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**Original Research**

# Neural Specificity of Acupuncture Stimulation at Pericardium 6: Evidence From an FMRI Study

Lijun Bai, PhD,[1] Hao Yan, PhD,[2,3] Linling Li, PhD,[4] Wei Qin, PhD,[4] Peng Chen, MD,[5] Peng Liu, PhD,[4] Qiyong Gong, MD,[6] Yijun Liu, PhD,[7] and Jie Tian, PhD[1,4*]

**Purpose:** To investigate the neural specificity of pericardium PC6, with the same meridian acupoint PC7 and a treatment-irrelevant acupoint GB37 as separate controls.

**Materials and Methods:** Functional magnetic resonance imaging (MRI) of the whole brain was performed in 36 healthy subjects receiving acupuncture at three acupoints, respectively: the study acupoint (PC6), and control acupoints (PC7 and GB37). A novel nonrepeated event-related (NRER) design paradigm was applied to separately detect neural activities related to different stages of acupuncture (needling manipulation and post-acupuncture rest epoch). Psychophysical responses (Deqi sensations) were also assessed.

**Results:** Neuroimaging studies of PC6 presented extensive signal attenuations in the cerebrocerebellar and subcortical areas, whereas acupuncture at GB37 induced widespread signal potentiations. In addition, acupuncture at PC6, in comparison with stimulations at PC7 and GB37, selectively evoked neural responses of the insula, hypothalamus, and flocculonodular lobe of cerebellum (nodulus and uvula).

**Conclusion:** These findings may provide preliminary evidence for specific involvements of the cerebellar-hypothalamus and insula following acupuncture at PC6, which underlies the autonomic regulation of vestibular functions. The predominantly time-prolonged deactivations in these areas may also serve the clinical efficacy of PC6 in producing a sedative or tranquilizing effect in antiemetic treatment.

**Key Words:** acupuncture; neural specificity; different meridian acupoints; functional magnetic resonance imaging (fMRI)
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ACUPUNCTURE, a traditional Chinese healing technique that can be traced back at least 2500 years, is gaining great popularity as an alternative and complementary therapeutic intervention in Western medicine. Since most researches have tended to focus on the analgesic mechanisms of acupuncture, little is known about probable nonanalgesic effects of acupuncture. In this field, the antiemetic efficacy of acupuncture, especially the acupoint Neiguan, pericardium 6 (PC6), has recently been confirmed in abundant clinical trials, such as treating postoperative and chemotherapy nausea and vomiting (1). In spite of its public acceptance, an unequivocal scientific explanation regarding the physiological mechanism of acupuncture has not been found and awaits further investigations.

Several possible explanations have been proposed for the effect of PC6 on nausea and vomiting. Data from animal research has provided direct evidence for the hypothesis that acupuncture involves the endogenous opioid system (2) as well as serotonin transmission via activation of serotonergic and noradrenergic fibers (3,4). Sato et al (5) further infer that the action of acupuncture on nausea and vomiting involved the somatovisceral reflex, revealed by the altered gastric motility in rats. Although most previous studies have been conducted on animal models, the modulatory effect of acupuncture at PC6 on humans is currently

[1]Institute of Automation, Chinese Academy of Sciences, Beijing 100190, China.
[2]School of Psychology, Shaanxi Normal University.
[3]School of Humanities and Arts, Xidian University.
[4]Life Science Research Center, School of Life Science and Technology, Xidian University, Xi'an 710071, China.
[5]Beijing TCM Hospital affiliated to Capital University of Medical Sciences.
[6]West China Hospital of Sichuan University.
[7]Departments of Psychiatry and Neuroscience, McKnight Brain Institute, University of Florida, Gainesville, FL 32610, USA.
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*Address reprint requests to: J.T., Institute of Automation, Chinese Academy of Sciences, Beijing 100190, China. E-mail: tian@ieee.org
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available. In a recent functional magnetic resonance imaging (fMRI) study, acupuncture at PC6 specifically elicited the activation of the cerebellar neuromatrix (6), unlike the sham control. The flocculonodular lobe of the cerebellum, serving as regulation of vestibular functions, may play a pivotal role in the antiemetic efficacy of PC6. Considering that nausea and vomiting can be affected by multiple physiological processes (7), we inferred that the neural modulatory mechanism exerted by acupuncture at PC6 may more widely involve brain areas that can regulate the antiemetic functions in a coordinated manner.

Up to now most fMRI studies on the brain correlates of acupuncture effects have adopted block designs with repeated stimuli, in which needle manipulation is typically started and stopped several times (6,8,9). This model-based experimental design implicitly presumes the temporal intensity profiles of certain events conforming to the "on-off" specifications (10). Under this assumption, typical visual or motor tasks can detect the simultaneously activated nuclei successfully. But this may not be valid in cases when limited or no prior temporal information is available, such as the study testing the acute effects of acupuncture stimulus on the brain. Given that acupuncture can provide long-acting efficacy even after the needling process terminated (11), we speculated that the interstimulus epochs of rest in a block-designed paradigm may remain acupuncture-related effects, and not return to the prestimulation baseline level. In the current study a novel experimental paradigm, the nonrepeated event-related fMRI (NRER-fMRI) design (12), was adopted to separately detect the neural activity related to different stages of acupuncture intervention (needling manipulation epoch and post-acupuncture rest epoch).

Since the effect of acupuncture is subject to the amount of improvement from a baseline read, a control group is therefore designed and the decision on which control should be imposed will ultimately depend on particular questions the research model plans to answer. In this study we used acupuncture at PC6 (Neiguan, an important acupoint for preventing nausea and vomiting) as the study acupoint to test 1) whether acupuncture at PC6 can specially induce the neural correlates underlying the control of nausea and vomiting, compared with acupuncture at antiemetic-irrelevant gallbladder 37 (GB37) (Guangming, located at different meridians serving as treatment for multiple vision-related disorders); and 2) whether there were some similarities and differences between PC6 and PC7 (belonging to the same meridian and median innervation). We assumed that the introduction of multiple controls can help elucidate the specificity of the neural expression underlying the antiemetic acupoint PC6.

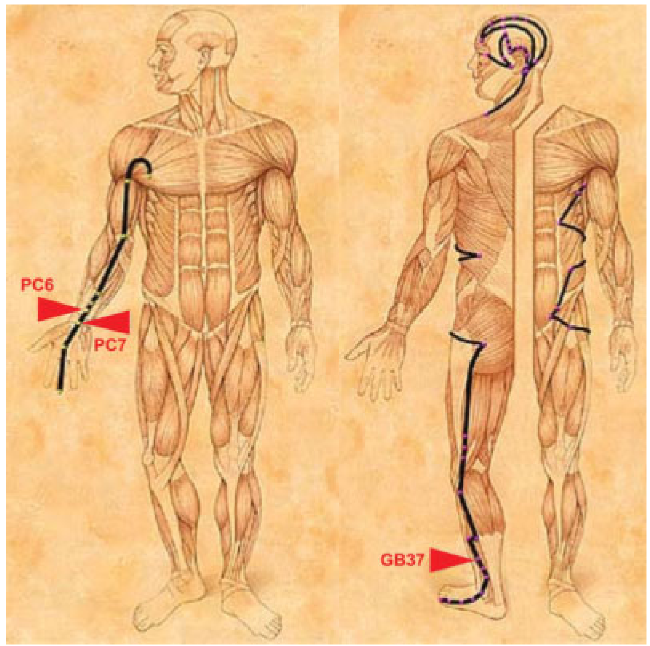


**Figure 1.** Illustration of the anatomical location and circuitry of there acupoints: PC6 (Neiguan), PC7 (Daling), and GB37 (Guangming). [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

## MATERIALS AND METHODS

### *Experimental Paradigm*

In order to reduce intersubject variabilities, all the subjects were recruited from a homogeneous group of 36 college students (18 males, ages 21.4 ± 1.3). Subjects were all acupuncture-naïve, and right-handed according to the Edinburgh Handedness Inventory (13). Subjects were screened and excluded for major medical illnesses, head trauma, neuropsychiatric disorders, intake of prescription medications within the last month, and any contraindications for exposure to a high magnetic field. Considering that nausea and vomiting can easily be affected by various psychological factors, such as anxiety, disgust sensitivity, and suggestibility (14), each participant filled out three trait questionnaires concerning disgust (Questionnaire for the Assessment of Disgust Sensitivity, QADS) (15), anxiety (State Trait Anxiety Inventory, STAI) (16), and suggestibility (17). On commencing the study, an envelope method was used to allocate subjects to receive one acupuncture at one of the three acupoints in a random sequence, with the gender ratio and psychological trait evaluations balanced (analysis of variance [ANOVA], $P > 0.6$) among different groups. After a complete description of the study was given to all subjects, written informed consent was obtained, as approved by a local Subcommittee on Human Studies.

The NRER-fMRI scanning lasted 5 minutes per run, including 2-minute needling manipulations preceded by a 1-minute rest, and followed by another 1-minute rest scanning. Acupuncture was performed on three acupoints (shown in Fig. 1): PC6 located ≈3 cm above the midpoint of the transverse crease of the wrist, between the tendon of palmaris longus and flexor carpi radialis (18); PC7 located at the midpoint of the crease of the wrist, between the tendons of the long palmar muscle and radial flexor muscle (19); GB37 located in the lateral aspect of the lower leg, with the needle being inserted on the anterior border of the fibula (20). Considering the anatomical differences, the needling depth ranged from 0.5–1.0 cm for PC6 and PC7 to 1.5–2.0 cm for GB37.

Acupuncture stimulation was delivered using a sterile disposable 38 gauge stainless steel acupuncture needle, 0.2 mm in diameter and 40 mm in length. The needle administration was delivered by a balanced "tonifying and reducing" technique (8), rotating clockwise and counterclockwise for 1 minute at a rate of 60 times/min. The procedure was performed by the same experienced and licensed acupuncturist on all subjects. The precise locations of needling, the presumed acupuncture effects, and the stimulation paradigm were not divulged. During the experiment the subjects were requested to keep their eyes closed and remain relaxed without engaging in any mental tasks.

At the end of each fMRI scanning the subjects completed a questionnaire that used a 10-point visual analog scale (VAS) to rate their experience (or "Deqi") of aching, pressure, soreness, heaviness, fullness, warmth, coolness, numbness, tingling, dull or sharp pain they felt during the scan (9,21). The VAS was scaled at 0 = no sensation, 1–3 = mild, 4–6 = moderate, 7–8 = strong, 9 = severe, and 10 = unbearable sensation. Because sharp pain was considered an inadvertent noxious stimulation, we excluded the subjects from further analysis if they experienced sharp pain (greater than the mean by more than two standard deviations) (9). Among the 36 participants, none experienced sharp pain.

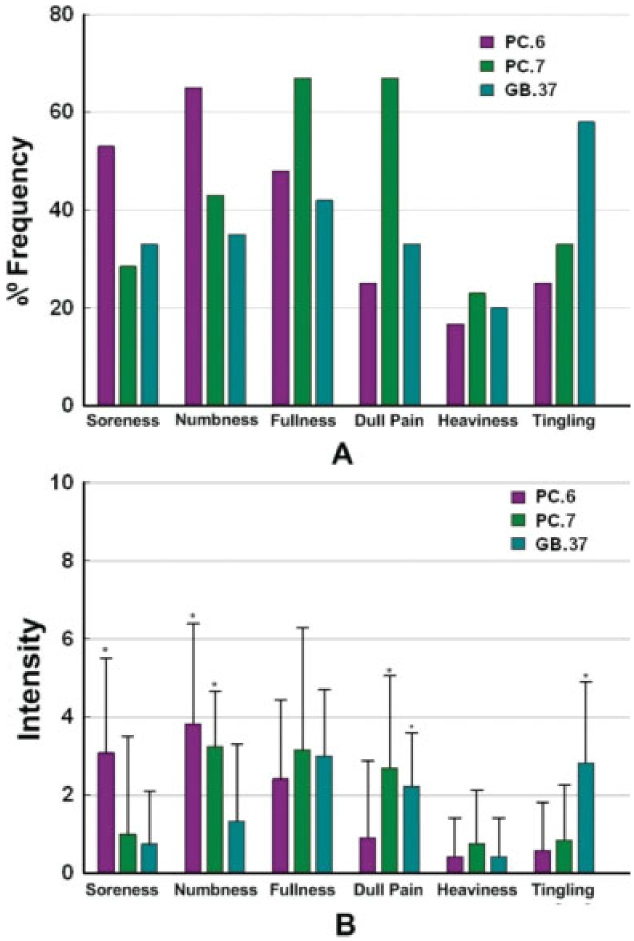


**Figure 2.** Averaged psychophysical response ($N = 36$). **A:** The percentage of subjects who reported having experienced the given sensation (at least one subject experienced the seven sensations listed). **B:** The intensity of reported sensations measured by an average score (with standard error bars) on a scale from 0 denoting no sensation to 10 denoting an unbearable sensation. *Significant differences under Fisher's exact test ($P < 0.005$). [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

### *Data Acquisition and Analysis*

The images were acquired on a 3.0 T Signa (GE Healthcare, Milwaukee, WI) MR scanner. A custom-built head holder was used to prevent head movements. Thirty-two axial slices (field of view [FOV] = 240 mm × 240 mm, matrix = 64 × 64, thickness = 5 mm), parallel to the AC-PC plane and covering the whole brain were obtained using a T2*-weighted single-shot, gradient-recalled echo planar imaging (EPI) sequence (TR = 2000 msec, TE = 30 msec, flip angle = 90°). After the functional run, high-resolution structural information on each subject was also acquired using 3D MRI sequences with a voxel size of 1 $mm^3$ for anatomical localization (TR = 2.7 sec, TE = 3.39 msec, matrix = 256 × 256, field of view [FOV] = 256 mm × 256 mm, flip angle = 7°, slice thickness = 1 mm).

All preprocessing steps were carried out using statistical parametric mapping (SPM5, http://www.fil.ion.ucl.ac.uk/spm/). The images were first slice-timed and then realigned to correct for head motions using least-squares minimization (none of the subjects had head movements exceeding 1 mm on any axis and head rotation greater than 1°). A mean image created from the realigned volumes was coregistered with the subject's individual structural T1-weighted volume image. The image data were further processed with spatial normalization based on the Montreal Neurological Institute (MNI) space and resampled at 2 mm × 2 mm × 2 mm (22). Finally, the functional images were spatially smoothed with a 6 mm full-width-at-half-maximum (FWHM) Gaussian kernel.

Since the needle insertion itself does not create significant effects on acupuncture's neural changes (9), signal intensity changes of the resting epoch prior to acupuncture manipulation can serve as an ideal baseline (BL). Due to the sustained effects of acupuncture, we specified a General Linear Model (GLM) design matrix that separates different conditions across each subject with regressors coded for the difference between the BL and subsequent epochs (needling manipulation and post-acupuncture rest), respectively. The resulting statistical maps indicated the voxel-wise signal changes for a particular condition relative to BL. These maps from each subject were then used to calculate one-sample *t*-tests in SPM5. The coordinates of activation foci were converted approximately from the MNI coordinates to Talairach

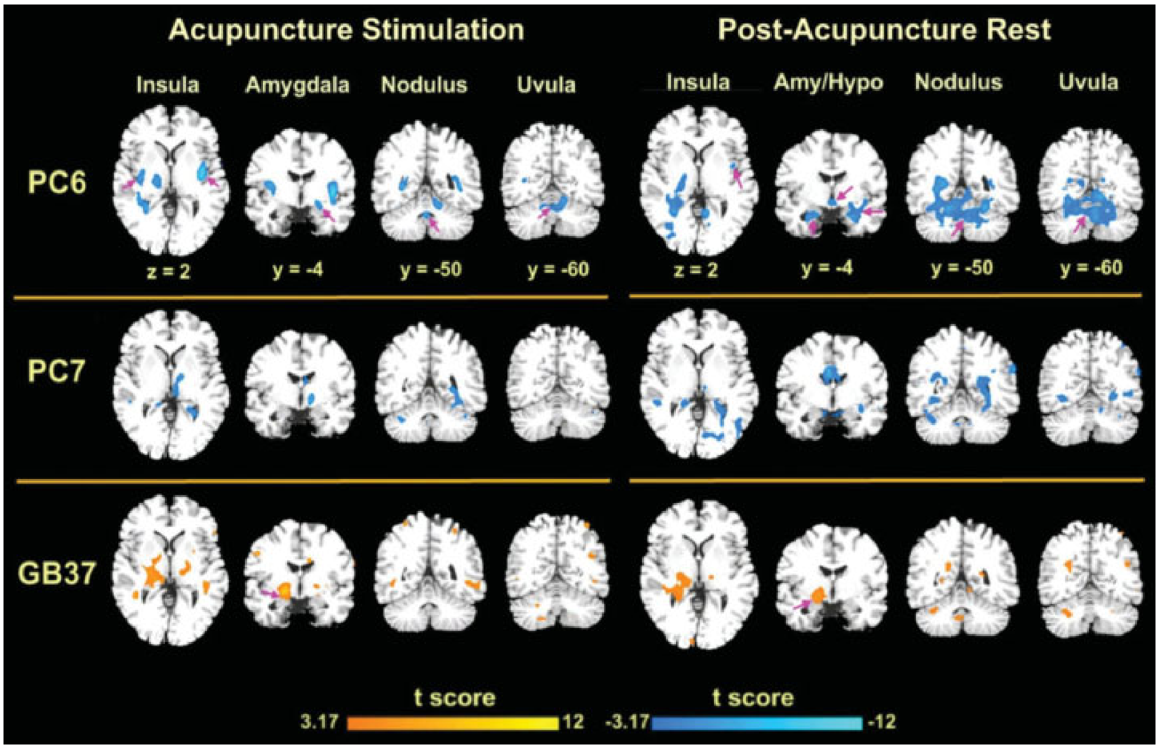


**Figure 3.** Group results of brain activity patterns under different epochs following acupuncture at PC6, PC7, and GB37. Statistical significance was thresholded at $P < 0.005$ (uncorrected) and a minimum cluster size of five voxels. Representative color-coded statistical maps exhibited the distribution of foci with significant increases (shown in the spectrum from orange to yellow) and decreases (shown in blue), relative to the respective baseline condition. Amy, amygdala; Hypo, hypothalamus. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

coordinates (23), and overlaid on MRIcro (www.sph.sc.edu/comd/rorden/mricro.html) for presentation purposes.

## RESULTS

### *Psychophysical Results*

The prevalence of these sensations was expressed as the percentage of individuals in the group who reported the given sensations (Fig. 2A). When grouped across all acupoints, no difference was found with regard to the prevalence of the listed sensations elicited by acupuncture stimulation ($P > 0.05$). However, differences did exist with respect to the type of sensations. Soreness and numbness were significantly more frequent for PC6 than PC7 and GB37 (53% vs. 28% and 33%; 65% vs. 43% and 35%). Fullness and dull pain occurred more commonly for PC7 than PC6 and GB37 (67% vs. 48% and 42%; 67% vs. 25% and 33%). Tingling was saliently more frequent for GB37 (58% vs. 25% and 33%). The average stimulus intensities (mean ± SE) were approximately similar during acupuncture on PC6 (1.85 ± 1.80), PC7 (1.93 ± 2.03), and GB37 (1.83 ± 1.79) under the ANOVA test ($P > 0.05$, Fig. 2B). However, soreness was more intense for PC6 than PC7 and GB37 ($P < 0.005$); numbness more intense for PC6 and PC7 than GB37 ($P < 0.005$). Dull pain was stronger for PC7 and GB37 than PC6 ($P < 0.005$), while tingling was more intense for GB37 than PC6 and PC7 ($P < 0.005$).

### *Sustained Neural Responses to Acupuncture at Different Acupoints*

Group results from acupuncture stimulation at three acupoints displayed distinct patterns of hemodynamic responses: negative predominantly for both PC6 and PC7 while positive following GB37 (Fig. 3, Table 1). Acupuncture stimulation at PC6 produced extensive signal decreases in the limbic/paralimbic-cerebellum and subcortical areas, such as amygdala, insula, periaqueductal gray (PAG), and flocculonodular lobe of cerebellum (nodulus and uvula). Interestingly, these remarkably decreased activities also occurred following acupuncture at PC7, but with relatively small spatial extent and less intensive signal changes (PAG, Pons, and culmen). In contrast, acupuncture at GB37 elicited saliently increased neural responses, mainly in the occipital cortex, with a limited extent of the limbic system.

More important, we observed that acupuncture-induced variance can sustain even beyond the stimulation phase, and the subsequent resting epoch can still retain "continuous" acupuncture-related effects (Fig. 3, Table 1). For PC6 this long-lasting neural response was widely presented in the limbic areas (amygdala; hypothalamus, Hypo; insula), cerebellum (nodulus, uvula, culmen) and brainstem structures (PAG); some of brain regions only became significant during the post-rest epoch of the acupuncture (PARS), including the Hypo and Pons. As for the PC7, we also observed similarly prolonged deactivations in the

Table 1
Foci With Significant Signal Changes Following Acupuncture at PC6, PC7, and GB37

| | | | PC6 | | | | | | PC7 | | | | | | GB37 | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | BA | Hem | Talairach x | Talairach y | Talairach z | *t* value | V voxels | Hem | Talairach x | Talairach y | Talairach z | *t* value | V voxels | Hem | Talairach x | Talairach y | Talairach z | *t* value | V voxels |
| Amygdala | C1 | | R | 22 | −4 | −12 | −4.27 | 27 | | | | | | | L | −18 | −8 | −11 | 10.74 | 36 |
| | C2 | | R | 26 | −7 | −18 | −4.10 | 72 | | | | | | | | | | | | |
| Insula | C1 | 13 | R | 40 | −6 | 2 | −6.68 | 144 | | | | | | | | | | | | |
| | C2 | 13 | R | 42 | 0 | 7 | −4.64 | 76 | | | | | | | | | | | | |
| Hypothalamus | C2 | | R | 4 | −6 | −7 | −4.12 | 12 | | | | | | | | | | | | |
| PAG | C1 | | L | −4 | −28 | −10 | −4.51 | 8 | R | 4 | −28 | −9 | −4.94 | 18 | | | | | | |
| | C2 | | L | −2 | −28 | −9 | −4.34 | 14 | L | −2 | −30 | −10 | −3.68 | 6 | | | | | | |
| Pons | C1 | | | | | | | | R | 1 | −18 | −19 | −4.62 | 48 | | | | | | |
| | C2 | | R | 10 | −26 | −19 | −4.59 | 49 | L | −12 | −40 | −28 | −5.09 | 100 | L | −6 | −11 | −20 | 6.23 | 64 |
| Occipital | C1 | 18 | | | | | | | R | 16 | −88 | 36 | −4.75 | 12 | L | −16 | −97 | 7 | 5.10 | 40 |
| Cortex | C2 | 17/19 | R | 14 | −60 | −2 | −5.66 | 22 | | | | | | | L | −15 | −92 | 1 | 5.74 | 126 |
| Cerebellar | C1 | | M | 4 | −48 | −27 | −5.22 | 33 | | | | | | | | | | | | |
| Uvula (X) | C2 | | M | 2 | −45 | −27 | −6.13 | 46 | | | | | | | | | | | | |
| Nodulus (X) | C1 | | M | 6 | −61 | −24 | −6.55 | 116 | | | | | | | | | | | | |
| | C2 | | M | −2 | −54 | −28 | −6.62 | 111 | | | | | | | | | | | | |

$P < 0.005$ uncorrected, cluster size > 5 voxels.
For bilaterally activated regions, we only selected the hemisphere anatomical area with a more significant *t*-value as the representative. Red color denotes positive activation, and blue for negative. C1, acupuncture stimulation condition; C2, postacupuncture rest condition; BA, Brodmann area; Hem, hemisphere; PAG, periaqueductal gray.

cerebellar system and brainstem nuclei. In contrast, long-lasting positive responses were identified in the Pons, occipital cortices, and a limited extent of the cerebellum in terms of GB37.

### *Distinct Neural Responses for PC6 vs. PC7 and PC6 vs. GB37*

Brain regions that exhibited the differential fMRI decrease in response to stimulation delivered to the PC6 and PC7 were only located in the posterior part of insula (Fig. 4). However, results from the comparison of acupuncture at PC6 and GB37 demonstrated widely spatial distributions of neural responses with relatively more intensive signal changes. These regions included the limbic/paralimbic system (amygdala and insula), thalamus, and cerebellum (uvula, nodule, fastigium, and culmen). On account of the sustained effects of acupuncture, such differential hemodynamic responses did overlap with the stimulation-induced discrepancies in our current findings.

## DISCUSSION

This was a systematic study on the examination of spatially specific neural circuits involved in acupuncture at PC6, compared with the separate controls of PC7 and GB37 (belonging to the same meridian and distinct meridian with respect to PC6). Neuroimaging results showed that acupuncture at PC6 can evoke prominently decreased neural responses in the wide cerebrocerebellar and limbic brain regions, other than increased activations following acupuncture at GB37. Even performed in the same meridian, acupuncture at PC6 and PC7 also exhibited differential hemodynamic neural responses in some limbic-cerebellar system, suggesting potentially selective efficacy-related actions. Intriguingly, such specific acupuncture-associated modulatory effects can sustain even beyond the stimulation phrase, and remain in the subsequent resting epoch; signal changes of some brain regions during the PARS were even higher than that of the stimulation epoch. These findings supported the view that the neural modulatory mechanism exerted by acupuncture at PC6 involved integrated limbic-cerebellar brain areas with a saliently prolonged action.

Following acupuncture at PC6 and PC7, we found widely negative signal changes in the limbic/paralimbic-cerebellum and subcortical areas. These regions, desensitized by acupuncture stimulation, are also reported in previous studies on neural responses involved in analgesic acupoints LI4 or ST36 (8,9). Given that limbic-cerebellum and subcortical areas are more engaged in affective motivation and autonomic drive of bodily responses, researchers speculate that acupuncture at these acupoints generally produces antistress and antianxiety effects (24). Along the same line, acupuncture at PC6 and PC7 (belonging to the pericardium

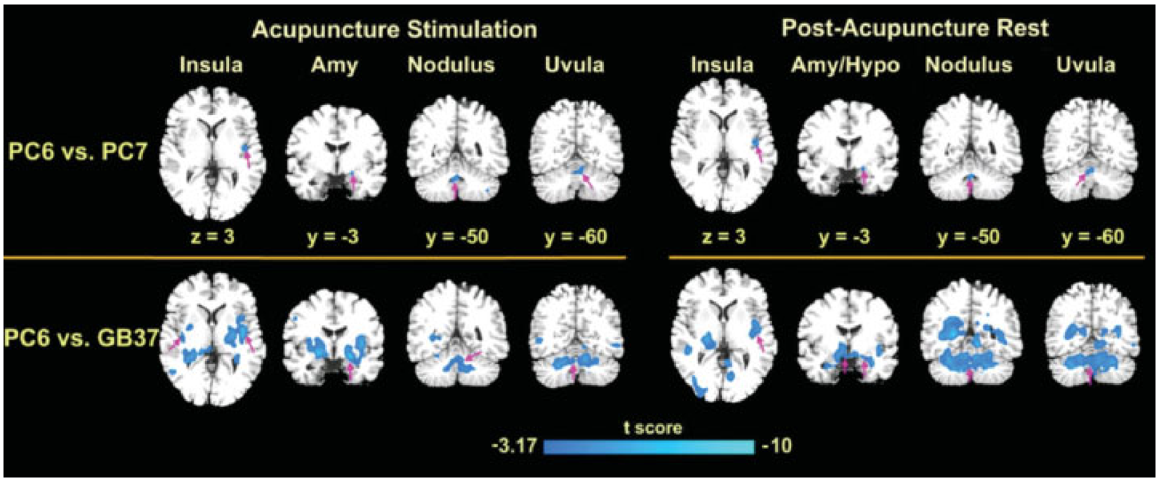


**Figure 4.** Comparison results from PC6 vs. GB37 and PC6 vs. PC7 under different epochs of acupuncture. Statistical significance was thresholded at $P < 0.005$ (uncorrected) and a minimum cluster size of five voxels. Representative color-coded statistical maps exhibited the distribution of foci with significant decreases (shown in blue). Amy, amygdala; Hypo, hypothalamus. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

meridian) has been used clinically to treat mental and psychosomatic disorders; the decreased tendency of these regions following acupuncture administration may be related to its clinical efficacy to produce a sedative or tranquilizing effect after a variety of stressors or depression (25). In contrast, these wider cerebrocerebellar and limbic areas presented consistently increased responses following acupuncture at GB37 (an acupoint of the gallbladder channel, which, as its name "brightness" implies, is described as a very effective acupoint influencing multiple vision-related disorders) (25,26). From these observations, we draw the conclusion that acupuncture stimulation at certain acupoints belonging to different meridians can elicit prominently opposite neural responses. We proposed that there were common neural substrates specific for stimulation at these acupoints, but with more flexible modulatory effects anchored by their efficacy-related actions.

We also identified several important limbic-cerebellar areas modulated only during the acupuncture stimulation at PC6. These regions included the posterior insula, hypothalamus, and flocculonodular lobe of cerebellum (nodulus and uvula). Recent noninvasive imaging studies in humans have supported a role of the insular cortex as a visceral sensory area (visceral sensations involving throat, esophagus, and possibly other areas of the gastrointestinal tract) (27,28). Penfield and Jasper (29) also reported that resection of the insula resulted in visceral motor dysfunction, nausea, vomiting, and gastrointestinal disorders. They concluded that the insula cortex was involved in psychosomatic functions with autonomic regulation of vestibular functions (27). The flocculonodular lobe of nodulus and uvula, as part of vestibulocerebellum, was only modulated following acupuncture stimulation at PC6. This may indicate that stimulation at PC6 can exert modulatory effects in the processing of vestibular functions, thereby alleviating the symptoms of vomiting and nausea. Furthermore, the hypothalamus was also involved in the central characteristic of acupuncture at PC6. This region, as an important high autonomic center for regulation of visceral functions, has recently been demonstrated in a series of neuroanatomical investigations on a variety of mammals and suggested to be potential pathways underlying the cerebellar vestibular modulation (30).

Activity observed in the cerebellar nodulus and uvula in this study was consistent with recent reports of neural responses following acupuncture at PC6 (6), whereas the hemodynamic neural response was in an opposite direction. Although this inconsistency between our findings and our predecessors may partly be due to various inherent factors in the fMRI experiments (different needling methods and diverse intensities of acupuncture stimulation), such varied detected hemodynamic response may also be attributed to the presence of significant activities during the sequential resting epoch (31,32). Response magnitudes of some part of the cerebellar during the PARS were even higher than that of the stimulation epoch (Table 1). Noticeably, it is these rest epochs that previous acupuncture studies always adopted as the baseline for comparison with signal intensity during stimulation, which led to the reversal sign of cerebellum activities during the stimulation condition.

In conclusion, the present study demonstrated that acupuncture at PC6 can selectively evoke the hemodynamic response of the insula and cerebellar-hypothalamus in order to exert modulatory effects on the regulation of vestibular functions. Although stimulation at three acupoints shared some spatial overlap of brain nuclei, neural response patterns induced by acupuncture at different meridians (treatment-irrelevant) exhibited an opposite effect. Even with the relatively similar treatment usage, PC6, compared with PC7, can particularly exert modulatory effects on the vestibulocerebellum and autonomic regulation areas. Not only can these findings support the notion of the sedative or tranquilizing effect underlying the antiemetic action of PC6, but also they provide a clue to elucidate the relatively function-oriented specificity of acupuncture effects. Further studies should also be adopted to elucidate the specificity of acupuncture at PC6 in comparison to that at a nearby nonacupoint. Apart from this, we also found generally sustained effects of acupuncture for all three acupoints. Considering that acupuncture-related changes is slow to develop and resolve (33,34), more flexible data-driven methods, allowing capturing both neural activations and temporal variations, may be an optimal choice for further investigations.

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