



Cortical responses to C-fiber stimulation by intra-epidermal electrical stimulation: An MEG study



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HIGHLIGHTS

- Cortical responses to C-fiber stimulation were recorded using MEG.
- For C-fiber stimulation, modified intra-epidermal electrical stimulation was used.
- Six out of seven subjects reported the evoked sensation as pricking.
- The conduction velocity calculated using S1 and opercular activation was 1.0 m/s.

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ABSTRACT

Intra-epidermal electric stimulation (IES) is an alternative to laser stimulation for selective activation of cutaneous A δ -fibers. IES is based on the fact that nociceptive fiber terminals are located in the epidermis, whereas receptors of other fibers end deep in the dermis. IES can selectively stimulate C-fibers if the electrode structure and stimulation parameters are carefully selected. However, stable selective stimulation of C-fibers using IES has proven difficult and cannot currently be used in clinical settings. The purpose of the present study was to determine if IES performed using a modified electrode reliably stimulates C-fibers. Magnetoencephalographic responses to IES to the foot were measured in seven healthy subjects. IES elicited somatosensory evoked fields in all subjects. The mean peak latency was 1327 ± 116 ms in the opercular region contralateral to the stimulated side, 1318 ± 90 ms in the opercular region ipsilateral to the stimulated side, and 1350 ± 139 ms in the primary somatosensory cortex. These results indicate that IES performed using the modified electrode can selectively stimulate C-fibers and may be a useful tool for pain research as well as clinical evaluation of peripheral small fiber function.

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1. Introduction

Selective stimulation of C-fibers is useful for pain research and clinical evaluation of peripheral nerves. Selective stimulation is of particular importance when one wants to observe cortical responses to C-fiber activation because C-fiber related cortical responses are only recorded when the concomitant activation of

A δ - and A β -fibers is avoided [1]. However, C-fibers are not easy to selectively stimulate. Several methods to stimulate C-fibers by laser beams have been proposed based on the differential characteristics of A δ - and C-fibers [2]. A first proposed method exploits the fact that unmyelinated C-fibers are more resistant to ischemic compression block than myelinated fibers [3,4]. A second proposed method is based on the difference in the thermal activation threshold between A δ - and C-fibers, and heats the skin above the threshold of C-fibers but below the threshold of A δ -fibers [5,6]. A third proposed method takes advantage of the fact that the distribution density of C-fiber free nerve endings in the epidermis is greater than that of A δ -fibers [7,8].

For reasons such as the expense of laser apparatus, intra-epidermal electrical stimulation (IES) has been proposed as an alternative method to selectively activate A δ -fibers [9]. Moreover, IES is superior to the inter-stimulus intervals and the synchronization of evoked response compared with the laser stimulation [10].

Abbreviations: IES, intra-epidermal electric stimulation; CV, conduction velocity; MEG, magnetoencephalography; RSS, root sum square; Op, the opercular region contralateral to the stimulated side; iOp, the opercular region ipsilateral to the stimulated side; S1, the primary somatosensory cortex.

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IES is based on the fact that nociceptive fiber terminals are located in the epidermis and superficial layer of the dermis, whereas other fibers end deep in the dermis. Selective activation of A δ -fibers by IES has been confirmed using the conduction velocity (CV) of the peripheral signals, cerebral responses, and sensitivity to local lidocaine or capsaicin [9–12]. A bipolar electrode configuration extends the effective range of the electric current for selective activation of A δ nociceptors [13], and the structure of the electrode can be modified to reduce the undesired loop current that reaches deeper skin layers [14]. IES can be used to selectively activate C-fibers if specific stimulation parameters, such as anodal stimulation, are employed [15]. However, Otsuru et al. [15] reported that IES failed to activate C-fibers in some subjects. Therefore, although IES is attractive due to the high level of control and low expense, a stable stimulation method is still lacking [16].

In preliminary studies we modified the IES electrode and some stimulation parameters, and found that IES under these conditions increased the chance of successful activation of C-fibers. This motivated us to use magnetoencephalography (MEG) to assess the cortical activation elicited by this stimulation. There are previous electroencephalography and MEG studies of cortical activation following C-fiber stimulation by lasers [17–21], contact heat [22,23] and brush stroke [24]. In the present study, we investigated whether stable cortical responses to C-fiber stimulation similar to those reported in previous studies could be obtained by IES.

2. Materials and methods

The experiment was performed on seven healthy right-handed volunteers (six males) aged 34–49 years (mean $\pm$ standard deviation [SD] age 40.4 ± 5.4 years). The study was approved in advance by the Ethics Committee of the National Institute for Physiological Sciences, Okazaki, Japan and written consent was obtained from all subjects.

2.1. Stimulus and procedures

IES was used to selectively stimulate cutaneous C-fibers. IES was performed as previously described for selective stimulation of A δ -fibers [11] but with some modifications. IES was performed using a concentric bipolar needle electrode [13] that consisted of an outer ring 1.3 mm in diameter and an inner needle that protruded 0.02 mm from the outer ring. For spatial augmentation, six concentric electrodes 6 mm apart were used. The electric stimulus was 10 triangular pulses of 1.0-ms duration (0.5-ms rise/fall) at an interstimulus interval of 20 ms. The inner needle was the anode and the outer ring was the cathode [15]. We used the stimulator (PNS-7000, Nihon Kohden, Tokyo, Japan) which is specialized for IES. The stimulus intensity was adjusted to produce a clear sensation. At first, the sensory threshold was determined by increasing the stimulus current in steps of 3.3 μ A per electrode and subjects were instructed to press a button as quickly as possible when they perceived a sensation. After the subject responded to the stimulus with an appropriate reaction time (~ 1.6 s), the sensory threshold was determined using an up-down-up procedure in order to check a repeatability. The current intensity for the test stimulus was set 17 μ A above the threshold. When the subject felt that the stimulus was too weak, the stimulus intensity was increased up to 83 μ A above the threshold. The reaction time was measured several times to confirm the stimulation of C-fibers. Quality of perception was assessed by asking subjects to choose one item among the following list of seven descriptors: 'not perceived', 'light touch', 'touch', 'tingling', 'warm', 'pricking', and 'burning' [25].

The stimulus was applied to the dorsum of both feet, which were kept at $\geq 32^\circ\text{C}$ using a hot-water bag. Since the used hot water

bag was highly pliable, pressure transferred to the electrodes was negligible. The left and right foot were stimulated randomly at an inter-trial interval of 13–18 s. One to three seconds before each stimulus, an LED signal was presented to the subject to reduce rejection of trials due to blink artifact. Subjects were instructed to attend the stimulus and to verbally report the pain rating by visual analog scale every 10–15 stimuli. At least 50 artifact-free trials were averaged for each stimulation site. In three subjects, the lateral aspect of the knee of one side was also stimulated in order to evaluate the CV of the peripheral signals activated by IES.

2.2. MEG recordings

The experiment was performed in a magnetically shielded room. Magnetic signals were recorded using a 306-channel whole-head type MEG system (Vector-view, ELEKTA Neuromag, Helsinki, Finland) as described elsewhere [19]. The signals were recorded with a bandpass filter of 0.1–300 Hz and digitized at 1004 Hz. The analysis was conducted from 100 ms before to 2000 ms after the onset of each stimulus. The 100-ms pre-stimulus period was used as the baseline. Epochs with MEG signals larger than 2.7 pT/cm were rejected from the averaging. The averaged waveform was filtered offline with a lowpass threshold of 30 Hz [26].

2.3. Analysis

Vector sums were calculated from the longitudinal and latitudinal derivations of the response recorded by the planar-gradiometers at each of the 102 sensor locations. This was obtained by calculating the root sum square (RSS) of the MEG signals from the two gradiometers at each sensor location, as described previously [27]. RSS waveforms were obtained for all 102 sensor locations and three locations with maximal amplitude at a latency around 1300–1500 ms were identified: one in the temporal region in each hemisphere and one in the vertex region, corresponding to the opercular region and the foot area of the primary somatosensory cortex (S1) respectively. In each subject, the magnitude and latency of the peak of the RSS waveform was measured for stimulation of each foot. The peak was accepted as an evoked component if the magnitude was $>3\text{SD}$ above baseline. The latency of the peak was compared across the three cortical areas using a one-way ANOVA.

Next, a multi-dipole analysis was performed using the brain electric source analysis (BESA) software package (NeuroScan, Mclean, VA), as described previously [28–30]. For each subject, the model was then superimposed on magnetic resonance (MR) images (Siemens Allegra, 3.0-T) to show the source location. The location was transformed into Talairach coordinates by BESA and Brain Voyager (QX 1.4, Maastricht, The Netherlands).

CV was calculated in three subjects by dividing the distance between electrode locations by the difference in peak latency of the somatosensory evoked field following stimulation of the dorsum of the foot (foot) and of the distal end of the fibular head (knee). CV was also calculated by dividing the distance between electrode locations by the difference in corresponding reaction times. Data are expressed as mean $\pm$ SD.

3. Results

3.1. Evoked sensation

The sensory threshold was 41.9 ± 17.9 and 33.1 ± 13.6 μ A per electrode for the left and right foot respectively. The mean reaction time was 1.63 ± 0.15 and 1.60 ± 0.14 s for the left and right foot respectively. Neither the sensory threshold ($p=0.26$) nor the reaction time ($p=0.67$) differed significantly between the two feet. Of

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