MRI was acquired using a T_1-weighted, three-dimensional (3-D), gradient-echo pulse-sequence to provide high-resolution (1 × 1 × 1 mm) images of the entire brain. Extraction of the brain from the 3-D T_1-weighted images was performed using the Statistical Parametric Mapping (SPM) software (Wellcome Department of Cognitive Neurology, London, UK).

Experimental design

The fMRI study employed a block design of RLRL for mapping the brain activation due to the word generation paradigm with R representing rest and L representing the language task. Each period lasted 30 sec. The subject would fix on a small crosshair during the resting period. There were 20 single Chinese characters in each stimulating period. Each character was shown through the goggle for 250 msec, and the subject would silently make up as many meaningful two-character Chinese words as possible during a fixation time of 1,250 msec [Tan et al., 2000]. To map the brain activation due to stimulation of the acupoints or non-acupoints, the fMRI study was repeated in a block design of RARBRBRARARB, with R representing rest with no stimulation, A representing stimulation over the non-acupoints (control acupuncture task), and B representing stimulation over acupoints (active acupuncture task). Each period lasted 45 sec. Bipolar electrical stimulation (Electronic Acupunctoscope, Model WQ-6F, Donghua Electronic Instrument Factory, Beijing, China) of the acupoints or non-acupoints at 2 Hz was made with the positive electrode over the left side and the negative electrode over the right side. Intensity of the stimulation was set at the mid-level between the barely perceptible and maximally tolerable levels, and subjects closed their eyes during the acupoint stimulation in order to reduce eye movements or visual sensory effects.

Data analysis

Post-processing of fMRI data was done using Matlab software (Math Works, Natick, MA) and SPM software. The fMRI images were grouped according to the period of data collection: resting state and language task as well as resting state, control acupuncture task, and active acupuncture task. Activation maps were calculated by comparing the images acquired during each task state with those acquired during the respective resting state except that images obtained during active acupuncture task were compared to that of control acupuncture task and resting state. The fMRI images were motion-corrected, coregistered to anatomical images and smoothed by a 8-mm full-width half-maximum Gaussian kernel. In addition, the fMRI images were normalized to the brain template adopted by the International Consortium for Brain Mapping (ICBM) [Mazziotta et al., 1995]. Physiological noise was filtered using a window function that corresponds to hemodynamic impulse response function (HRF). The first level SPM *t*-contrast map was generated for each subject under each task state using a boxcar function convolved with an empirically derived HRF at a threshold of $P = 0.001$ (uncorrected). The second level analysis of random effects was used for comparisons within each group of subjects under each task state at a threshold of $P = 0.01$ (uncorrected). Brodmann's area (BA) designations were applied using the Talairach Daemon [Lancaster et al., 2000]. In this study, significant activation in the inferior frontal (BA 9, 44, 45, 46), superior temporal (BA 22, 42), angular (BA 39), supramarginal (BA 40), and fusiform (BA 19, 37) gyri was considered relevant to the language task [Binder et al., 1994; Booth et al., 2002; Brunswick et al., 1999; Buchel et al., 1998; Noppeny and Price, 2002; Poldrack et al., 1999; Tan et al., 2000; Thierry et al., 1999]. One subject did not contribute to the group activation map during language task or stimulation of acupoints and non-acupoints related to SJ 8 because no activation was seen in the first level SPM *t*-contrast map. Thus, 17 subjects contributed to the activation map of the language task; there were 11 and 6 subjects, respectively, for electro-acupuncture over SJ 8 and du 15.

RESULTS

Age of the subjects ranged from 19 to 26 years (median = 22 years). Table I summarizes the regions of significant activation due to the language task or acupoint stimulation. During the language task, positive activation was seen in the left inferior frontal gyrus (BA 44, 45) and the left superior temporal gyrus (BA 22, 42) as well as in the right inferior frontal gyrus (BA 44; Fig. 1A and Table I). The volume of the activated region was larger in the inferior frontal gyrus (BA 44, 45) than the superior temporal gyrus (BA 22, 42). In addition, stronger activation of a larger volume was seen in the left than right hemisphere. During stimulation of SJ 8, the right inferior frontal gyrus (BA 44, 46) gyri showed positive activation (Fig. 1B and Table 1). During stimulation of du 15, the left (BA 22, 42) and right (BA 22, 42) superior temporal gyri showed positive activation with a larger volume of activation on the left side (Fig. 1C and Table 1). No activations were found in the typical language area of the left inferior frontal gyrus during stimulation of

TABLE I. Regions of significant activation during language task or during stimulation of SJ 8 or Du 15 relative to the respective resting state

		Language task (n = 17)				Stimulation of SJ 8 (n = 11)				Stimulation of Du 15 (n = 6)			
		Coordinates			Vol.	Coordinates			Vol.	Coordinates			Vol.
Activated regions	BA	*x*	*y*	*z*	(mm^3)	*x*	*y*	*z*	(mm^3)	*x*	*y*	*z*	(mm^3)
R inferior frontal gyrus	44	55	18	16	14,192	48	12	16	17,899				
R inferior frontal gyrus	46					40	32	16	8,949				
L inferior frontal gyrus	44, 45	−55	15	16	48,256								
L superior temporal gyrus	22, 42	−64	−40	16	880					−62	−44	16	20,960
R superior temporal gyrus	22, 42									63	−30	16	11,648

BA, Brodmann's area.

these two language-disorder–related acupoints. The volume of activated regions was smaller than that obtained during the language task. Electrical stimulation of the adjacent non-acupoints did not produce any significant brain activation.

DISCUSSION

Previous studies have reported the important left cortical sites for language in right-handed subjects. Left fusiform gyrus (BA 19, 37) appears to contain orthographic representations of words [Brunswick et al., 1999; Buchel et al., 1998]. Wernicke's area (BA 22) within the left superior temporal gyrus (BA 42) and the surrounding left angular (BA 39) and supramarginal (BA 40) gyri are involved in the integration of auditory and visual signals as well as the interpretation of words [Binder et al., 1994; Booth et al., 2002; Thierry et al., 1999]. Broca's area (BA 44, 45) and the surrounding left inferior frontal gyrus (BA 9, 46) are important for language output [Noppeny and Price, 2002; Poldrack et al., 1999; Thierry et al., 1999]. In the present study, intense activation is seen over the left and right inferior frontal gyri (BA 44, 45) as well as the left superior temporal gyrus (BA 22, 42) during the language task of generating meaningful two-character Chinese words. Stronger activation of a larger volume is seen over the left hemisphere, which is dominant for language in right-handed people. Our results are in accordance with the literature. In addition, the right homologous areas of the left cortical sites are active during a language task [Luke et al., 2002; Tan et al., 2000].

SJ 8 and du 15 are two important treatment points for language disorders [Zmiewski, 1994]. It is interesting to explore the neuromatrix associated with stimulation of these two acupoints and compare the activated sites with that of common language tasks. Stimulation of SJ 8 but not non-acupoint near SJ 8 activates the right inferior frontal gyrus (BA 44, 46), which is also involved in the processing of some language tasks [Tan et al., 2000]. Stimulation of du 15 but not non-acupoint near du 15 activates the left and right superior temporal gyri (BA 22, 42) with a larger volume of activation on the left hemisphere. Activation of the superior temporal gyrus is more related to semantic than syntactic processing of Chinese [Luke et al., 2002]. However, the pattern of brain activation associated with language task is not consistent with that associated with electro-acupuncture. While distinctive brain sites are activated upon stimulation of these two language-implicated acupoints, the left inferior frontal gyrus, which is the typical site activated by the language task, is not involved. Given the complexity of the language system and simplicity of the current stimulation paradigm as compared to actual acupuncture therapy, the present results should not be taken to refute the potential benefit of these two acupoints in language disorders. It is possible that modulation of the activity of the right homologues of the left inferior prefrontal areas during stimulation of SJ 8 or du 15 is beneficial in some specific types of language disorders. Further studies using functional neuroimaging should be conducted to compare the acupoint-related neuromatrix with other language tasks.

In conclusion, applying acupuncture at SJ 8 or du 15 does not activate the typical language areas in the left inferior frontal cortex. Nevertheless, our results support the notion of acupoint–brain correlation and the proposition that acupuncture at disease-implicated acupoints modulates the activity of the disease-related neuromatrix. The present results also suggest that acupuncture treatment at SJ 8 or du 15 may improve certain language disorders by activating the right ho-

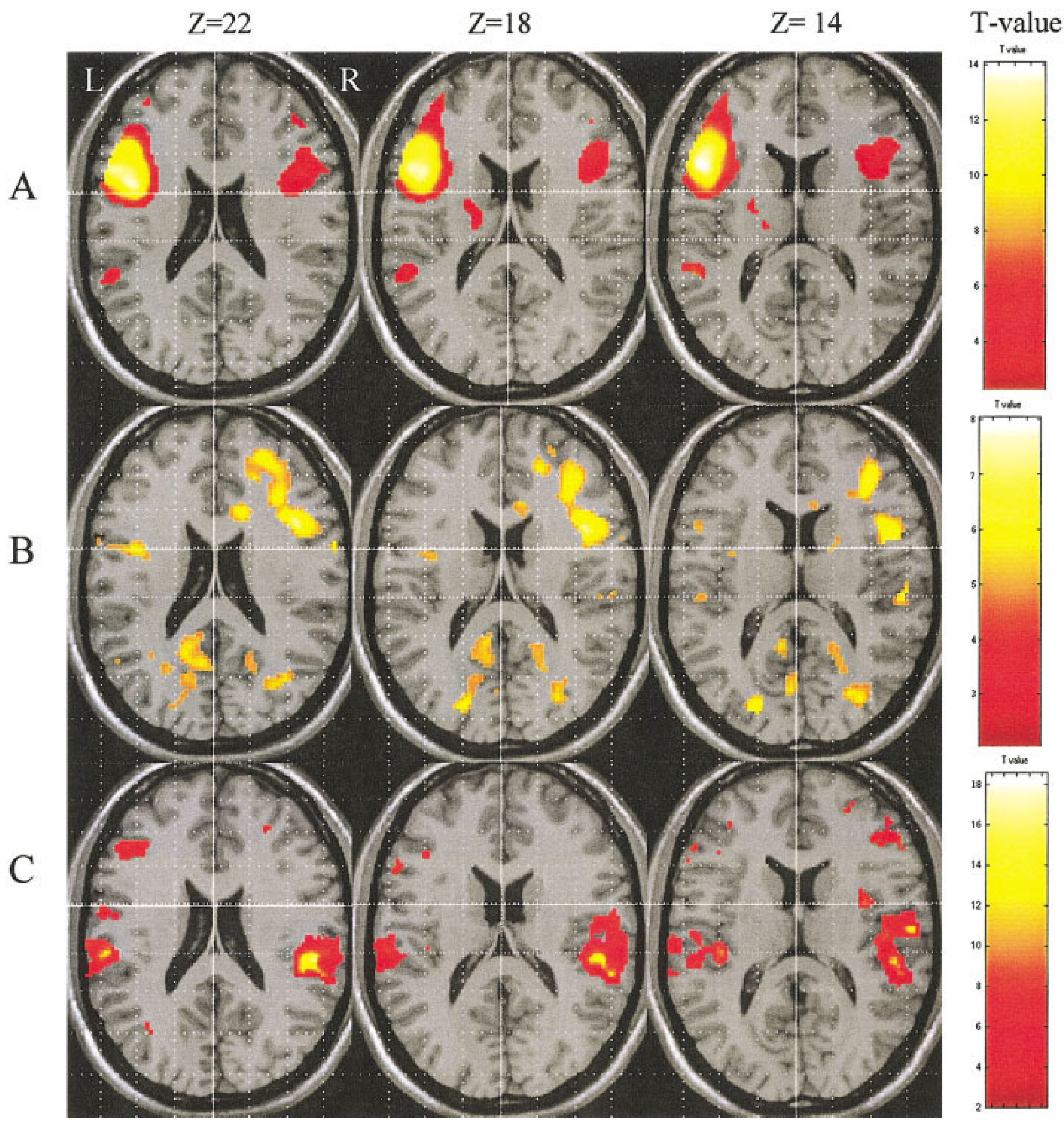

Figure 1.

Normalized SPM *t*-maps (in color) overlaid on the corresponding axial T_1-weighted images (in gray scale labeled with the height [Z] in mm relative to the bicommissural line) showing statistically significant ($P < 0.01$) brain activations due to the language task in a group of 17 subjects (**A**) or bipolar electrical stimulation of SJ 8 in a subgroup of 11 subjects (**B**) or of du 15 in a subgroup of 6 subjects (**C**). During the language task (A), activation is seen in the left inferior frontal (BA 44, 45) and superior temporal (BA 22, 42) gyri as well as the right inferior frontal gyrus (BA 44). Activation is also seen in the left thalamus and left deep white matter. Stimulation of SJ 8 (B) produces activation in the right inferior frontal gyrus (BA 44, 46). Smaller areas of activation are also seen in the right frontal white matter, right deep white matter, left frontal white matter, left occipital lobe, and right occipital lobe. Stimulation of du 15 (C) produces activation in the left and right superior temporal gyri (BA 22, 42). Small areas of activation are also seen in the white matter underneath the right and left middle frontal gyri.

mologous areas of the typical language areas. Exploring the brain activation during acupoint stimulation may reveal the central neural mechanism of acupuncture treatment. Further functional neuroimaging studies on treatment-relevant acupoints are warranted.

ACKNOWLEDGMENTS

We appreciate the assistance of Miss Queenie C.C. Chan in processing the fMRI data and the help of Mr. Jian-Chuan Chen in collecting the MRI data.

REFERENCES

Biella G, Sotgiu ML, Pellegata G, Paulesu E, Castiglioni I, Fazio F (2001): Acupuncture produces central activations in pain regions. Neuroimage 14:60–66.

Binder JR, Rao SM, Hammeke TA, Yetkin FZ, Jesmanowicz A, Bandettini PA, Wong EC, Estkowski LD, Goldstein MD, Haughton VM, Hyde JS (1994): Functional magnetic resonance imaging of human auditory cortex. Ann Neurol 35:662–672.

Booth JR, Burman DD, Meyer JR, Gitelman DR, Parrish TB, Mesulam MM (2002): Functional anatomy of intra- and cross-modal lexical tasks. Neuroimage 16:7–22.

Brunswick N, McCrory E, Price CJ, Frith CD, Frith U (1999): Explicit and implicit processing of words and pseudowords by adult developmental dyslexics. Brain 122:1901–1917.

Buchel C, Price CJ, Friston K (1998): A multimodal language region in the ventral visual pathway. Nature 394:274–277.

Bullock ML, Kiresuk TJ, Sherman RE, Lenz SK, Culliton PD, Boucher TA, Nolan CJ (2002): A large randomized placebo controlled study of auricular acupuncture for alcohol dependence. J Subst Abuse Treat 22:71–77.

Cho ZH, Chung SC, Jones JP, Park JB, Lee HJ, Wong EK, Min BI (1998): New findings of the correlation between acupoints and corresponding brain cortices using functional MRI. Proc Natl Acad Sci 95:2670–2673.

Cho ZH, Hong IK, Kang CK, Kim JS, Na CS, Park KJ, Jeong KW, Wong EK (2000): Acupuncture-stimulated auditory-cortical activation observed by fMRI: a case of acupoint SJ5 stimulation. Proc Int Soc Mag Reson Med 8:327.

Gareus IK, Lacour M, Schulte AC, Hennig J (2002): Is there a BOLD respoinse of the visual cortex on stimulation of vision-related acupoint GB 37? J Magn Reson Imaging 15:227–232.

Hardware B, Lacey A (2002): Acupuncture and other alternative therapies in rheumatoid arthritis. Prof Nurse 17:437–439.

Hsieh JC, Tu CH, Chen FP, Chen MC, Yeh TC, Cheng HC, Wu YT, Liu RS, Ho LT (2001): Activation of the hypothalamus characterizes the acupuncture stimulation at the analgesic point in human: a positron emission tomography study. Neurosci Lett 307:105–108.

Hui KK, Liu J, Makris N, Gollub RL, Chen AJ, Moore CI, Kennedy DN, Rosen BR, Kwong KK (2000): Acupuncture modulates the limbic system and subcortical gray structures of the human brain: evidence from fMRI studies in normal subjects. Hum Brain Mapp 9:13–25.

Johnstone PA, Niemtzow RC, Riffenburgh RH (2002): Acupuncture for xerostomia. Cancer 94:1151–1156.

Kam E, Eslick G, Campbell I (2002): An audit of the effectiveness of acupuncture on musculoskeletal pain in primary health care. Acupunct Med 20:35–38.

Kaptchuk TJ (2002): Acupuncture: theory, efficacy, and practice. Ann Intern Med 136:374–383.

Lancaster JL, Woldorff MG, Parsons LM, Liotti M, Freitas CS, Rainey L, Kochunov PV, Nickerson D, Mikiten SA, Fox PT (2000): Automated Talairach Atlas labels for functional brain mapping. Hum Brain Mapp 10:120–131.

Leibing E, Leonhardt U, Köster G, Goerlitz A, Rosenfeldt JA, Hilgers R, Ramadori G (2002): Acupuncture treatment of chronic low-back pain: a randomized, blinded, placebo-controlled trial with 9-month follow-up. Pain 96:189–196.

Luke KK, Liu HL, Wai YY, Wan YL, Tan LH (2002): Functional anatomy of syntactic and semantic processing in language comprehension. Hum Brain Mapp 16:133–145.

Mazziotta JC, Toga AW, Evans A, Fox P, Lancaster J (1995): A probabilistic atlas of the human brain: theory and rationale for its development. The International Consortium for Brain Mapping (ICBM). Neuroimage 2:89–101.

NIH Consensus Conference (1998): Acupuncture. JAMA 280:1518–1524.

Noppeney U, Price CJ (2002): A PET study of stimulus- and task-induced semantic processing. Neuroimage 15:927–935.

Plummer JP (1980): Anatomic findings at acupuncture Loci. Am J Chin Med 8:170–180.

Poldrack RA, Wagner AD, Prull MW, Desmond JE, Glover GH, Gabrieli JDE (1999): Functional specialization for semantic and phonological processing in the left inferioir prefrontal cortex. Neuroimage 10:15–35.

Siedentopf CM, Golaszewski SM, Mottaghy FM, Ruff CC, Felber S, Schlager A (2002): Functional magnetic resonance imaging detects activation of the visual association cortex during laser acupuncture of the foot in humans. Neurosci Lett 327:53–56.

Snyder PJ, Harris LJ (1993): Handedness, sex and familiar sinistrality effects on spatial tasks. Cortex 29:115–134.

Tan, LH, Spinks JA, Gao JH, Liu HL, Perfetti CA, Xiong JH, Stofer KA, Pu YL, Liu YJ, Fox PT (2000): Brain activation in the processing of Chinese characters and words: a functional MRI study. Hum Brain Mapp 10:16–27.

Thierry G, Boulanouar K, Kherif F, Ranjeva JP, Demonet JF (1999): Temporal sorting of neural components underlying phonological processing. Neuroreport 10:2599–2603.

Wang WK, Hsu TL, Huang ZY, Wang YY (1995): Collective effect of a Chinese formula: a study of xiao–jian–zhong–tang. Am J Chin Med 23:121–130.

Wu MT, Xiong J, Yang PC, Hsieh JC, Tsai G, Rosen BR, Kwong KK (1997): Acupuncture modulating the limbic brain detected by functional MR imaging. Neuroimage 5:S15.

Wu MT, Hsieh JC, Xiong J, Yang CF, Pan HB, Chen YCI, Tsai GC, Rosen BR, Kwong KK (1999): Central nervous pathway for acupuncture stimulation: localization of processing with functional MR imaging of the brain: preliminary experience. Radiology 212:133–141.

Wu MT, Sheen JM, Chuang KH, Yang P, Chin SL, Tsai CY, Chen CJ, Liao JR, Lai PH, Chu KA, Pan HB, Yang CF (2002): Neuronal specificity of acupuncture response: a fMRI study with electroacupuncture. Neuroimage 16:1028–1037.

Yoon SH, Koga Y, Matasumoto I, Ikezono E (1987): An objective method of pulse diagnosis. Am J Chin Med 15:147–153.

Zhu S, He Q and Meng Z (1986): Studies of phenomenon of latent PSC and preliminary study of its skin electrical conductance. In: Zhang X, editor. Research on acupuncture, moxibustion and acupuncture anesthesia. Beijing: Springer-Verlag; p 721–728.

Zmiewski P (1994): Chinese acupuncture. Brookline, MA: Paradigm.