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EEG and MEG responses following stimulation of unmyelinated C fibers

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Abstract— **Cerebral processing of first pain, associated with A-delta fibers, has been studied intensively, but the cerebral processing associated with C-fibers, relating to second pain, remains to be investigated. We selectively activated C-fibers by the stimulation of a tiny area of skin with a CO_2 laser. As for the primary component (1M), in the hemisphere contralateral to the stimulation, two regions in the hand area of the primary somatosensory cortex (SI) and secondary somatosensory cortex (SII)-insular were activated. In the hemisphere ipsilateral to the stimulation, only one source was estimated in SII-insular. Our findings suggest that parallel activation of SI and SII-insular contralateral to the stimulation represents the first step in the cortical processing of C-fiber-related activities. In addition to SI and SII-insular, cingulate cortex and medial temporal area (MT) around amygdala and hippocampus in bilateral hemispheres were also activated for the subsequent component, 2M. All components of EEG and MEG responses were significantly reduced in amplitude during distraction and diminished during sleep, particularly 2M component. These findings indicate that these regions are related to the cognitive aspect of second pain perception, particularly activities in cingulate cortex.**

Keywords— **Attention, C fiber, Pain**

I. Introduction

There are two systems for nociceptive perception, one ascending through A-delta fibers relating to first or sharp pain, and one ascending through C-fibers relating to second or burning pain. A CO_2 laser beam is frequently used to record pain-related brain potentials (laser evoked potentials, LEP) and magnetic fields (LEF) in humans. Recently, Bragard et al., [1] and Opsommer et al., [2] reported a simple method for recording ultra-late LEP by selective activation of C afferent sensory terminals in the skin using a CO_2 laser to stimulate a tiny surface area. The physiological background of this method is that the C afferent sensory terminals in the skin have a higher density and lower activation threshold than the A-delta terminals. We have recorded a clear ultra-late LEP by modifying the method and reported that the conduction velocity of the peripheral nerve and spinal cord following this specific stimulation was approximately 1-4 m/s, which is within the range for unmyelinated fibers [3,5,7,8]. We reported that 3-dipole model of SI and bilateral SII sources could explain the 1M component of MEG responses following stimulation of C-fibers [9], and that cingulate cortex and medial temporal area (MT) around amygdala and hippocampus in bilateral hemisphere were also activated for the subsequent component, 2M [6], and also clarified the mechanisms underlying the effects of attention/distraction on second pain perception in detail by using EEG [4] and MEG [6].

II. Methods

Thirteen healthy male volunteers participated in this study. For recording the ultra-late LEP and LEF by selective stimulation of C-fiber, we used a thin aluminum plate reported in detail in our previous papers [5,7]. The ultra-late LEF were recorded with two probes (BTi, San Diego, CA) placing at C3 and C4.. We used the brain electric source analysis (BESA) software package made by Scherg (BESA 2000, NeuroScan Inc., McLean, VA) for the computation of theoretical source generators in a 3-layer spherical head model. The ultra-late LEP was also recorded with three exploring electrodes that were placed at Cz (vertex), C3 and C4 referred to linked earlobes (A1+A2). Ultra-late LEP were recorded under five different sets of conditions. (i) Control condition in which subjects did not have any task, (ii) Attention in which the subjects were instructed to mentally count the number of laser pulses paying close attention to the stimuli, (iii) Distraction in which the subjects were asked to calculate, (iv) Drowsiness (stage 1 in sleep) and (v) Stage 2 in sleep. Ultra-late LEF was recorded under two different conditions between Control and Distraction.

III. Results

A. Effects of attention, distraction and sleep on ultra-late LEP

The ultra-late LEP, negative component (N1) and positive component (P1), were recorded. We mainly analyzed the results recorded at the Cz.. Results of ANOVA indicated a significant relationship between the P1 amplitude and attention level (P=0.0011). The P1 amplitude was slightly increased during the attention task (P=0.19) but significantly decreased during the distraction task (P=0.0068), relative to the control by post-hoc comparison. The P1 amplitude was significantly larger during the attention task than the distraction task (P=0.0003) (Fig. 1). The P1 amplitude was much decreased in 5 subjects, and was absent in the other 5 subjects during drowsiness. The mean amplitude decrease during drowsiness was significantly relative to the control condition (P=0.0044, n=5; P=0.0001, n=10) (Fig. 1).

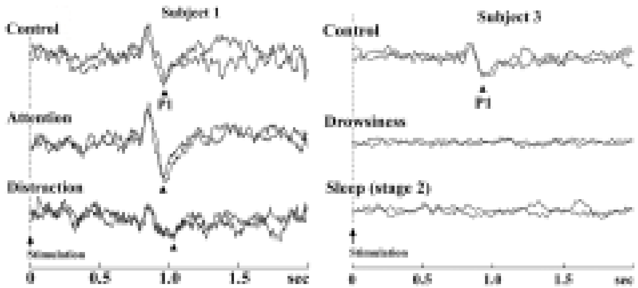

Fig. 1. Effects of attention, distraction and sleep on ultra-late LEP

B. Effects of distraction on ultra-late LEF

In the Control condition, the mean peak latencies of first component (1M) and second component (2M) were 744±72 ms and 926±85 ms, respectively in the contralateral hemisphere, and 765±77 ms and 958±96 ms, respectively, in the ipsilateral hemisphere(Fig. 2). The 1M and 2M recorded from the ipsilateral hemisphere was significantly longer in latency in all the subjects, and the inter-hemispheric difference in mean latencies were 21±26 ms ($P<0.01$) and 32±26 ms ($P<0.002$) (Fig. 2). The RMS of 1M and 2M was significantly smaller than in the Control, $P<0.01$ for 1M and $P<0.005$ for 2M, in the contralateral hemisphere (Fig. 2). In the ipsilateral hemisphere, the RMS of 1M and 2M was significantly smaller than the Control value, $P<0.005$ for 1M and $P<0.002$ for 2M (Fig. 2).

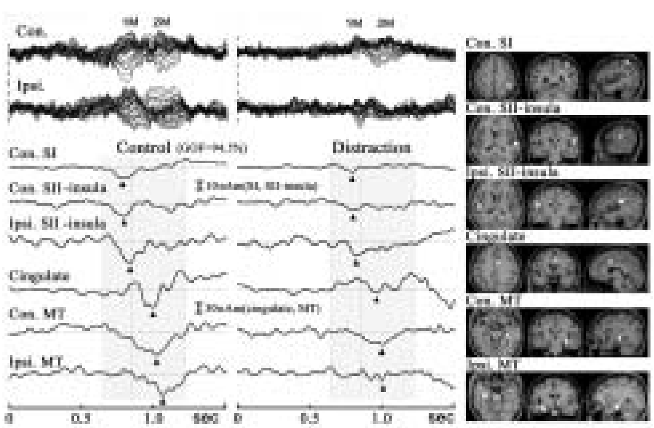

Fig. 2. Effects of distraction on ultra-late LEF and results using BESA

C. Results using BESA

We made a 6-source model by locating Source 1 in SI of the contralateral hemisphere, Source 2 and 3 in SII-insula of bilateral hemispheres, Source 4 in the cingulate cortex and Source 5 and 6 in MT of bilateral hemispheres (Fig. 2). The GOF value for this 6-dipole model in the Control was 92.9±1.1%. The current strength of SI and SII was significantly smaller in the Distraction than Control condition, $P<0.05$ for SI and $P<0.01$ for SII-insula (Fig. 2). The current strength of the cingulate cortex and MT was significantly smaller in Control than in Distraction, $P<0.001$ for the cingulate and $P<0.05$ for the MT (Fig. 2). The SII-insula and cingulate were more effectively attenuated than SI and MT, particularly activities in cingulate cortex.

IV. Discussion

Our new technique, based on reports from a Belgian group [1,2], enabled us to record clear ultra-late LEP and LEF. Since the subjects felt touch, pressure or a slight burning pain, we have to consider one fundamental and important question; Does this stimulus really relate to second pain? In conclusion, we believe the C-fiber responses in our study represent the second pain-related cerebral activation. There are 3 types of C-fibers, (1) polymodal or mechano-heat responsive C-fibers, (2) warm or heat responsive C-fibers, and (3) silent or mechano- and heat-insensitive C-fibers, and second pain is transmitted by (1). In normal subjects, CO_2 laser stimulation can activate (1) and (2). However, it is found that (2) have a higher heat threshold (48 °C) than (1) (40 °C). In the present study, we used a CO_2 laser to stimulate a tiny area of skin at weak intensity. Therefore, this stimulation probably activated polymodal C-fibers.

The most important finding in this study is that we found activated regions following the stimulation of C-fibers and clarified their changes during the Distraction condition. Only one study has reported ultra-late LEF following C-fiber stimulation using the same stimulus methods as the present study [9]. They focused on the primary activities corresponding to our 1M component, and found that SI and SII were simultaneously activated in the contralateral hemisphere, and only SII was activated in the ipsilateral hemisphere. These findings were compatible with our results, and we added activities in the cingulate cortex, the MT, and probably the insula as mainly later activities in the present study.

V. Conclusion

We confirmed that the cerebral response relating to signals ascending through C-fibers was much affected by the level of consciousness, possibly corresponding to second pain perception. Moreover, since the activities in the SI, SII-insula, cingulate cortex and MT were significantly reduced when the subject was distracted from the stimuli, the level of attention should be strictly controlled when the ultra-late LEP and LEF recording technique is used for clinical purposes.

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