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Activation of the hypothalamus characterizes the acupuncture stimulation at the analgesic point in human: a positron emission tomography study

Jen-Chuen Hsieh[a,b,c,*], Chung-Haow Tu[a,b], Fang-Pey Chen[c,d], Min-Chi Chen[a], Tzu-Chen Yeh[a,c], Hui-Cheng Cheng[a,c], Yu-Te Wu[a,e], Ren-Shyan Liu[c,f], Low-Tone Ho[a,c]

[a]*Integrated Brain Research Unit, Department of Medical Research and Education, Taipei Veterans General Hospital, No.201, Section 2, Shih-Pai Road, Taipei 112, Taiwan*

[b]*Institute of Neuroscience, School of Life Science, National Yang-Ming University, Taipei, Taiwan*

[c]*Faculty of Medicine, School of Medicine, National Yang-Ming University, Taipei, Taiwan*

[d]*Center of Traditional Medicine, Taipei Veterans General Hospital, Taipei, Taiwan*

[e]*Institute of Radiological Sciences, National Yang-Ming University, Taipei, Taiwan*

[f]*National PET/Cyclotron Center, Taipei Veterans General Hospital, Taipei, Taiwan*

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Abstract

We performed a positron emission tomography study, using regional cerebral blood flow as the index of brain activity, to address the specificity of brain activation pattern by acupuncture stimulation of short duration at the classical analgesic point. Needling manipulation at 2 Hz was performed at a classical point of prominent analgesic efficacy (Li 4, Heku) and a near-by non-classical/non-analgesic point, respectively, in normal subjects. Regions activated by acupuncture stimulation at Li 4 included the hypothalamus with an extension to midbrain, the insula, the anterior cingulate cortex, and the cerebellum. Of note, it was only the stimulation at Li 4 that activated the hypothalamus under the similar psychophysical ratings of acupuncture sensation (*deqi*) as elicited by the stimulation at the two points, respectively. The data suggested that the hypothalamus might characterize the central expression of acupuncture stimulation at the classical analgesic point and serve as one key element in mediating analgesic efficacy of acupuncture stimulation.

Keywords: Acupuncture; Pain; Hypothalamus; Positron emission tomography; Brain; Insula; Brain stem; Cerebellum

Acupuncture has been used as a treatment in Asia for more than 3000 years and is gaining widespread popularity in the modern medicines as an alternative and complementary treatment for many health conditions [14]. Among them, pain alleviation is one of the most common applications. Animal and clinical studies suggested that the analgesia efficacy of acupuncture might be achieved by the endogenous opioid ligands [7,11]. Several structures of the descending antinociceptive pathway, e.g. the hypothalamus, the nucleus accumbens, the mesencephalon (including periaqueductal gray matter and raphe nuclei), and the limbic systems are believed to participate in the analgesic mechanism of acupuncture [7,18,21].

The suggested mechanisms have been corroborated by recent functional brain imaging studies in which modulation of the activities of hypothalamus–limbic systems were demonstrated when contrasting the acupunctural needle manipulation with the controlled superficial tactile or pricking stimulation at the analgesic acupuncture points [10,20]. Using functional magnetic resonance imaging (fMRI), Wu et al. [20] had previously demonstrated that acupuncture stimulation at the analgesic acupuncture points, Large Intestine 4 (Li 4) and Stomach 36 (St36), activated the hypothalamic–limbic system. In addition, a correlation between activation of specific areas of brain cortices and corresponding acupuncture stimulation at the therapeutic points had been well illustrated [3]. To further address the specificity of central expression of acupuncture stimulation, we conducted a PET study, using rCBF as the index of brain activity, on acupuncture stimulation at the classical

* Corresponding author. Tel.: +886-2-28757480; fax: +886-2-28745182.

E-mail address: jchsieh@vghtpe.gov.tw (J.-C. Hsieh).

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acupuncture point (Li 4) of prominent analgesic efficacy and a near-by non-classical/non-analgesic point on the right hand, respectively. The hypothalamus, brainstem, insula, and anterior cingulate cortex were pre-selected for analysis based on our previous PET and fMRI imaging studies on pain and acupuncture [8,9,20].

All procedures were approved by the local Ethics and Radiation Safety Committees. Informed consent was given by all the healthy subjects ($n = 16$, right-handed, 20–30 years of age, gender balanced, randomly allocated into two groups). Subjects participated in a short training session with actual acupuncture stimulation 1 day before the PET experiment. Acupuncture needling stimulation (performed by FPC on all subjects) was carefully administered during the rehearsal session (left Li 4) and the PET experiment (right Li 4) to generate acupuncture sensation (*deqi*; a mixture sensation including soreness, numbness, fullness, and heaviness) with little or no pain [10,15,20]. For the verification, subjects were questioned immediately after each rCBF study as to the type of and intensity of sensation they experienced during the needling stimulation [10,20]. The needle was manipulated in *minimal* and *deqi* conditions by twirling and balanced reinforcing-reducing technique at about 2 Hz [20]. The frequency of needle manipulation was selected according to the previous observations that hypothalamus, being a nucleus densely aggregated with β-endorphinergic neurons, is central to the analgesic mechanisms of low frequency acupuncture stimulation [18,19].

In experiment one (group I, $n = 8$), we studied the central representation of acupuncture stimulation and sensation. Subjects underwent nine rCBF investigations (Scanditronix PC 4096–15 WB, ~30 mCi [15O] water, and 180-s scan). PET scanning was commenced (subjects' eyes closed) simultaneously with the injection of [15O] water via left antecubital vein. The acupuncture needle (0.25 mm in diameter) was inserted perpendicular to the skin surface to a depth of ~3 mm deep before the PET scanning. The needle remained in place throughout the experiment. Acupuncture stimulation was performed at Li 4 on the right hand. The stimulation commenced ~15 s after the injection of [15O] water and lasted for ~30 s to coincide with the bolus arrival in the brain [8,17]. In the *rest* condition, the acupuncturist (FPC) kept her hand near the needle with sham manipulation during the scanning. In the *minimal* condition, the needle was gently manipulated at the same depth as that of *rest*(~3 mm). In the *deqi* condition, the needle was advanced deeper into the tissue (~1 cm depth). After scanning (180 s), the needle was retracted to the depth of *rest* condition. The three conditions were consecutively studied once and thereafter twice in a randomized manner.

In experiment two (group II, $n = 8$), we investigated the differences between the stimulation at the classical analgesic point (Li 4, Heku) and the non-analgesic point (non-classical point at the space between the 3rd and 4th metarcapals; Fig. 1), respectively, on the right hand. Acupuncture sensation (*deqi*) could be obtained from needling stimulation at both sites. Needles were inserted at both sites and retained in place before the PET scanning. Since we targeted at the central representations of acupuncture sensation, only the *minimal* and the *deqi* paradigms were studied. Measurement orders (two repetitions, 8 rCBF scans in total) were balanced within and between subjects.

The images were processed using SPM96 (SPM96, Welcome Dept. of Cognitive Neurology, Institute of Neurology, University College London, London, UK), implemented in Matlab (Mathworks Inc., Sherborne, MA, USA). Images were realigned, normalized to the standard space, and smoothed with a Gaussian filter (FWHM = 16 mm). The effect of variance due to global blood flow was removed by using a voxel-based ANCOVA. The global cerebral blood flow across the scans was normalized to 50 ml/100 g-min. Significant changes in rCBF in different brain regions associated with *minimal* and *deqi* were identified by comparing the condition-specific levels of adjusted mean rCBF with *rest* level on a voxel-by-voxel basis with *t*-statistics in the experiment 1. Comparisons between *deqi* and *minimal* on the two sites were respectively conducted in experiment 2. These analyses generated SPM{t} maps which were subsequently transformed to SPM{Z} maps. Significant differences were accepted at a threshold of $P < 0.001$ (uncorrected). Stereotaxic co-ordinates of peak activation are expressed in millimeters and refer to medial-lateral position (x) relative to midline (positive = right), anterior-posterior position (y) relative to the anterior commissure (positive = anterior), and superior-inferior position (z) relative to the commissural line (positive = superior).

In the experiment 1, *deqi* significantly activated the

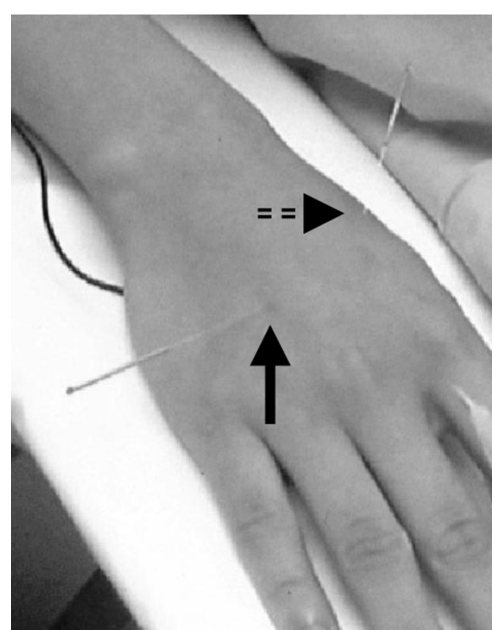

Fig. 1. Acupuncture needle manipulation was performed at analgesic point Li 4 (dotted arrow) and at the non-analgesic point in the 3rd interosseous muscle (filled arrow), respectively.

hypothalamus ($x = 2$, $y = -10$, $z = 0$, Z-max = 4.32; bilaterally extended) and insula ($x = 32$, $y = -22$, $z = 16$, Z-max = 3.38) when compared with *minimal* condition (Fig. 2a). *deqi* activated the hypothalamus more spatially and with an extension to midbrain (encompassing periaqueductal gray matter) when compared with *rest* condition ($x = -2$, $y = -6$, $z = -4$, Z-max = 4.85; bilaterally extended; Fig. 2b). *Minimal* stimulation activated neither the hypothalamus nor the insula when compared with *rest* situation (Fig. 2b). We inadvertently observed a strong activation of cerebellar vermis extending to left cerebellar hemisphere by *deqi* in comparison with both *minimal* ($x = -8$, $y = -80$, $z = -24$, Z-max = 4.17; Fig. 2a) and *rest* conditions (Z-max = 5.00; Fig. 2b), respectively. In experiment 2, the activation pattern by *deqi* at the analgesic point (Li 4) was similar to that of experiment 1 as contrasted with the *minimal* condition (Fig. 2d). Stimulation at the non-analgesic point (with similar acupuncture sensation and intensity as that of *deqi*) neither activated the hypothalamus, the midbrain/brain stem, nor the insula (Fig. 2e).

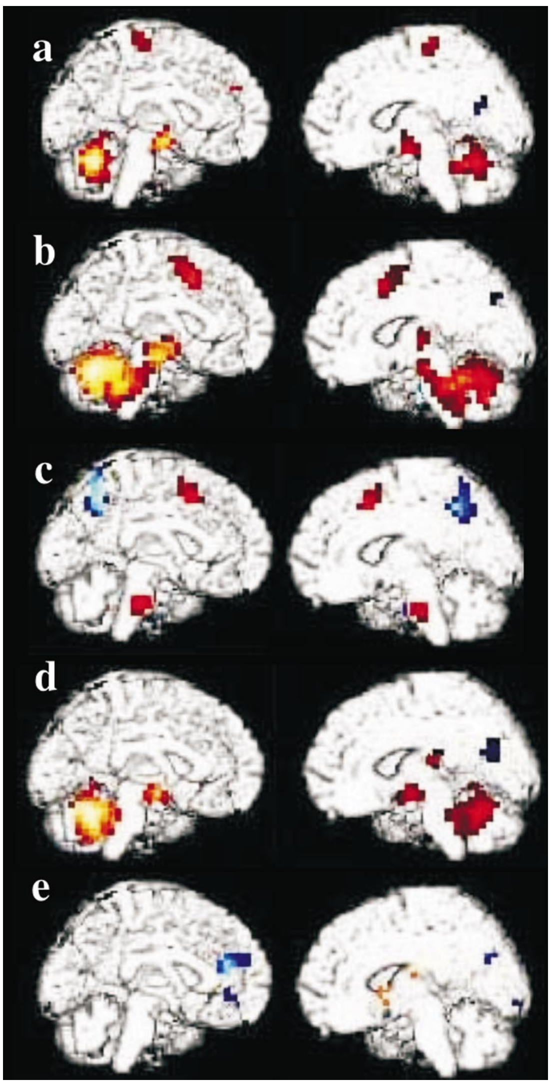

Fig. 2. The activation maps depicting the neuronal activities in different conditions. The warm color (red-yellow) denoted activation and the cold color (blue-cyan) denoted deactivation (not discussed) in experiment 1 (a,b,c) and experiment 2 (d,e). (a) *deqi,* as contrasted with *minimal,* activated the hypothalamus and the cerebellum. (b) The activation by *deqi* in the hypothalamus extended to the midbrain/brain stem when contrasted with *rest*. (c) *Minimal* stimulation in experiment 1 did not activate the hypothalamus. (d) Similar activation by *deqi* at Li 4 as contrasted to *minimal* stimulation. (e) No activation observed in the hypothalamus by *deqi* stimulation at non-analgesic point, comparing *minimal* stimulation.

The data further corroborated our previous fMRI findings [20]. Acupuncture stimulation with *deqi* at the analgesic point engages neural substrates of the endogenous anti-nociceptive modulation system, especially the hypothalamus and the midbrain structures. The hypothalamus, with the most abundant endorphinergic neurons and long descending projections to the raphe nucleus and periaqueductal gray matter of the mesencephalon, has been suggested to be critical for acupuncture analgesia [18,19,21]. The absence of hypothalamus/midbrain activation by the stimulation at the non-analgesic point implies that the hypothalamus might characterize the central expression of acupuncture stimulation at the acupuncture point of prominent analgesic efficacy and serve as one of the key neural substrates in mediating analgesic efficacy of acupuncture stimulation [7,18,21].

In the past decade, confirmation has been given to the insula as a visceral sensory area, visceral motor area, motor association area, vestibular area, and language area [13]. Activation of insula by *deqi* and *minimal* conditions was in agreement with the recent idea, based on the functional brain imaging studies [8,9,20] and neuroanatomical knowledge, that insula can be a multifaceted-sensory area and serves as a critical integration cortex [1].

Activation of the anterior cingulate cortex was significant only when contrasting *deqi* with *rest* ($x = 0$, $y = -20$, $z = 36$, Z-max = 3.86; Fig. 2d). We did not observed any significant activation of the anterior cingulate cortex when contrasted *deqi* with *minimal* (Fig. 2c). Attention and arousal to needling manipulation could account for the activation in this sub-region of the anterior cingulated cortex [9]. The role of the anterior cingulate cortex might be minor in the mediation of *deqi* phenomenon per se.

Prominent activation of cerebellum (mainly the vermis) by acupuncture stimulation with *deqi* was unexpected. The cerebellar activity survived even using a more stringent corrected threshold of $P < 0.01$ [5]. The brain activation pattern did not code the mild musculocutaneous discomfort due to the stimulation [16]. Neuroanatomical studies have shown that the cerebellum and hypothalamus are interconnected by direct hypothalamo-cerebellar and cerebello-hypothalamic projections and by a multitude of indirect pathways [4]. The reciprocal connections between the cerebellum and hypothalamus may be part of the circuits through which the cerebellum participates in the modulation and co-ordination of a wide range of central nervous activities, somatic as well as non-somatic [6]. The relevance of cerebellum activity to acupuncture stimulation and sensation mandates further exploration.

The findings of differential activation patterns tailoring possible functional specificities of acupuncture points/meridian are supported by one human fMRI study [3] and our recent work with manganese-enhanced animal fMRI methodology [12] on experimental animal acupuncture [2]. We demonstrated in rabbits that different acupuncture points of different meridians have respectively different patterns of cerebral representations and corresponding time-courses of activation [2].

The clinical effect of acupuncture analgesia usually necessitates longer and multiple stimulation sessions [7]. We in this study only investigated the central representation of acupuncture stimulation of short duration in normal subjects without pain. We demonstrated a correlation between activation of specific areas of brain cortices and corresponding acupuncture stimulation at the analgesic point. It remains to be explored whether high frequency acupuncture stimulation at the analgesic point can activate the hypothalamus/midbrain of endogenous pain modulation system. Furthermore, it is conceivable that the CNS representation of acupuncture stimulation can be different between pain and non-pain subjects. Studies on acupuncture stimulation at different acupuncture points of different meridians and acupuncture modulation on patients in pain are currently undertaken to better elucidate the central mechanisms of acupuncture medicine.

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