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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 Aδ-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.

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 Aδ- and Aβ-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 Aδ- 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 Aδ- and C-fibers, and heats the skin above the threshold of C-fibers but below the threshold of Aδ-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 Aδ-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 Aδ-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 Aδ-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 Aδ 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 ± 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 Aδ-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 μA 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 μA above the threshold. When the subject felt that the stimulus was too weak, the stimulus intensity was increased up to 83 μA 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 ≥32 °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 planer-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 >3SD 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 ± SD.

3. Results

3.1. Evoked sensation

The sensory threshold was 41.9 ± 17.9 and 33.1 ± 13.6 μA 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

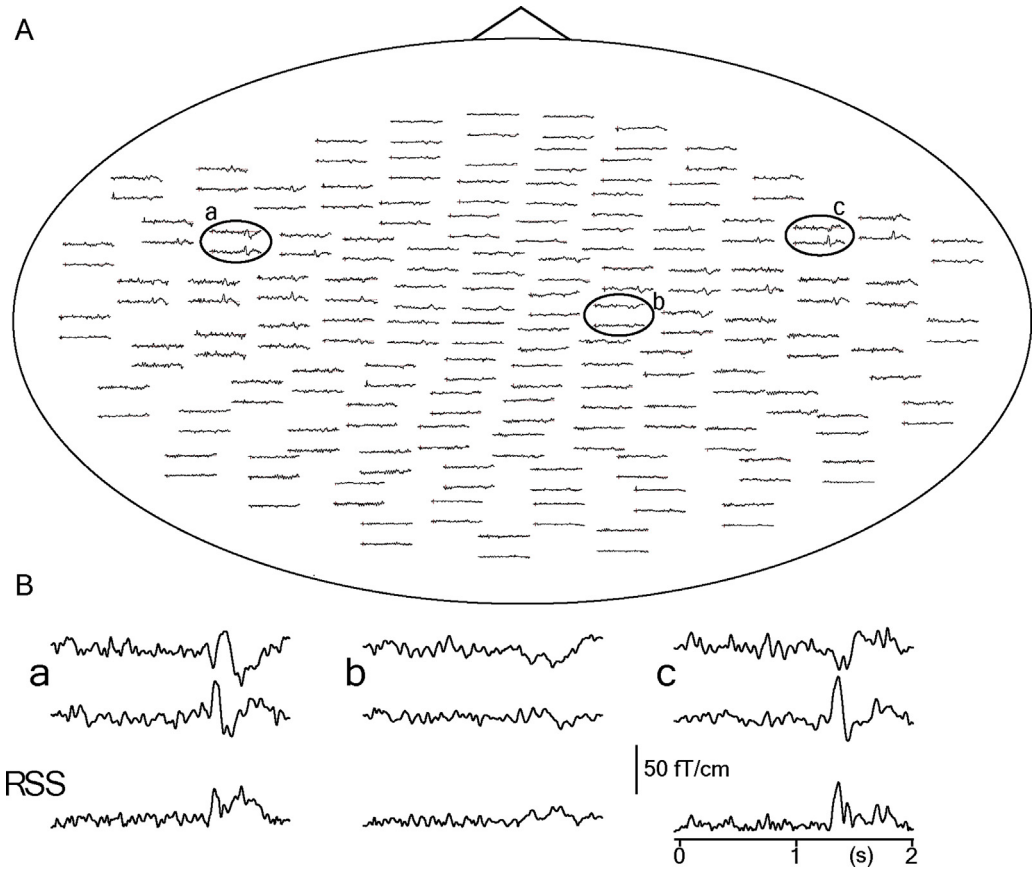

Fig. 1. Evoked magnetic fields following intra-epidermal electrical stimulation to the dorsum of the foot in a representative subject. (A) Waveforms of all 204 sensors. Ovals indicate the sensor of interest in the parietal (b) and bilateral temporal (a and c) regions selected for the root sum square (RSS) analysis. (B) The waveforms of the two planer-gradiometers in each sensor of interest marked in 1A (upper traces) and their RSS (lower trace).

the 14 feet tested, a clear pricking sensation was elicited in 12 and a burning sensation was elicited in two.

3.2. Evoked waveforms and RSS signals

In all subjects, IES to the foot evoked clear cortical responses at around 1300–1500 ms in the temporal region of both hemispheres, corresponding to the opercular region. For all but one foot, additional clear responses were observed in the vertex region, corresponding to the foot area of S1. Fig. 1 shows the magnetic responses to left-foot stimulation in a representative subject. The three sensor locations indicated in Fig. 1A were used for further analyses of the RSS signals. Fig. 1B shows the RSS waveforms for the selected locations. Across all subjects, the mean peak latency was 1327 ± 116 ms ($n = 14$) in the opercular region contralateral to the stimulated side, 1318 ± 90 ms ($n = 14$) in the opercular region ipsilateral to the stimulated side, and 1350 ± 139 ms ($n = 13$) in the S1 ($F = 0.27$, $p = 0.77$).

3.3. Dipole analysis

Fig. 2 shows results of the multi-dipole analysis in a representative subject. Like cortical responses to A-delta stimulation using IES [31], stimulation of C-fiber nociceptors activated S1 in the hemisphere contralateral to the stimulation and S2 in bilateral hemispheres. A clear dipolar pattern field distribution was observed in the temporal region of both hemispheres. This corresponded to the sensor of interest in the temporal region for the RSS analysis. In the subject shown in Fig. 2 there was an additional dipolar pattern consistent with a dipole in the parietal midline area with a posteriorly directed current, which corresponds to the S1 dipole. Fig. 2B shows the source strength as a function of time for each dipole and Fig. 2C shows the location of the dipoles superimposed on the subject's own MR images. The mean location of each dipole across subjects is shown in Fig. 3.

3.4. CV

Table 1 shows CV in three subjects calculated using the peak latency of each cortical activity and calculated using reaction time. Both calculations resulted in CV of around 1 m/s, which suggests C-fibers mediated the observed responses.

4. Discussion

In the present study, IES-induced peripheral signals ascended through C-fibers activated S1 and opercular regions of the brain, resulting in a pricking sensation. Cortical responses were similar to those reported in previous MEG studies using laser stimulation [26]. These findings indicate that IES selectively activated cutaneous C-nociceptors, and suggest that IES may be a useful method for selective C-fiber stimulation.

4.1. Sensation

Six of seven subjects felt the IES-evoked sensation as pricking and one felt the sensation as burning. In a previous study, the sensations produced by IES were weak and painful, described as "flicking", "burning", or "long-lasting weak pricking" (50%), or light touch, described as a "faint touch" or "light pressure" (50%)

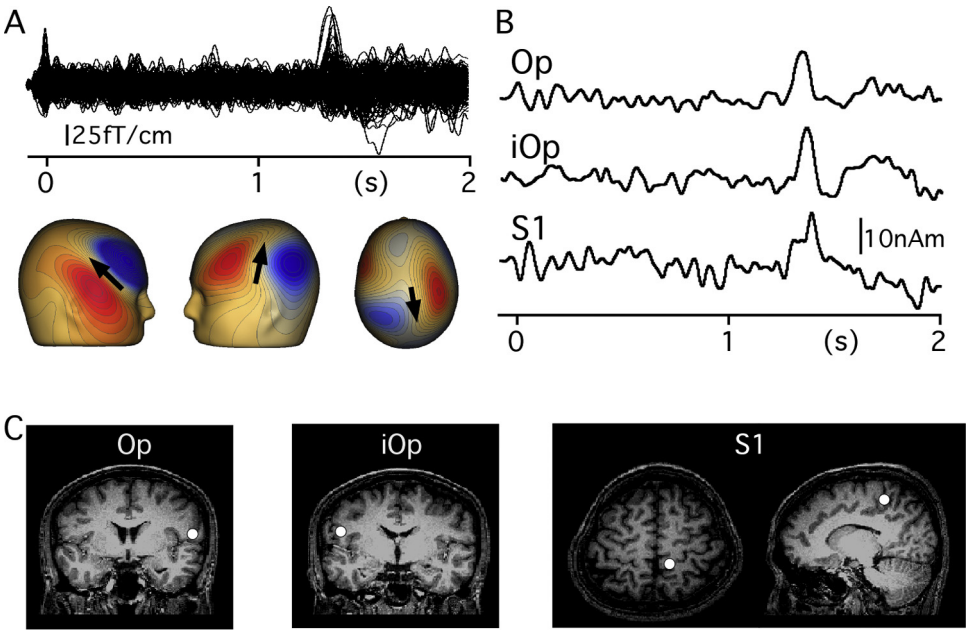

Fig. 2. Source analyses of evoked magnetic fields. The results of the multi-dipole analysis for the waveforms in A are shown. (A) Superimposed waveforms (top) and isocontour maps at three selected latencies (bottom). (B) The source strength as a function of time in the obtained dipoles. (C) The location of each dipole superimposed on the subject's own magnetic resonance images.

[15]. Similarly, C-fiber stimulation by laser beams caused "warm" (20%), "tingling" (16%), or "light touch" (13%) sensations [25]. In studies that used contact thermal stimulation, the evoked sensation was usually "warm" [22]. Therefore the evoked sensation of clear pricking in this study is apparently different from those reported previously. IES might have stimulated different C-fibers from thermal or laser stimulation, or the different stimulation parameters, such as stimulus duration, may have determined the sensation.

4.2. Dipole analysis and CV

Results of the source analysis were in agreement with previous studies using laser stimulation, showing the major cortical

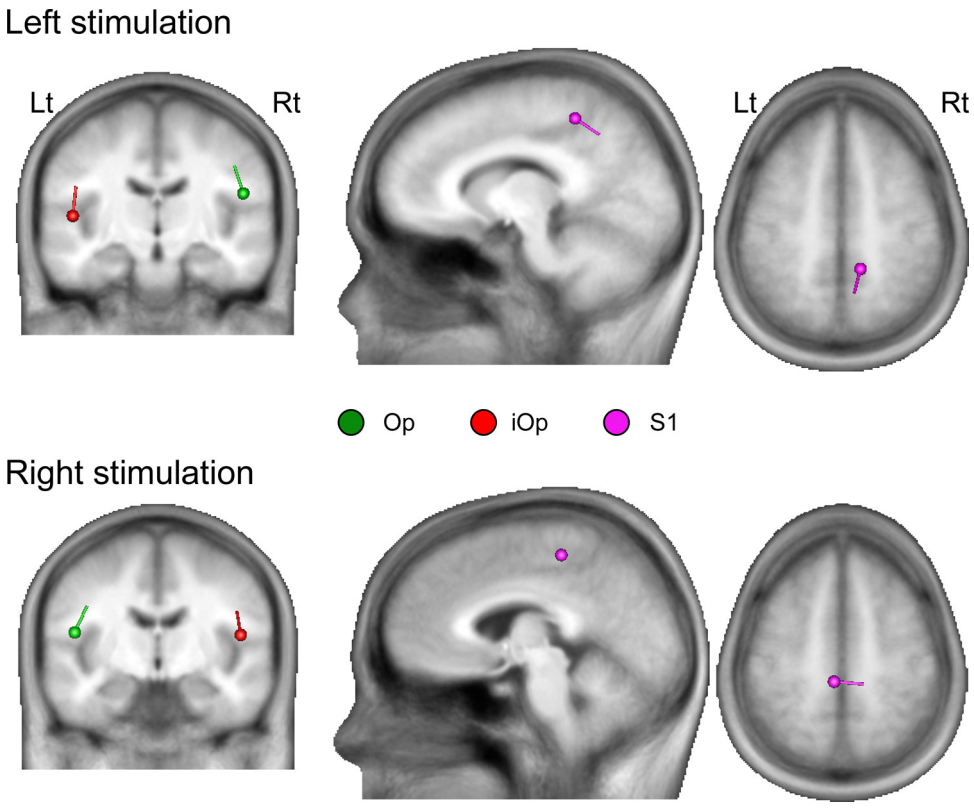

Fig. 3. The mean location of estimated dipoles from seven subjects superimposed on standard brain slices.

Table 1
Conduction velocity.

Subject	Location	Distance (mm)	Peak latency (ms)		CV (m/s)	Reaction time (s)		CV (m/s)
			Foot stimulation	Knee stimulation		Foot stimulation	Knee stimulation	
1	S1	400	1380	989	1.02	1.34	1.08	1.53
	iOp		1356	910	0.90			
	Op		1452	934	0.77			
2	S1	375	1188	880	1.22	1.58	1.00	0.65
	iOp		1196	786	0.91			
	Op		1194	851	1.09			
3	iOp	410	1300	923	1.09	1.74	1.32	0.98
	Op		1351	954	1.03			
Mean		393	1302	903	1.00	1.55	1.13	1.05
SD		16	100	64	0.14	0.20	0.17	0.45

The peak latency of root sum square (RSS) waveforms and the estimated conduction velocity (CV) in the foot area of the primary somatosensory cortex (S1), the opercular region contralateral to the stimulated side (Op), and the opercular region ipsilateral to the stimulated side (iOP).

source in the opercular region [26,32,33]. When the site of stimulation is taken into consideration, the latency of each cortical source activity, including parallel activation of S1 and the opercular region, was consistent with previous findings [26,32]. One previous study observed S1 activation following C-fiber stimulation [34], but another did not [35]. Pain related to C-fiber activation is considered to be vague and non-localized, which implies that C-fiber signals are mainly processed outside the lateral system and supports the absence of S1 activation following C-fiber stimulation. On the other hand, Moore and Schady [36] demonstrated that the ability to localize a stimulus on the body surface did not differ among touch, sharp pain, and burning pain, which supports the observation of S1 activation following C-fiber stimulation. In the present study, S1 activation was observed following stimulation of nine of the 14 feet, and the evoked sensation was usually sharp pricking and well-localized, which supports the notion that S1 is involved in the processing of the sensory aspect of C-fiber signals, as it is in processing the sensory aspect of A-δ signals [37].

CV calculated by both the cortical responses and the reaction time was approximately 1.0 m/s, which is within the range of CV of C-fibers measured in a microneurographic study [38] and is consistent with previous EEG studies reporting CVs of 0.5–2.5 m/s [6,39]. The reaction time of longer than 1 s also indicates that C-fibers were responsible for the evoked sensations. The present findings, together with the fact that C-fiber cerebral responses cannot be obtained with concomitant activation of thicker fibers, indicate clearly that IES selectively activated C-fibers in the present study.

4.3. Electrode configuration and stimulation parameters

The difference in stimulus conditions between the present and previous [15] studies is that the present study used a shorter needle (0.02 vs. 0.1 mm) and more pulses for the stimulus train (10 vs. 3). Our preliminary studies showed that a shorter needle expanded the effective range of electric current over which C-fibers were selectively stimulated, i.e. increased the current threshold for stimulation of Aδ-fibers. This may suggest that C-fiber terminals are located in a shallower skin layer than Aδ-fiber terminals. Furthermore, Zylka et al. [40] identified peptidergic and non-peptidergic C-fibers terminate in different epidermal layers. Regarding the pulse number for IES, it is clear that C-receptors or their axon terminals are sensitive to train stimulation. Therefore, more pulses with a shorter inter-stimulus interval provide a wider effective range for selective C-fiber stimulation.

4.4. Limitations

The optimal stimulus parameters are not known, and there is room for improvement in this technique. In future studies, several stimulus parameters should be compared using a larger sample of subjects. In this study, we used six electrodes to acquire a spatial enhancing effect. To reduce the cost, it is necessary to identify the minimum number and optimal arrangement of electrodes for C-fiber stimulation by IES.

4.5. Conclusion

IES using the modified electrode selectively stimulated C-fibers in all healthy subjects tested. This suggests that IES is a useful tool for evaluation of peripheral thin fibers and pain research. IES is simple and easy to control, and may also be suitable for clinical testing.

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