The cerebral representation of pain perception in humans is poorly understood compared with other modalities of sensation such as touch or vibration. This is mainly because of a lack of the appropriate instrumentation for stimulation and recording. A low-power and long-wavelength CO₂ laser beam induces sensations of pain or heat when applied to the skin. From studies in normal subjects and in patients with various types of sensory impairment, it has been established that CO₂ laser stimuli cause the excitation of nociceptive receptors in the skin and that their signals ascend through small myelinated fibers (Aδ) of the peripheral nerves and are probably mediated through the spinothalamic tract. We have, therefore, studied electroencephalography (EEG) and magnetoencephalography (MEG) following painful CO₂ laser stimulation to elucidate the mechanisms of pain processing in the human brain. Since recording EEG is much easier than MEG, EEG is usually used for clinical application. In contrast, since the spatial resolution of MEG is higher than EEG, in order of mm, MEG is usually used for detecting cortical activities in pain perception. In addition to the conventional CO₂ laser stimulation stimulating Aδ fibers, we recently found various new methods and findings. In this review article, therefore, we introduce our recent studies on pain perception and review clinical application of these methods.

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EEG and MEG following painful laser beam stimulation

The ideal pain stimulation is pain-specific, controllable, safe and repeatable. Laser beam stimulation such as CO₂ and Tm:YAG to the skin satisfies all the above. Laser beam does not actually contact the skin, therefore, only nociceptive receptors of the skin are activated, not mechanoreceptors. The time difference between the stimulus period and the triggering period is very small, probably almost zero. This is the best characteristic for recording evoked potentials in the order of msec. The biggest disadvantage of laser stimulation is that it burns the superficial skin (erythema) with high intensity, though the burn heals completely.

Chen et al.²² proposed 1 standard for recording EEG using CO₂ laser stimulation, but it is still controversial. In our understanding, the following method is now probably a standard, based on comments by most researchers.

As for stimulus parameters, they are 2- to 10-mm beam diameter, 10- to 50-msec duration, 3- to 10-sec random interstimulus interval, and rotation of stimulation spot to avoid sensitization and burn. Stimulus strength must be changed depending on the above factors, but both slight pain to measure the pain threshold and moderate-strong pain for recording EEG are necessary. As for recording parameters, the bandpass filter is 0.1 to 30 or 50 Hz, and sampling rate is 512 Hz or 256 Hz. Non-cephalic reference (sternovertebral, chin or nose) is ideal, but linked earlobes or the cephalic electrode such as Fz are also available when the signal-to-noise ratio is small. 25-50 trials are averaged, but the number for averaging actually depends on the quality of the waveforms. Only 10-20 trials are enough in some recordings. At least Cz is necessary, since EEG is maximal there. T3 and T4 are appropriate for recording the early components, and Fz, Pz, C3 and C4 can be added to know the scalp topography. Electrode placement is based on the 10-20 International System. As for subjects’ state, it should be calm, vigilant, attentive, relaxed, and with eyes open to minimize boredom and drowsiness and to avoid an effect by large α wave of EEG. A subjective pain rating scale (0-10 scales) such as the visual analogue scale (VAS) is useful.

Consistent negative and positive potentials, termed N2 and P2, were identified at Cz in all subjects.⁵ The mean peak latencies of N2 and P2 following stimulation of the hand were about 200-240 and 300-360 msec, respectively, and 250-300 and 350-420 msec following the foot stimulation, respectively (Fig. 1). By calculating the difference of latency and the distance between 2 separate stimulus sites, for example hand and elbow, the conduction velocity (CV) of Aδ fibers of the upper and lower limb of this subject were 7.1 and 7.3 m/sec, respectively, slightly slower than the mean value of normal subjects, approximately 9-10 m/sec. Adopted from Kakigi et al.³

There were several MEG reports using painful laser stimulation ascending through Aδ fibers,¹⁵,¹⁷,¹⁸,²¹,²⁴,²⁵ but the detailed findings will be shown in the next section.

preferential stimulation of Aδ fibers by intra-epidermal needle electrode in humans

We recently recorded EEG and MEG induced by
epidermal electrical stimulation (ES) using a specially-made needle electrode (Fig. 2). For the ES, the tip of a very short stainless steel needle electrode was inserted in the epidermis of the skin (0.2 mm in depth). Since only free nerve endings, which receive pain stimuli, are present in epidermis, the ES method is considered to selectively activate Aδ fibers. Recording methods except those for stimuli were almost the same as those using laser stimulation.

At first, we evaluated the activated fibers by epidermal stimulation by assessing the CV of the peripheral nerves using EEG. Distal and proximal sites of the upper limb were stimulated by ES with an intensity which induced a definite pain sensation. A major positive response (P1) was obtained by stimulation. The P1 latency for the ES was 302 +/- 17 ms and the CV of the peripheral nerve was 15.1 m/s. The CV indicated that the fibers activated by ES were mainly Aδ fibers. We considered that the ES with our newly developed needle electrode was a very convenient method for the selective stimulation of the Aδ fibers, since it was very simple, not requiring any special apparatus, did not cause bleeding or burns, and caused minimal uncomfortable feeling.

We recorded MEG using dual sets of 37-channel devices (Magnes, BTi, CA, USA) and EEG simultaneously produced by ES method and conventional transcutaneous electrical stimulation (TS) applied to the left hand in healthy volunteers to compare cortical responses to noxious and innocuous somatosensory stimulations. Our MEG results revealed that cortical processing following noxious and innocuous stimulations was strikingly similar except that the former was delayed approximately 60 ms relative to the latter, which was well explained by a difference in peripheral CV mediating noxious (Aδ fiber) and innocuous (Aβ fiber) inputs. The first cortical activity evoked by both ES and TS was in the SI in the hemisphere contralateral to the stimulated side. The following activities were in the bilateral SII, insular cortex, cingulate cortex, and anterior medial temporal (MT) area around the amygdala and hippocampus (Fig. 3). The source locations did not differ between the 2 stimulus modalities except that the dipole for insular activity following ES was located anterior to that following TS.

As for EEG recording, both ES and TS evoked vertex potentials consisting of a negativity followed by a positivity at a latency of 202 and 304 ms, and 134 and 243 ms, respectively. The time course of the vertex potential corresponded to that of the activity of the MT area. Our results suggested that cortical processing was similar between noxious and innocuous stimulation in SI and SII, but different in insular cortex. Our data also implied that activities in the amygdala/hippocampal formation represented common effects of noxious and tactile stimulations.

**Effects of various factors on pain-related EEG and MEG**

We previously investigated various factors affecting subjective pain perception (VAS) and EEG/MEG. By applying continuous tactile and vibratory stimulation to the
site where the CO₂ laser beam was applied, EEG was significantly decreased in amplitude. This finding was consistent with the gate control theory proposed by Melzack and Wall. We also analyzed the effects of noxious heat and cold stimulation on pain perception. When a limb was placed in hot water at 46 °C or cold water with ice at 0 °C which caused a noxious feeling in all subjects, VAS was markedly decreased and EEG was significantly decreased in amplitude. This finding was consistent with the gate control theory proposed by Melzack and Wall.

Fig. 3. Temporal profile of cortical activities following painful ES. Cortical responses to ES in Subject 3. The upper 3 traces are superimposed waveforms recorded from 37 channels in both hemispheres and evoked potentials recorded in Cz. The lower 7 traces are temporal profiles of each source strength. Filled circles indicate a group of early SI activities. Arrowheads indicate the peak latency of early and late SI activity. (Right) Locations of source generators overlaid on MRI scans. Magnetic fields were recorded from 2 probes that were centered on the C4 (hemisphere contralateral to the stimulation) and C3 (hemisphere ipsilateral to the stimulation) positions as based on the International 10-20 System. Adopted from Inui et al. 27
decreased in amplitude. This finding was clearly observed even when a limb other than the laser-stimulated hand was placed in hot or cold water. We considered that this finding was due to the theory of diffuse noxious inhibitory control (DNIC).31

We often move our limbs when they receive a painful stimulation. To evaluate the effects of movement on cortical activities evoked by noxious stimulation, we recorded EEG13 and MEG21 following laser stimulation.

Results of MEG (VectorView, Elekta Neuromag Yo, Helsinki, Finland) can be summarized as follows (Fig. 4):

1. Active movement of the hand ipsilateral to the side of noxious stimulation resulted in significant attenuation of both SI and SII in the hemisphere contralateral to the stimulated hand (cSI and cSII). Activity in the hemisphere ipsilateral to the side of stimulation (iSII) was not affected.
2. Active movement of the hand contralateral to the side of noxious stimulation resulted in significant attenuation of cSII. Activity in cSI and iSII was not affected.
3. Passive movement of the hand ipsilateral to the side of noxious stimulation resulted in significant attenuation of cSI. Activity in cSII and iSII was not affected.
4. Visual analogue scale (VAS) changes showed a similar pattern to the amplitude changes of cSII.

These results suggest that activities in the 3 regions are modulated by movements differently. Inhibition in cSI was considered to be mainly due to an interaction in SI by the signals ascending from the stimulated and movement hand. Inhibition in cSII was considered to be mainly due to particular brain activities relating to motor execution and/or movement execution associated with a specific attention effect. In addition, since VAS showed a similar relationship with the amplitude changes of cSII, cSII may play a role in pain perception.

Other important factors causing a change of EEG and MEG waveforms are attention or distraction effects.18,32 The amplitude of both EEG and MEG components were significantly reduced during sleep32,33 and during distraction.18 This change positively correlated with a decrease of subjective pain feeling (VAS). In contrast, both EEG and MEG amplitudes were significantly increased during attention to the stimulated site.33 These results indicated that vigilance and attentiveness to the painful stimuli should be monitored during the recording.

Cerebral responses following stimulation of unmyelinated C-fibers in humans

There are 2 kinds of pain, a sharp pain ascending through Aδ fibers (first pain) and a second burning pain ascending through C fibers (second pain). By using a novel method, the application of a low intensity CO₂ laser beam to a tiny area of skin using a very thin aluminum plate with numerous tiny holes as a spatial filter, we succeeded in selectively stimulating unmyelinated C fi-
bers of the skin in humans, and could record consistent and clear brain responses using EEG and MEG (Fig. 5).\textsuperscript{34-41} The CV of the C fibers of the peripheral nerve\textsuperscript{34,39} and spinal cord,\textsuperscript{35,37} probably via the spinothalamic tract, is approximately 1-4 m/sec, which is significantly slower than that of A\textdelta fibers, approximately 10-20 m/sec, and A\textbeta fibers, approximately 50-70 m/sec (Fig. 6). This method should be very useful for clinical applications. Following C fiber stimulation, SI and SII are activated in the cerebral hemisphere contralateral to the stimulation, and then SII in the hemisphere ipsilateral to the stimulation is activated.\textsuperscript{36} Then, limbic systems such as the insula, cingulate cortex and medial temporal (MT) region are activated, and those activities are reflected in EEG components.\textsuperscript{40} Investigations of the cortical processing in pain perception including both first and second pains should provide a better understanding of pain perception and therefore contribute to pain relief in clini-

![Fig. 5.](image1)

![Fig. 6.](image2)
EEG and MEG components were also remarkably reduced in amplitude or disappeared during distraction task and sleep\(^{38,40}\) like those following A\(\delta\) fiber stimulation\(^{18,32,33}\). However, their degree of reduction were much larger than that of A\(\delta\) fibers. We confirmed that SI in the contralateral hemisphere and SII-insula, cingulate cortex and MT in bilateral hemispheres play a main role for second pain perception, and all sites were much affected by a change of attention, indicating that these regions are related to cognitive aspect for second pain perception. This finding also suggested us the usefulness of psychotherapy for patients suffering from cancer pain or chronic pain relating to second pain.

**Clinical application**

EEG is usually used for clinical application, since it is much easier to record than MEG. We use the term laser-evoked potential (LEP) for EEG following laser stimulation in this section.

**Peripheral nerve and muscle**

Patients showing various types of sensory disturbance caused by lesions in the peripheral nerves are good subjects for clinical application. Recording conventional somatosensory evoked potential (SEP) following non-painful electrical stimulation simultaneously was also useful. We examined 30 patients with peripheral neuropathies, and the results were compared with clinical sensory findings\(^7,10\). The LEP findings showed a significant correlation with the clinical impairment of pain sensation, but not with the impairment of deep sensation (Fig. 7). In contrast, SEP showed a significant correlation with deep sensation, but not with the impairment of pain sensation. A histological examination of the sural nerve was done in 10 out of 30 patients. The LEP and SEP findings showed a positive relationship with densities of small myelinated fibers and large myelinated fibers, respectively. Examinations of both LEP and SEP, therefore, are considered to be very useful to evaluate physiological functions of sensory nerves in patients with peripheral neuropathies. Wu et al.\(^{42}\) reported LEP findings in 2 patients with neuropathic pain in whom increased pain sensation (hyperalgesia) to laser stimulation was, on the contrary, associated with a delayed, dyssynchronized and attenuated LEP. They considered that LEP reflects the activity of a “lateral” pain system of spinothalamic tracts and thalamocortical projections, but may not index adequately the affective-emotional aspects of pain sensation conveyed by the “medial” pain system, which subserves the affective-motivational aspects of pain.

The fibromyalgia syndrome is a disease of unknown etiology defined by chronic diffuse musculoskeletal pain and a low mechanical pain threshold\(^{43,44}\). Lorenz et al.\(^{43}\) found a significantly enhanced LEP and decreased pain threshold in 10 female patients with FS. They speculated that the results in FS patients were due to greater attention and cognitive processing of nociceptive stimuli and/or reduced cortical or subcortical inhibition of nociception.

**Spinal cord and brainstem**

Signals following non-painful electrical stimulation applied to the peripheral nerve or skin ascend mainly through the dorsal column of the spinal cord, but signals following painful CO\(_2\) laser stimulation applied to the peripheral skin ascend mainly through the spinothalamic
tract. Therefore, some patients show so-called “dissociated sensory disturbance,” that means, tactile or deep sensation are preserved but the pain-temperature sensation is disturbed, and vice versa. Combining studies of LEP and SEP are useful to know the pathophysiology of such diseases.

We reported the findings of LEP and SEP in patients with 3 diseases affecting the spinal cord, syringomyelia, multiple sclerosis and HTLV-I (human T-lymphotropic virus type-1) associated myelopathy (HAM). In 8 patients with syringomyelia who showed various forms of dissociated sensory loss, LEP findings showed a positive correlation with the clinical disturbance of pain-temperature sensation in all patients. By applying CO2 laser stimulation to the dermatomes where clinical impairment of pain sensation was not identified, some abnormal results (subclinical abnormality) were found in 3 patients. In contrast, the SEP was normal in 7 of 8 patients. In patients on whom a syringosubarachnoid shunt operation was done, LEP findings were improved, showing a positive correlation with clinical improvement. These results suggested that the impairment of both clinical and neurophysiological findings before the operation were mainly caused by compression rather than direct invasion by the syrinx.

Hansen et al. reported LEP and SEP in 4 patients with Wallenberg’s syndrome, which shows specific clinical symptoms caused by lateral brainstem (medulla oblongata) infarction. In the acute stage of the disease, their SEP was normal but the LEP following stimulation of the affected site was absent or markedly reduced and/or delayed. However, in the second study recorded at 7 months to 4 years after the first, LEP findings were much improved along with the clinical symptoms.

**Cerebral hemisphere**

Yamamoto et al. reported both LEP and SEP in 12 patients with stroke in the putamen, the thalamus and corona radiata. In 5 patients with a putaminal lesion, LEP was absent or its latency was delayed, and SEP was absent or reduced in amplitude. In 3 patients with a thalamic lesion, LEP and SEP showed various patterns according to the involved sites. In 4 patients with a lesion in the corona radiata, both LEP and SEP were normal. Abnormalities of LEP and SEP in the stroke location were related to impairment of the pain and vibration senses, respectively.

LEP were recorded in 11 patients with central pain. Five of 11 patients showed normal LEP, and the other 6 patients showed no consistent LEP and had lateralized increased thresholds for warmth, heat pain, or deep pain, or reduced ratings of laser pulse sensation. These results reflect primarily a deficit in spinothalamic tract function and do not suggest excessive responses to synchronous activation of cutaneous heat nociceptors in patients with central pain.

There is a general consensus that cortical reflex myoclonus is induced mainly by muscle stretch, touch or pressure. This is compatible with the fact that cortical components of SEP are considerably enhanced (giant SEP) in most patients with cortical reflex myoclonus. We recorded LEP and SEP in 4 patients with cortical reflex myoclonus to elucidate the sensitivity to pain stimuli. The P25 component of SEP was markedly enhanced in all 4 patients, but LEP was normal in amplitude. In addition, myoclonus was not induced by CO2 laser stimulation. Therefore, patients with cortical reflex myoclonus are not sensitive to pain stimuli.

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