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Modulation of cerebellar activities by acupuncture stimulation: evidence from fMRI study

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Recent neuroimaging studies have revealed that acupuncture stimulation modulates human central nervous system including cerebral limbic/paralimbic and subcortical structures. Due to the wide and intricate connections with cerebrum, we hypothesized that anatomically specific areas in human cerebellum are also modulated by acupuncture stimulation beyond classical involvement of cerebellum in motor coordination. Functional MRI (fMRI) was used to investigate neural substrates responding to the acupuncture stimulation of Pericardium 6 (PC6, *Neiguan*), an acupoint relevant for the management of nausea including vestibular-related motion sickness. Sham stimulation near the acupoint and tactile stimulation on the skin of the acupoint were given as separate conditions. Psychophysical scores as well as the heart and respiratory rates were measured during each condition. Acupuncture manipulation on PC6, in comparison to the sham acupuncture and tactile stimulation conditions, selectively activated left superior frontal gyrus, anterior cingulate gyrus, and dorsomedial nucleus of thalamus. Acupuncture-specific neural substrates in cerebellum were also evident in declive, nodulus, and uvula of vermis, quadrangular lobule, cerebellar tonsil, and superior semilunar lobule. Negative MR signal changes, often seen during the acupuncture of analgesic points, were not observed in the present study. Our data suggest that cerebellum serves as important activation loci during the acupuncture stimulation of PC6, and clinical efficacy of PC6 may be mediated by the cerebellar vestibular neuromatrix.

Keywords: Neuroimaging; Complementary medicine; Cerebellum; Vestibular system; Acupuncture

Introduction

Acupuncture is used extensively in Oriental Medicine and has emerged as an important modality of complementary and alternative therapy to Western Medicine (Eisenberg et al., 1993,1998; Kaptchuck, 2000; Richardson and Vincent, 1986). In the United States, a panel of experts concluded that acupuncture showed efficacy in treating postoperative and chemotherapy nausea and vomiting (National Institute of Health Consensus Development Panel, 1997). In spite of its long history and public acceptance, an unequivocal scientific explanation regarding the physiological mechanism of acupuncture has not been found and awaits further investigation. Various animal data and clinical observations suggest that acupuncture modulates activities in the central nervous system (CNS) and influences treatment areas via release of neurotransmitters/hormones or direct modulation of neural pathway (Bing et al., 1991; Kho et al., 1993; Kiser et al., 1983; Peets and Pomeranz, 1978; Shen, 2001). Cho et al. (1998), from their pioneering functional MRI (fMRI) investigation of acupuncture, proposed CNS to be an important mediator of acupuncture effects. Subsequent fMRI investigations on several acupuncture points demonstrated that regionally specific, quantifiable activation in CNS elicited by acupuncture can be detected, providing further information for the hypothesized neuro-functional modulation (Cho et al., 1998; Hui et al., 2000; Li et al., 2003; Siedentopf et al., 2002; Wu et al., 1999, 2002). Involvement of limbic/paralimbic systems and subcortical brain structures such as nucleus accumbens, amygdala, and hippocampus during the acupuncture stimulation was discovered from these imaging studies (Hui et al., 2000; Wu et al., 1999).

Human cerebellum, with its complicated afferent and efferent connections with the cerebrum and adjacent midbrain regions, provide a crucial role in high-order cognitive functions and affective behavior in addition to its classical role in motor coordination and gating (Allen et al., 1997; Desmond et al., 1997; Houk and Wise, 1995; Vaina et al., 2001). For example, pain- and attention-related loci in cerebellum (Iadarola et al., 1998; Ploghaus et al., 1999) have been identified along with its role in perceptual learning (Vaina et al., 2001). A recent fMRI investigation by Wu et al. (2002) found cerebellar activity associated with electro-acupuncture of the analgesic acupoint GB34. This study provides the initial evidence of a modulatory effect of acupuncture on the cerebellum. Based on the previous findings of modulatory effects of acupuncture on the CNS, together with existing knowledge on the presence of extensive neural connections with the cerebrum (Afifi and Bergman, 1998; Houk and Wise, 1995), we hypothesized that acupuncture modulates anatomically specific cerebellar neural substrates in addition to cerebral involvement.

Based on the postulation that different acupoints modulate distinct cortical networks and related symptom/disease conditions

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(Cho et al., 1998), we endeavored to identify symptoms associated with lesions or abnormalities in cerebellum to find a subsequent treatment acupoint. Clinical symptoms associated with lesions or strokes in the cerebellum include nausea, vomiting, dizziness, and vertigo with the presence of ataxia (Adams, 2001). Although it is not used in the treatment of stroke, Pericardium 6 (PC6, *Neiguan*), in the flexor aspect of the forearm between the tendons of palmaris longus and flexor carpi radialis, is a commonly used acupoint for relieving some of these symptoms (Deadman and Al-Khafaji, 1998; Stux and Pomeranz, 1997). PC6 is traditionally known to be effective in treating nausea and vomiting associated with motion sickness (Boehler et al., 2002; Pomeranz and Stux, 1989). It also has been used in alleviating nausea accompanying the early stage of pregnancy (morning sickness) or chemotherapy (de Aloysio and Penacchioni, 1992; Shen et al., 2000; Stux and Pomeranz, 1997). Although the nausea is the result of multiple physiological processes that may not necessarily involve cerebellum, for example, mediation via vagal/sympathetic visceral nervous system, the vomiting center (VC) and a chemoreceptor trigger zone (CTZ) in medulla (Adams, 2001), we hypothesized that the cerebellum may contain important neural substrates for the clinical efficacy of PC6 with its role in vestibular control.

We performed functional MRI (fMRI) on healthy volunteers and examined the neural substrates modulated by the acupuncture stimulation of PC6. To investigate the anatomical specificity of the real acupuncture compared to classical tactile stimulation or placebo control, the acupuncture condition was contrasted to the perception of simple tactile stimulation and then to the 'sham' stimulation of a non-acupoint proximal to PC6. Several psychophysical parameters such as pain, unpleasantness, and anxiety, as well as respiratory and heart rates were measured from subjects.

Method and materials

Participants

All procedures were conducted in accordance with the ethical guidelines set forth by the IRB. Twelve healthy volunteers (female/male = 5:7, aged 27.2 $\pm$ 6.3, all right-handed) participated in the study with informed consent. Subjects had no history of head trauma, neurological disease, substance abuse, or dependency. Subjects at the time of study were free of any transient medical problems or symptoms including chronic pain and headache. Four participants had previous experience and cultural exposure to acupuncture. All other participants were naïve to acupuncture stimulation.

Pre-fMRI testing

Before the fMRI exam, acupuncture stimulation on PC6 was given to all participants to lessen the psychological uneasiness toward the needle stimulation. We intended to reduce confounding effects of any emotions and cognitive behaviors toward first-time exposure to acupuncture. The subjects lied comfortably in a reclined supine position, and PC6 stimulation was given to the right wrist for 10 s using the technique of Traditional Manual Acupuncture (TMA) (Hui et al., 2000). A disposable, individually wrapped, one time use only, sterile MR-compatible silver #36-gauge acupuncture needle was inserted to a depth of less than 1 cm. Stimulation was delivered by gentle manual rotation of about 2 Hz, using a balanced 'tonifying and reducing' technique. Each subject was able to describe the sensation associated with typical *deqi* phenomena (which is often described as numbness, distention, heaviness, fullness, or soreness; Baldry, 1998; Park et al., 2002a,b; Streitberger and Kleinhenz, 1998). Additionally, we examined the subject's tolerance to acupuncture. All subjects endured the pre-fMRI acupuncture session without emotional distress to the acupuncture.

Stimulation paradigm

The subject lied supine in the center of the MR magnet bore during which the hand and wrist areas were exposed outside of the opening of the bore so that the acupuncturist could have access to the acupoint. The acupuncturist monitored the scan time inside the MR room and delivered the stimulation to PC6. The study consisted of three different conditions: (1) real acupuncture stimulation, (2) 'sham' acupuncture stimulation close to the designated acupuncture point with no particular clinical relevance, and (3) simple tactile stimulation on the skin of the PC6 point.

Acupuncture stimulation was delivered to the PC6 point of the right wrist using the same method in the pre-fMRI tests. During the sham condition, the skin near the PC6 (about 1.5–2 cm proximal to the PC6 area targeting palmaris longus and flexor carpi ulnaris using palpation) was stimulated with a needle depth and frequency similar to the real acupuncture. Since sham acupoints may have therapeutic effects similar to the real acupuncture (Margolin et al., 1993; Wu et al., 2002), great care was given to avoid nearby lung and heart-related acupoints (*LU6 Kongzui* and *PC5 Jianshi*). With their eyes closed, subjects were not able to spatially distinguish the sham and real acupuncture points. Tactile stimulation, as one of the control condition, was delivered by gentle brushing of a MR-compatible vonFrey monofilament (pressure rating of 133 g/mm^2, Somedic Inc., Horby, Sweden) at 2 Hz frequencies.

Since needle insertion itself does not create significant effects on overall acupuncture effects (Hui et al., 2000), each fMRI session began with the needle in place about a minute before the start of the scan. The sequence of the presentation of each stimulation condition was randomized and balanced throughout the subject population. Two stimulation blocks, each 1 min in duration, were interleaved by three 1-min rest periods. During the stimulation periods, subjects were asked to passively attend to incoming sensation or listen to the gradient noise to prevent possible distraction by imagery, which was often reported by subjects from our previous experience. The process resulted in two stimulation periods interleaved by three rest conditions with equal length in time. Subject's head motion was limited using MR-compatible cushions (X-Ray products, New York).

Measurement of psychophysical parameters

Visual analogue scale (VAS) rating on pain, unpleasantness, and anxiety level was measured using a VAS questionnaire (ranging from 0 to 10, 0 being minimum to 10 being maximum) following each functional session (Wu et al., 1999). Heart and respiratory rates were measured using a MR-compatible monitoring device (GE Medical Systems, Wisconsin) at the middle of each rest and stimulation period. The rates were then grouped for rest and stimulation period and compared using paired t test to determine the presence of modulation of the autonomic nervous system controlling heart and respiratory rates.

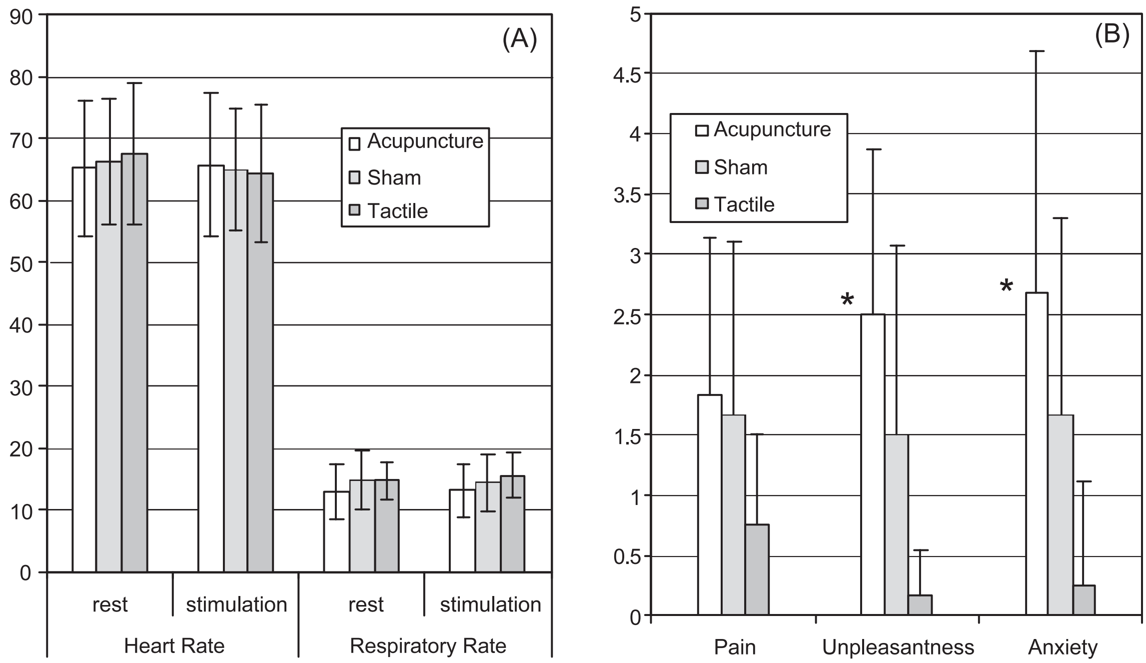

Fig. 1. Bar graphs of (A) heart/respiratory rates and (B) psychophysical ratings averaged across 12 subjects. Significant difference ($P < 0.01$) of real acupuncture stimulation compared to the tactile stimulation condition was observed in unpleasantness and anxiety level (marked with *).

MR imaging

Images were acquired with a three-axis gradient head-coil in the 1.5-T MR scanner (GE Medical) equipped for echo planar imaging. Spin-echo T_1-weighted three-plane images [three slices in each direction, TE/TR = 10/700 ms, 24 × 24 cm field-of-view (FOV), matrix size of 128 × 256, 5 mm slice thickness, 1.5 mm slice gap] were acquired for anatomical localization. Following the anatomical localizer sequence, high-resolution structural information on each subject was obtained using 3D SPGR (Spoiled Gradient Recalled) sequence (sagittal orientation, TR/TE = 35/7 ms, FA = 45°, 1.5 mm slice thickness, 256 × 192 in-plane matrix, 24 × 24 cm FOV).

Table 1
Group activation results across 12 subjects for three different conditions

Anatomy	BA	Side	Real acupuncture vs. rest				Sham acupuncture vs. rest				Tactile stimulation vs. rest			
			x	*y*	*z*	*Z* score	*x*	*y*	*z*	*Z* score	*x*	*y*	*z*	*Z* score
Postcentral gyrus (SI)	3/1/2	L	−55	−25	44	4.53	−53	−32	41	2.86	−57	−27	43	3.16
Insula		L	−40	−2	−8	3.16	−39	13	1	3.56	−40	17	6	3.52
		R	48	7	−7	2.82	49	9	1	2.68	48	26	8	4.03
Medial frontal gyrus	8	L	−3	24	43	3.22								
Transverse temporal gyrus	42	L	−57	−11	13	4.17	−57	15	3	4.34	−55	−5	8	4.40
		R	51	−10	2	3.43	55	−22	6	2.82	51	−15	10	3.61
Superior temporal gyrus	22	L	−57	−51	19	3.54								
		R	59	−52	19	3.62	64	−40	8	3.31				
	38	L	−53	15	−7	3.19	−58	13	−6	3.52	−52	10	−6	3.29
		R	57	4	−7	2.93					58	6	−6	3.28
Middle temporal gyrus	37	L					−55	−58	−2	3.66	−50	−65	12	3.74
		R					53	−53	−2	4.41				
Inferior parietal lobule	40	L	−46	−48	52	3.02	−53	−39	41	3.31				
Parietal operculum (SII)	40/43	L	−57	−22	21	3.73	−65	−26	23	3.58	−60	−32	23	3.37
		R	−55	−22	20	3.72	53	−34	24	3.89	53	−34	16	3.15
Thalamus (dorsomedial nucleus)		L	−12	−19	10	3.43								
Cerebellar vermis/declive (VI)[a]		m	2	−70	−12	2.64								
Cerebellar vermis/nodulus (X)		m	0	−51	−28	3.34								
Cerebellar sup. semilunar lobule		L	−22	−73	−18	4.2								
(Crus I)		R	24	−68	−15	3.57								
Cerebellar quadrangular lobule		L	−23	−61	−16	2.75								
(HVI)		R	−24	−62	−17	2.83								

None of the gray matter areas were noted examining the negative signal changes during the stimulation period. Hemisphere: L, left; R, right; m, middle.
[a] Anatomical labels based on Larsell nomenclature in parenthesis (Larsell, 1970; Schmahmann et al., 1999).

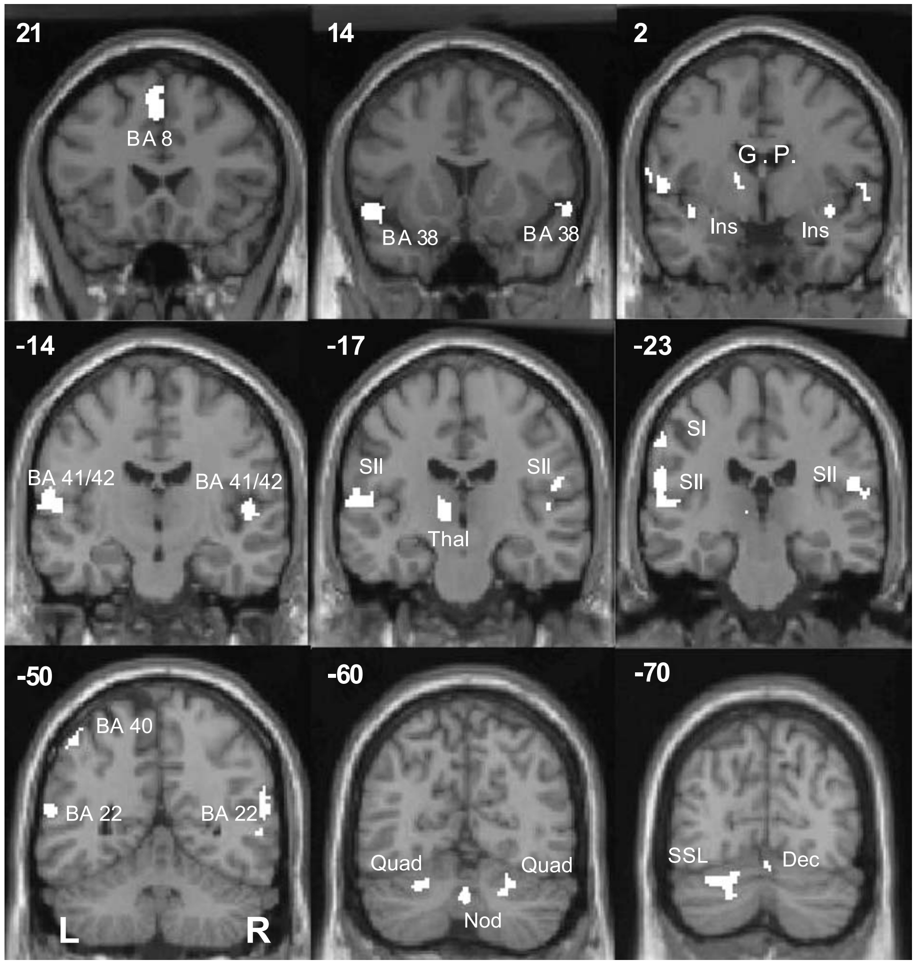

Fig. 2. The group activation map thresholded at $P < 0.005$ (spatial extent thresholded at $P < 0.05$) for the real acupuncture > rest condition with Brodmann's area nomenclature. Talairach coordinates, from anterior to posterior direction, are shown in the upper left corner of each slice. SI, primary somatosensory area; SII, secondary somatosensory area; Ins, insula; Thal, thalamus; Quad, cerebellar quadrangular lobule; SSL, cerebellar superior semilunar lobule; Nod, cerebellar nodulus; Dec, declive of vermis; Uvl, cerebellar uvula; Tns, cerebellar tonsil.

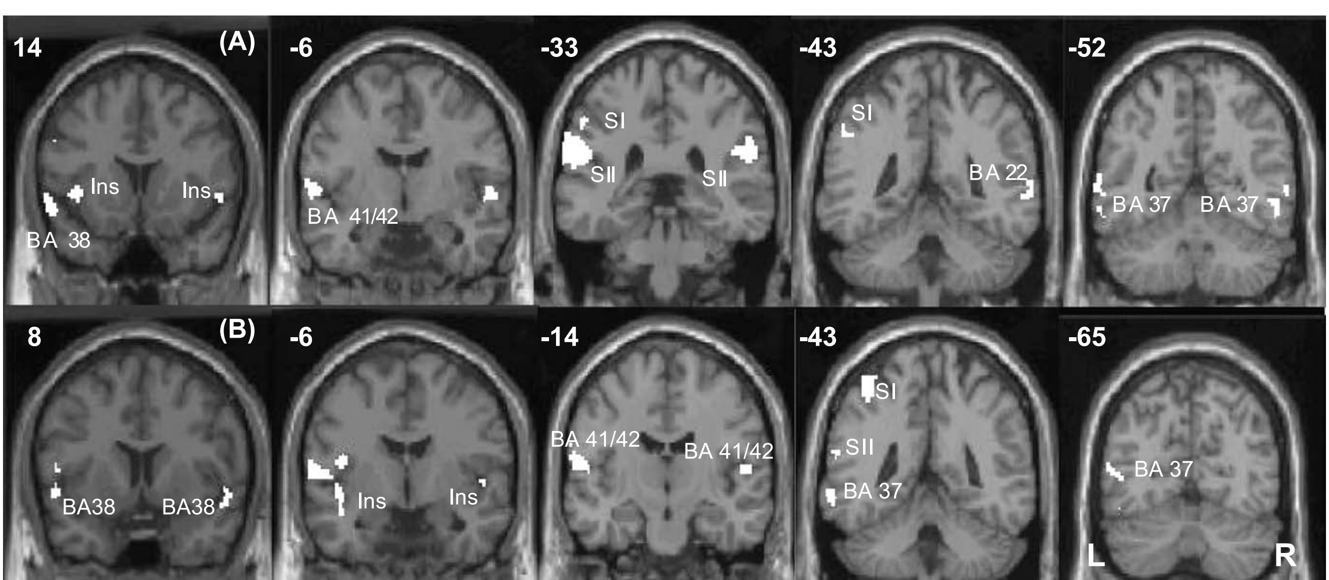

Fig. 3. The group activation map for the (A) sham acupuncture > rest condition and (B) tactile stimulation > rest condition.

Table 2
Group activation results of real acupuncture stimulation compared to the sham acupuncture and tactile stimulation conditions

Anatomy	BA	Side	Real acupuncture > sham acupuncture				Real acupuncture > tactile stimulation			
			x	*y*	*z*	*Z* score	*x*	*y*	*z*	*Z* score
Precentral gyrus	4	L	−46	−18	22	4.04				
Superior frontal gyrus	10	L	−26	55	5	3.43	−24	59	12	3.85
Superior temporal gyrus	22	R					61	−48	13	4.2
Anterior cingulate	24	m	1	19	23	3.51	−3	33	6	5
Precuneus	7	L					−3	−52	45	3.75
		R					4	−52	45	3.78
Thalamus (dorsomedial nucleus)		L	−11	−19	5	3.25	−10	−23	3	3.42
Cerebellar vermis/declive (VI)[a]		m	−1	−72	−10	3.46	−1	−69	−8	3.67
Cerebellar vermis/nodulus (X)		m	2	−48	−29	3.65	−2	−49	−28	2.98
Cerebellar vermis/uvula (X)		m	−4	−62	−33	3.36	−3	−65	−33	3.31
Cerebellar tonsil (IX)		L	−6	−60	−37	3.43	−5	−65	−36	3.52
Cerebellar sup. semilunar lobule (Crus I)		L	−24	−74	−18	3.24	−23	−73	−17	3.94
		R					24	−67	−18	3.13
Cerebellar quadrangular lobule (HVI)		L	−18	−55	−19	3.69				
		R					20	−59	−16	3.49

[a] Anatomical labels based on Larsell nomenclature in parenthesis.

Functional images were collected with T2*-weighted gradient echo planar imaging sequence, with in-plane resolution of 3.75 mm (64 × 64 matrix, 24 × 24 cm FOV). TR/TE = 2500/55 ms and flip angle of 90° were used to detect a blood oxygenation level-dependent (BOLD) signal changes associated with neuronal activation. The regions covering entire cerebrum and cerebellum were imaged with 28 axial slices of 5 mm in slice thickness. After the acquisition of five sets to allow for the T1 equilibration, each functional scan session generated 120 sets of images. Considering the stimulation paradigm, 24 sets of volume images were acquired during each stimulation/rest block.

Data processing

After the storage, the fMRI data was subjected to detailed analysis. Each image volume was motion-corrected and registered to the image space of the first scan session using SPM99 software. Subsequently, each image volume was normalized to the standardized Talairach coordinates (Talairach and Tournoux, 1998). Normalized images were smoothed with 6 mm full-width-at-half maximum (FWHM) isotropic Gaussian kernel to decrease the spatial noise. Group-level activation across the subjects was examined using SPM's random effect model that employs a hierarchical two-stage procedure (Friston et al., 1999). In the first stage, the individual contrast images for the effect of interest were generated by calculating voxel-wise *t* statistics with respect to the reference waveform that is designed to conform to the task paradigm using the canonical hemodynamic response function (Friston et al., 1996). Confounding effects of fluctuations in the global mean were removed by scaling the signal intensity of each voxel to the global mean for each time point. In the second stage, one-tailed *t* test was applied to a set of contrast images to determine

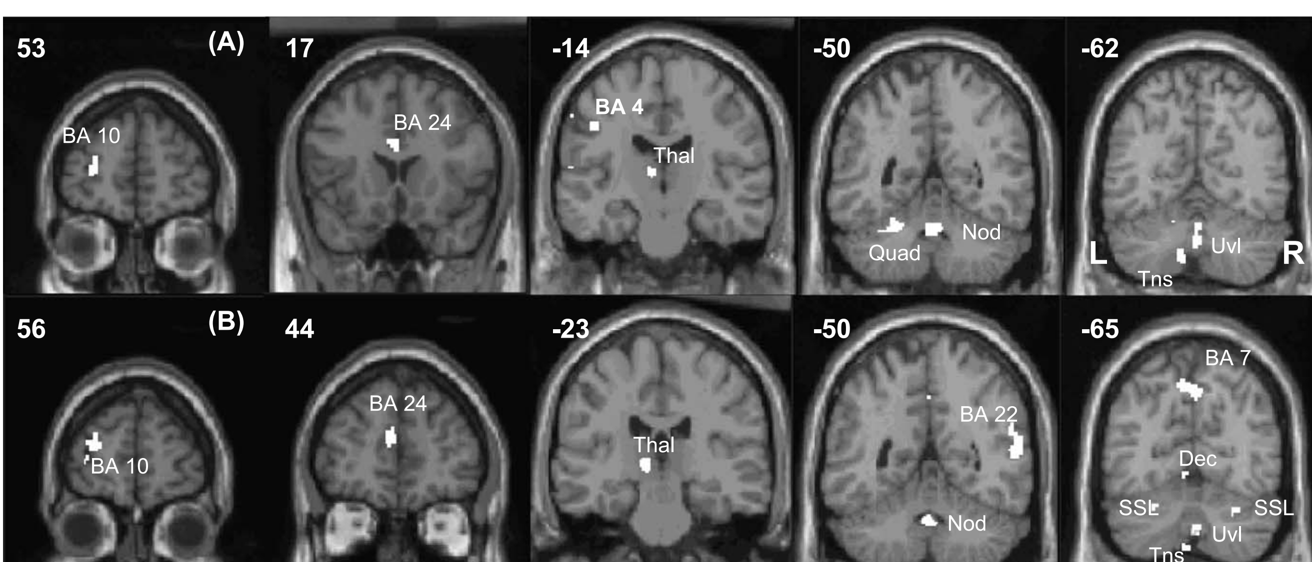

Fig. 4. The group activation map of the (A) real acupuncture > sham acupuncture condition, and (B) real acupuncture > tactile stimulation condition.

the group-level activation. Resulting t statistics were normalized to Z scores, and clusters of significant activation were defined using the joint expected probability distribution of height ($Z > 2.58$; $P < 0.005$) and spatial extent ($P < 0.05$) of the activation. The location of activation in Talairach space was converted to the corresponding anatomical and Brodmann's area (BA) nomenclature. For the cerebellar activation, we jointly used the anatomical name provided by Larsell nomenclature (Larsell, 1970; Schmahmann et al., 1999) and by Dubernoy (1995).

We constructed the matrix of activation/deactivation functional maps comparing (1) real acupuncture condition > rest, (2) sham acupuncture > rest, and (3) tactile condition > rest. To examine the acupuncture-specific neural substrates, combinations of (4) real acupuncture > sham stimulation and (5) real acupuncture > tactile stimulation were also examined. The converse of all contrast conditions was examined to probe for any negative BOLD signal changes or relative signal decrease.

Results

Psychophysical parameters

All subjects successfully underwent acupuncture stimulation. Fig. 1 shows the analysis of the three psychophysical scores and heart and respiratory rates. Across the stimulation condition, there were no significant changes in heart and respiratory rates (paired t test, $P > 0.05$). Neither imagery nor excessive pain was reported from any of the subjects. Level of pain was kept low throughout all conditions (paired t test across the pairs of conditions, $P > 0.01$). In comparison between acupuncture and tactile stimulation, unpleasantness and anxiety levels were significantly elevated during the acupuncture stimulation (paired t test, $P < 0.01$), primarily due to the low scores (typically less than 1) measured during the tactile stimulation. One subject (female, 26 years old) reported transient mild vertigo felt only during the acupuncture stimulation, which promptly disappeared when the acupuncture stimulation was removed.

Functional neural substrates

Stimulation vs. rest conditions

Table 1 lists the group activation results for three different stimulation conditions compared to the rest periods. As also seen in Figs. 2 and 3, primary (SI) and secondary (SII) somatosensory areas in parietal operculum, as well as the bilateral insula, were activated. Other areas that were mutually activated across all the conditions include transverse temporal gyrus (BA 42) and anterior aspect of superior temporal gyrus (BA 38). Sham acupuncture and tactile stimulation shared similar neural substrates except for the recruitment of additional cortical areas such as right superior/middle temporal gyrus and left inferior parietal lobule during the sham acupuncture stimulation. During the real acupuncture stimulation, activation in the dorsomedial nucleus of thalamus, ipsilateral to the side of stimulation, was observed together with cerebellar activation in vermis, bilateral quadrangular lobules, and superior semilunar lobules. Cortical areas with negative MR signal changes were searched, however, none was detected from any of the three conditions used. From the examination of individual stimulation conditions contrasted to the rest period, it was notable that cerebellar activation was not identified either from the sham acupuncture or from the tactile stimulation condition.

Real acupuncture vs. sham acupuncture/tactile stimulation

The results from comparing real acupuncture vs. sham acupuncture and tactile stimulation demonstrated that real acupuncture on PC6 elicited activation from spatially distinct neural substrates (Table 2 and Fig. 4). For example, left precentral gyrus (BA4), dorsomedial nucleus of thalamus, and superior frontal gyrus (BA10) showed relative signal increase during real acupuncture stimulation. In addition to the selective engagement of cerebral structures, we found extensive neuro-matrices in cerebellum that were involved only during the real acupuncture stimulation. These included declive, nodulus, and uvula in vermis, quadrangular/superior semilunar lobules, and left cerebellar tonsil. The detailed map of cerebellar activity is shown in Fig. 5.

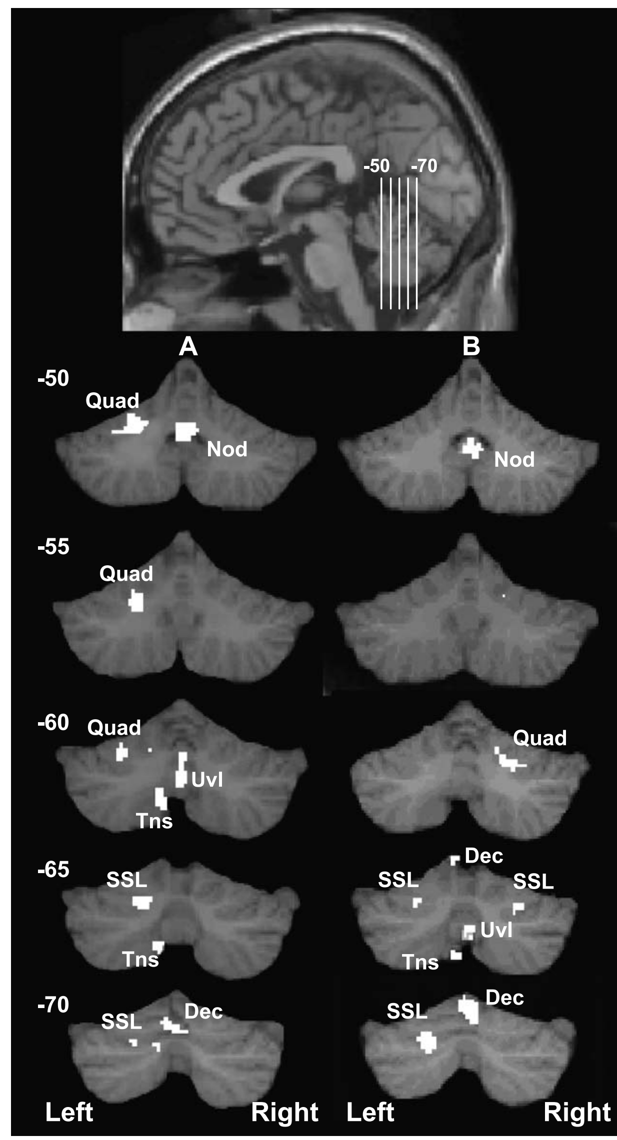

Fig. 5. Group activation map in cerebellar ROIs for (A) real acupuncture > sham acupuncture condition and (B) real acupuncture > tactile stimulation from anterior to posterior direction. Talairach coordinates are shown in upper left corner.

Discussion

We examined the neural substrates responding to the acupuncture stimulation of PC6. Sham stimulation near the acupoint and tactile stimulation on the skin of the acupoint were given as separate conditions to examine the spatially selective efficacy of the acupoint. Primary (SI) and secondary somatosensory areas (SII) as well as bilateral insular activities were detected throughout the conditions, suggesting that the neural pathway for tactile perception was commonly engaged. Activation in auditory areas in bilateral transverse temporal gyri (BA42) and superior temporal gyrus (BA38) were also observed for all stimulation conditions. Electro-acupuncture on GB34 yielded similar activation in both sham and real electro-acupuncture of the same acupoint (Wu et al., 2002); however, the activation in the temporal gyri was an unexpected finding, especially during the tactile stimulation. We conjecture that the activation in these auditory-related areas was not specific to acupuncture stimulation and may be associated with the cognitive attention given to the rhythmic scanner noise during the stimulation period, which we asked subjects to listen to prevent possible imagery (Jancke et al., 1999).

In the examination of the neural substrates activated during each stimulation condition, sham acupuncture and tactile stimulation shared similar activation patterns, suggesting that the effect of sham acupuncture does not elicit significantly different neural activation compared to the simple tactile stimulation. During the real acupuncture on PC6, however, we found distinctive activation loci distributed in the cerebellum (Table 2), in addition to the activation in left superior frontal gyrus, anterior cingulate gyrus, and dorsomedial nucleus of thalamus in cerebrum. Activation in precentral gyrus and anterior cingulate gyrus was similar to the previous observation seen in the acupuncture stimulation on GB34 (Wu et al., 2002). Activation in anterior cingulate gyrus, as a part of limbic system, was also identified in the acupuncture of LI4 (Hui et al., 2000), suggesting there are common neural substrates specific for stimulation of these acupuncture points.

In the present study, we identified several important cerebellar areas modulated only during the acupuncture stimulation on PC6. Cerebellar nodulus and uvula, a part of the flocculonodular lobe, participates in the vestibular control as the phylogenetically oldest regions in the cerebellum (Afifi and Bergman, 1998). The cerebellar uvula-nodulus receives vestibular projections from primary and secondary vestibular afferents, as well as vestibular climbing fibers (Ito, 1993; Pettorossi et al., 2001). Other cerebellar locations such as quadrangular/semilunar lobules and cerebellar tonsil have been identified as the cerebellar loci engaged in selective attention (Allen et al., 1997), verbal working memory (Desmond et al., 1997), and response to hypercarbia (Parsons et al., 2001). We initially suspected that the activation in cerebellar loci could be attributed to the perception of pain or the possible hand motion that was associated with needling in the proximity of radial or ulnar nerve. However, the patterns of brain activation, from both cerebrum and cerebellum, were different from those of pain perception and motor-related tasks, especially in the nodular–uvular complex in the cerebellum (Biella et al., 2001; Houk and Wise, 1995; Iadarola et al., 1998). Our psychophysical measurement also indicates that pain was not the differential factor among the stimulation conditions.

Based on our findings, the following hypothesis was constructed to provide a framework to investigate the neuro-modulatory effect on cerebellum by acupuncture stimulation. PC6 stimulation modulates the activity in cerebellar neuromatrix relating to vestibular function, especially in the flocculonodular lobe, subsequently alleviating the symptoms with motion-related sickness and nausea. An episode of transient vertigo experienced by one female subject can be postulated that the PC6 stimulation resulted in cerebellar activation significant enough to disturb the vestibular perception of that individual. It is important, however, to mention that our data do not provide a thorough explanation of PC6-specific treatment effects on nausea of non-vestibular origin, such as morning sickness. It is postulated that the vomiting center, in the lateral medullar oblongata of the brain, could be indirectly modulated by the acupuncture via extensive cerebellar–medullary connections. Alternative postulation can be made that acupuncture modulates the release of neurotransmitter, which in turn desensitizes the response of the vomiting center (VC) or chemoreceptor trigger zone (CTZ) in medulla. Further study is required to investigate the hypothesized modulation at the level of brain stem. In this case, the adoption of gated fMRI acquisition schemes (Guimaraes et al., 1998) is conducive to compensate for the high susceptibility of the region to pulsatile motion of surrounding cerebral spinal fluid.

From the examination of the negative BOLD-related signal component compared to the rest period, we were not able to locate any neural correlates from any conditions. Negative BOLD signal change, which is believed to be associated with the suppression of neural activity, has been observed in the limbic structures and hippocampus in stimulation of LI4 (Hui et al., 2000; Wu et al., 1999), anterior cingulate gyrus in stimulation of ST36 and GB34 acupoints (Wu et al., 1999, 2002). These studies, which mostly examined the analgesic component of acupuncture, hypothesized that signal decrease was related to the deactivation of the pain-related neural substrates. Several cerebral structures identified in the present study, that is, left superior frontal gyrus, anterior cingulate gyrus, and dorsomedial nucleus of thalamus, have shown increased activity compared to the sham acupuncture and tactile simulation. We determined that the physiological mechanism of PC6 acupuncture does not necessarily accompany the neural deactivation of limbic system.

From the examination of the psychophysical scores, we found that emotional responses such as anxiety and unpleasantness were kept in the reasonably low level. In addition, we also determined that sham acupuncture, as reported in a recent fMRI investigation (Li et al., 2003), could be reasonably used as the placebo control in an acupuncture fMRI setting. Although the utility of using sham stimulation has been debated due to its lack of specificity (Richardson and Vincent, 1986; Vincent and Lewith, 1995; Wu et al., 2002), careful design and execution of sham acupuncture paradigms/procedures would effectively reduce the subjects' bias toward the stimulation. For example, White et al. (2001) suggested the use of retractable nonpenetrating sham needle device (Park et al., 2002a,b) or blinding observers and the analysts participating in the studies. The utility of other acupuncture modalities for placebo control, such as laser acupuncture (Siedentopf et al., 2002) or minimal 'shallow' acupuncture techniques (Wu et al., 2002), also needs further investigation. In case the manual needle manipulation is necessary, adoption of electro-acupuncture (Li et al., 2003; Wu et al., 2002) may help to minimize the stimulation variation introduced by manual acupuncture.

Although PC6 has been used in the treatment of tachycardia and arrhythmia (Deadman and Al-Khafaji, 1998), we did not find any modulatory effects on respiration and heart rate from acupuncture of the PC6 point. Previous study on acupuncture of LI4 in the hand resulted in the significant level of bradycardia (Wu et al., 1999). Possible sources of the disparities seen in the results may be attributed to many factors, such as location and method (manual or electro-acupuncture for example) of stimulation delivery, timing of the stimulation, difference in subject's susceptibility to acupuncture, and imaging parameters. One of the crucial questions remaining from our investigation is regarding the reproducibility of the activation in a test–retest setting (Gareus et al., 2002). Several fMRI studies were conducted to show that activations in major eloquent cortical as well as subcortical neural substrates during motor and visual task could be reliably detected across the subjects and sessions (Machielsen et al., 2000; Miki et al., 2000). However, the examination of the session-to-session reproducibility of fMRI activation in the context of acupuncture stimulation has not been thoroughly studied and constitutes a compelling subject for investigation. A test–retest experimental design will also help to determine the effect of repetitive application of acupuncture, so-called 'cumulative effect' typically necessary in clinical treatment.

Conclusion

We demonstrated that the human cerebellum, in addition to the cerebral loci, selectively responded to the acupuncture stimulation of the PC6 acupoint. Modulation of cerebellar areas, especially relevant to vestibular neuromatrix, was found from our investigation. Further research, such as fMRI examining the brain stem, is needed to elucidate the neural circuitries involved in PC6's anti-emetic effect. The role of the cerebellum in producing therapeutic effects of acupuncture, in addition to the cerebral involvement, requires further investigation to better understand the mechanism of acupuncture. An inter-session and intra-session reproducibility/variability of fMRI results in the context of acupuncture stimulation needs to be established as well.

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