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Differential neural responses to acupuncture revealed by MEG using wavelet-based time-frequency analysis: A pilot study

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Abstract—**Acupoint specificity, lying at the core of the Traditional Chinese Medicine, still faces many controversies. As previous neuroimaging studies on acupuncture mainly adopted relatively low time-resolution functional magnetic resonance imaging (fMRI) technology and inappropriate block-designed experimental paradigm due to sustained effect, in the current study, we employed a single block-designed paradigm together with high temporal-resolution magnetoencephalography (MEG) technology. We applied time-frequency analysis based upon Morlet wavelet transforming approach to detect differential oscillatory brain dynamics induced by acupuncture at Stomach Meridian 36 (ST36) using a nearby nonacupoint (NAP) as control condition. We observed that frequency power changes were mainly restricted to delta band for both ST36 group and NAP group. Consistently increased delta band power in contralateral temporal regions and decreased power in the counterparts of ipsilateral hemisphere were detected following stimulation at ST36 on the right leg. Compared with ST36, no significant delta ranges were found in temporal regions in NAP group, illustrating different oscillatory brain patterns. Our results may provide additional evidence to support the specificity of acupuncture modulation effects.**

I. Introduction

ACUPUNCTURE is an ancient therapeutic technique in Traditional Chinese Medicine (TCM). It has been used increasingly in Western medicine to treat a range of clinical conditions as an alternative and complementary therapy [1]. A promising efficacy of acupuncture has been shown in the effective treatments of postoperative and chemotherapy nausea and vomiting as well as beneficial effectiveness for pain relief [2][3]. However, the scientific explanation regarding the physiological mechanisms underlying acupuncture has not been found totally yet, which hindered better acceptation and significance in the modern medicine practice. The recently great progress in noninvasive imaging techniques, such as functional magnetic resonance imaging, electroencephalography and magnetoencephalography have opened a window to the human brain, allowing us to obtain an appreciation of the anatomy and physiological function involved during acupuncture in humans noninvasively [4]-[6].

The clinical effectiveness of acupuncture per se is said to depend on the specific placement of the needles at designated acupoint [7]. Although acupoint specificity lied at the core of traditional acupuncture theory, controversy regarding its representation still remains. Cho et al found that the visual cortex can be activated by peripheral acupuncture at visual associated acupoints, while such neural activities did not emerge after stimulation at a nearby nonacupoint [8]. Further investigation by others also supported that acupuncture at traditional vision-related acupoints can elicit activity selectively within the visual cortex [9][10]. Nevertheless, these results were hard to be replicated by other researches [11][12]. On the whole, the representations of acupoint specificity remain debatable and further work is needed to test the neurological basis of acupoint specificity to promote its acceptance as a viable clinical treatment in the modern medicine practice.

Having a review of previous neuroimaging research on acupuncture, we found that fMRI has been the dominant imaging technology for exploring brain activity. However, fMRI only measures the secondary effect of neural activity on cerebral metabolism and hemodynamics, unable to directly track neuronal electrical activity following acupuncture stimuli on a millisecond timescale [13]. Since acupuncture can induce complex temporal neural responses in wide brain area [14], careful interpretations of interactions between acupuncture intervention and brain processing depend on how effectively we can characterize the nature of temporal variations underlying neural activities that give rise to hemodynamic responses.

Recent neuroimaging studies on acupuncture-induced neural responses have mainly adopted a block-designed experimental paradigm combined with general linear model (GLM) method [12][15][16]. With this approach, detection of brain activation is based on probable assumptions of the temporal activation patterns suggested by the experimental paradigm. This approach, however, is not valid to the cases with limited temporal information. According to the acupuncture theory of TCM and amount of clinical reports and studies, the acupuncture effects can sustain even after acupuncture needling being terminated [17][18]. Due to the sustained effects, the temporal aspects of Blood Oxygen Level-Dependent responses to acupuncture may violate the assumptions of the block-designed GLM estimates [19]-[23].

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Therefore, conclusions derived from this method may not reveal the intrinsic relation between the acupuncture effect and the corresponding activated brain regions.

In this study, we adopted MEG technique as well as a newly non-repeated event-related (NRER) experimental paradigm. Time-frequency analysis, which quantifies signals on the basis of the amount of frequency power present in different frequency bands, was also introduced to determine the band-limited power change of neural response patterns induced by acupuncture at ST36 (an important acupoint for analgesia) and a nearby nonacupoint (NAP). By comparing the differential brain oscillatory patterns, we expected to provide further evidence to support acupoint specificity.

II. Methods

A. Subjects

In order to reduce intersubject variabilities, 28 college students (14 male, ages of 24.5±1.8) were recruited in this study. They were all right-handed and acupuncture naïve with no psychiatric or neurological disorders. All subjects gave written, informed consent after the experimental procedures had been fully explained. All research procedures were approved by the Tiantan Hospital Subcommittee on Human Studies and conducted in accordance with the Declaration of Helsinki.

B. Experimental paradigm

28 participants were evenly divided into two groups, the groups being matched by age and gender. Every subject received only once acupuncture stimulation. The experiment consisted of two functional runs. Resting-state (RS) run lasted 6 min. Acupuncture at ST36 and nonacupoint employed the single-block design paradigm, incorporating 2 min needle manipulation, preceded by 1 min rest epoch and followed by 6 min rest (without acupuncture manipulation) scanning. All participants were instructed to sit comfortably in a dark and magnetically shielded room with their eyes closed and asked to remain relaxed without engaging in any mental tasks.

Acupuncture was performed at acupoint ST36 on the right leg. This is one of the most frequently used acupoints and proved to have various efficacies in pain-management in both humans and animals [14]. Sham acupuncture was exerted with needling at non-meridian points (NAP, 2-3 cm apart from ST36) with needle depth, stimulation intensity, and manipulation method all identical to those used in the verum acupuncture. Stimulation consisted of rotating the needle clockwise and counterclockwise for 2 min at a rate of 60 times per minute. The procedure was performed by the same experienced and licensed acupuncturist on all participants.

C. Data acquisition

The MEG data were recorded while subjects were comfortably seated inside a magnetically shielded room using a 151-channel whole-head MEG system (CTF Systems Inc., Port Coquitlam, BC, Canada). Average distance between sensors in this system is 3.1 cm. The head position was monitored during the measurement using head position indicator coils (HPI). MEG data were recorded at the sample rate of 600 Hz. A third-order gradient noise reduction (computed with CTF software) was applied to all MEG signals to remove noise. During the MEG recording, patients were instructed to close their eyes to reduce artifact signals due to eye movements. At the beginning and at the end of each recording, the head position relative to the coordinate system of the helmet was recorded by leading small alternating currents through three head position coils attached to the left and right pre-auricular points and the nasion on the subject's head. Head position changes during the recording up to approximately 0.5 cm were accepted.

D. Data analysis

The MEG sensors were grouped into five regions of interest (ROIs) roughly corresponding to the major cortical areas (frontal, temporal, central, parietal and occipital) for each hemisphere. A schematic distribution of these areas is shown in Fig.1A. As ROIs were based on the extra-cranial position of the MEG sensors, underlying cortical areas are to be considered as indicative [24]. Of the original 151 channels, two channels were not available due to technical problems during recording for all participants. The MEG raw data were filtered offline with a band pass of 0-48 Hz and further down sampled to 300 Hz to reduce computation load. In order to improve signal-to-noise ratio, the 6-min resting state data before acupuncture and 6-min post-stimulus data were averaged respectively for each participant. Then time-frequency analysis based on complex Morlet wavelet transformation were performed to determine changes in power within the following frequency bands: delta (0.5-4Hz), theta (4-8Hz), alpha (8-13Hz), beta (13-30Hz) and gamma band (30-48Hz) [25]. The complex Morlet wavelet is a continuous wavelet often used in MEG studies [26][27], with its definition as $w(t,f) = (\sigma_t\sqrt{\pi})^{-1/2}\exp(-t^2/2\sigma_t^2)\exp(2i\pi ft)$, having temporal resolution of $2\sigma_t$ and frequency resolution of $1/\pi\sigma_t$. Time-frequency analysis computes the convolution of complex wavelet with the MEG signal (S) to get the time-frequency decompositions (wavelet coefficients) for each of the time points [28]. $C(t,f) = S * w$, where ($*$) denotes the convolution operator, and $C(t,f)$ are the complex wavelet coefficients. After getting coefficients for each frequency bands, the power of every MEG channel was computed within each frequency band according to $E(t,f) = |C(t,f)|^2$. Finally, we averaged the 14 subjects' time-frequency results by condition (resting state before and after acupuncture) and compared the difference between these two averaged power results. All analysis was conducted using Brainstorm toolbox [29] in Matlab R2008a.

III. Results

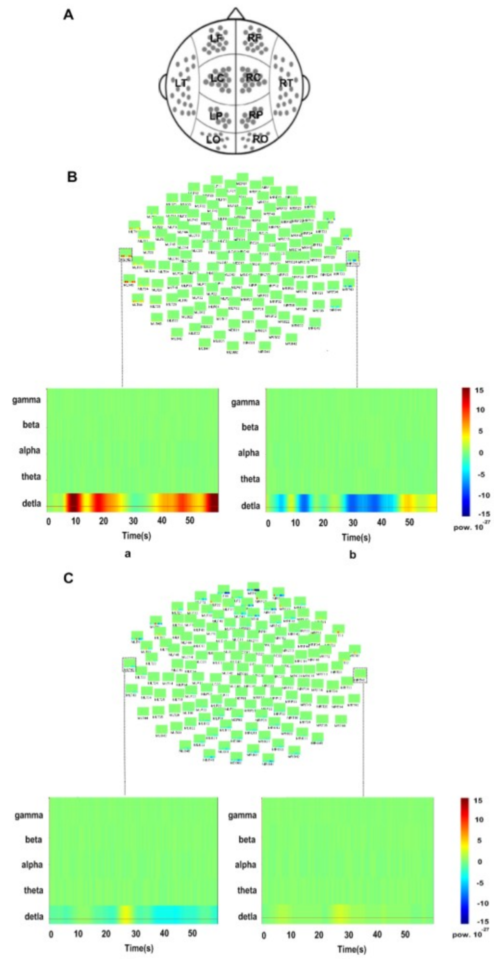

Figure 1. Group time-frequency analysis results based on morlet wavelet transformation. A. Schematic projection of MEG-channels and head drawing to illustrate the groups into which the MEG channels were clustered based upon the approximate underlying cortical areas. L or R, cortical area on the left (L) or right (R) side of the head; C, central; F, frontal; O, occipital; P, parietal; T, temporal. B. The overall view of time-frequency representations following acupuncture at ST36. a. Increased delta band-limited power change reflected by the sensor overlying the temporal region (contralateral hemisphere) b. Decreased delta band-limited power change results (ipsilateral hemisphere). C. The overall view of time-frequency results following acupuncture at NAP. c,d. frequency band-limited power change in temporal regions for NAP group.

Time-frequency analysis results illustrated differential oscillatory brain activity change pattern between acupuncture stimulation at ST36 and NAP. To be specific, a consistent increase in the delta band power in temporal regions in contralateral hemisphere together with a decrease in the amplitude of delta band power in ipsilateral hemisphere were found following acupuncture at ST36 on the right leg, whereas no significant amplitude changes in other frequency bands were detected (see Fig.1B).

In line with ST36 group, the frequency power changes were mainly confined to delta range following acupuncture at NAP. Nevertheless, time-frequency analysis results demonstrated conspicuously differential oscillatory brain activity. No significant power change as ST36 group was detected in temporal regions both in contralateral and ipsilateral hemispheres (see Fig. 1C). Furthermore, a slight decrease in delta power was recorded by MEG sensors outlying the occipital regions (see Fig.2B).

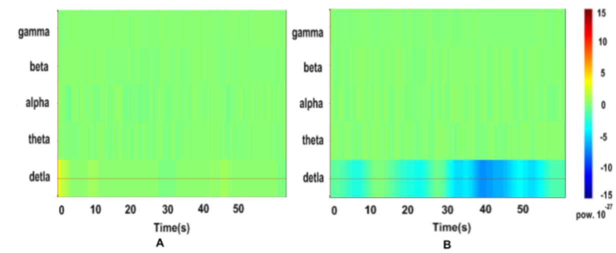

Figure 2. Time-frequency decomposition of MEG signal recorded by sensors outlying occipital lobe. A. Group results for acupuncture at ST36. B. Group results for acupuncture at NAP.

IV. Discussion and Conclusion

To our knowledge, this is the first study adopting wavelet transforming based time-frequency analysis to investigate the representation of acupuncture at ST36 using a nearby nonacupoint as control condition in terms of power changes measured by MEG. A consistent increase in the delta band power recorded by sensors outlying temporal area in contralateral hemisphere together with a decrease in the delta band power in ipsilateral hemisphere were observed following acupuncture at ST36 on the right leg. While distinct band-limited power changes were found after acupuncture at a nearby nonacupoint. Our results illustrated the conspicuously differential oscillatory brain activity following acupuncture at different designated place.

Previous studies of Hui et al and Wu et al on acupoint ST36 demonstrated that acupuncture can produce significant modulatory effects on the limbic system, paralimbic and subcortical gray structures [4][16][30]. The limbic system is a set of brain structures including hypothalamus, hippocampus, amygdala, nucleus accumbens and anterior cingulate cortex. Animal studies have illustrated that the high density of opioid receptor (a kind of neurotransmitter, related with analgesia) in amygdala can conspicuously increase the threshold of pain [31]. Meanwhile, amount of fMRI researches have discovered the activation of amygdala following acupuncture at ST36 [4][16]. Besides, considering the acupoint on the right leg was used, we expected to observe neural response reflected in the left hemisphere. Therefore, we inferred that the increased delta band power in the temporal MEG channels of contralateral hemisphere may result from the increased amplitude in amygdala which is located deep within the middle temporal gyrus of the brain. By the way, the finding of decreased delta band power in the temporal channels of ipsilateral hemisphere was intriguing. Previous studies have demonstrated the relation between homologous regions in opposite hemispheres [32][33]. We thus speculated that probability of existing delta band-limited energy flow between these energy-increased and energy-decrease regions. Further studies need to explore the interaction between these two regions combining anatomical information from MRI.

The slight energy decrease in occipital region following acupuncture at NAP indicated that the visual activity during eye-closed condition may stay at a relatively low level [34]. As exerting peripheral stimulation into skin at nonacupoint mostly elicit pain, brain regions concerning pain transmission and perception should gather more energy than usual. Therefore, it was possible that there may exist energy modulation from visual cortex to these brain regions, mainly including thalamus, primary (SI) and secondary (SII) somatosensory cortex.

Note that the present work was performed on MEG data at the level of sensor space, limiting anatomical inferences drawn from the data. Given the sparsity of work on acupuncture together with MEG, it is difficult to generate clear hypotheses about oscillatory neuronal dynamics of power changes induced by acupuncture. Future work will include a source reconstruction of the activity in the brain, which will allow improved extrapolation to anatomical locations.

In the current study, we attempted to detect the differential spectral neural responses following acupuncture at ST36 and a nearby nonacupoint with efficacy-irrelevant. Wavelet transformation based time-frequency analysis elucidated the distinct band-limited power change patterns between ST36 group and NAP group. Our findings may provide additional evidence to support the specificity of acupoint.

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