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Abbreviation:
CNS = central nervous system

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Central Nervous Pathway for Acupuncture Stimulation: Localization of Processing with Functional MR Imaging of the Brain—Preliminary Experience[1]

PURPOSE: To characterize the central nervous system (CNS) pathway for acupuncture stimulation in the human brain by using functional magnetic resonance (MR) imaging.

MATERIALS AND METHODS: Functional MR imaging of the whole brain was performed in two groups of nine healthy subjects during four stimulation paradigms: real acupuncture at acupoints ST.36 (on the leg) and LI.4 (on the hand) and control stimulations (minimal acupuncture and superficial pricking on the leg). Stimulations were performed in semirandomized, balanced order nested within two experiments. Psychophysical responses (pain, *De-Qi* effect [characteristic acupuncture effect of needle-manipulation sensation], anxiety, and unpleasantness) and autonomic responses were assessed. Talairach coordinates–transformed imaging data were averaged for a group analysis.

RESULTS: Acupuncture at LI.4 and ST.36 resulted in significantly higher scores for *De-Qi* and in substantial bradycardia. Acupuncture at both acupoints resulted in activation of the hypothalamus and nucleus accumbens and deactivation of the rostral part of the anterior cingulate cortex, amygdala formation, and hippocampal complex; control stimulations did not result in such activations and deactivations.

CONCLUSION: Functional MR imaging can demonstrate the CNS pathway for acupuncture stimulation. Acupuncture at ST.36 and LI.4 activates structures of descending antinociceptive pathway and deactivates multiple limbic areas subserving pain association. These findings may shed light on the CNS mechanism of acupuncture analgesia and form a basis for future investigations of endogenous pain modulation circuits in the human brain.

Acupuncture originated in ancient China and has been used to manage various clinical disorders. Acupuncture techniques are based on the theory of meridians and energy flow, which evolved after painstaking observation against a background of Chinese philosophy. However, acupuncture was not widely introduced as an alternative medicine in the West until the scientific basis of acupuncture analgesia began to be explored in the middle of the 1970s (1–5). In recent years, acupuncture has gained increasing popularity in modern health care and increasing support among scientific investigators (6–8).

Of the versatile clinical uses of acupuncture, acupuncture analgesia was one of the earliest, and so far most advanced, aspects to be explained on the basis of physiology and anatomy (1,9). Results from human and animal studies (2,9–13) suggest that acupuncture acts as a neuromodulating input into the central nervous system (CNS) that can activate multiple analgesia systems and stimulate pain modulation systems to release neurotransmitters such as endogenous opioids.

The exact CNS pathway mediating acupuncture analgesia has been explored in animal studies (2,4,9,14–17) with lesion creation or microinjection of naloxone hydrochloride (a narcotic antagonist) in a variety of hypothesized areas. Up to now, the most important and repeatedly demonstrated pathway has been the descending antinociceptive system, including the hypothalamus (the arcuate nucleus), the nucleus accumbens, and the mesencephalon (the periaqueductal gray matter and raphe nuclei) to the dorsal horn of the spinal cord (2,4,9,14–17). In addition, several areas of the limbic system have been found to participate in the nervous system circuit for acupuncture analgesia (17,18). Because it has long been hypothesized that limbic areas encode the affective-cognitive aspects of pain (19–23), the limbic system may be as important as the descending antinociceptive pathway for the CNS mechanism of acupuncture analgesia.

Although the underlying neurophysiologic mechanism remains unclear, it is generally accepted (2,4,5,24,25) that *De-Qi* (the acupuncture effect of characteristic needle-manipulation sensation, which manifests as numbness, heaviness, distention, and soreness, with spreading sensation) is the sine qua non of acupuncture for the achievement of a clinical therapeutic effect. Although the correlation between the stimulation of certain acupoints and human cortical activation has recently been explored (26), the CNS pathways that mediate *De-Qi* have not been characterized in the human brain.

Knowledge of how acupuncture stimulation proceeds centrally during the state of *De-Qi* may shed light on the CNS mechanism of acupuncture analgesia, as well as provide a common explanation for nonanalgesic effects of acupuncture. Because functional magnetic resonance (MR) imaging, a technique that is sensitive to changes in regional blood oxygenation as an index of neuronal activity (27), has been used with wide success in the mapping of human brain functions (28), we hypothesized that functional MR imaging may be useful for characterization of the CNS pathway for acupuncture stimulation. On the basis of results from the aforementioned animal studies of acupuncture analgesia, we hypothesized that acupuncture stimulation may activate the hypothalamus and limbic system to mediate the acupuncture effect (29).

In the present study, we performed functional MR imaging in healthy subjects to map the CNS pathway for real acupuncture at two acupoints, ST.36 and LI.4 (30), which are the two most widely used acupoints in experimental studies of acupuncture analgesia (2,14-18). In addition, two control stimulations were performed to test our hypothesis.

MATERIALS AND METHODS

Study Design

General protocol.—We used four stimulation paradigms nested within two experiments. In experiment 1, nine right-handed, healthy subjects (six men, three women; age range, 20–35 years) underwent two stimulation paradigms in a balanced, semirandomized order. Four subjects first underwent a real acupuncture paradigm at acupoint ST.36 (traditionally known as the *Zusanli* acupoint) (30) on the left leg; 20 minutes later, a control stimulation paradigm was performed, which consisted of superficial pricking of the skin at ST.36. The other five subjects underwent the same series of stimulations in reverse order. Experiment 2 was conducted in similar fashion: Another nine right-handed, healthy subjects (five men, four women; age range, 22–38 years) underwent a real acupuncture paradigm at acupoint LI.4 (traditionally, the *Hegu* acupoint) (30) on the left hand; 20 minutes later, a control stimulation paradigm, which consisted of minimal acupuncture (31,32) at a nonacupoint area near ST.36 on the left leg, was performed.

Acupoints ST.36 and LI.4 were chosen because they are the two most frequently used acupoints in experimental studies of acupuncture analgesia (2,14–18). Minimal acupuncture and superficial pricking were used as the control stimulations for the ST.36 stimulations, whereas acupuncture at LI.4 was used to demonstrate common brain activation patterns after stimulation of different acupoints.

Subject preparation and instructions.—The subjects were blinded about the type, block design, and order of stimulations and were instructed that all stimulations would be endurable. To minimize the effect of anticipation, subjects were instructed that any combination of different or same types of stimulation may be performed in a paradigm (although, for the purpose of group analysis, the stimulation paradigms were performed with a fixed block design in a balanced order). Before performance of the second stimulation paradigm, we determined that each subject's psychophysical state and autonomic function had returned to neutral baseline levels after approximately 20 minutes. Informed consent was obtained from all subjects, and both the acupuncture and functional MR imaging arms of the experiment were approved by the institutional ethics committees at Massachusetts General Hospital (Boston) and Kaohsiung Veterans General Hospital (Taiwan).

Stimulation paradigm design.—The block design for all four stimulation paradigms consistently was B_{120}-*A*-B_{150}-*A*-B_{90}, in which two stimulation periods (*A*, needle manipulation for 60 seconds) were interposed within three rest periods (B_{120}, B_{150}, and B_{90}, no needle present for 120, 150 and 90 seconds, respectively). All stimulation paradigms were performed by one experienced acupuncturist (J.X.).

Experiment 1.—In the first paradigm (real acupuncture at ST.36), a stainless steel acupuncture needle (Lhasa Medical, Accord, Mass) with a diameter of 0.25 mm and a length of 30 mm was inserted to a depth of about 2 cm into acupoint ST.36, which is located four finger breadths below the lower margin of the patella and one finger breadth laterally from the anterior crest of the tibia. The needle was manipulated by twirling approximately 90° and lifting-thrusting approximately 0.6–1.0 cm coordinately in a balanced reinforcing and reducing manner at about 1–2 Hz (24,30).

In the second paradigm (superficial pricking), an acupuncture needle was used to gently prick (approximately 1 mm deep at 1 Hz) the skin at ST.36.

Experiment 2.—In the first paradigm, real acupuncture was performed at acupoint LI.4, which is located at the first dorsal intermetacarpal space with a depth of approximately 1 cm (24,30). Manipulation of the needle was similar to that for ST.36. In the second paradigm (minimal acupuncture), the needle location was chosen at a nonmeridian focus near ST.36 (approximately 2–3 cm distant laterally) on the left leg. The manipulation was performed more lightly than in real acupuncture, with a depth of approximately 5 mm (31,32).

Data Acquisition

Psychophysical and autonomic function assessment.—After completion of each stimulation paradigm, subjects used a 10-point scale to self rate the perceived intensities of pain, the *De-Qi* effect, unpleasantness, and anxiety. A score of 0 indicated no intensity at all, and a score of 10 indicated the strongest imaginable intensity. Heart rate and end-tidal CO_2 level were continuously monitored (Omni-Trak 3100; Invivo Research, Orlando, Fla) throughout the experiments.

MR imaging.—MR imaging was performed with a quadrature head coil and a 1.5-T MR imager (Signa; GE Medical Systems, Milwaukee, Wis) that had been modified for echo-planar imaging (Advanced NMR System; Advanced NMR, Wilmington, Mass). To reduce head motion, subjects were immobilized with foam support cushions and adhesive strips.

Imaging involved the following protocol. First, a sagittal localizer image was obtained with a conventional T1-weighted spoiled gradient-echo sequence (25/5 [repetition time msec/echo time msec]; flip angle, 35°; field of view, 23 cm; matrix, 192 × 256; through-plane resolution, 2.8 mm; 60 sections) to orient, for subsequent acquisitions, 17 contiguous axial sections along the anterior commissure–posterior commissure line and to cover both cerebral hemispheres. This localizer image also was used as the structural image for transformation to Talairach coordinates of the imaging data.

Next, an automated shimming technique was used to optimize B_0 (constant magnetic induction field) homogeneity (33). This was followed by acquisition of a spoiled gradient-echo T1-weighted flow-compensated MR image (170/8; flip angle, 60°; resolution, 1.6 × 1.6 × 7.0 mm; field of view, 20 cm; matrix, 128 × 128), which was obtained primarily to aid in Talairach transformation during data analysis. The third imaging sequence was a T1-weighted echo-planar inversion-recovery sequence (∞/5/1,200 [repetition time/echo time msec/inversion time msec]; resolution, 1.6 × 1.6 × 7.0 mm), which was used to obtain structural images for the construction of preliminary statistical maps (but not Talairach-transformed or averaged maps).

Finally, a gradient-echo T2*-weighted sequence (∞/40; flip angle, 90°; field of view, 20 cm; matrix, 64 × 64 for a voxel resolution of 3.125 × 3.125 × 7.000 mm; 17 contiguous axial sections along the anterior commissure–posterior commissure line and covering both cerebral hemispheres) was performed. This sequence, which is sensitive to signal changes that arise from small changes in blood oxygenation, was used for measurements of brain activation (27). One complete set of 17 sections was obtained repeatedly every 3.5 seconds to obtain 136 time points during 8 minutes.

Autonomic Function and Psychophysical Data Analysis

Autonomic function and psychophysical data (heart rate and end-tidal CO_2 level) were averaged across the two stimulation periods and across the three rest periods separately, to calculate the mean values in the stimulation and rest states, respectively. Heart rates and end-tidal CO_2 levels in the stimulation and rest states for each paradigm were compared by using both the paired Student *t* test and the Wilcoxon signed-rank test to determine whether there were significant stimulation-related changes in autonomic function. The changes induced by means of stimulation were further normalized to percentage changes, as indexed to the mean values of the rest periods.

Multivariate analyses of variance (with four indicator variables for the four types of stimulation and one indicator variable for order effects of stimulation) were used in the analysis of differences among the four psychophysical scores and among heart rate changes associated with the four stimulation paradigms. Multivariate analyses of variance also were used in the analysis of differences among psychophysical scores and heart rate changes between the two true acupuncture paradigms and between the true acupuncture paradigm and the control stimulation paradigm. Comparisons among individual psychophysical score and heart-rate changes were performed with analyses of variance, with a threshold *P* value of less than .003 (ie, type I error rate $\alpha = .05/[3 \times 5]$; Bonferroni correction).

Image Analysis

Motion correction.—The echo-planar imaging data were motion corrected by using a ratio-variance minimization algorithm (called ''automatic image registration'', or AIR) (34) adapted from Woods et al (35). After motion correction, residual motion was reduced to less than 0.5 mm, and no time-series data evidenced residual motion in the form of cortical rim or ventricular artifacts for either the acupuncture or the control stimulations.

Talairach transformation, normalization, and averaging.—Both morphologic and functional imaging data for each subject were transformed to correspond to the Talairach stereotactic system (36) and were resectioned in coronal orientation over 57 sections with isotropic voxel dimensions of 3.125 × 3.125 × 3.125 mm. If movement was apparent between acquisitions of structural and functional images, the functional data were further fit to the structural data by translating exterior contours.

Talairach-transformed functional data were intensity scaled so that all mean baseline raw MR signal intensities were equal. Group data for each stimulation paradigm were obtained by averaging the Talairach-transformed functional data across nine subjects. The structural imaging data also were obtained by averaging across nine subjects.

Voxel-by-voxel statistical mapping and anatomic localization.—Stimulation-induced changes in functional MR imaging signal intensity were assessed by using nonparametric Kolmogorov-Smirov statistical maps (28,37–39) constructed from these averaged data sets. These maps were used for the comparisons among the two stimulation and three rest periods of each paradigm. Kolmogorov-Smirov maps were constructed after an in-plane Hanning spatial filter was applied that smoothed adjacent voxels. The Kolmogorov-Smirov probability map was converted to a logarithmic color scale and was overlaid on anatomic T1-weighted images of the same location for visual inspection. Kolmogorov-Smirov maps for group results were created with a threshold for significant changes in signal intensity established with a *P* value of less than .00001. Kolmogorov-Smirov maps also were constructed for individuals, to determine the percentage of subjects who showed activation or deactivation (with a threshold of $P < .01$) of the areas noted in the group data. Brain areas with increased signal intensity during stimulation periods were defined as activated areas, and those with decreased signal intensity during stimulation periods were defined as deactivated areas.

The time courses of signal intensity changes were evaluated for each putative activation or deactivation identified on statistical maps derived from averaged data. These signal intensity–versus-time determinations were assessed to ascertain that the changes in signal intensity did not precede stimulus presentation and that the changes specifically followed performance of the stimulation paradigm. All activations and deactivations had to meet these two criteria.

Statistical maps were superimposed on conventional T1-weighted images that also had been transformed into the Talairach domain.

RESULTS

Autonomic Function and Psychophysical Assessments

The autonomic function assessments showed that the average heart rate (± SD) was significantly decreased by means of

acupuncture at ST.36 (from 64.4 beats per minute ± 7.3 in the rest periods to 60.5 beats per minute ± 7.8 in the stimulation periods, $P < .001$) and at LI.4 (from 68.1 beats per minute ± 4.8 to 64.2 beats per minute ± 5.3 , $P < .001$). No significant changes were induced by the control stimulations (Fig 1). End-tidal CO_2 level was not significantly changed in any subject.

The analysis of the four psychophysical scores and changes in heart rate indicated no significant order effects ($F_{5,27} = 0.907$, $P = .491$) for the stimulations. Because there were no significant differences between assessments of acupuncture at ST.36 and LI.4 ($F_{5,27} = 0.483$, $P = .786$), we combined the two data sets to represent the results of real acupuncture. We found significant differences between real acupuncture and minimal acupuncture ($F_{5,27} = 14.45$, $P < .001$), as well as between real acupuncture and superficial pricking ($F_{5,27} = 27.15$, $P < .001$). Comparisons among each psychophysical score and change in heart rate showed that real acupuncture resulted in significantly higher degrees of *De-Qi* and a more severe bradycardia response ($P < .001$ for both) than did minimal acupuncture, whereas real acupuncture caused significantly less pain, a higher degree of *De-Qi*, and a more severe bradycardia effect ($P < .001$ for all) than did superficial pricking (Fig 1).

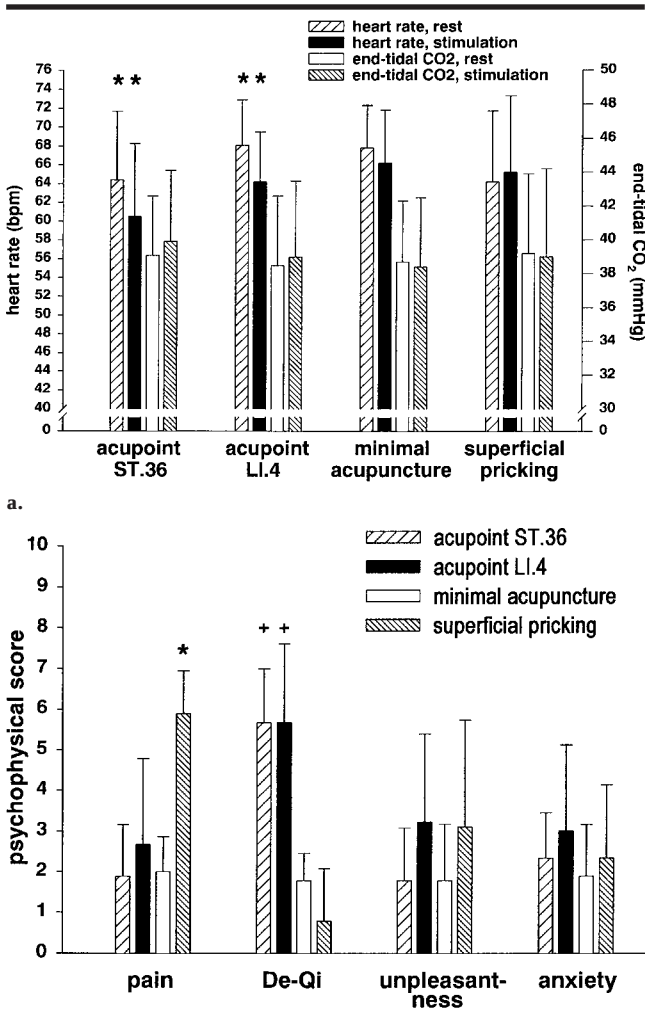

Figure 1. **(a)** Bar graph shows heart rate averaged across nine subjects in the rest and stimulation periods for each stimulation paradigm. *bpm* = beats per minute, ∗ = significant difference ($P < .001$). **(b)** Bar graph shows average psychophysical responses reported by the subjects, who used a score of 0–10 for each variable on the horizontal axis. ∗ = significantly different from other stimulations ($P < .001$), + = significantly different from control stimulations ($P < .001$) but not between two real acupuncture stimulations.

Functional MR Imaging Findings

Group results for functional MR imaging (Figs 2, 3; Table) during acupuncture at ST.36 showed an activation pattern in the hypothalamus and limbic system, that is, activation (signal intensity increased during stimulation as compared with that during rest) in the contralateral hypothalamus and nucleus accumbens. Deactivation (signal intensity decreased during stimulation as compared with that during rest) was noted bilaterally in the anterior cingulate cortex (rostral part, Brodmann area 24b [22]), ipsilaterally in the orbital and basal gyri, contralaterally in the amygdala formation, and bilaterally in the hippocampal complex. In addition, activation occurred in the contralateral primary somatosensory cortex, ipsilateral parietal operculum (Brodmann area 40), and bilateral prefrontal cortex (Brodmann areas 8, 9, and 10). The involvement of the limbic system was replicated with acupuncture at LI.4 in experiment 2; however, the hypothalamus appeared to show more extensive activation bilaterally.

With regard to the control stimulations, minimal acupuncture induced activation over the contralateral supplementary motor area and the anterior cingulate cortex (Brodmann area 32), the contralateral frontal operculum (Brodmann area 44 and primary motor area M1), and the ipsilateral parietal operculum (Brodmann area 40). Superficial pricking induced activation over the primary somatosensory cortex, the thalamus, the anterior cingulate cortex (Brodmann areas 32 and 24′), the contralateral supplementary motor area, the bilateral prefrontal cortex (Brodmann areas 8, 9, and 10), the bilateral frontal operculum (Brodmann area 44 and primary motor area M1), and the bilateral parietal operculum (Brodmann area 40). In addition, there was activation in the ipsilateral lentiform nucleus and the bilateral insula. No area showed a significant decrease in signal intensity (Fig 2, Table).

DISCUSSION

The distinction between the two real acupuncture stimulations and the two control stimulations was clearly reflected in the autonomic function results and psychophysical responses. The bradycardia associated with real acupuncture is a rather characteristic autonomic response that has been widely observed clinically

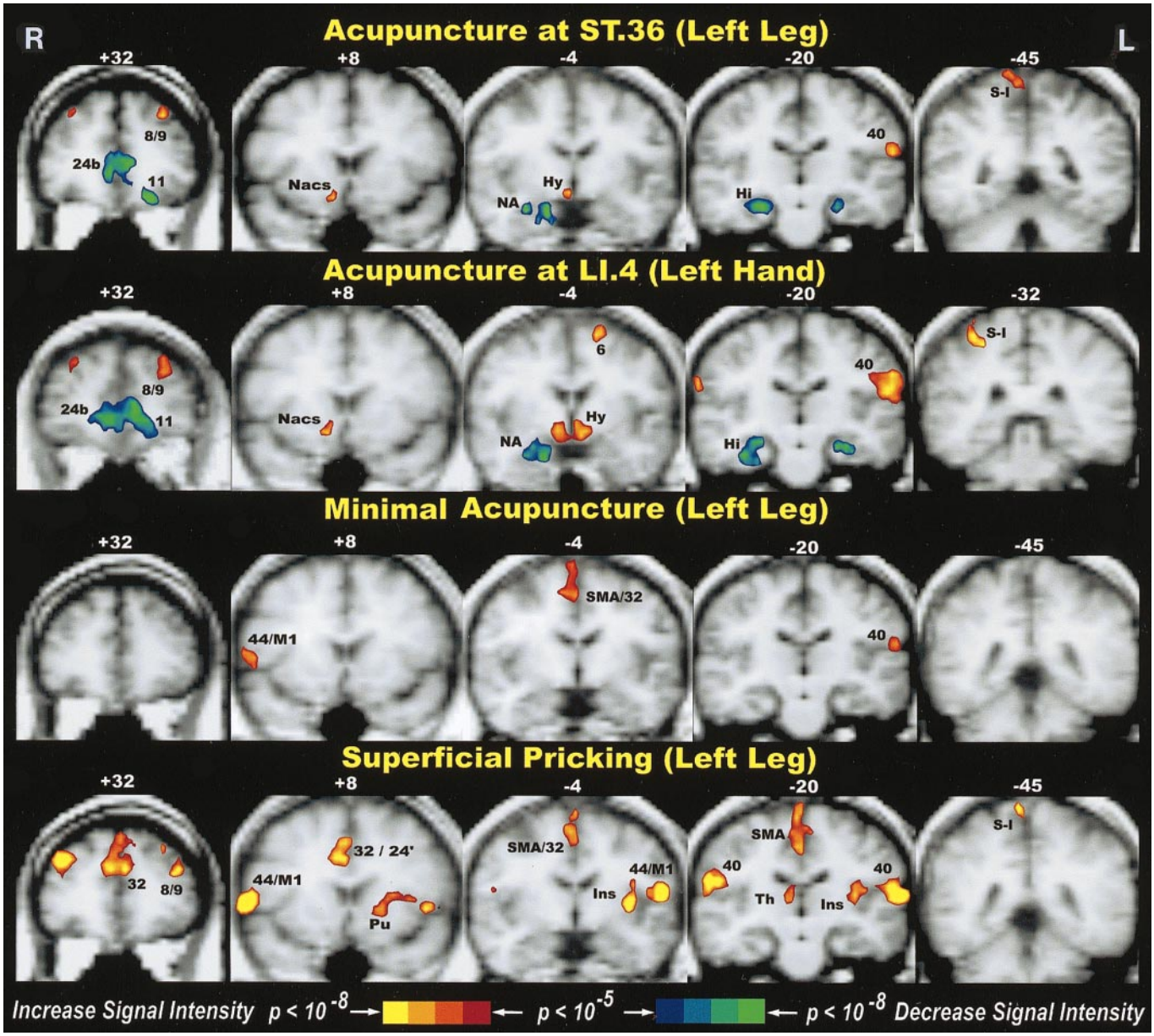

Figure 2. Functional MR images of brain activation show mean results for nine subjects in each stimulation paradigm. Representative color-coded statistical maps derived from data obtained during the four stimulation paradigms (overlaid on morphologic MR images [25/5, 35° flip angle]) show the distribution of foci with significant increases (shown in the spectrum from red to yellow) and decreases (shown in the spectrum from blue to green) in signal intensity, relative to that of the respective rest states. The threshold for a significant change in signal intensity was a *P* value of less than .00001 (Kolmogorov-Smirov method). Numbers above each image indicate the distance in millimeters anterior (+) and posterior (−) to the anterior commissure. Numbers in cortical areas of the images correspond to Brodmann areas. *Hi* = hippocampus, *Hy* = hypothalamus, *Ins* = insula, *M1* = primary motor cortex, *NA* = amygdala, *Nacs* = nucleus accumbens, *Pu* = putamen, *S-I* = primary somatosensory cortex, *SMA* = supplementary motor cortex, *Th* = thalamus.

and experimentally and hypothesized to be triggered by sufficient activation of characteristic acupuncture afferent pathways, concomitant with the state of *De-Qi* (4,24,40). It is unlikely that such bradycardia could cause substantial changes in brain activation patterns. Instead, the bradycardia reinforced the psychophysical assessment results and was supportive of the notion that our subjects achieved the state of *De-Qi* specifically by means of real acupuncture stimulation.

Of note, in the healthy subjects in our study, none of whom had a painful condition, it was difficult to demonstrate an analgesic effect of acupuncture. Furthermore, the clinical effect of acupuncture analgesia usually necessitates longer and multiple stimulation sessions; thus, it is difficult to assess the analgesic effect in an experimental functional MR imaging setting. However, presence of the *De-Qi* state, which is a prerequisite for and often an indicator of a clinical acupuncture effect (2,4,5,24,25), was sufficient to support our hypothesis that functional MR imaging findings indeed reflected the CNS pathways that mediate the acupuncture effect.

The activation of the hypothalamus

and nucleus accumbens by means of acupuncture at both acupoints was consistent with the results from animal experiments and supported the notion that acupuncture afferent pathways engage the structures of the descending antinociceptive system, particularly the hypothalamus (2,4,10,11,14,16,17). The hypothalamus, with the most abundant endorphinergic neurons and long descending projections to the raphe nucleus and periaqueductal gray matter of the mesencephalon, has repeatedly been shown (15–17,41) to be critical for acupuncture analgesia. The nucleus accumbens, with interconnections to the descending pathway from the hypothalamus to the raphe nucleus and periaqueductal gray matter, is another important structure for both opioid- and acupuncture-induced analgesia (14,15,18,41).

An important finding was that the hypothalamus showed a tendency for sustained activation on the MR images obtained after acupuncture (Fig 3). Such sustained activation of the hypothalamus may have a bearing on the long-lasting analgesic effect of acupuncture in the clinical setting (2–4,11,24,42). The finding that acupuncture at LI.4 activated the hypothalamus more extensively than did acupuncture at ST.36 may be in agreement with the clinical observation that acupuncture at the LI.4 acupoint has a stronger analgesic effect.

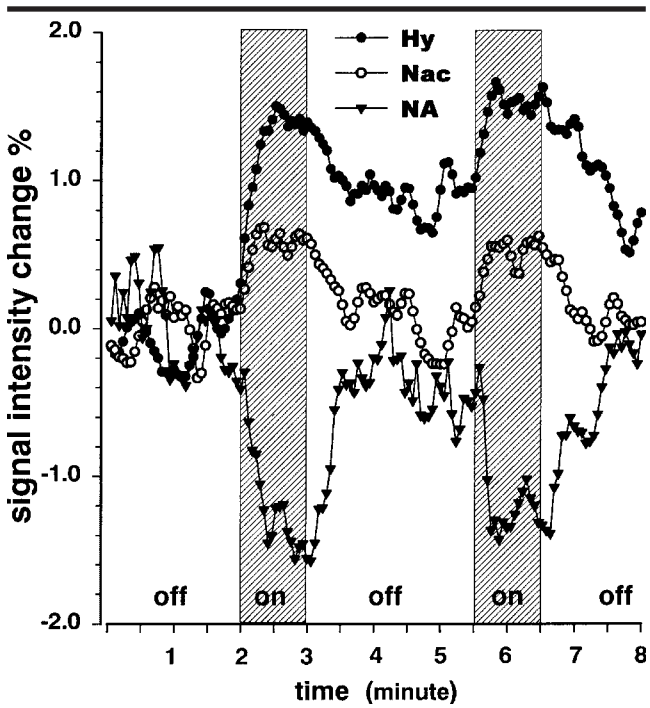

Figure 3. Graph shows the time course of changes in signal intensity (averaged across nine subjects) during acupuncture at ST.36. *Hy* = hypothalamus, *Nac* = nucleus accumbens, *NA* = amygdala. Signal intensity was normalized to the average of that measured at the first rest period and is expressed as percentage change. Note that the signal intensity of the hypothalamus showed prolonged elevation through postacupuncture MR acquisitions. The time courses of signal intensity during acupuncture at LI.4 (not shown) were similar.

Although it has been generally accepted (27) that increases in signal intensity at functional MR imaging indicate neuronal excitation (ie, activation), the physiologic meaning of a decrease in signal intensity awaits further investigation. A plausible explanation is a summed decrease in neuronal activity (ie, deactivation) (43). In the present study, the only areas of deactivation that we observed were in the limbic system during real acupuncture. This finding is noteworthy because it has been suggested (19,20,22) that the limbic system participates in pain perception, particularly the affective-cognitive aspect. Results of animal studies have demonstrated that the amygdala formation has abundant opiate receptors and participates in both opioid analgesia and acupuncture analgesia (18,44). Hippocampal activity can be strongly modulated by means of both pain and acupuncture stimulation (17,45). Furthermore, the rostral part of the anterior cingulate cortex, which has extensive connections to the amygdala and periaqueductal gray matter, is a key modulator of the internal emotional response to pain (22). On the basis of these linkages, we hypothesized that an important mechanism of acupuncture analgesia may be deactivation of limbic areas and attenuation of the affective response to pain as a result of acupuncture stimulation.

We ascribed the discrepancy between the activation pattern associated with real acupuncture and that associated with minimal acupuncture to the notably lower degree of *De-Qi* in minimal acupuncture as rated by the subjects. Minimal acupuncture has recently been recommended as an appropriate control for real acupuncture, because minimal acupuncture minimizes the specific effects of the needle manipulation while maintaining the psychologic effect (31,32). The activation of the supplementary motor cortex, parietal operculum, and frontal operculum in minimal acupuncture may be suggestive of an orientation of attention toward incoming sensory stimulation (46,47). We did not use "sham acupuncture," in which the needle manipulation and depth are identical to those used in real acupuncture, but the manipulations are performed at a nonacupoint. It has been pointed out (3,4,31,32) that sham acupuncture produces a substantial acupuncture effect that overlaps that of real acupuncture, and a huge number of subjects are needed to differentiate the effects of these two types of stimulation. On the other hand, the multiple distributed activations noted at superficial pricking—such as those of the contralateral anterior cingulate cortex (Brodmann area 24′) and thalamus, the ipsilateral lentiform nucleus, and the bilateral insula, frontal operculum (Brodmann area 44 and primary motor area M1), and parietal operculum (Brodmann area 40)—are consistent with activations identified in previous human experimental neuroimaging studies of pain (21,23,47–51). Such activation patterns were consistent with the higher pain scores given by the subjects for superficial pricking relative to those given for the deep-tissue stimulation of acupuncture.

We emphasized the group results in the present study. Given that the hypothalamus and limbic system are close to the skull base, which contains air and bone structures, it is possible that substantial susceptibility artifact (ie, decreased functional MR signal) will be produced, along with an increased potential for a type II

Foci with Significant Change in Signal Intensity between Rest and Stimulation Periods

Region	ST.36 Acupuncture					LI.4 Acupuncture					Minimal Acupuncture					Superficial Pricking				
	Side	Signal Intensity	Coordinates*	*P* Value†	No. of Subjects‡	Side	Signal Intensity	Coordinates*	*P* Value†	No. of Subjects‡	Side	Signal Intensity	Coordinates*	*P* Value†	No. of Subjects‡	Side	Signal Intensity	Coordinates*	*P* Value†	No. of Subjects‡
Hypothalamus	Right	Increase	−5, −11, +3	$<10^{-7}$	8	Right	Increase	−3, −2, +4	$<10^{-8}$	8										
						Left	Increase	−4, −4, −5	$<10^{-8}$	7										
Nucleus accumbens	Right	Increase	+8, −7, +8	$<10^{-7}$	7	Right	Increase	+10, −4, +10	$<10^{-8}$	7										
Anterior cingulate gyrus (rostral, Brodmann area 24b)	Right	Decrease	+33, +10, +4	$<10^{-9}$	8	Right	Decrease	+35, +10, +4	$<10^{-9}$	8										
	Left	Decrease	+32, +9, −7	$<10^{-10}$	8	Left	Decrease	+33, +8, −4	$<10^{-9}$	8										
Anterior cingulate gyrus (posterior-caudal, Brodmann area 24)							Increase	0, +32, +4	$<10^{-5}$	5						Right	Increase	+8, +34, +3	$<10^{-9}$	9
Anterior cingulate gyrus (Brodmann area 32)											Right	Increase	−3, +45, +4	$<10^{-6}$	7	Right	Increase	+32, +29, +5	$<10^{-10}$	9
																Left	Increase	+30, +26, −6	$<10^{-9}$	9
Amygdala formation	Right	Decrease	−8, −12, +21	$<10^{-9}$	8	Right	Decrease	−4, −13, −20	$<10^{-10}$	8										
Hippocampal complex	Right	Decrease	−20, −12, +28	$<10^{-10}$	9	Right	Decrease	−22, −10, +30	$<10^{-8}$	7										
	Left	Decrease	−24, −13, −25	$<10^{-7}$	7	Left	Decrease	−20, −18, −39	$<10^{-8}$	7										
Thalamus																Right	Increase	−20, +5, +9	$<10^{-6}$	9
Primary somatosensory	Right	Increase	−44, +65, +6	$<10^{-6}$	9	Right	Increase	−33, +60, +35	$<10^{-9}$	9						Right	Increase	−45, +66, +7	$<10^{-9}$	9
Prefrontal (Brodmann areas 8, 9, 10)	Right	Increase	+28, +45, +40	$<10^{-5}$	7	Right	Increase	+30, +44, +39	$<10^{-5}$	7						Right	Increase	+32, +31, +50	$<10^{-11}$	9
	Left	Increase	+32, +43, −33	$<10^{-8}$	7	Left	Increase	+30, +40, −38	$<10^{-6}$	7						Left	Increase	+30, +28, −48	$<10^{-10}$	9
Prefrontal (Brodmann areas 44/M1)											Right	Increase	+7, +19, +57	$<10^{-6}$	6	Right	Increase	+8, +15, +50	$<10^{-11}$	9
																Left	Increase	+0, +20, +12	$<10^{-11}$	9
Prefrontal (Brodmann area 6)						Left	Increase	−6, +61, +21	$<10^{-7}$	8										
Supplementary motor cortex						Right	Increase	−12, +56, +5	$<10^{-5}$	6	Right	Increase	−6, +60, +5	$<10^{-6}$	6	Right	Increase	−16, +58, +4	$<10^{-7}$	9
Insula																Right	Increase	0, +2, +32	$<10^{-6}$	8
																Left	Increase	+10, −4, −37	$<10^{-10}$	9
Lentiform nucleus																Left	Increase	+7, +4, −17	$<10^{-6}$	8
Posterior parietal (inferior, Brodmann area 40)						Right	Increase	−20, +28, +61	$<10^{-7}$	7						Right	Increase	−35, +30, +58	$<10^{-10}$	9
	Left	Increase	−23, +21, −53	$<10^{-7}$	9	Left	Increase	−24, +30, −57	$<10^{-8}$	9	Left	Increase	−21, +20, −54	$<10^{-7}$	6	Left	Increase	−28, +30, −51	$<10^{-11}$	9

Note.—Blank cells indicate areas in which change in signal intensity did not reach the significance threshold (ie, $P < .00001$).

* Data are Talairach coordinates (anterior-posterior, superior-inferior, right-left) of maximal change in signal intensity in terms of group results.

† *P* values calculated with the Kolmogorov-Smirov method.

‡ Data are number of subjects with significant change in signal intensity in the vicinity of the coordinates for the entire group.

statistical error; therefore, we used group averages in the data analyses to increase the contrast-to-noise ratio (39). On the other hand, the fact that not all subjects showed activation in the foci determined from the group results (Table) may reflect the clinical observation that individual variation is common in the treatment response of acupuncture therapy (2,4,24). Future studies with large groups of patients in which correlations among functional MR imaging findings, psychophysical and autonomic responses, and treatment effectiveness are investigated may provide results that are relevant to this clinical issue.

Although acupuncture analgesia is among the earliest, and so far most advanced, aspects of acupuncture application to be explained in scientific terms, it has been suggested (5) that a proposed mechanism for the acupuncture effect must be able to account for its action in both painful and nonpainful conditions. Given that the hypothalamus and limbic system provide multidimensional integration of neuroendocrinal and autonomic homeostasis (41), our finding that acupuncture activates the hypothalamus and limbic system also may provide a basis for the versatility of acupuncture for use in conditions other than pain disorders, such as management of nausea and vomiting, asthma, and substance addiction (4,5,52,53).

These preliminary results suggest that functional MR imaging is useful for demonstrating brain activation associated with acupuncture stimulation. We also characterized a nervous pathway in the hypothalamus and limbic system that may mediate the *De-Qi* state. Activation of the hypothalamus and nucleus accumbens of the descending antinociceptive system and deactivation of limbic areas, which are associated with pain perception, provide a neurophysiologic mechanism for the analgesic effect of acupuncture. Our findings also provide a basis for future comprehensive investigations of endogenous pain modulation circuits in the human brain.

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References

1. Nathan PW. Acupuncture analgesia. Trends Neurosci 1978; 21–23.
2. Han JS. Neurochemical basis of acupuncture. Annu Rev Pharmacol Toxicol 1982; 22:193–220.
3. Melzack R. Folk medicine and the sensory modulation of pain. In: Wall PD, Melzack R, eds. The textbook of pain. 3rd ed. London, England: Churchill Livingstone, 1994; 1209–1218.
4. Pomeranz B. Scientific basis of acupuncture. In: Stux G, Pomeranz B, eds. Basics of acupuncture. 3rd ed. New York, NY: Springer-Verlag, 1995; 4–60.
5. Filshie J, White A. Medical acupuncture: a Western scientific approach. London, England: Churchill Livingstone, 1998.
6. Eisenberg DM, Kesseler RC, Foster C, Norlock FE, Calkins DR, Delbanco TL. Unconventional medicine in the United States: prevalence, costs and patterns of use. N Engl J Med 1993; 328:246–252.
7. Fisher P, Ward A. Complementary medicine in Europe. Br Med J 1994; 309:107–111.
8. 1993 exploratory grants for alternative medicine: National Institutes of Health guide. Bethesda, Md: National Institutes of Health, 1993.
9. Bowsher D. Mechanisms of acupuncture. In: Filshie J, White A, eds. Medical acupuncture: a Western scientific approach. London, England: Churchill Livingstone, 1998; 69–82.
10. Peets JM, Pomeranz B. CXBK mice deficient in opiate receptors show poor electroacupuncture analgesia. Nature 1978; 273:675–676.
11. Clement-Jones V, McLoughlin L, Tomlin S, Besser GM, Rees LH, Wen HL. Increased beta-endorphin but not met-enkephalin levels in human cerebrospinal fluid after acupuncture for recurrent pain. Lancet 1980; 2:946–949.
12. Kiser RS, Khatami MJ, Gatchel RJ, Huang XY, Bhatia K, Altshuler KZ. Acupuncture relief of chronic pain syndrome correlates with increased plasma met-enkephalin concentrations. Lancet 1983; 2:1394–1396.
13. Ng LKY, Katims JJ, Lee MHM. Acupuncture, a neuromodulation technique for pain control. In: Aronoff GM, ed. Evaluation and treatment of chronic pain. 2nd ed. Baltimore, Md: Williams & Wilkins, 1992.
14. Jin WQ, Zhou ZF, Han JS. Electroacupuncture and morphine analgesia potentiated by bestatin and thiorphan administered to the nucleus accumbens of the rabbit. Brain Res 1986; 380:317–324.
15. Yu LC, Han JS. Involvement of arcuate nucleus of hypothalamus in the descending pathway from nucleus accumbens to periaqueductal gray subserving an antinociceptive effect. Int J Neurosci 1989; 48: 71–78.
16. Wang Q, Mao L, Han JS. The arcuate nucleus of hypothalamus mediates low but not high frequency electroacupuncture in rats. Brain Res 1990; 513:60–66.
17. Takeshige C. The acupuncture point and its connecting central pathway for producing acupuncture analgesia. Brain Res Bull 1993; 30:53–67.
18. Zhou Z, Du M, Wu W, Jiang Y, Han J. Effect of intracerebral microinjection of naloxone on acupuncture- and morphine-analgesia in the rabbit. Sci Sin 1981; 24: 1166–1177.
19. Melzack R, Casey KL. Sensory, motivational and central control determinants of pain. In: Kenshalo DR Jr, ed. The skin senses. Springfield, Ill: Thomas, 1968.
20. Bonica JJ. Basic considerations of pain. In: The management of pain. 2nd ed. Philadelphia, Pa: Lea & Febiger, 1990; 2–208.
21. Hsieh JC, Belfrage M, Stone-Elander S, Hansson P, Ingvar M. Central representation of chronic ongoing neuropathic pain studied by positron emission tomography. Pain 1995; 63:225–236.
22. Devinsky O, Morrell MJ, Vogt BA. Contributions of anterior cingulate cortex to behavior. Brain 1995; 118:279–306.
23. Rainville P, Duncan GH, Price DD, Carrier B, Bushnell C. Pain affect encoded in human anterior cingulate but not somatosensory cortex. Science 1997; 277:968–971.
24. Beijing College of Traditional Chinese Medicine, Shanghai College of Traditional Chinese Medicine, Nanjing College of Traditional Chinese Medicine, Acupuncture Institute of the Academy of Traditional Chinese Medicine. Essentials of Chinese acupuncture. Beijing, People's Republic of China: Foreign Language Press, 1980.
25. Vincent CA, Richardson PH, Black JJ, Pither CE. The significance of needle placement site in acupuncture. J Psychosom Res 1989; 33:489–496.
26. Cho ZH, Chung SC, Jones JP, et al. New findings of the correlation between acupoints and corresponding brain cortices using functional MRI. Proc Natl Acad Sci USA 1998; 95:2670–2673.
27. Kwong KK, Belliveau JW, Chesler DA, et al. Dynamic magnetic resonance imaging of human brain activity during primary sensory stimulation. Proc Natl Acad Sci USA 1992; 89:5675–5679.
28. Cohen MS, Bookheimer SY. Localization of brain function using magnetic resonance imaging. Trends Neurosci 1994; 17:268–277.
29. Wu MT, Xian J, Kwong KK, Yang P, Rosen BR. Central processes of acupuncture assessed by functional MR imaging (abstr). Radiology 1997; 202(2):56A.
30. State Administration of Traditional Chinese Medicine. The location of acupoint: state standard of the People's Republic of China. Beijing, People's Republic of China: Foreign Language Press, 1995.
31. Vincent CA, Lewith G. Placebo controls for acupuncture studies. J R Soc Med 1995; 88:199–202.
32. Lewith GT, Vincent CA. The clinical evaluation of acupuncture. In: Filshie J, White A, eds. Medical acupuncture: a Western scientific approach. London, England: Churchill Livingstone, 1998; 205–224.
33. Reese TG, Davis TL, Weisskoff RM. Automated shimming at 1.5 T using echo planar image frequency maps. JMRI 1995; 5:739–745.
34. Jiang A, Kennedy DN, Baker JR, et al. Motion detection and correction in functional MR imaging. Hum Brain Mapp 1995; 3:1–12.
35. Woods RP, Cherry SR, Mazziotta JC. Rapid automated algorithm for aligning and reslicing PET imaging. J Comput Assist Tomogr 1992; 16:620–633.
36. Talairach J, Tournoux P. Co-planar stereotaxic atlas of the human brain. New York, NY: Thieme Medical, 1988.
37. Stuart A, Ord JK, eds. Kendall's advanced

theory of statistics. New York, NY: Oxford University Press, 1991.
38. Baker JR, Weisskoff RM, Stern CE, et al. Statistical assessment of functional MRI signal change (abstr). In: Book of abstracts: Society of Magnetic Resonance in Medicine 1992. Berkeley, Calif: Society of Magnetic Resonance in Medicine, 1992; 626.
39. Breiter HC, Etcoff NL, Whalen PJ, et al. Response and habituation of the human amygdala during visual processing of facial expression. Neuron 1996; 17:875–887.
40. Nishijo K, Mori H, Yosikawa K, Yazawa K. Decreased heart rate by acupuncture stimulation in humans via facilitation of cardiac vagal activity and suppression of cardiac sympathetic nerve. Neurosci Lett 1997; 227:165–168.
41. Angevine JB, Cotman CW. The limbic system and hypothalamus. In: Principles of neuroanatomy. New York, NY: Oxford University Press, 1981; 253–293.
42. Lewith GT, Machin D. On the evaluation of the clinical effects of acupuncture. Pain 1983; 16:111–127.
43. Le Bihan D, Dohi M. Can fMRI detect decreased neuronal activity? (abstr). In: Proceedings of the Society of Magnetic Resonance in Medicine and the European Society of Magnetic Resonance in Medicine. Berkeley, Calif: Society of Magnetic Resonance in Medicine, 1995; 452.
44. Manning BH, Mayer DJ. The central nucleus of the amygdala contributes to the production of morphine antinociception in the rat tail-flick test. J Neurosci 1995; 15:8199–8213.
45. Khanna S, Sinclair JG. Responses of the CA1 region of the rat hippocampus to a noxious stimulus. Exp Neurol 1992; 117: 28–35.
46. Posner MI, Rothbart MK. Attentional mechanisms and conscious experience. In: Milner AD, Rugg MD, eds. The neuropsychology of consciousness. London, England: Academic Press, 1991; 91–111.
47. Derbyshire SW, Jones AK, Gyulai F, Clark S, Townsend D, Firestone LL. Pain processing during three levels of noxious stimulation produces differential patterns of central activity. Pain 1997; 73:431–445.
48. Coghill RC, Talbot JD, Evans AC, et al. Distributed processing of pain and vibration by the human brain. J Neurosci 1994; 14:4095–4108.
49. Hsieh JC, Stahle-Backdahl M, Hagermark O, Stone-Elander S, Rosenquist G, Ingvar M. Traumatic nociceptive pain activates the hypothalamus and the periaqueductal gray: a positron emission tomography study. Pain 1995; 64:303–314.
50. Hsieh JC, Hannerz J, Ingvar M. Right-lateralized central processing for pain of nitro-glycerine–induced cluster headache. Pain 1996; 67:59–68.
51. Derbyshire SWG, Jones AKP, Devani PFKJ, et al. Cerebral responses to pain in patients with atypical facial pain measured by positron emission tomography. J Neurol Neurosurg Psychiatry 1994; 57:1166–1172.
52. Clement-Jones V, McLoughlin L, Lowry PJ, Besser GM, Rees LH, Wen HL. Acupuncture in heroin addicts: changes in met-enkephalin and beta-endorphin in blood and cerebrospinal fluid. Lancet 1979; 2:380–383.
53. Jobst K, Chen JH, McPherson K, et al. Controlled trial of acupuncture for disabling breathlessness. Lancet 1986; 2:1416–1419.