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Neuromagnetic SII responses do not fully reflect pain scale

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To elucidate the role of somatosensory cortices in coding pain magnitude, we recorded the neuromagnetic responses of ten subjects to mild, moderate, and severe pain stimulation by delivering thulium-laser pulses on the dorsum of the left hand. The stimulus intensities for producing different pain levels were determined individually, and the mean values across subjects were 255, 365, and 490 mJ for mild, moderate, and severe pain, respectively. We obtained 40 responses for each intensity condition, and analyzed the averaged cortical signals by multi-dipole modeling. All subjects showed consistent activation over the bilateral secondary somatosensory (SII) cortices for each intensity level, peaking around 150–230 ms, with 15-ms earlier on the contralateral hemisphere. The SII dipole strength was significantly larger for the moderate than for the mild pain stimulation, but lacked further increase as the pain magnitude elevated to the severe level. In contrast, the primary somatosensory cortical response was detected in only half of our subjects, and thus it seemed difficult to evaluate its role in pain intensity coding. Our results suggest that activation strength in human SII cortices reflects the magnitude of peripheral noxious inputs only up to the moderate level, and some other cerebral correlates may get involved in sensing a further increment of pain magnitude.

Keywords: Secondary somatosensory (SII) cortex; Primary somatosensory (SI) cortex; Magnetoencephalography (MEG); Pain magnitude; Pain intensity; Laser evoked magnetic field (LEF); Thulium-YAG laser; Visual analogue scale (VAS); Human

Introduction

Pain perception is an essential function for humans, and the awareness of pain magnitude ensures the individual take immediate aversive behavior to avoid harm. Earlier functional imaging and electrophysiological studies on human pain processing have already shown consistent activations around the secondary somatosensory (SII) cortex (see Kakigi et al., 2005; Peyron et al., 2000 for a review). Additional responses from the primary somatosensory (SI) cortex, insula, anterior cingulate, and prefrontal cortices are otherwise inconsistently demonstrated (Kakigi et al., 2005; Peyron et al., 2000). The extent to which these pain-relevant brain responses correlate with pain intensity is not yet settled.

Cutaneous noxious laser pulses activate exclusively Aδ and C nociceptive receptors without eliciting responses from Aβ mechanoreceptors (Bromm and Treede, 1984). The recording of laser-evoked potentials (LEP) has been therefore used as a powerful method to study cortical processing of pain information. Early studies have observed that the late LEP component correlates with subjective pain magnitude and, to a lesser degree, with the stimulus intensity (Bromm et al., 1983; Carmon et al., 1978, 1980; Kakigi et al., 1989). Recent studies were further devoted to the relationship between laser evoked responses and noxious stimulus intensities in isolated cerebral regions. For example, using subdural electrode recordings, Ohara et al. (2004) have shown that LEP over the SI, parasylvian, and frontal cortices correlate with the intensity of noxious stimuli perceived as mild to moderate pain. Timmermann et al. (2001) demonstrated a significant positive correlation of SI and SII amplitudes with mild pain intensity (rated as less than 20 with a visual analogue scale (VAS) of 0–100), but interestingly a sharp increase in SII activation was already obtained well above pain threshold. However, it is not clear whether somatosensory

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cortical responses would increase further as the subject receives even stronger painful stimulation.

In the present study, we investigated how the human brain responses reflected pain magnitude using a wide range of laser stimulus intensities, starting from a mild level and increasing up to a severely painful level. By comparing the cortical activations in varying pain conditions, we evaluated the functional roles of the activated cortices in coding perceived pain magnitude. Based on the differential coding of pain intensity in SI and SII cortices as well as the S-shaped stimulus–response function in bilateral SII in response to low levels of pain stimuli (Timmermann et al., 2001), we hypothesized that the neuronal correlate of perceiving severe pain might not necessarily be reflected by the amplitude of somatosensory cortical activations.

Materials and methods

Ten healthy right-handed volunteers (2 women and 8 men; age 27–39 years, mean 32.1 ± 4.3 years) gave their informed consent and participated in this study. This research adhered to the tenets of the Declaration of Helsinki, and the experimental protocol had a prior acceptance by the institutional review board of Taipei Veterans General Hospital.

Stimulation

Cutaneous nociceptive laser stimuli were produced by a thulium-YAG stimulator (BLM 1000 Tm:YAG®, Baasel Lasertech, Starnberg, Germany). The laser beam was conducted via an optical fiber, which entered the magnetically shielded room through a small hole. An assistant held the hand piece at the end of the optical fiber and applied the stimuli upon the lateral dorsum of the subject's left hand; the distance of the lens (within the hand piece) from the skin was about 1.5 cm. The laser pulse was kept at 1 ms in duration to stimulate a spot skin area of 10 mm^2. After each stimulus, the hand piece was slightly moved within an area of 3–4 cm in diameter to avoid skin burns and fatigue of primary nociceptive afferents.

Pain rating

Before the recordings, the subject learned how to differentiate the first (stabbing or pinprick like) and second (warm or heat sensation) pain sensations following laser pulse stimulation (Ploner et al., 2002). We started laser pulses at 100 mJ, and increased the intensity at 50-mJ steps. The subject was instructed to rate the perceived intensity of the first stabbing-like pain on the VAS. Pain threshold (PT) was determined as the lowest intensity level (VAS = 1) that elicited clear stabbing or pinprick-like pain. We defined VAS 0 as no pain, and VAS 10 as the worst imaginable pain. To ensure reproducibility, we repeated the pain rating with three randomized stimulus intensities that had been delivered to the subject. For those subjects whose estimation was incongruent with their own earlier reports, the stimulus trials and pain rating were repeated after half an hour.

The lowest strengths of laser pulses for eliciting pain levels at VAS 2–3, VAS 5–6, and VAS 8–9 were determined individually and further applied on each subject to produce mild, moderate and severe pain, respectively.

MEG recordings

During MEG recordings, the 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). The neuromagnetometer comprised 102 identical triple sensor elements, and each sensor element consisted of two orthogonal planar gradiometers and one magnetometer. In this study, data analysis was based on signals of the 204 planar gradiometers.

We determined the exact location of the head with respect to the MEG sensors by measuring magnetic signals produced by currents led to four head indicator coils at known sites on the scalp. The coil locations with respect to anatomical landmarks on the head were then found with a three-dimensional digitizer to allow further alignment of the MEG and magnetic resonance (MR) imaging coordinate systems. The positive x, y, and z axes in the head–coordinate system go towards the right preauricular point, the nasion, and the head vertex, respectively.

Each subject underwent three sessions (mild, moderate and severe pain) of laser pulse stimulation in a random order. For each session, the interstimulus interval varied between 8 and 12 s, and forty responses were averaged. All subjects gave a subjective estimate of the pain magnitude after each session. The signals were recorded with a passband of 0.1–160 Hz, digitized at 500 Hz, and stored on a disk for subsequent analysis. Epochs coinciding with signals exceeding 300 μV in the simultaneously recorded vertical electro-oculogram were automatically rejected from being averaged.

Source modeling

In this paper, the analysis period of 500 ms included a prestimulus baseline of 100 ms. To identify the sources of the evoked responses, we visually searched those channels with signal deflections clearly exceeding the prestimulus background level and select the time windows for further analysis. Equivalent current dipoles (ECDs) that best described local source currents at the response peaks were found one by one by a least-squares

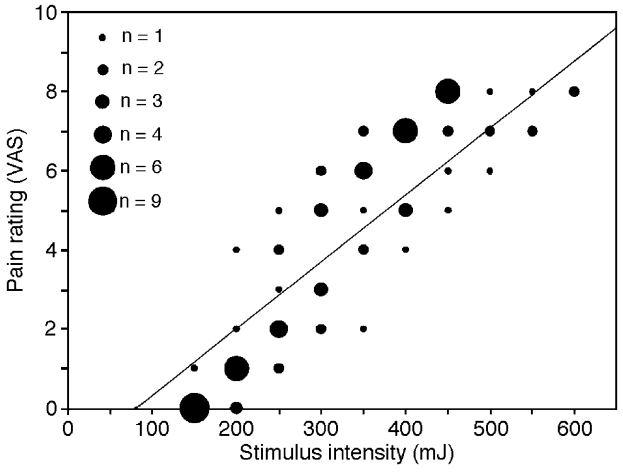

Fig. 1. The linear relationship between the subjective pain rating and the intensity level of painful laser stimulation over the left hand dorsum. The subjects reported 1 on the visual analog scale (VAS) as the pain threshold, and 10 as the worst imaginable pain.