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Somatosensory event-related potentials evoked by painful and non-painful electrical stimuli

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Abstract The aim of this study is to compare the somatosensory event-related potentials (SERPs) elicited by painful and non-painful electrical stimuli, and to investigate the central processing of nociceptive input from skin. The thumb and index fingers of the right hand were stimulated. The index finger stimuli (80% of the total stimulus number) which were non-target stimuli, and the thumb stimuli (20% of the total stimulus number) which were target stimuli were delivered at random. SERPs were recorded from 5 scalp sites. The latency and amplitude of each SERP component were analyzed mainly in terms of N140 and P300. Furthermore, topographical maps and dipole localization maps of SERPs were also produced.

Our results revealed that the amplitudes of the N140 and P300 components were larger and the latency of the P300 component shorter in SERPs elicited by painful stimuli. However, there was no significant difference in the topographical distribution of the N140 and P300 components and the dipole location of the P300 component between painful and non-painful stimuli. These findings may suggest that painful sensations and non-painful sensations are generated through similar cortical pathways, and that the velocity and intensity of cognitive cerebral processing of the sensations are faster and stronger in painful stimuli.

1. Introduction

The intracerebral cognitive pathway induced by pain has been studied for the past 30 years. Pain evoked potentials (EPs) with a variety of painful stimuli, including mechanical, electrical, laser, chemical and heat stimuli[1-7], have been used to investigate the origin of pain perception. However, in part, the mechanisms of pain processing in the brain are still controversial.

Two popular patterns of stimulation induced pain are produced by CO_2 laser and electrical stimuli.[3,4] Electroencephalographic (EEG) and magnetoencephalographic (MEG) studies have been applied for analyzing the brain areas involved in pain perception .[1,8,9] The peaks of EPs in response

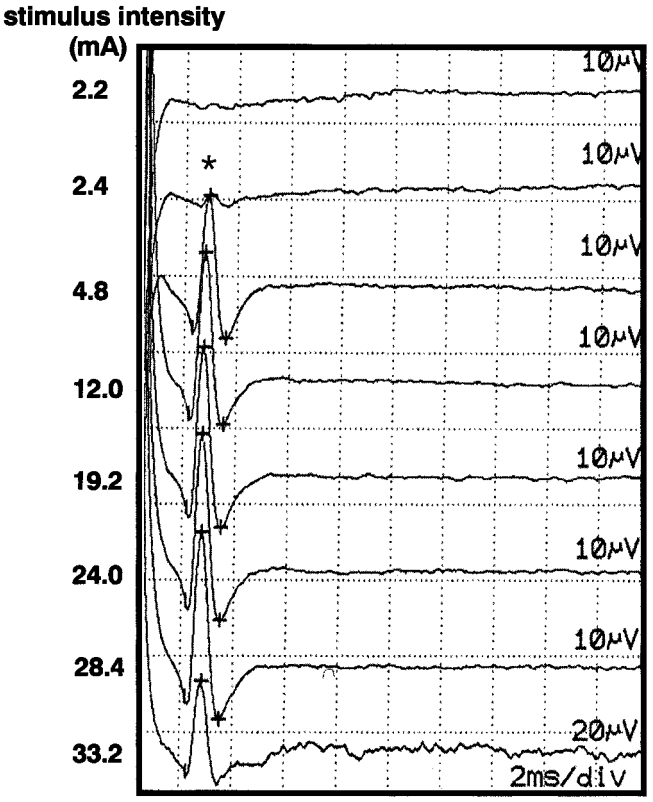

Fig. 1 Sensory nerve action potentials (SNAPs) recorded from the right median nerve at the wrist, changing stimulus intensities of ring electrodes attached to the right thumb. The threshold stimulus intensity (*) producing the SNAP is determined by these procedures.

to painful stimuli, which are commonly used in the EEG study, are divided into two groups (early and late somatosensory components). Early somatosensory components which appear before 80 msec reflect the entrance of the stimulated afference in the primary sensorimotor cortex , and have not been observed in response to painful stimuli. However, late components, which are components of so-called somatosensory event-related potentials (SERPs), are broadly agreed to reflect cognitive processing of the stimuli with or without pain .[10] They are characterized by a negative peak at 130-240 msec, and a subsequent positive peak at 230-390 msec .[11–15] In a previous study, it was found that electrical stimulation of fingers with an oddball paradigm elicited the long-latency component N140, which corresponds to the component N120 of Allison et al. following median nerve stimulation at the wrist [16], and the late cognitive component P300 .[11] We concentrated on these two components of SERPs in response to painful and non-painful electrical stimuli.

The aim of this study is to compare the late components of SERPs elicited by painful and non-painful electrical stimuli, and to investigate the central processing of nociceptive input from skin. In the present study, we methodologically analyzed SERP latencies/amplitudes, topographical maps, and current dipole sources generated by non-painful and painful stimulation of the skin.

2. Methods

2-1 Subjects

Seventeen normal subjects were included in this study, 12 males and 5 females ranging in age from 20 to 28 years old, with a mean age of 25. They were all right-handed and in good health. They had no neurological problems and

were not taking medication. The subjects were instructed to get plenty of sleep the night before the experiment, in order to maintain alertness throughout the procedure. The subjects were reclined comfortably with their eyes closed in an armchair, in a quiet, semi-darkened room.

2-2 painful or non-painful stimuli

The stimulus conditions were determined before the measuring event related potentials. First, the motor nerve action potentials (MNAPs) were recorded from the right abductor pollicis brevis, when changing the stimulating positions of the right median nerve at the wrist. The position at which the highest MNAP was recorded was determined as an appropriate position of the median nerve at the wrist, and was marked. Next, the sensory nerve action potentials (SNAPs) were recorded from electrodes attached on the marking place at the wrist, changing stimulus intensities of ring electrodes attached to the right thumb. The threshold stimulus intensity producing the SNAP was determined by these procedures (Figure 1). After the determination of the threshold intensity of the SNAP, stimulus intensity levels producing a cutaneous silent period (CSP) were determined in each subject. CSPs were recorded from the right opponens pollicis for 40 msec and 70 msec after the right median nerve stimulation at the wrist, when increasing the stimulus intensities from twice to 14 times of the threshold intensity of the SNAP (Figure 2). The stimulus intensity producing CSPs was regarded as the objective index of painful stimuli, and the stimulus intensity which did not produce CSPs was regarded as non-painful stimuli. The mean threshold intensity producing the SNAP and CSPs in 17 subjects were 2.8± 0.5 mA and 22.4±6.6 mA, respectively.

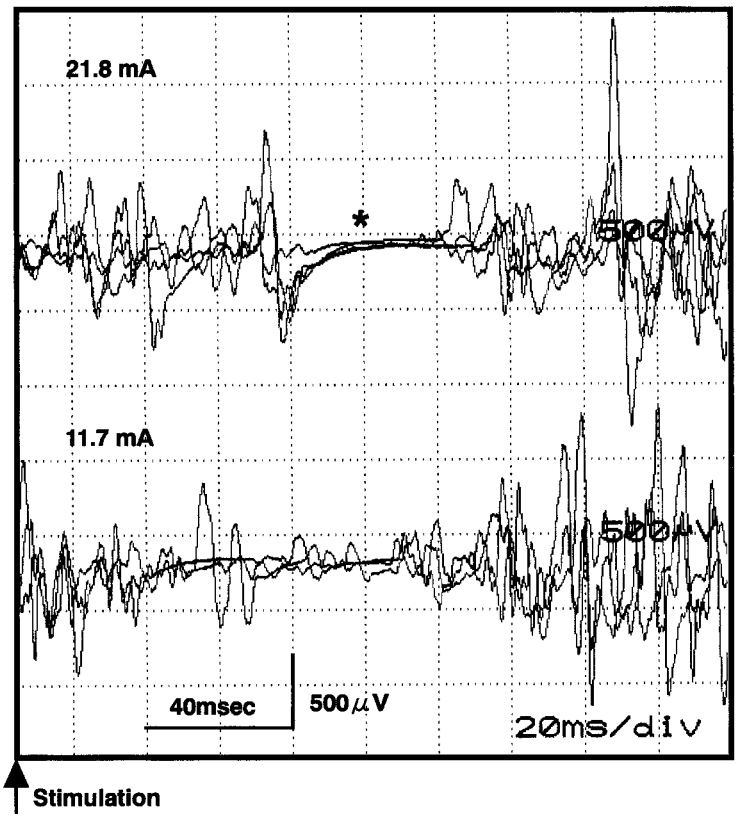

Fig. 2 Cutaneous silent period (CSP) recorded from the right opponens pollicis for 40 msec (*), 70 msec after the right median nerve stimulation at the wrist, when increasing the stimulus intensities from 11.7 mA (bottom tracing) to 21.8 mA (top tracing). The stimulus intensity producing CSP is regarded as the objective index of painful stimuli.

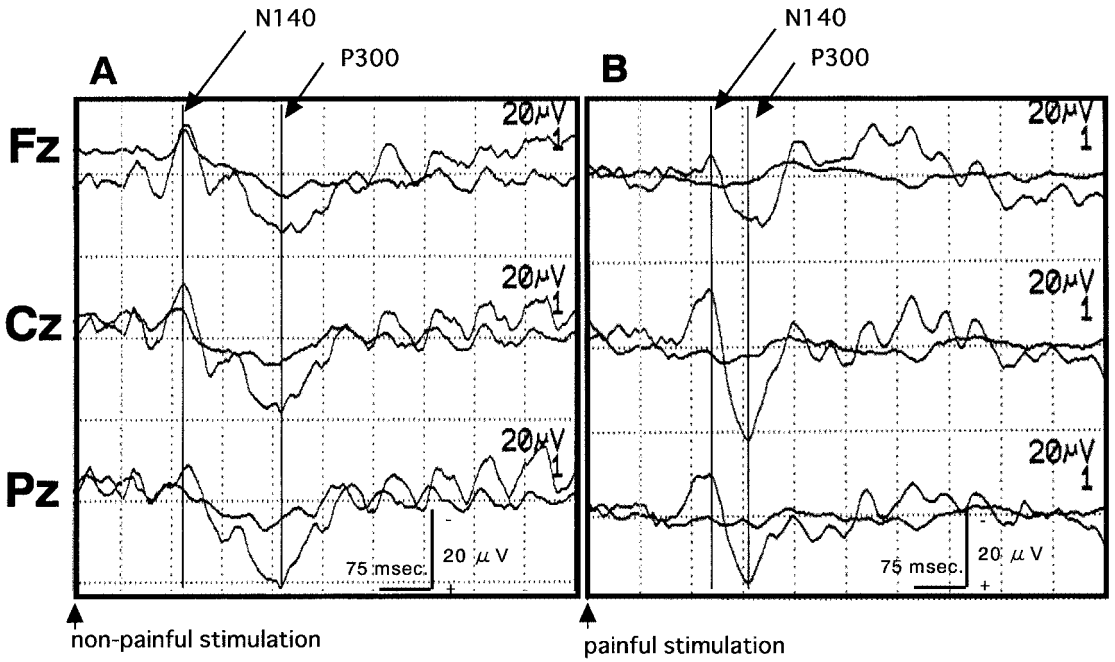

Fig. 3 Representative somatosensory event related potentials (SERPs) obtained from one subject (23 year-old male). A: non-painful stimulation, B: painful stimulation. Two peaks of N140 and P300 components are clearly discernible in the traces. The highest and deepest portions of the traces are considered as the peaks of N140 and P300. The amplitudes of the N140 and P300 components (Cz, Pz) evoked by the painful stimuli are higher than those evoked by the non-painful stimuli. The latency of P300 was shorter in the painful electrode stimuli.

2-3 Stimulation for SERPs

The thumb and index fingers of the right hand were stimulated with two ring electrodes. The distal sites were anodes, and the proximal sites were cathodes. Rectangular pulses of 1 msec duration were delivered at 1 Hz frequency. The index finger stimuli (80% of the total stimulus number) which were non-target stimuli and the thumb stimuli (20% of the total stimulus number) which were target stimuli were delivered at random. In all subjects, the intensity of the non-target stimuli was twice of the threshold intensity of the SNAP which did not form CSP. The intensities of the target stimuli were 3-4 times of the threshold intensity of the SNAP for non-painful stimuli, and 7-10 times for painful stimuli. The means and standard deviations of stimulus intensities were 5.6±0.6 mA for non-target stimuli, 15.2±5.6 mA for non-painful target stimuli, and 25.2±5.1 mA for painful target stimuli, respectively.

2-4 Recording system

Event related potentials (ERPs) were recorded from 5 scalp sites (Fz, Cz, Pz, C3, and C4) according to the International 10-20 system, and the linked earlobes were used as the reference. Electrode impedances were kept below 5 kΩ and the bandwidth was set from 0.1 to 50 Hz. The all waveforms obtained by electrical stimuli through a Neuropack 8 (Nihon Koden Co. Ltd.Japan) were input on-line into a personal computer, then 15 to 20 waveforms were subjected to average off-line addition for the data obtained with the target stimuli after the waveforms contaminated with artifacts had been excluded. All waveforms obtained by the non-target stimuli were also stored into a personal computer. The reproducibilities of the waveforms were always checked, and only those wavelets

which showed good accordance between three trials were considered in the following analysis. An individual final waveform was consisted of 45 - 60 sweeps.

The latency and the amplitude of each ERP component were analyzed mainly in terms of N140 and P300 based on the above data for both painful stimuli and non-painful stimuli. The highest and deepest portions of the traces were considered as the peaks of N140 and P300. The latencies and amplitudes were measured at the Cz for the N140 component and the Pz for the P300 component, respectively. The Wilcoxon signed-rank test was used to compare values of the latency and the amplitude, and differences at $p<0.05$ were considered statistically significant.

2-5 Topographical map

Topographcal maps of ERPs for painful and non-painful stimuli were produced with a digital EEG system (AllianceWorks ™, Nicolet Biomedical Inc. USA) in 7 volunteers by the waves obtained from 17 scalp electrodes, based on the International 10-20 System.

2-6 Dipole localization

Seven of 17 volunteers were included in this study to detect the differences of cerebral generators of the cognitive function between painful and non-painful stimuli. Two mathematical techniques, the dipole localization method and the cortical imaging technique, were used to analyze the ERPs induced by painful and non-painful electric stimuli. The dipole locations of the ERPs were identified from potential distributions in 28 EEG leads, using the brain electrical source analysis (BESA) program and topography. EEG data were collected from 28 recording channels in each subject, with other conditions being the same as previous procedures. Based on the ground average EEG data, a single-dipole model and simulated cortical surface maps were constructed for each subject in both painful and non-painful electrical stimuli. Three-dimensional coordinates of the surface electrodes and the scalp, skull and brain geometry of the subjects were measured by a special device (SynaPoint Pro, NEC Medical Systems Inc. Japan).

3. Results

Representative SERP traces obtained from one subject (a 23 year-old male) are presented in Figure 3. Two peaks of the

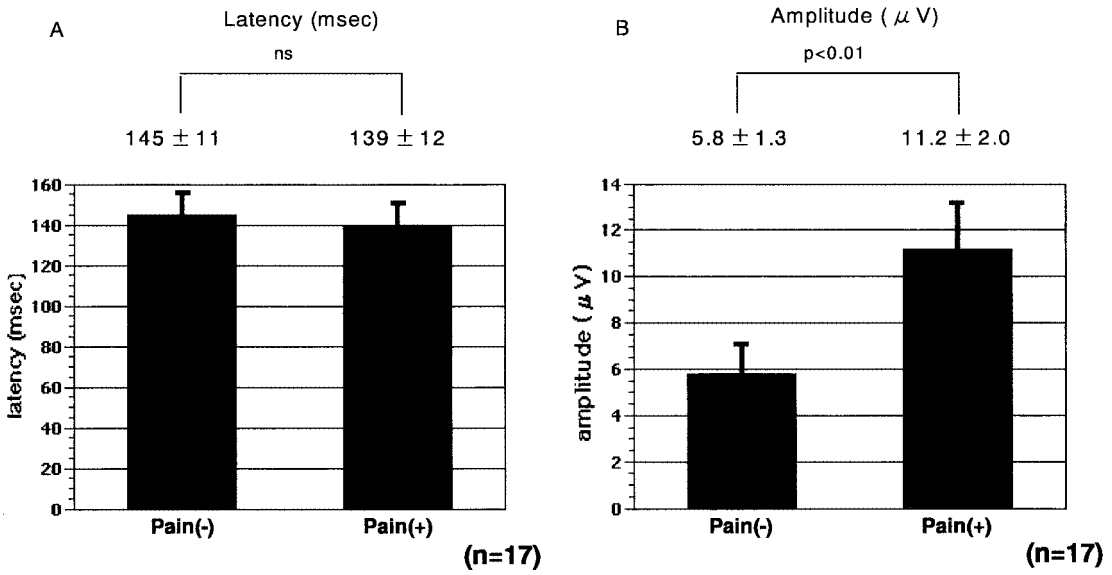

Fig. 4 Mean latencies (A) and amplitudes (B) of N140 components measured at the Pz in 17 subjects. Although no difference is observed between the painful and non-painful stimuli for the N140 latency, a statistically significant difference is observed for the N140 amplitude ($p<0.01$).

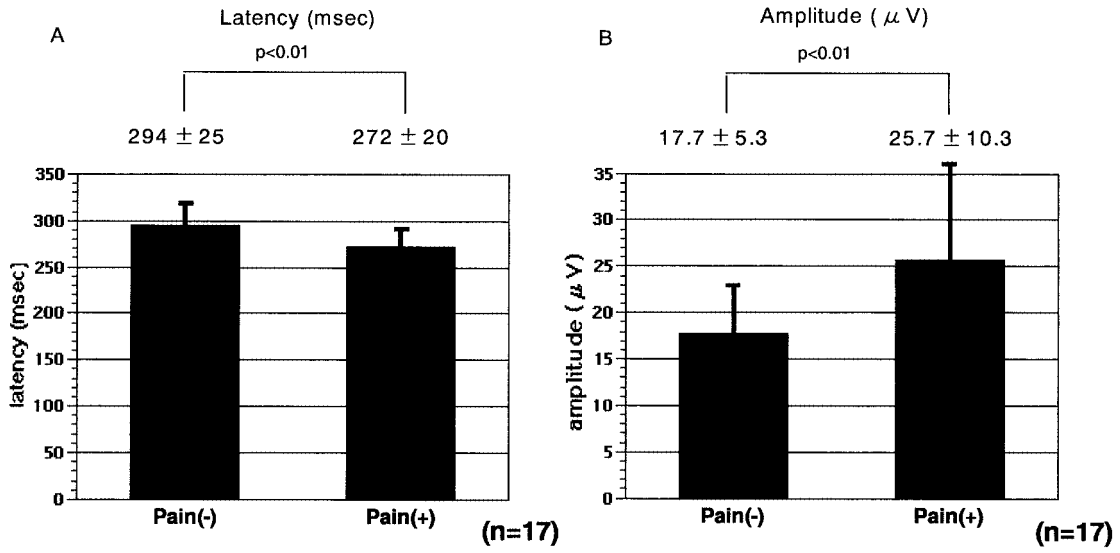

Fig. 5 Mean latencies (A) and amplitudes (B) of P300 components measured at the Pz in 17 subjects. The latency and the amplitude of the P300 component evoked by painful stimuli are statistically shorter and higher ($p<0.01$) than those of the P300 components evoked by non-painful stimuli.

N140 and P300 components were clearly discernible in the traces. The amplitudes of the N140 and P300 components evoked by painful stimuli were higher than those evoked by non-painful stimuli. The latency of P300 was shorter in the painful electrode stimuli. The mean latencies and amplitudes of the two components in 17 subjects are summarized in Figures 4 and 5. The latencies and amplitudes of the N 140 components were 145±11 msec and 5.8±1.3 μV for the non-painful stimuli, and 139±12 msec and 11.2±2.0 μV for the painful stimuli, respectively (Figure 4). The latencies and amplitudes of the P300 components were 294±25 msec and 17.7± 5.3 μV for the non-painful stimuli, and 272±20 msec and 25.7±10.3 μV for the painful stimuli, respectively (Figure 5). Although no difference was observed between the painful and non-painful stimuli for the N140 latency (Figure 4), a statistically significant difference was observed for the P300 latency ($p<0.01$, Figure 5). The amplitudes of the N140 and P300 components evoked by the painful stimuli were statistically larger ($p<0.01$) than those of the N140 and P300 components evoked by the non-painful stimuli (Figuers 4 and 5).

Representative topographical maps of the ERPs for the painful and non-painful stimuli are shown in Figure 6. The N 140 component was distributed over the fronto-central scalp regions (Fz, Cz) and the P300 component was distributed over the centro-parietal scalp regions (Cz, Pz) without laterality. Visual inspection showed no significant difference in the distribution of the N140 and P300 components between the painful and non-painful stimuli.

Representative three-dimensional views of the equivalent current dipole are illustrated in Figure 7. At the peak of P300, a dipole was located in the deep midline area beneath the vertex, which was slightly contralateral to the stimulus site over 95% goodness-of-fit. The location of the dipole was similar in both the painful and non-painful stimuli.

4. Discussion

The present results revealed that the amplitudes of the N140 and P300 components were larger and the latency of the P300 component was shorter in the somatosensory ERP elicited by painful stimuli, but there was no significant difference in the distribution of the N140 and P300 com-

ponents between the painful and non-painful stimuli, and a dipole of the P300 component was located in the deep midline area beneath the vertex, which was slightly contralateral to the stimulus site.

It is critically important that painful stimuli might be clearly and definitely painful. Although several reports have described pain evoked potentials, their criteria for determining the pain threshold were obscure.[17,18] To ensure that the painful stimuli were well above the objective pain threshold, cutaneous silent periods (CSPs) were applied in this study, because it is agreed that afferent impulses producing CSP are mediated by pain related slow-conducting fibers, probably A δ fibers.[19,20] However, electrical stimulation on the skin may not elicit a pure sensation of pain, but may activate some nociceptive processes related to pain.[2,21]

The painful and non-painful effect of somatosensory ERPs, that is, the increase of amplitude, was noted on the N140 component in the present study. The amplitude increase of N140 may correspond to an attention for noxious stimuli, and may indicate strong activation of the cortical cognitive related regions. Tarkka et al. suggested that the N140 component might be generated by a bilateral activity in the secondary somatosensory cortices from dipole source analysis [11], which has been supported by several other studies.[22,23] Sev-

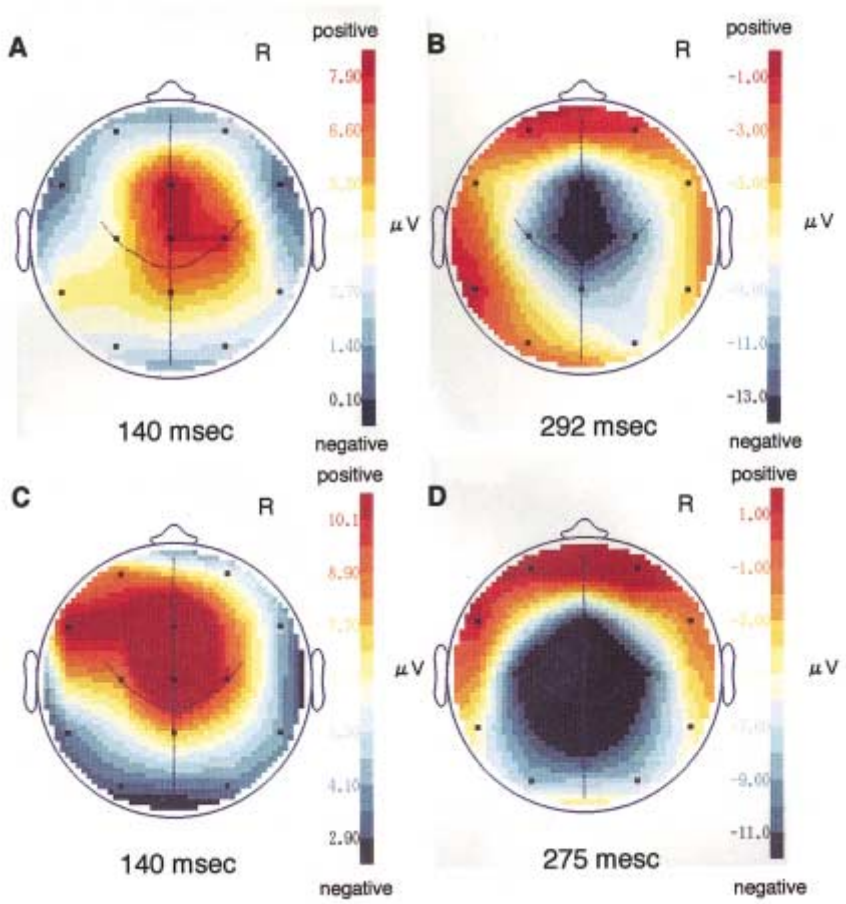

Fig. 6 Representative topographical maps of N140 and P300 components of somatosensory event-related potentials for non-painful (A,B) and painful stimuli (C, D). The N140 component is distributed over the fronto-central scalp regions (Fz and Cz) and the P300 component is distributed over the centro-parietal scalp regions (Cz and Pz) without laterality. Visual inspection shows no significant difference in the distribution of the N140 and P300 components between the painful and non-painful stimuli.

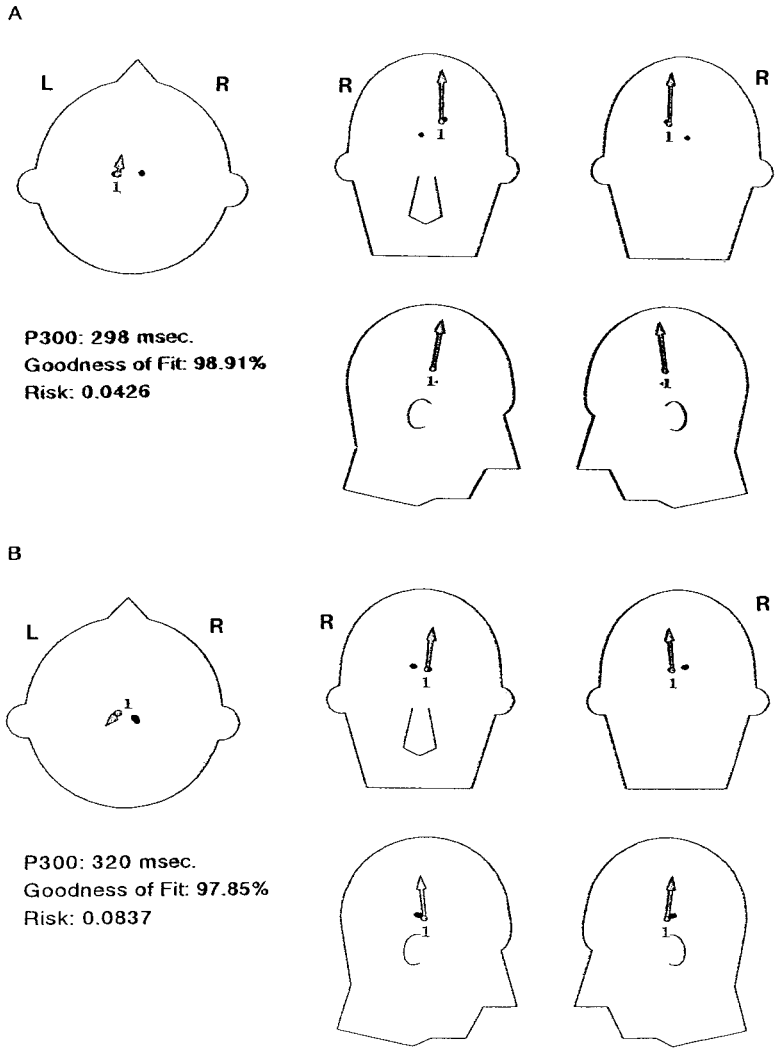

Fig. 7 Representative three-dimensional views of the equivalent current dipole of P-300 components with painful (A) and non-painful stimuli (B) are illustrated. At the peak of P300, a dipole is located in the deep midline area beneath the vertex that is slightly contralateral to the stimulus site with a 95% goodness-of-fit. The location of the dipole is similar in both the painful and non-painful stimuli.

eral positron-emission-tomography (PET) studies also showed that painful stimulation indicated more activation of the secondary somatosensory cortices.[24–26] Changes in the amplitude of the N140 component may be related to the activation of the secondary somatosensory cortex for processing of nociceptive information. However, Shimojo et al. reported that this component exhibited no significant correlation with painful stimuli .[27] This may be explained by the difference in sites studied and differences in the intensities of electrical stimulation used.

The present results revealed that the P-300 components elicited by painful stimuli had an earlier and larger positive peak than those elicited by non-painful stimuli, which was supported by Becker et al.[17] Miltner et al. pointed out that the pain SEPs from individual subjects often showed two late positive peaks (at means of 215 msec and 332 msec), and that, due to latency variability, the grand averages across subjects resulted in a single peak at about 260 msec .[28] I also found that SERPs from some subjects had two positive peaks in both stimulus conditions.

I speculate that earlier P300 components were emphasized in the SERP with painful stimuli (noxious conditions), and later P300 components was emphasized in the SERP with non-painful stimuli (cognitive conditions).

Several studies with PET have also shown that the contralateral somatosensory cortex, anterior insular cortex, anterior cingulate cortex, and thalamus participate in the processing of painful cutaneous stimuli .[24-26] The P300 components elicited by painful stimuli had been thought to be generated by the thalamus [29], but later studies suggested that they could be generated by the anterior cingulate gyrus and bilateral secondary somatosensory cortex .[22,30] The present result that the P300 components were distributed over the centro-parietal scalp regions (Cz, Pz) may indicate that the generators of P300 could be either thalamus, cingulate gyrus or bilateral secondary somatosensory cortex. The topographic distribution of the P300 components induced by painful stimuli were very similar to those induced by non-painful stimuli. However, there was a difference in the amplitudes and latencies in both stimuli. These findings may suggest that the painful sensation and non-painful sensation are generated through similar cortical pathways, and that the velocity and intensity of the cognitive cerebral processing of the sensations are faster and stronger in painful stimuli. The present results regarding the distributions and latencies of the N140 and P 300 components were consistent with a previous report by Shimojo et al. [27]

In the equivalent current dipole study, at the peak of P300, a dipole was located in the deep midline area beneath the vertex that was slightly contralateral to the stimulus site with 95% goodness-of-fit. The location of the dipole was similar in both the painful and non-painful stimuli. From these results, I speculate that the P300 component might be generated in the midline subcortical regions, such as the thalamus or cingulate cortex, or the bilateral secondary somatosensory corteces. Tarkka et al. reported that the P300 components of SERPs originated from the deep medial temporal lobes, including the hippocampus and parahippocampal cortex.[11] However, their conclusions were inconsistent with the Johnson's report that only minor changes in the morphology of the P 300 wave forms were found in patients with unilateral temporal lobe resections.[31] As the origin of the P300 component is in part still controversial, and the measurement of the P300 component on the scalp with the equivalent current dipole study has a limitation with regards to detecting the precise origin, further assessment with a new equipment or intracranial EEG recordings is needed.

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