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Oscillatory characteristics in the secondary somatosensory (SII) cortex in response to nociceptive stimuli

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Abstract

We used a whole-head neuromagnetometer to study the oscillatory characteristics in the secondary somatosensory (SII) cortex in response to nociceptive stimuli. Laser pulses were delivered to the left hand dorsum of 10 right-handed healthy adults to elicit mild, moderate, and severe pain. Using Morlet wavelet-based analyses and equivalent current dipole (ECD) modeling, we analyzed the temporal and spatial characteristics of bilateral SII pain-elicited oscillatory activities. In each pain condition, pronounced theta (4-8 Hz) and alpha (8-13 Hz) activities are clearly found at 180-210 ms after stimulus onset in the bilateral temporoparietal regions. Our results suggest that the 4-13 Hz theta and alpha oscillations, peaking from 180 to 210 ms, have an important role in the processing of nociceptive inputs in the bilateral SII areas; but their power may code the magnitude of pain stimuli only up to moderate intensity, as rated subjectively.

Keywords: theta and alpha oscillations, secondary somatosensory cortex, nociceptive laser stimulation, wavelet analysis, magnetoencephalography

Introduction

Unlike electric stimulation, laser stimulation has the advantage of being able to selectively activate cutaneous nociceptive receptors without simultaneously eliciting a tactile sensation response (Bromm *et al.*, 1984). The resultant laser evoked potential (LEP) and magnetic filed (LEF), recorded by electroencephalography (EEG) and magnetoencephalography (MEG), respectively, have been found to be generated by an ascending signal transmitted via the peripheral A-delta (Aδ) and C fibers as well as through the spinothalamic tract of the spinal cord (Bromm and Treede, 1991; Kakigi *et al.*, 1995, 1996; Mor and Carmon, 1975). With a much better spatial resolution, the measurement of LEF is especially suitable for pain research (Kakigi *et al.*, 1995; Timmermann *et al.*, 2001; Forss *et al.*, 2005; Chen *et al.*, 2006). Most biosignals that vary around a mean value can be reconstructed as a sum of sines and cosines occurring at different frequencies (Samar *et al.*, 1995). The spectral wavelet analysis allows the overall variance of a biosignal to be split into its various underlying frequency components (Samar *et al.*, 1995). Differences in the magnitudes of these different frequencies or oscillations can be attributed to differences in the neural influences that are responsible for pain modulation. We therefore hypothesized that a particular neural oscillation band might specifically reflect the correlation between SII activation and subjective pain rating. To explore this hypothesis, this study investigation involves: a) evaluating the quantitative changes of pain-related oscillatory activities, b) analyzing the correlations between perceived pain levels and the oscillatory activities of the SII cortex.

Materials and Methods

Ten healthy volunteers (8 men and 2 women; mean age 32.1 ± 4.3 years; all right-handed) were included to participate in this study. None had any neurological or psychiatric deficits. Cutaneous nociceptive stimuli were produced using a thulium-YAG laser stimulator (BLM 1000 Tm:YAG®, Baasel Lasertech, Starnberg, Germany) set up in the MEG lab at Taipei Veterans General Hospital. The stimuli were applied to the lateral dorsum of the left hands of the volunteers. Each subject was instructed to rate the perceived intensity of a stabbing pain using the Visual Analogue Scale (VAS). We firstly determined the strengths of laser pulses for eliciting pain levels at VAS 2-3, VAS 5-6, VAS 8-9 for each subject and then applied the stimuli on each subject to elicit mild, moderate and severe pain, respectively. During the recordings, each subject sat comfortably in a magnetically shielded room with the head supported against the helmet-shaped bottom of a whole-scalp 306-channel neuromagnetometer (Vectorview™, Elekta Neuromag, Helsinki, Finland). Each subject underwent three sessions (mild, moderate, and severe pain) of laser pulse stimulation in a randomized order. Forty responses were averaged in each session. The signals were bandpass filtered (0.1-160 Hz) and digitized at 500 Hz. Epochs were excluded from being averaged whenever the amplitudes of the corresponding electro-oculogram and MEG signals were larger than 300 μV and 6000 fT/cm, respectively. MR images of the brain of each of the subjects were acquired with a 3 T Bruker Medspec300 scanner (Germany). LEF responses of the gradiometer channels were computed using the continuous wavelet transform. The analysis period of 1100 ms included a prestimulus baseline of 100 ms. We used the Morlet wavelet (Kronland-Martinet *et al.*, 1987), which is a function of time t and frequency f_0 defined as:

$$w(t,f_0) = A\exp(-t^2/(2\sigma_t^2))\exp(i2\pi f_0 t),$$

$$\text{where } \sigma_t = 1/(2\pi\sigma_f) \text{ and } A = 1/(2\pi\sigma_t^2)^{1/2}$$

The width of the wavelet ($m = f_0/\sigma_f$) was chosen to be 7 (Grossmann *et al.*, 1989; Lachaux *et al.*, 1999; Rodriguez *et al.*, 1999; Hsiao *et al.*, 2006). The time-varying amplitude of the neuromagnetic responses in a frequency band around f_0 is the result of the convolution of the complex wavelet $w(t,f_0)$ with the signal $s(t)$:

$$E(t,f_0) = w(t,f_0)*s(t)$$

This procedure was performed by using a set of wavelets with f_0 ranging from 0.5 to 25 Hz at intervals of 0.5 Hz. The spatial distribution, power and temporal features of the stimulus-related oscillatory activities were exhibited. The time-frequency plots for the selected channels were averaged across individual frequency bands of 0.5–4 Hz, 4–8 Hz, 8–13 Hz and 13–25 Hz to provide the time-varying measures of delta, theta, alpha and beta activities, respectively.

Because of the non-parametric nature of the oscillatory activities in the present study, the peak powers, latencies and ECD locations for the conditions of pain intensity (mild, moderate and severe), frequency band (delta, theta, alpha and beta), hemisphere (contra- and ipsi-lateral SII) were examined by using non-parametric repeated measures ANOVA (Friedman ANOVA) and Wilcoxon's signed ranks test.

Results

Fig.1A shows time-frequency representation of the evoked neuromagnetic responses of Subject 1 by moderate painful stimulation. It shows the spatial distribution of 0.5-25 Hz activities 100 ms before and 1000 ms after stimulus onset. The enhanced oscillatory activities are clearly discernible in the bilateral temporoparietal areas. Fig.1B displays the time-frequency plots from the two channels of interest located around the bilateral SII of Subject 1 in response to mild, moderate, and severe painful stimuli. A power increase was found in all conditions around 150-220 ms following stimulus onset, with maximal power ranging between 5 and 10 Hz.

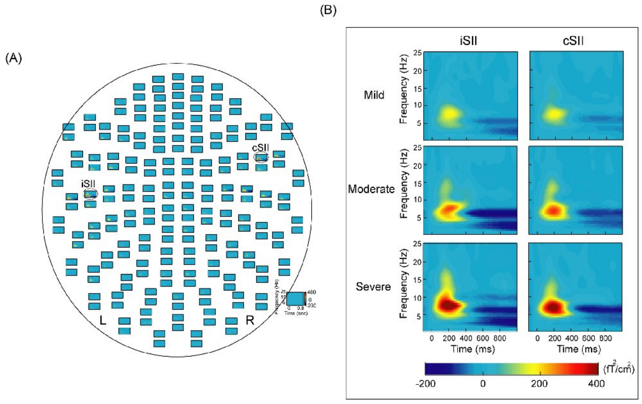

Fig. 1. (A) Time-frequency representations of the neuromagentic responses following moderate painful stimulation over planar gradiometers of Subject 1. (B) the inserts showing the time-frequency plots over two selected channels around ipsilateral SII (iSII) and contralateral SII (cSII) for mild, moderate and severe pain conditions.

Fig.2 shows the power (mean ± SEM) of the delta to beta frequency bands from the two channels of interest in the bilateral hemispheres in response to mild, moderate and severe pain. We observed significant bilateral power increases in the delta, theta and alpha activities to all the three pain intensities (all $p < 0.01$). With respect to the hemispheres, no significant power difference was found in any of the pain intensity conditions (all $p > 0.2$). Finally, pain intensity elicited significant differences in the theta ($\chi2 = 7.8$, $p < 0.05$) and alpha ($\chi2 = 9.8$, $p < 0.01$) activities in the bilateral hemispheres. Wilcoxon testing showed that the power of the theta and alpha bands under mild painful stimulation were significantly smaller than when moderate and severe pain stimuli were used (for theta, $p < 0.02$; for alpha, $p < 0.05$).

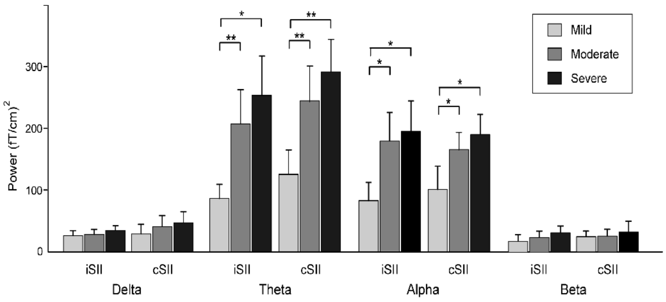

Fig. 2. Mean power of delta to beta activities of iSII and cSII responses to laser stimulation with varying pain intensities. * P < 0.05; ** P < 0.01

Figs. 3A and 3B show the spatial distribution of time-varying theta and alpha activities for moderate painful stimulation from Subject 1 and Subject 2, respectively. Clear response deflections are observed in the bilateral temporoparietal areas. The isocontour map appeared to show the presence of a single ECD. ECDs from theta and alpha activity were estimated in the superior bank of the Sylvian fissure, around SII, in bilateral hemispheres.