Mode and site of acupuncture modulation in the human brain: 3D (124-ch) EEG power spectrum mapping and source imaging

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This study determined: (a) if acupuncture stimulation at a traditional site might modulate ongoing EEG as compared with stimulation of a control site; (b) if high-frequency vs. low-frequency stimulation could exert differential effects of acupuncture; (c) if the observed effects of acupuncture were specific to certain EEG bands; and (d) if the acupuncture effect could be isolated at a specific scalp field, with its putative underlying intracranial source. Twelve healthy male volunteers (age range 22–35) participated in two experimental sessions separated by 1 week, which involved transcutaneous acupoint stimulation at selected acupoint (Li 4, HeGu) vs. a mock point at the fourth interosseous muscle area on the left hand in high (HF: 100 Hz) vs. low-frequency (LF: 2 Hz) stimulation by counter-balanced order. 124-ch EEG data were used to analyze the Delta, Theta, Alpha-1, Alpha-2, Beta, and Gamma bands. The absolute EEG powers (µV²) at focal maxima across three stages (baseline, stimulation, post) were examined by two-way (condition, stage) repeated measures ANOVA. The activity of the Theta power significantly decreased (P = 0.02), compared with control during HF but not LF stimulation at acupoint stimulation, however, there was no study effect at the mock point. A decreased Theta EEG power was prominent at the frontal midline sites (FCz, Fz) and the contralateral right hemisphere front site (FCC2h). In contrast, the Theta power of low-frequency stimulation showed an increase from the baseline as those in both controlled mock point stimulations. The observed high-frequency acupoint stimulation effects of Theta EEG were only present during, but not after, stimulation. The topographic Theta activity was tentatively identified to originate from the intracranial current source in cingulate cortex, likely ACC. It is likely that short-term cortical plasticity occurs during high-frequency but not low-frequency stimulation at the HeGu point, but not mock point. We suggest that HeGu acupuncture stimulation modulates limbic cingulum by a frequency modulation mode, which then may damp nociceptive processing in the brain.

Keywords: Acupuncture; Theta EEG; 3D topographic field potential mapping; Current source imaging; Cortical plasticity; Frequency modulation

Introduction

Acupuncture has been considered an important milieu in complementary medicine and has received an increase interest by the public. The scientific community on acupuncture therapy has been summarized by a recent NIH Consensus on Acupuncture (Berman, 2001). The controversial issues surrounding acupuncture are (a) whether it works and (b) how it works, as is evident by the 30 systematic reviews in recent years.

Essential mechanisms of the acupuncture effect have been hypothesized (Kaptchuk, 2002): (1) the short-term effect caused by frequency modulation of neuroplasticity and (2) the long-term effect caused by gene transformation of protein synthesis demonstrated by specific brain activations in neuroimaging (Biella et al., 2001; Uchida et al., 2003). Central to the basic mechanisms of the acupuncture effect is a theory of frequency modulation of brain function (Han, 2003). The contemporary electroacupuncture (EA) was shown to be more effective than traditional manual acupuncture for anti-nociception (Wang et al., 1992). As a result, EA is used more often than manual acupuncture for its convenience and high repeatability of stimulus control. Aside from proving the efficacy of acupuncture in treatment of several medical problems, basic neuroscience research has been focused on the modulation of the brain activities during acupuncture stimulation. The physiological or psychophysical effects of acupuncture are often depending on stimulus parameters (site, intensity, mode, etc.). Of these parameters, stimulus frequency has been proven to be most important to impact on brain activities (cf. Zhang et al., 2003c; Napadow et al., 2004).
Different neuro-acupoint stimulation frequency can induce different neurochemical effects. Stimulation at a frequency of 15–30 Hz was more effective than a lower frequency of 2–3 Hz in triggering peptide release (Racke et al., 1989). Burst stimulation was more effective than constant frequency stimulation on cortical excitation (Cazalis et al., 1988). Both low-frequency and high-frequency stimulation reducing or increasing cortical excitation has been shown to induce analgesia, but there were differential effects of low- and high-frequency acupuncture on the types of endorphins released (Shen, 2001). Low-frequency (2 Hz) and high-frequency (100 Hz) EA selectively induced the release of enkephalins and dynorphins in both experimental animals and humans (Ulett et al., 1998). Therefore, endogenous opioid peptides could play an important role in acupuncture-induced analgesia. In human subjects, low-frequency (2 Hz) high-intensity stimulation could induce a partial naloxone reversible acupuncture effect compared with high-frequency (100 Hz) low-intensity stimulation on the nociceptive R-III component of the blink reflex (Willer et al., 1982). In patients, preoperative EA stimulation between low-frequency and high-frequency on the post-operative pain of abdominal surgery and drug demands under patient controlled analgesia (Lin et al., 2002) showed that a morphine required in 24 h was decreased more in high-frequency group than the low-frequency and sham group and that (b) vomiting and nausea were lower in the acupuncture group than in the sham and control groups.

In a recent report of EA-induced analgesia, as examined by using behavioral withdrawal index and FMRI, a positive correlation of analgesic effects was observed in the contralateral motor area, the supplementary motor area, and the ipsilateral superior temporal gyrus for low-frequency 2 Hz stimulation compared with the contralateral inferior parietal lobule, ipsilateral anterior cingulate cortex, nucleus accumbens, and pons for high-frequency 100 Hz stimulation (Zhang et al., 2003b).

It is also known that intense stimulation may induce “wind-up” and/or hypersensitization in the spinal cord (Herrero et al., 2000) and the brain in monkeys (Tommerdahl et al., 2002). Of particular interest is whether high-frequency and low-frequency stimulation may also modulate human EEG records. Little information has been reported in literature. EEG and acupuncture stimulation have been studied with various effects (e.g. Rosted, 2001; Litscher, 2004), however, specific examination of high- vs. low-frequency effects has yet to be investigated. This study uses a modern EEG recording methods, 3D high-resolution 124-ch EEG topographic mappings, to study the acupuncture effects.

The aim of the present study was to examine (a) if acupuncture stimulation at a traditional site modulates ongoing EEG compared with a control site; (b) if high-frequency and low-frequency stimulation exerted differential effects on the EEG; (c) if the observed effects were specific for EEG frequency bands, (d) if specific cortical areas were affected by the topographic examination analysis, and finally (e) whether any EEG changes were only present during stimulation or lasted to the post stage.

### Materials and methods

#### Subjects

Twelve healthy male volunteers (age range 22–35 years-old, mean 24.3 years) participated in the study. Subjects were excluded from the study if they had any sore, pain, cut, serious skin problems on the hands, or using medication. Written consent was obtained from each subject in accordance with the Helsinki Declaration, and the study was approved by the local ethical committee.

#### Acupuncture stimulation and experimental design

Each subject was asked to sit in an armchair throughout the duration of the experiment in a quiet room (mean temperature of 20–22°C). Each subject attended two experimental sessions (acupoint stimulation and control mock point stimulation) separated by at least 1 week. The order of stimulation mode was counterbalanced across the subject; all subjects were blind to the stimulation mode and effect. Transcutaneous electric acupoint stimulation (HANS: Han’s acupoint nerve stimulator, Model LH202H TEAS) was used. The selected acupoint stimulation was LI4 (HeGu point) and applied to the first inter-terosseous muscle of the left hand. The control point was at the area overlaying the fourth interosseous muscle (see Fig. 1A), as reported by other MRI studies (Hsieh et al., 2001; Wu et al., 2002). The frequency of stimulation was 100 Hz vs. 2 Hz. The intensity was adjusted slightly below the pain or discomfort threshold. The stimulation level varied between 7 and 32 mA for 2 Hz in low-frequency stimulation, and 6–18 mA for 100 Hz in high-frequency stimulation for all subjects. Each subject was instructed to pay attention to the sensation induced at the stimulated site and to fully relax.

Across the sessions, three study stages consisted of 5 min baseline EEG; (B); 15 min stimulation EEG (S); and 20 min post-stimulation EEG (P). At the stimulation stage, four study conditions were designated as acupoint stimulation with high-frequency (A/HF); acupoint stimulation with low-frequency (A/LF); mock point stimulation with high-frequency (C/HF); mock point stimulation with low-frequency (C/LF).

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**Table 1**

<table>
<thead>
<tr>
<th>Study stage</th>
<th>Baseline (B, 5 min)</th>
<th>Stimulation (S, 15 min), and Post (P, 20 min) stages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acupoint (A)</td>
<td>A/HF</td>
<td>A/LF</td>
</tr>
<tr>
<td>Mock point (C)</td>
<td>C/HF</td>
<td>C/LF</td>
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</table>
LF); control point stimulation with high-frequency (C/HF); control point stimulation with low-frequency (C/LF). The design protocol is outlined in Table 1.

EEG recordings and pre-treatment of EEG

A high-resolution 124-channel EEG recording and two channels of electro-oculogram (EOG) channels were continuously gathered across three study stages (see below) with the A.N.T. EEG System (A.N.T. Enschede, Netherlands). The electrodes were mounted according to the 10/5 montage system (Oostenveld and Praamstra, 2001). The 3D 128-ch montage and nomenclature is depicted in Fig. 2.

Bilateral EOG was recorded from the horizontal and vertical sites to monitor blinking or eye movements. The portion of EOG contamination of each scalp trace was removed in the off-line analysis. All the EEG channels were recorded in reference to the left mastoid but were offline bilaterally re-referenced (averaged A1 + A2). EEG data were sampled at 512 Hz, and electrode impedance was kept lower than 5 kΩ. Ongoing EEG was recorded with eyes closed in three stages: before stimulation (Baseline 5 min), during stimulation (Stimulation, 15 min), after stimulation (Post, 20 min).

Fig. 2. Superior-anterior view (left panel) and superior-posterior view (right panel) perspectives of the 128-ch EEG electrode nomenclature in 10/5 montage.

Fig. 3. EEG power spectrum topography of grand average at the baseline stage. Delta activity was focal at the prefrontal site on the top of both eyes and maximal at the AF8 electrode site. Theta activity was clustered at the frontal midline area, maximal at the FCz electrode site. Alpha-1 activity was centered on the parietal–occipital midline area and maximal at the PO8 electrode site. Alpha-2 activity was focal at the occipital area and maximal at the PO4 electrode site. Beta activity was highly diffused across the scalp, and a maximal site at the FCz electrode site was selected. Gamma activity was focal at bilateral temporal areas and maximal at FFT7h electrode site.
EEG data were filtered with 0.5–100 Hz bandpass filter off-line and were subjected to epoching (2 s each), linear-detrend, artefact rejection, and averaging. The artefact rejection methods consisted of exclusion in epoch with large amplitude (over ±80 μV), DC bias, blinks, and slow eye movement coincident with EOG. Bad electrodes were replaced with the extrapolated values from the neighboring electrodes. After rejection of EOG contamination and non-specific artefacts, each set of EEG data (2-s epoch) was subjected to Fast-Fourier Transform (FFT) analysis to obtain the absolute EEG band power (μV²) at each electrode in the following 6 bands: Delta (0.5–3.5 Hz), Theta (4–7 Hz), Alpha-1 (7.5–9.5 Hz), Alpha-2 (10–12 Hz), Beta (13–30 Hz), and Gamma (35–45 Hz). These broad bands were defined by the conventional IFCN guideline (Nuwer et al., 1999), but not according to individuals’ spectral characteristics (cf. Doppelmayr et al., 1998).

For each condition and stage, the six band powers of valid epochs were averaged. The group averages and FFT maps of different stages were performed by ASA 3.0 software (A.N.T. Enschede, Netherlands). Topographic maps (256 hues) of the mean amplitude of the surface EEG power were calculated on a 3D “quasi-realistic” cortical model by a spline interpolating function (Babiloni et al., 1996).

### Data management and statistical analysis

For each of the 6 EEG bands, a scalp field power spectral map was interpolated from 124-ch of EEG, and the site/electrode of maximal power was isolated with its value calculated. A grand average of the four baseline conditions was computed, as shown in Fig. 3. Statistical effects of study conditions and experimental stages were conducted on the maximal values at the focal site in each of the six bands.

Statistical comparisons were performed on the scalp field maxima of EEG power by two-way repeated measures ANOVA, and Tukey test was used for post-hoc comparisons (P < 0.05). The study conditions A/HF, A/LF, C/HF, and C/LF were used for factor-1, and study stages Baseline, Stimulation, Post were used for factor-2. The statistical program SigmaStat (SPSS Inc., Chicago, USA) was used for statistical measure.

### Results

#### 3D topographic mapping of the grand average of baselines at resting stage

The field power topography and focal maximal site/electrode in each of the six EEG bands at the resting Baseline are respectively displayed in Fig. 3. Delta activity was focal at the prefrontal site on the top of both areas above the eyes. This site likely reflected the slow wave of eyes blinking, even after serious artefact rejection routine, and was maximal at the electrode site of AF8. Theta activity was clustered at the frontal midline area, maximal at FCz, likely reflecting ACC (anterior cingulate cortex) activation as demonstrated in EEG literature (Asada et al., 1999; Luu et al., 2003). Alpha-1 was centered on parietal midline area, maximal at PO8. PO8’s origin is unknown but has been modeled from centroparietal contribution (Manshanden et al., 2002). Alpha-2 was focal at occipital area, maximal at PO4, and is of visual cortex origin. Beta band was shown to be highly diffused across the scalp and was maximal at FCz. Gamma band was focal at bilateral temporal areas, maximal at FFT7h, and is likely due to muscle tension of both temporal jaws.

#### Statistical effects of study conditions across stages

The results of two-way ANOVA with repeated measures indicate systematic effects on the EEG power of focal maxima. The full statistical results are presented in Table 2 below.

The main results indicated: (A) the significant effects in the Theta and Alpha-1 powers and (B) no significant effects in the Delta, Alpha-2, Beta, or Gamma powers. The Theta power showed significant condition by stage effects (F = 2.277, P = 0.047), while the Alpha-1 power only showed significant stage effect (F = 6.12, P = 0.008). Since there was no significant interaction between

![Fig. 4. Significant effect of the stage on Alpha-1 activities. “Acupoint stimulation” and “mock point stimulation” resulted in a significant increase of Alpha-1 power at the occipital during the Stimulation and Post stages compared to Baseline stage. These effects were non-specific to the study site and study conditions, i.e. high vs. low frequency. The heightened Alpha-1 may indicate greater relaxation state both during and after stimulation (bar: standard error of mean; ★ denotes P < 0.05).](Image)
condition and stage effects in Alpha-1 power, the observed results could be due to non-specific changes of Alpha-1 EEG across time, from Baseline to Stimulation and Post changes (see Fig. 4). The results of the Theta EEG were even clearer, when compared with the results of Alpha-1.

The power spectrum maps of the grand average in each of the four stimulation conditions are shown in the middle column of Fig. 5. Only the acupoint stimulation at high-frequency (A/HF) condition resulted in decreased Theta EEG power compared with the Baseline stage. The other three conditions resulted in

Fig. 5. Theta EEG power changes between Stimulation and Baseline stages. These graphs illustrate the maximal differences at sites (A) FCC2h between high-frequency acupoint stimulation (A/HF) and Baseline, (B) Cz between low-frequency acupoint stimulation (A/LF) and Baseline, (C) FCC2h between high-frequency control stimulation (C/HF) and Baseline, and (D) FCC2h between low-frequency control stimulation (C/LF) and Baseline. The Theta EEG power is decreased by 31.04% from the Baseline to A/HF, compared with those increased by 39.95% at A/LF, by 34.29% at C/HF, and by 53.23% at C/LF.
increased activity for the Theta power when compared with the Baseline stage.

The Theta power showed a significant decrease from Baseline to A/HF, but, conversely, Theta power increased significantly when compared to Baseline stage during low-frequency control stimulation (C/LF), as shown in Fig. 6A.

In all 4 stimulation conditions (see Fig. 6B), the Theta EEG power was shown to be significantly lower at A/HF than the other three stimulation conditions, and no significant differences were noticed among these conditions.

To further substantiate the study effects in the Theta EEG power, a new automatic quantification method was introduced for measuring (1) the focal peak site from a MNI Standard Brain with 10/5 EEG montage, (2) the focal power (\(\mu V^2\)) at the focal maximal site, FM, (3) the field area (cm\(^2\)) calculated from the effective threshold of the peak amplitude, and (4) the field effective magnitude. Thus, these measures include the peak activity of the single electrode nearest to the maximal site, in addition to the topography of 20 neighboring electrodes within the field area. The effective magnitude now captures the full topography information of the field energy.

In order to make the map details more clear, only the Theta activities of the first 3 subjects and the group average of 12 subjects are displayed in each study stage. The individual maps of the 12 subjects are similar to each other and to the maps of the group average in 12 subjects, as well as consistency within the individuals (see Fig. 7A: top view, face/nose up, in millimeters).

In Fig. 7B, the statistical analyses of the 4 parameters across the study stage of Baseline, A/HF, and Post indicated: (A) no significant change in “focal site” (Fig. 7B-a), (B) no significant change in “field area” (Fig. 7B-c) but a significant decrease during the treatment of “focal power” (Fig. 7B-b) and for “field effective magnitude” (Fig. 7B-d). However, these changes were not long-lasting after the acupoint stimulation.

Initial isolation and tentative identification of ACC from the frontal Theta EEG

To easily convey the site and mode of acupuncture effects for this study, results of a single subject are shown in Fig. 8. As shown in Fig. 8, the topographic somatosensory field potentials and tomographic current source imagines (CSI) during the acupoint stimulation at high-frequency (A/HF) compared with low-frequency (A/LF) stimulation are clearly distinct. Higher SFP can also be seen at the A/LF than the A/HF (note: scaling difference). The distributions of the filtered Theta EEG in both conditions are shown in the middle panel. These EEGs are typical examples of single epoch of 2 s EEG and thus were used for

Fig. 6. (A) Statistical effect within-condition on Theta activities/FCC2h. Panel A-a illustrates that the Theta activity was significantly decreased from Baseline to Stimulation A/HF (★ denotes \(P < 0.05\)). Panel A-b illustrates no significant difference between Stimulation A/LF and Baseline. Panel A-c illustrates no significant difference between Stimulation C/HF and Baseline. Panel A-d illustrates an increase of Theta activity at Stimulation C/LF as compared with Baseline (bar: standard error of mean; ★ denotes \(P < 0.05\)). (B) Statistical effect between conditions on Theta activities/FCC2h. The significant decrease of Theta activity during the A/HF, compared with the other conditions (bar: standard error of mean; ★ denotes \(P < 0.05\)).
A

Baseline

A/HF

Post

B

a. Focal Sites (x, y; mm)

b. Focal Power ($\mu$V^2)

c. Field Area (cm^2)

d. Effective Magnitude ($\mu$V^2 x cm^2)

Group: n=12
extraction of CSI by MUSIC method (Mosher et al., 1999). A larger magnitude of CSI can be seen in the A/LF compared with that in the A/HF. The CSI of this single subject was superimposed onto the Montreal Standard Brain (MRI average of 305 normal healthy subjects), however, the fitting of ACC might not fully comparable. In general, it is not possible here to describe the procedure of our frequency-domain EEG source imaging. But, the conceptual background and methodological principles of the current source imaging in EEG have recently gained strong interest (Jensen and Vanni, 2002; Gross et al., 2003; Komssi et al., 2004).

These results depict the main effect of acupoint stimulation (A/HF): reduced midline current source magnitudes, likely from damping of cingulate activity in ACC, which would result in slower and smaller Theta activities in the midline EEG recorded as shown in the attenuated SFP. Through the damped ACC, the acupoint stimulation (A/HF) could exert its analgesic effect by blockage of incoming noxious afferents. This effect of neurophysiological regulation would (as one of the main factors) trigger cascades of slow PET/fMRI hemodynamic changes as reported in literature (see review, Shen, 2001).

Furthermore, we isolated the cingulate-related activation in all subjects (nine of them are displayed in Fig. 9), showing that these current sources are distributed from the rostral sites to anterior loci on the cingulate cortex when these sources in the individuals are superimposed on the MNI Standard Brain.

Discussion

Acupuncture effect induced by stimulation at HeGu vs. mock point

The traditional site of HeGu acupoint of this study lies at the first inter-terosseous muscle. This juncture is rich in peripheral nerve extension from the sensory nerve and muscle tendon (Lu, 1983), with great focal electrical conductivity measurable percutaneously. In contrast, the locus of mock point selected is overlaying the fourth interosseous muscle with few neural fibers in the dorsal hand. Thus, the observed EEG effect in this study could be due to the differences in nerve conduction and excitability between the traditional HeGu acupoint and the selected mock point. Stimulation of the HeGu point has been reported to inhibit a peripheral finger flexion reflex (Takakura et al., 1996), sympathetic outflow (Wang et al., 2002), and modulation of some esthetic afferents in the primary somatosensory area of the brain (Abad-Alegria et al., 1995). Using identical comparison of acupoint vs. mock point in this study in a report on PET imaging, HeGu stimulation induces activation in midbrain, hypothalamus, insular,
anterior cingulate, and cerebellum (Hsieh et al., 2001). Whether the element of de-chi is essential for central activation of the acupuncture effect still remains unknown. At least, the stimulation effects between true acupoint vs. mock point on the Theta EEG power found in this study encourage the use of mock point or sham stimulation for the study of brain function and associated acupuncture effects.

Acupuncture effect induced by stimulation in high- vs. low-frequency

Previously, EEG has been used to explore acupuncture effects, however, the real effect and mode of action remain controversial (Tanaka et al., 2002; Rosted et al., 2001; Pilloni et al., 1980). In fact, available literature on EEG and acupuncture is slim. Increased EEG powers at all band densities were associated with decreased blood pressure during acupuncture (Tanaka et al., 2002). No EEG change associated with acupuncture has been reported due to great individual variability (Rosted et al., 2001). Some Theta and Alpha modulation was briefly noted in auricular acupuncture (Pilloni et al., 1980). Of interest was a recent report of acupuncture effects on EEG bispectral index and spectral edge frequency (Litscher, 2004) and the effect of acupuncture on noxiously induced SEP under anesthesia (Meissner et al., 2004). Of interest was a recent report of acupuncture effects on EEG bispectral index and spectral edge frequency (Litscher, 2004) and the effect of acupuncture on noxiously induced SEP under anesthesia (Meissner et al., 2004). To date, most studies lack multiple EEG recordings and thus have inadequate control, poor stimulus parameters, and incomplete statistical analyses: to draw more conclusive results. Our current study was designed to rectify these inadequacies.

Our study has demonstrated that only high-frequency stimulation (100 Hz), but not low-frequency (2 Hz), at HeGu point induced specific EEG modulation of the Theta activity in the midline frontal area. Although the effect of high-frequency acupoint stimulation on Theta EEG was not long-lasting after the termination of stimulation in this study, the significant decrease during acupoint stimulation is of particular interest. This modulatory effect of stimulus specificity is consistent with several recent studies that have demonstrated differential brain EEG effects from varying stimulation frequencies. For example, the high- vs. low-frequency acupuncture stimulation can differentially modulate cerebral blood flow (Backer et al., 2002), autonomic responses (Suter and Kistler, 1999), heart-rate variability (Li et al., 2003), genotype noxious sensitivity (Wan et al., 2001), experimental pain threshold (Chesteron et al., 2002), abdominal surgery (Lin et al., 2002), orofacial muscular pain (Widerstrom-Noga et al., 1998), and stroke recovery (Johansson et al., 2001). Hence, we propose a plausible “frequency modulation” (FM Theorem) for the neural regulation of bodily function by peripheral and central stimulation. This modulation can be induced by manual acupuncture twist, galvanic acupoint stimulation, or even transcranial magnetic stimulation on the brain (Siebner and Rothwell, 2003), via neural excitatory and inhibitory mechanisms to regulate physiological effects. The effects of systematic visual stimulation frequencies on the human EEG have been reported (Herrmann, 2001). Furthermore, frequency modulation of fMRI hemodynamics can also be demonstrated (Iidaka et al., 2004).

The frequency specificity of acupuncture effect is particularly interesting with two likely explanations. One relates to the known effect of wind-up in central sensitization and cortical plasticity. The other relates to neurochemical modulations in the brain. Repeated high-frequency peripheral stimulation can induce wind-up effects (for reviews, see Dickinson, 1997; Eide, 2000). The cortical plasticity hypothesis postulates that the short-term effect of wind-up can lead to central sensitization (Baranauskas and Nistri, 1998; Petrenko et al., 2003) and long-term neuronal plasticity changes (Melzack et al., 2001; Ambrosini and Schoenen, 2003), which ultimately may induce cellular modulation of chemical structures, such as gene transformation. Another hypothesis is that differential neurotransmitter and...
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neuromodulator is released by high- vs. low-frequency stimulation. Comparatively, the hypothesis of neurochemical induction in the brain by differential frequency modulations has gained strong support (see review, Han, 2003). This hypothesis postulates that both high- and low-frequency-stimulation-induced analgesia are mediated by opioid peptides via different receptor effects: low-frequency effects mediated by the mu/delta opioid receptors, whereas the high-frequency effects mediated by the kappa opioid receptors. The low-frequency modulation exerts effects on the central hypothalamus, which has descending inhibition via enkephalin at PAG, medulla, and dorsal horn of spinal cord on mu receptors, while high-frequency stimulation exerts effect directly at parabrachial nuclei, periaqueductal gray, medulla, and dorsal horn via dynorphine on kappa receptors. Of importance, a recent fMRI neuroimaging study of acupuncture compared low- vs. high-frequency stimulation has revealed extensive overlapping and specific central effects in the human brain (Zhang et al., 2003a).

**Frontal Theta activity and anterior cingulate cortex (ACC)**

The site and mode of main EEG effect at the frontal midline field in the Theta band are of special interest. Since the initial identification of the putative ACC (Fig. 8 for one subject and Fig. 9 for the major subset of subjects under the high-frequency acupuncture condition) by primary current source imaging (a full analysis to be reported elsewhere) is a technical innovation in EEG frequency-domain source analysis, similar effects have also been recently reported in MEG (Jensen and Vanni, 2002). Nevertheless, this effect collaborates with a recent report using similar acupuncture stimulation, at the Zusani point in the leg (Zhang et al., 2003a). The frontal midline Theta (Fmθ) EEG has long been modeled as source from various parts of the lateral frontal cortex of both hemispheres (Sasaki et al., 1996) or large area of medial prefrontal cortices including anterior cingulate cortex (ACC) (Ishii et al., 1999). The function of ACC has been well established. The ACC has been associated with task difficulty (Smith et al., 2001), attention (Kubota et al., 2001), cognitive operation (Gevins and Smith, 2000; Inanaga, 1998), attention disorders (Clarke et al., 2003), and altered state of attention (e.g. meditation) (Aftanas and Golochekine, 2002). The ACC is also modulated by analgesics (Bromm and Meier, 1989) and acupuncture analgesia (Zhang et al., 2003b). In general, human brain mechanisms subserving attention involve prefrontal, midfrontal, and posterior parietal cortices, anterior cingulate, and thalamus (Posner and Rothbart, 1992). The features of ACC in brain functions, including pain, are reviewed in the contemporary PET/fMRI neuroimaging research (van Veen and Carter, 2002; Barch et al., 2001; Allman et al., 2001; Peyron et al., 2000). In this study, the area of Theta activity was modulated by the high-frequency acupoint stimulation and was topographically overlaying the anterior–central midline, contralateral prefrontal area, likely reflecting the subcortical ACC modulation and cortical sensorimotor areas. These areas are presumably involved in the affective and cognitive dimension of pain. The effect of Theta reduction may implicate damping of ACC activity by high-frequency acupoint stimulation and thus reduce the processing capacity of ACC to impending noxious stimuli and resulting in anti-nociception as pain modulation. From our work, it remains to be investigated if these effects, including A/HF, would regulate Theta by (a) shifting 7 Hz down to 4 Hz as exemplified in Fig. 7 and/or (b) modulating the amplitude/power without frequency alteration.

**Non-specific increase of Alpha-I power in the stimulation and post stages**

In addition to the above described specific Theta modulation, this study also showed Alpha-I enhancement in the posterior focal maxima during stimulation and post stages. This effect is considered non-specific since it was induced by both acupoint and mock point stimulation of high and low frequency (Fig. 4). In general, alpha reduction is well known in response to sensory stimuli, but little has been reported on alpha enhancement. The posterior Alpha-I maxima observed in this study may not originate from occipital but parietal area. In somatosensory area, mu rhythm of Alpha-I can be inhibited by stimulation of human hand (Cheyne et al., 2003). Why our results show a strong and significant alpha enhancement is not understood. Nevertheless, long-lasting effect of Alpha-I EEG in the post-stimulation stage was shown but not specific to stimulation mode and site. In contrast, the above Theta EEG changes are considered specific to stimulation mode and site in this study. Hence, this effect can be considered a short-term cortical plasticity modulation. Yet, it is not known if repeated stimulation over days and weeks may also induce long-term cortical plasticity in the brain, a contention of therapeutic acupuncture effects.

**Issue of cortical plasticity**

It seems that the following aspects have to be considered with regard to the contention for "cortical plasticity" in this study: (A) temporal aspect—in Fig. 6A, the main Theta EEG modulation showed significant reduction during the high-frequency acupoint stimulation at HeGu acupoint, but not to the low-frequency HeGu acupoint stimulation, or the high- and low-frequency stimulation at the placebo-point. In contrast, a persistent post-stimulation enhancement was noted in the Alpha EEG for all study conditions (Fig. 4). In this context, the observed effect during high-frequency acupuncture stimulation at HeGu is unique and genuine. It showed specific effect, but not the non-specific post-stimulation effect in alpha-EEG. (B) Frequency aspect—only the Theta band power was modulated significantly, but not the other EEG broad bands. (C) Spatial aspect—the observed effect was considered central in origin, but not from peripheral blockage at the HeGu stimulation site. In this context, if it were modulated at the peripheral site, all EEG frequencies at other broad bands would be equally modulated. When only the Theta EEG at the frontal–central site was affected, our contention of its central source (i.e. ACC) is highly plausible. Based on the above considerations, a rephrased “short-term cortical plasticity” (Chen et al., 2000) shall be more appropriate in this study.

**Conclusion**

Short-term cortical dynamic changes occur in Theta EEG at the frontal midline site, during high-frequency but not low-frequency stimulation for the HeGu point only. This cortical plasticity is hypothesized as the intracranial modulation of the anterior cingulate cortex during acupoint stimulation. High-frequency acupoint stimulation at a rich nerve junction such as HeGu point may reduce pain-induced cingulate processing that would result in hypo-algesia. A generalized “frequency modulation” (FM Theorem) of neural system is proposed.
Acknowledgment

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