or had been made by the authors (only for images showing painful events). Examples of images showing painful events made by authors are shown in Figure 1. Images showing painful events in Figure 1 depict arms and hands punctured by needles and syringes, using the author's arm and hand and red ink for simulating blood; a needle appears to have punctured the hand or arm in the images presented but actually it has not. The subjects were not informed of this setup. Other images showing painful events extracted from the IAPS included a man's face with a dental needle inserted into his tooth pulp, an arm wherein the cubital vein is punctured for taking blood samples, and a woman's face in agony caused by a severe headache. Images evoking fear from the IAPS included a hand holding a knife in a stabbing position, a gun pointed at the viewer, a giant shark attacking the viewer at any moment, and a man covered with a mask. Images evoking rest from the IAPS included beautiful landscapes. During the pain condition, the subjects were instructed specifically to feel their own pain as if they were in the same painful situation similar to the images presented showing painful events. That is, the subjects were instructed to imagine their own sharp acute pain as if it were their own arm while viewing images showing an arm punctured by needles, for example. Likewise, they were instructed to feel fear as if they were in the same fearful situation during the fear condition and to relax and feel free during the rest condition.

Following the scanning session, we ascertained verbally whether the subjects were able to imagine their own pain as they viewed the images showing painful events. The subjects provided ratings of their arousal level and the valence of each of the images showing painful events, images evoking fear, and images evoking rest presented during the experiment, using the self-assessment manikin (SAM), a 9-point visual analog scale (Bradley and Lang, 1994). The scale ranged from 1 (calm) to 9 (very excited) for the rating of emotional arousal and 1 (very negative/unpleasant) to 9 (very positive or pleasant) for the rating of emotional valence. One-way ANOVA was used to compare valence and arousal ratings between the images used in the pain, fear, and rest conditions.

Magnetic Resonance Imaging Acquisition

Magnetic resonance imaging (MRI) was performed using a Shimadzu-Marconi's Magnex Eclipse 1.5-T PD250 (Kyoto, Japan) at the Advanced Telecommunications Research Institute International, Brain Activity Imaging Center (Kyoto, Japan). Functional T_2-weighted images were acquired using a gradient echo-planar imaging (EPI) sequence (repetition time = 3000 ms, echo time = 49 ms, flip angle = 90°, field of view = 192 × 192 mm, and matrix size = 64 × 64 pixels). Thirty consecutive axial slices (thickness 5 mm) covering the entire cortex and cerebellum were acquired. T_2-weighted anatomical images (voxel size = 0.75 × 0.75 × 5 mm) were acquired in the same plane. T_1-weighted anatomical images (voxel size = 1 × 1 × 1 mm) were also acquired. Before the acquisition of functional images (voxel size = 3 × 3 × 5 mm), these 2 sets of anatomical images were used to improve spatial normalization (Seki and others 2004). First, T_2-weighted image was coregistered to the mean EPI (functional) image. Second, T_1-weighted image was coregistered to the T_2-weighted image. Then, coregistered T_1-weighted image was used to calculate parameters for spatial normalization, and the parameters were used to normalize EPI (functional) images (voxel size = 3 × 3 × 5 mm).

Image and Statistical Analyses

Image analysis was performed using SPM2 (Wellcome Institute of Cognitive Neurology, London, UK). Slice time was corrected, and reconstructed data were realigned, spatially normalized, high-pass filtered, and smoothed with a Gaussian filter (6 × 6 × 10 mm full width at half maximum) to minimize noise and residual differences in gyral anatomy (Friston and others 1995; Worsley and Friston 1995). Preprocessed MRI data were analyzed statistically on a voxel-by-voxel basis using SPM2. Serial correlations were corrected using an autoregressive model, and global signal changes were removed by scaling. Task-related neural activities were modeled using a boxcar function convolved with a hemodynamic response function.

To identify which cerebral networks were activated under the pain condition and fear condition, we analyzed the blood oxygenation level-dependent (BOLD) response under the different emotional conditions by calculating 3 contrasts: For each subject, a boxcar model convolved with the hemodynamic response function was applied to the fMRI time series at each voxel, and t-maps for the contrasts pain minus rest (contrast name: pain - rest contrast), fear minus rest (contrast name: fear - rest contrast), and pain minus fear (contrast name: pain - fear contrast) were computed. Then, the subject-specific contrast images of parameter estimates were used as inputs for the second (random effect) level analysis. At the second level, the 1-sample t-test was conducted and a threshold of $P < 0.001$ (uncorrected) was employed. To minimize false-positive activations, we only used activations exceeding 5 contiguous voxels as described by Phan and others (2003). The sites of activation for each contrast are listed in Table 2 with their number of voxels, corrected P at the cluster level, coordinates, and t-value at the voxel level. The coordinates and labels of anatomical localizations were defined in accordance with the macroscopic anatomical parcellation of the Montreal Neurological Institute MRI single-subject brain as described by Tzourio and others (2002).

Table 1
Emotional ratings for image categories: images showing painful events (pain condition), images evoking fear (fear condition), and images evoking rest (rest condition)

	Pain (Mean ± SD)	Fear (Mean ± SD)	Rest (Mean ± SD)
Postscan SAM valence (1-9)	2.25 ± 1.02*	2.33 ± 1.15*	7.52 ± 1.36
Postscan SAM arousal (1-9)	7.21 ± 1.46*	7.48 ± 1.45*	2.10 ± 1.20

Note: SD, standard deviation.
*$P < 0.01$ versus rest using 1-way analysis of variance.

Table 2
Local statistical maxima in activated brain regions in each contrast

Number of voxels	Cluster level corrected P	Brain region	MNI coordinates (mm) x	y	z	t-Value
Pain − rest						
57	0.001	(R) Anterior insula	40	8	−8	8.23
18	0.309		36	−4	12	7.61
117	0.000	(R) SII	64	−32	36	8.12
27	0.081		52	6	8	7.02
54	0.002	ACC (BA 24)	8	10	52	7.53
26	0.093		4	14	32	9.06
9	0.885		8	−6	48	6.19
67	0.000	(R) PPC	34	−52	60	9.67
26	0.093	(L) PPC	−34	−50	52	7.44
35	0.025	Cerebellum	−24	−62	−56	7.23
32	0.039		−12	−74	−48	5.62
7	0.968		4	−64	−48	5.11
193	0.000	(R) LOC	48	−70	−4	8.22
91	0.000	(L) LOC	−54	−66	−16	7.18
Fear − rest						
30	0.129	(L) Amygdala	−20	4	−16	6.98
18	0.487	ACC (BA 24)	−4	8	40	7.01
9	0.940	Brain stem	2	−32	−4	6.03
24	0.254	Cerebellum	−10	−74	−40	6.35
443	0.000	(R) LOC	44	−80	−12	13.45
61	0.005		42	−60	−24	7.69
317	0.000	(L) LOC	52	−78	0	8.43
Pain − fear						
283	0.000	(R) SII	58	−32	16	9.07
13	0.657	(R) PPC	18	−48	72	6.68
24	0.157	(L) SII	−62	−26	20	7.59
32	0.053	(L) PPC	−58	−48	48	11.61
5	0.997		−54	−34	52	8.27
19	0.314	(R) Insula	42	−6	−12	8.90
186	0.000		8	−54	−56	7.72
24	0.157	Cerebellum	−26	−50	−48	7.78
17	0.409		−14	−56	−48	7.21

Note: Results are superimposed on MNI coordinates. Coordinates refer to local cluster maxima. The voxel size is 3 × 3 × 5 mm. MNI, Montreal Neurological Institute; (R), right; (L), left; LOC, lateral occipital cortex. Uncorrected $P < 0.001$ was adopted as the height threshold, and the extent threshold of 5 voxels was adopted.

Result

Subjective Self-Reports

All the subjects reported that they could imagine their own pain on their body as they viewed the images showing painful events in the MRI scanning set. Postscanning emotional ratings by the SAM method revealed that all the subjects reported comparable valence and arousal estimates among images showing painful events, evoking fear and rest (Table 1). *ANOVA* showed significant differences in both the valence and arousal ratings in rest versus pain, and rest versus fear conditions. On the other hand, for pain and fear conditions, no differences were found between valence and arousal ratings. Arousal and valence ratings were highly correlated (Pearson's correlation coefficient, $r = 0.93$, $P < 0.001$).

Representation of Imagination of Pain While Viewing Images Showing Painful Events

The pain - rest contrast revealed several increased activations in pain-related regions that are known to be activated during the perception of nociceptive stimulation (shown in the pain - rest contrast in Fig. 2 and Table 2), namely, the right upper bank of the Sylvian fissure, corresponding to the SII, right anterior insula, caudal portions of the bilateral ACC (BA 24), and the cerebellum. Additionally, an increased activation was located in the rostral part of the posterior parietal cortex (PPC) (right > left) in both hemispheres (BAs 5 and 7). The other peaks of increased changes in activity were found in the bilateral lateral occipitotemporal cortices around the fusiform gyrus corresponding to an extrastriate region, which is involved in the recognition of visual objects. At the subcortical level, in the thalamus as such, no activation was found in the pain - rest contrast.

To determine cerebral activations specific to the pain condition, we compared cerebral activations during the viewing of images showing painful events with those during the viewing of images evoking fear (i.e., pain - fear contrast). This contrast revealed clear activations in the bilateral SII regions and posterior parietal cortices (PPCs), with stronger activations on the right side than on the left side (shown in the pain - fear contrast in Fig. 2 and Table 2). The other activations observed in this contrast were in the right insula and cerebellum. Activations in the bilateral lateral occipitotemporal cortices were not observed in the pain - fear contrast.

Representation of Viewing Images Evoking Fear

Different patterns of brain activation were found during the viewing of fearful images (fear - rest contrast) as compared with the viewing of painful images (pain - rest contrast) (shown in the fear - rest contrast in Fig. 2 and Table 2). There were activations in the left amygdala and the caudal portions of the ACC (BA 24), cerebellum, and bilateral lateral occipitotemporal cortices. The locations of the activation in ACC and lateral occipital cortices mostly overlapped with those of ACC and lateral occipital cortices activations noted in the pain - rest contrast.

Discussion

In this study, we investigated the cerebral hemodynamic response of the imagination of pain while viewing images showing painful events in comparison with those while viewing images evoking fear and rest. Our results show that the imagination of pain induced a different cortical representation and engage the brain region associated with pain-related neural network more extensively in comparison with the emotions of fear and rest, notably the ACC (BA 24), anterior insula, cerebellum, PPC, and the SII region.

Brain Regions Related to Subject Experience of Pain

Our general findings in imagination of pain are in agreement with the recent findings that Jackson and others (2006) have reported, in which they differentiated empathic responses to witnessed pain between imagining others versus imagining our own personal distress in similar painful situation. Recent functional imaging studies in humans have provided evidence that multiple regions of the brain are involved in pain perception (Treede and others 1999; Kakigi, Inui, and Tamura 2005; Qiu and others 2005). Despite their diversity, recent many studies have shown that the pain-related neural brain regions and network exhibit activation related to the subjective experience of pain. For example, we have shown, in a yoga master who claims not to feel pain during meditation, that BOLD signals of fMRI in these pain-related regions including the primary somatosensory cortex (SI) and SII were not increased while he received pain by applying a laser pulse (Kakigi, Nakata, and others 2005). Koyama and others (2005) showed that expectations of decreased pain strongly reduced both the subjective experience of pain and the activation of pain-related brain regions including the SI, SII, insula, prefrontal cortex, and ACC. In suggestion-prone subjects, Raij and others (2005) showed that the dorsal ACC and insula were activated during both physical and psychological induced pain, although the SII region and posterior insula were activated more strongly during physical than psychological induced pain. Seymour and others (2005) showed that prediction and expectation of pain relief is reflected by neural activities in the amygdala and midbrain and mirrored by activities in the lateral orbitofrontal cortex (OFC) and ACC. These findings, taken together with our results, suggest that the subjectivity of pain encompasses a widespread and functionally diverse set of brain regions.

Parasylvian Cortex and PPC Activations during Imagination of Pain While Viewing Images Showing Painful Events

The main findings of this study are activations in the SII region in the parasylvian cortex and PPC during the imagination of pain while viewing images showing painful events, in which activations in the SII region and PPC were considered to be relatively specific to the pain condition compared with fear and rest conditions. The SII region has been consistently shown as the main activity area in many pain imaging studies, suggesting that the SII region plays a major role in pain perception in humans (Treede and others 1999; Schnitzler and Ploner 2000; Kakigi, Inui, and Tamura 2005; Qiu and others 2005). However, the location of nociceptive cortical areas around the sylvian fissure is still a matter of controversy. It has been difficult to determine whether the nociceptive area is situated within the classic SII (parietal operculum) or within adjacent somatosensory areas such as the frontoparietal operculum or insula. Many previous studies have shown that noxious stimuli activate at least one cortical area around the sylvian region other than the SII. For example, fMRI (Brooks and others 2002, 2005; Bingel and others 2003; Iannetti and others 2005) and electroencephalographic (Lenz and others 2000; Frot and Mauguiere 2003) studies have

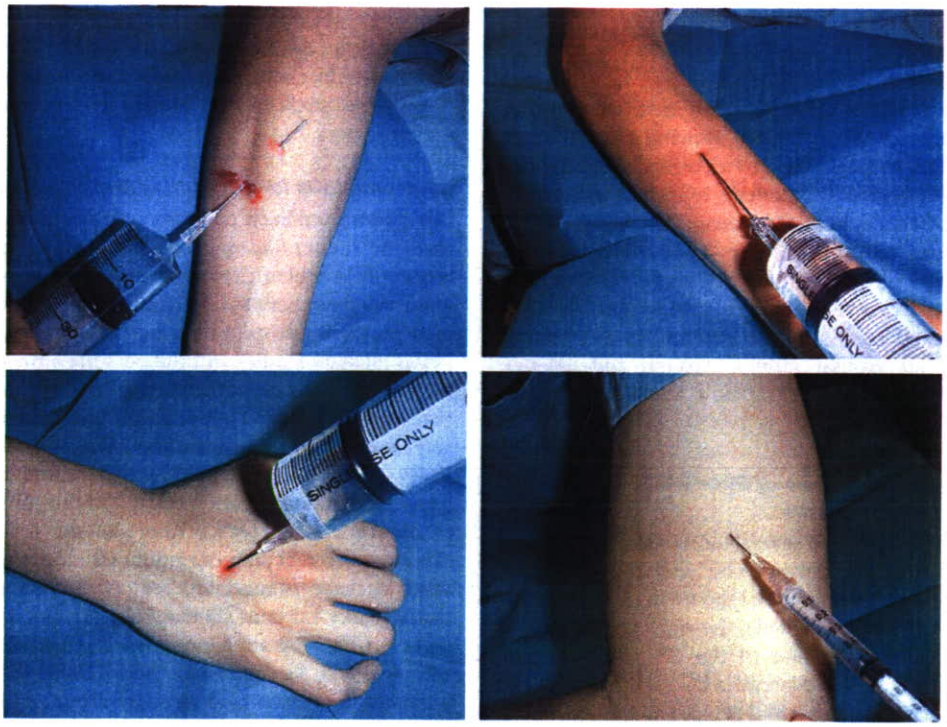

Figure 1. Sample painful images. We used 15 images for each condition (pain, fear, and rest conditions). In addition to the "images showing painful events" taken from IAPS (Lang and others 2005), we used 8 pictures made by the authors in the pain condition to fill up the deficit of images showing painful events taken from IAPS. Images shown in Figure 1 are the examples of images showing painful events, which were made using the author's arm and hand punctured by needles and syringes and red ink for simulating blood; a needle appears to have punctured the hand or arm in the images presented, but actually it has not. The subjects were not informed of this setup.

shown activation in the posterior insula following noxious stimulation. Our previous studies also showed that activity from the insula may contribute to major magnetoencephalographic signals evoked by noxious stimuli (Inui and others 2003; Kakigi, Inui, and Tamura 2005). In this study, the pain – rest contrast showed activations in the right upper bank of the Sylvian fissure, and the pain – fear contrast showed activations in the same area bilaterally. Therefore, we consider that activations in the sylvian region in this study may be a summation of activities from the SII region and other adjacent areas, although the former appears to be the major contributor.

In spite of the constant finding of activation in the SII region following noxious stimuli among the fMRI, electroencephalographic, and magnetoencephalographic studies, the functional role of the SII region remains largely unknown. Using a nociceptive stimulus, some studies suggested that the SII region is associated more with the cognitive evaluative aspects of the painful nature of a stimulus than with the sensory discriminative aspects of pain (Treede and others 1999; Schnitzler and Ploner 2000; Timmermann and others 2001). Otherwise, attention to images showing painful events may also influence SII region activity; it is known that attention enhances SII region and PPC responses (Mauguiere and others 1997). Task-related responses to visual inputs suggest the role of the SII region in directing attention toward noxious stimuli (Dong and others 1994). Downar and others (2002) reported an interesting finding that activation in the temporoparietal junction, which is generally consistent with our observed activation in the SII region, showed sensitivity to stimulus salience across multiple sensory modalities, suggesting this region may play a general role in identifying salient stimuli. Therefore, activations in the SII region observed in this study may likewise functionally reflect attention capture or awareness entry in identifying salient features to the self, although they are situated within adjacent areas consistently showing activation following noxious stimuli.

Another main finding in this study is PPC activations during the imagination of pain. It is suggested that the role of the PPC is to integrate afferent information from multimodalities, such as vision, touch, and proprioception, and to convert it into common spatial representations (Andersen and others 1997). In this study, all the images showing painful events presented to the subjects (the examples are shown in Fig. 1) contain human body parts, and the bodies in the images are those of other individuals not those of the subjects themselves. The subjects were instructed to imagine pain on their own body as if they were the subjects in the images showing painful events, and we consider that such a task necessarily requires self-body image within the subjects. To project the pain imagined onto the self-body image, the transformation of spatial coordinates from the images of body parts of other individuals into the corresponding self-body coordinates is required. Therefore, PPC activation during the imagination of pain may reflect a transformation processing of the pain imagined to the self-body–centered coordinates. The role of the PPC in such a transformation is well established (Anderson 1995; Andersen and others 1997).

ACC and Right Anterior Insula Activation during imagination of Pain While Viewing Images Showing Painful Events

First, the activations in the ACC (BA 24) during imagination of pain are similar to those in previous imaging studies of pain perception, whether pain is actually experienced (Rainville and

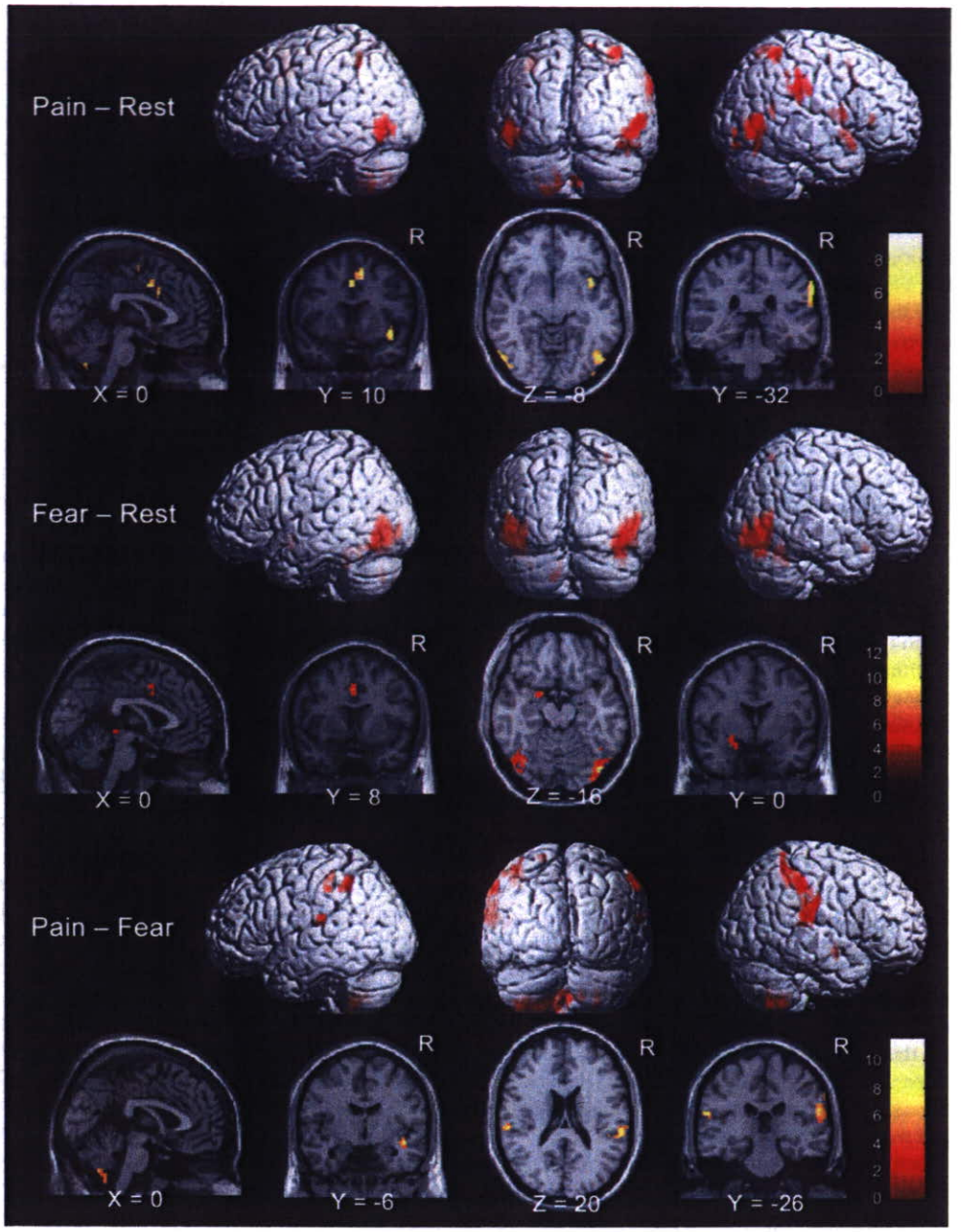

Figure 2. Brain activations in each contrast. Activated brain areas in each contrast: pain – rest, fear – rest, and pain – fear conditions. Pain – rest and pain – fear contrasts revealed activations in the SII region and PPC areas and in the affective components of the pain matrix such as the ACC, anterior insula, and cerebellum while viewing images showing painful events. The fear – rest contrast revealed activations in the left amygdala and ACC. The brain region is superimposed with orthogonal sections (sagittal, coronal, and axial) of a structural scan rendered in standard space, and the corresponding *t*-value is also shown in the color scale on the lower right side for each contrast. Uncorrected $P < 0.001$ was adopted as the height threshold, and the extent threshold of 5 voxels was adopted.

others 1997; Singer and others 2004), visually perceived from other's pain (Jackson and others 2005), hypnotically induced (Derbyshire and others 2004), imagined by self's perspective (Jackson and others 2006), or even induced by listening to pain-evoking words, compared with listening to nonsense syllables (Osaka and others 2004). This region is considered as a key cortical area involved in the regulation of subjective feelings of pain-related unpleasantness in humans and is particularly associated with the cognitive values of pain (Bush and others 2000; Rainville 2002). Also, note that neurons that respond specifically to painful stimulation have been identified using intracortical electrode recordings in a very similar region as the dorsal ACC (Hutchison and others 1999).

Second, we discuss whether anticipatory mechanisms were involved in our findings because viewing images showing painful events or evoking fear may prompt the anticipation of pain or fear in oneself. Our results showed that dorsal ACC activations during the fear condition mostly overlapped with ACC activations observed during the pain condition. It is well known that the prefrontal cortex, anterior insula, and rostral ACC are activated during the anticipation of pain (Ploghaus and others 1999; Petrovic and others 2002; Porro and others 2002).

Furthermore, the anticipation of emotionally aversive visual stimuli activates the rostral ACC, anterior insula, dorsolateral prefrontal cortex, and medial OFC (Simmons and others 2004; Nitschke and others 2006); in particular, the medial OFC is uniquely associated with the anticipation of aversive pictures, on the other hand, the main areas activated both in anticipation and in response to aversive pictures were amygdala, anterior insula, and dorsal ACC (Nitschke and others 2006). In our results, we failed to observe activations in the dorsolateral prefrontal cortex and medial OFC in every contrast. Neither the subjects were actually inflicted with a pain stimulus nor were they led to believe that they will receive a pain stimulus during the course of our experiment. Therefore, we consider that activations in the dorsal ACC were positively associated with responses to aversive stimuli rather than an anticipatory mechanism.

Third, the pain – rest and pain – fear contrasts revealed right insula activation, particularly the anterior part, whereas the fear – rest contrast did not show any increased insula activation. Functional imaging studies consistently demonstrated pain-related activations in the insula, and most studies are in agreement that pain-related activations are located in the anterior parts of the insula, whereas tactile activations are distinctly located more posteriorly (Coghill and others 1994; Davis and others 1998; Inui and others 2003). The anterior insula activity was dependent on the attention of painful stimulation and was significantly attenuated when subjects were distracted from pain (Brooks and others 2002). The activation in the right anterior insula correlates with the subjective intensity rating of painful thermal stimulation, whereas posterior insula activation correlates with stimulus temperature (Craig and others 2000). The anticipation of pain activates more the anterior insular regions, whereas the actual experience of pain activates more the posterior insula, which suggests that the former is associated with affective dimensions, such as the anticipatory arousal and anxiety of pain, and the latter is associated with the actual sensory experience of pain (Ploghaus and others 1999). Anders and others (2004) reported that negative emotional valence varied with insular activity. Our psychological ratings (SAM method) showed that the imagination of pain induces a complete contrastive valence and arousal scores in comparison with rest emotion, suggesting that the imagination of pain places subjects in a significantly negative affective state.

Thus, our results support the model proposed by Craig (2000, 2003) that suggests the insula as an "interoceptive" cortex that reflects the internal condition of pain, similar to temperature, sensual touch, itch, hunger, or thirst. The activation in the right anterior insula during imagination of pain is in agreement with the finding that only the right insula would serve to compute a higher order "metarepresentation of the primary interoceptive activity," which is related to the feeling of pain and its emotional awareness (Craig 2003). The activation in the right anterior insula is assumed to subserve subjective feelings of pain imagined while viewing images showing painful events. The activations of both the insula and ACC in this study may correspond to the simultaneous generation of a feeling and an emotional motivation because afferents also project to the ACC via the medial dorsal thalamic nucleus to produce behavioral drive (Craig 2000, 2003).

The insula as well as the PPC and SII activations in the pain condition tended to be stronger on the right side than on the left. Canli and others (1998) using IAPS showed that negative emotions are mostly represented in the right hemisphere, whereas positive emotions are lateralized to the left hemisphere. Brooks and others (2002) observed a right hemispheric lateralization of nociceptive processing in the anterior insula during a rating task of painful heat stimulation. Hari and others (1997) also showed that the unpleasant nature of a pain stimulus is associated with the right hemisphere predominance of SII responses, thereby suggesting the involvement of the right hemisphere in the emotional motivational aspects of pain processing. In contrast, Schlereth and others (2003) reported a left hemisphere predominance for the early sensory discriminative aspects of pain processing using brain electrical source analysis of laser-evoked potentials.

Amygdala Activation during Viewing Images Evoking Fear

The amygdala is suggested to play a crucial role in the processing of fear emotion (Calder and others 2001). The activation of the left amygdala during the fear condition in this study is consistent with its involvement in the processing of fear emotion found in most studies in which subjects were presented with images of human faces expressing fear (Breiter and others 1996; Morris and others 1998; Wright and others 2001). However, the notion that the amygdala is specific to fear-related emotions seems to be questionable; an alternative interpretation would be that unspecific negative emotional states such as fear, disgust, personal distress, and anxiety have a common neuronal circuitry. A number of studies have suggested that negative emotions are related to not only activation in the ACC but also activation in the amygdala (Irwin and others 1996; Davidson 2002; Stark and others 2003).

Conclusion

Imagination of pain while viewing images showing painful events involves activations in the ACC (BA 24), right anterior insula, cerebellum, SII region, and PPC. Activations in the SII region and PPC were detected specifically during the imagination of pain compared with emotions of fear and rest. These findings are in good agreement with the activation patterns associated with the perception of nociceptive stimulation. These results suggest that the activations during the imagination of pain elicited by viewing images showing painful events may be based on the cortical representations of the pain matrix in the human brain, which reflects the multidimensional nature of pain experience including sensory, affective, and cognitive components.

Notes

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RESEARCH ARTICLE

Early cortical activities evoked by noxious stimulation in humans

Xiaohong Wang · Koji Inui · Ryusuke Kakigi

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Abstract Lasers can selectively activate the nociceptors of A-delta fibers. Since nociceptors in the skin are activated via temperature conduction by the laser beam, a latency jittering of cortical responses among trials would affect results obtained with a conventional averaging (C-AVE) technique. We therefore used a new method, latency-adjusted averaging (L-AVE), to investigate cortical responses to noxious laser stimulation in normal subjects. L-AVE was done by averaging trials after adjusting the latency so that the peak latency of an activity in the temporal region of all trials matched on the time axis. Both in C-AVE and in L-AVE, clear activations were found in the contralateral primary somatosensory cortex (SI) and bilateral parasylvian regions, whose activities peaked 163–181 ms after the stimulation. In addition to these three main activities, weak activities peaking at around 109–119 ms could be identified in only L-AVE in similar cortical regions. Since the direction of the source differed between early and main activities, we considered that the early weak activities were cancelled out by the later main activities with an opposite orientation. The results suggested that early cortical processing of noxious information occurs earlier than previous neurophysiological studies have estimated and that the temporal sequence of activations should be reconsidered.

Keywords Magnetoencephalography · Pain · Somatosensory

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Introduction

Functional neuroimaging studies using positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) have provided unequivocal evidence of the participation of the cerebral cortex, including the primary somatosensory cortex (SI), secondary somatosensory cortex (SII), and insula, in pain processing (Talbot et al. 1991; Casey et al. 1994; Gelnar et al. 1999; Apkarian et al. 2000; Qiu et al. 2006). In contrast to PET and fMRI, magnetoencephalography (MEG) has excellent temporal resolution, and can be used to investigate the temporal aspect of the processing of information in the cortex. In previous MEG studies, parasylvian regions were consistently activated by noxious stimulation (Huttunen et al. 1986; Kakigi et al. 1995; Hari et al. 1997). In addition, recent studies found activation in SI following laser (Ploner et al. 1999; Kanda et al. 2000; Timmermann et al. 2001; Nakata et al. 2004) and intraepidermal electrical (Inui et al. 2002b, 2003a, b) stimulation. Some studies found a parallel activation pattern of SI and SII (Ploner et al. 1999; Kanda et al. 2000; Timmermann et al. 2001; Inui et al. 2002b; Nakata et al. 2004) showing a similar onset latency between SI and SII activities, while others (Inui et al. 2003a, b) showed an early SI

activity prior to the main SII activity, implying serial processing through SI and SII. In addition to MEG, laser-evoked potentials (LEPs) have been used for the temporal assessment of cortical pain processing. Although the SII area was the major cortical region responsible for LEPs in most studies (for review, see Apkarian et al. 2005), several studies reported the involvement of the contralateral SI in pain processing (Tarkka and Treede 1993; Schlereth et al. 2003; Ohara et al. 2004). Tarkka and Treede (1993) reported that a N1 component at a latency of 160 ms was generated in SI and SII, whereas others demonstrated an activity in the contralateral SI helped to shape the N2 component (Schlereth et al. 2003; Ohara et al. 2004). Valeriani et al. (2000) reported an early component with a peak latency of 83 ms originating from SII or the insular area, suggesting that the opercular cortex is also involved in early processing. Therefore, the temporal aspect of the processing of noxious information in the cortex still remains to be elucidated.

A laser can activate nociceptors of thinly myelinated A-delta fibers without stimulating tactile afferents, and therefore is a good tool with which to investigate the nociceptive system. However, since the skin's nociceptors are activated via temperature conduction by the laser beam, there is considerable jitter in the latency of the activation of nociceptors among trials (Bromm and Treede 1984), which is problematic for studies using an averaging technique. The main activations in SI and SII reported previously (Ploner et al. 1999; Kanda et al. 2000; Timmermann et al. 2001; Nakata et al. 2004) are less affected by latency jittering because of their long duration. However, the possibility cannot be excluded that some weak and short-lasting activities at an earlier latency were overlooked due to the problem of jittering in conventional averaging (C-AVE). In the present study, we used latency-corrected averaging to test this possibility.

Methods

Subjects

The experiment was performed on nine healthy male volunteers, aged 27–43 years (32.1 ± 5.3). Informed consent was obtained from all participants prior to the study, which was first approved by the Ethics Committee at our Institute.

Laser stimulation

A thulium:YAG laser stimulator (Carl Baasel Lasertech, Starnberg, Germany) was used to elicit noxious stimuli. Laser pulses (1 ms in duration, 2,000 nm in wavelength, and 3 mm in spot diameter) were delivered to the dorsum of the left hand at an interval of between 8 and 12 s. The interstimulus interval of 8–12 s was employed to avoid habituation of evoked cortical responses (Raij et al. 2003). The irradiated points were moved slightly for each stimulus to avoid tissue damage and habituation of the receptors. The mean intensity was 211 mJ, ranging from 200 to 250 mJ, with which a painful sensation having a visual analysis score (VAS) of around 7 was evoked in each subject. Since the laser stimulator caused large magnetic artifacts, it was set outside the shielded room, and the laser beam was conducted through optical fibers, approximately 6.5 m in length, into the shielded room. In order to maintain the distance between the laser outlet and the skin surface, the optical fiber was attached to the MEG device and subjects were instructed to attach the palm of the left hand to the table during the recording.

MEG recording

Laser-evoked magnetic fields (LEFs) were recorded with a helmet-shaped 306-channel detector array (Vectorview; ELEKTA Neuromag, Helsinki), which comprises 102 identical triple sensor elements, in a magnetically shielded room. Each sensor element consists of two orthogonal planar gradiometers and one gradiometer magnetically coupled to a multi-superconducting quantum interference device (SQUID) and thus provides three independent measurements of the magnetic fields, though in this study, results recorded from 204 planar gradiometers were analyzed. The signals were recorded with a 0.1–100 Hz band-pass filter and digitized at a sampling rate of 900 Hz. The period of analysis was 500 ms including a prestimulus period of 100 ms. Sixty trials following laser stimulation were recorded.

Prior to the recording, the exact location of the head with respect to the sensors was found by measuring the magnetic signals produced by currents leading to four indicator coils placed at known sites on the scalp. The four indicator coils attached to the subject's head were measured with respect to the three anatomical landmarks using a 3D digitizer to allow alignment of the MEG and magnetic resonance (MR) image coordinate systems (3.0-T Siemens Allegra). The x-axis was fixed with the preauricular points, the positive direction being to the right. The positive y-axis passed through the nasion and the z-axis thus pointed upward. Current was then fed to the indicator coils and the resulting magnetic fields were measured with the magnetometer, which allowed for aligning the individual head coordinate system with the magnetometer coordinate system.

Averaging of trials

First, C-AVE using the onset of the noxious stimulation was done. In C-AVE waveforms, the largest response was

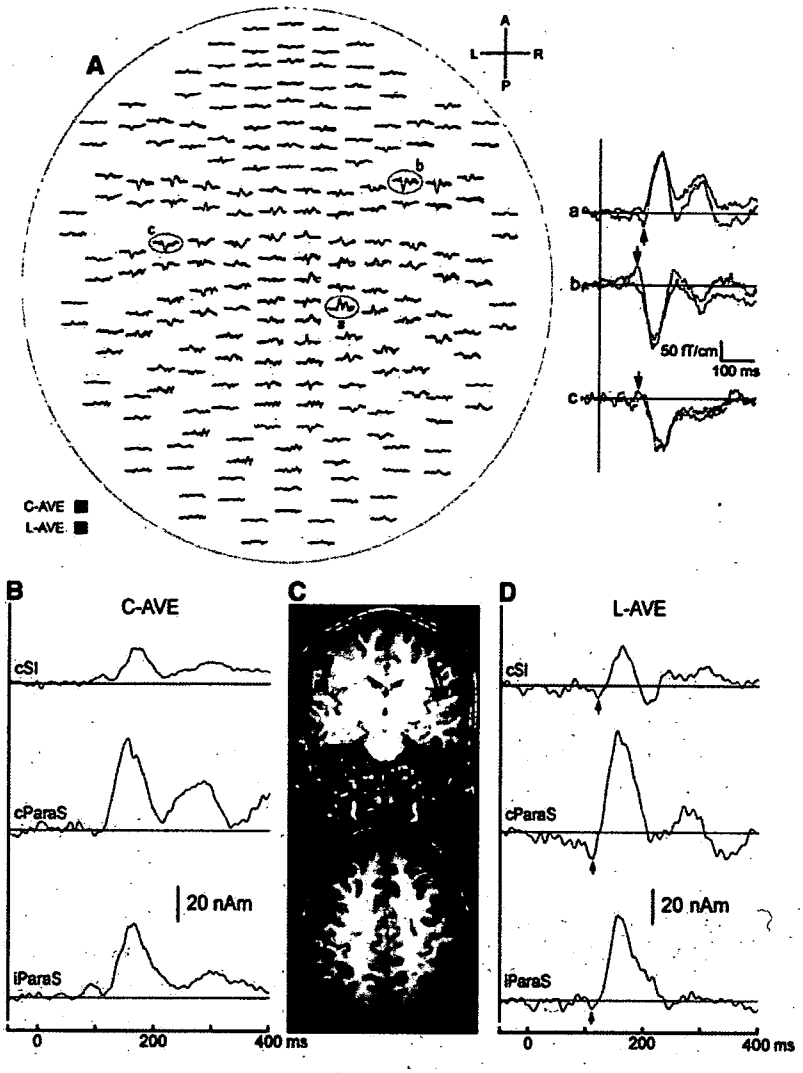


Fig. 2 Magnetic fields following noxious laser stimulation applied to the dorsum of the left hand. **a** Waveforms of evoked magnetic fields obtained in conventional averaging (C-AVE) and latency-adjusted averaging (L-AVE) were superimposed. The *upper right figures* show enlarged waveforms recorded from **a**, **b**, and **c**. *Arrows* show the early activities. **b**, **d** The time-varying source strength of cSI, cParaS, and iParaS in C-AVE (*lower left*) and L-AVE (*lower right*), respectively. **c** The location and orientation of each source are superimposed on the MRI scans. *cSI* contralateral primary somatosensory cortex, *cParaS* contralateral parasylvian region, *iParaS* ipsilateral parasylvian region

were used to compute the time-varying multidipole model allowing the strengths of the previously found ECDs to change over the entire period of analysis while the source locations and orientations were kept fixed. The data acquisition and analysis followed Hamalainen et al. (1993).

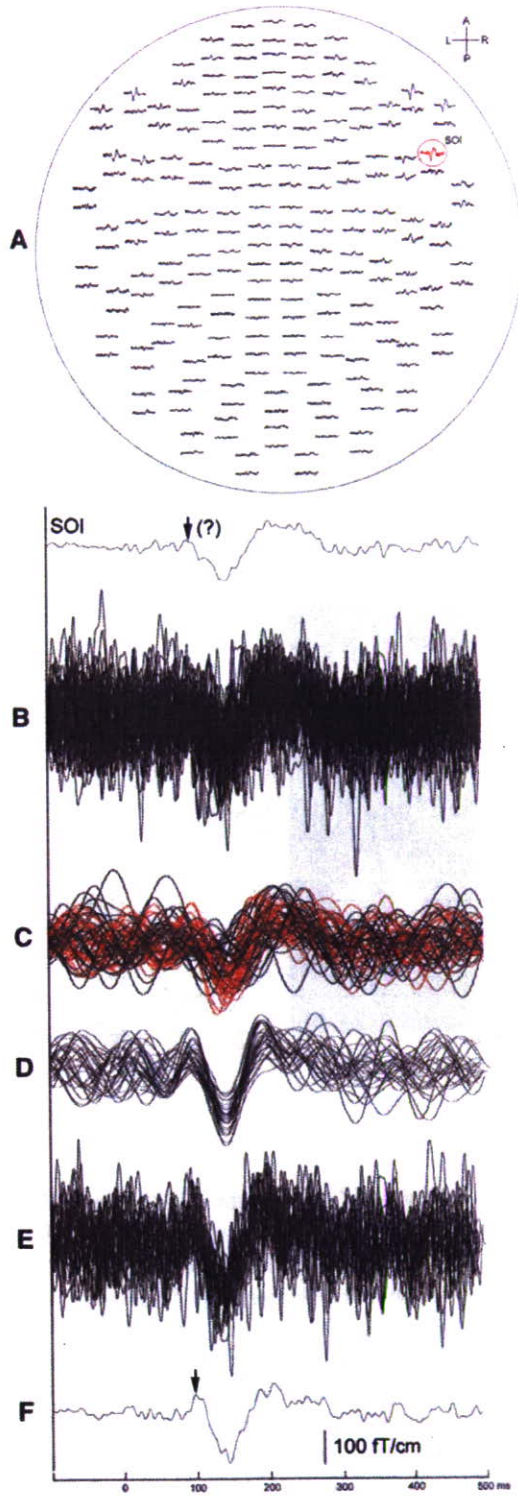
Second, the possibility that there emerge additional components at an early latency in L-AVE was examined. When a new deflection had a peak amplitude larger than the baseline + 3 times the standard deviation (SD), we accepted it as a significant component. In the present study, the onset latency of a component was defined as a latency point where the amplitude first exceeded the baseline + 2 SD.

Data were expressed as the mean ± SD. A paired *t*-test was used to compare the source's location and peak amplitude between the C-AVE and L-AVE. A one-way analysis of variance (ANOVA) was used to compare the latency among cortical sources. *P* values less than 0.05 were considered to be significant.

Results

After the application of our criteria, 27–35 (mean 30.7) trials were included for L-AVE in each subject, which corresponded to 45–58% of the 60 trials used for C-AVE.

Figure 2a shows evoked magnetic fields recorded from 204 planar gradiometers in C-AVE (black lines) and L-AVE (red lines). Both in C-AVE and L-AVE, a clear and consistent main component, which has been reported in previous studies, was recorded in three cortical areas; the left (contralateral) parietal region and bilateral temporal regions. An ECD analysis and subsequent superposition of sources on individual MR images revealed that ECDs responsible for these three main components were located around the postcentral gyrus of the contralateral hemisphere and around the upper bank of the Sylvian fissure or near the insular circular sulcus of both hemispheres, corresponding to the contralateral SI (cSI), contralateral parasylvian region (cParaS), and



◀ **Fig. 1** Procedures followed for latency-adjusted averaging (L-AVE) in a single subject. **a** Laser-evoked magnetic fields recorded from 204 planar coils and the SOI with the largest amplitude in the right temporal area. **b**, **c** Superimposed waveforms of 60 trials of the SOI obtained with a low-pass filter of 100 and 15 Hz, respectively. **c** *Waveforms in red* show the trials selected for L-AVE. **d** Selected trials were latency-corrected. **e** Latency-adjusted trials with a bandpass of 0.1–100 Hz. **f** Averaged waveform of selected trials after latency-adjustment. *SOI* sensor of interest. *Arrows* indicate the early activity that appeared after L-AVE

usually recorded in the right (hemisphere contralateral to the stimulated side) temporal area (Fig. 1A) at around 150–200 ms after stimulation consistent with previous studies (Kakigi et al. 1995; Ploner et al. 1999; Kanda et al. 2000; Timmermann et al. 2001; Nakata et al. 2004). We selected the channel with the largest amplitude around the temporal region as a sensor of interest (SOI, Fig. 1A). The peak latency of the SOI was determined in each subject and was used for latency-adjusted averaging (L-AVE).

Second, L-AVE was done, in which each trial had been latency-adjusted before the averaging. One problem with a single-trial analysis is that the signal-to-noise ratio (S/N) is very low for single epochs. Notably, high frequency noises superimposed on the evoked response were problematic when determining the peak of the response. After several attempts, we found that a cutoff frequency of 15 Hz is appropriate for determination of the peak latency of the main component. Therefore as a first step, MEG signals of each trial were filtered with a low-pass of 15 Hz. Then we used the SOI to select trials to include averaging (Fig. 1C). That is, only the trials whose SOI had an unambiguous peak within the range of the peak latency of the C-AVE waveform ±20 ms were selected by visual inspection (red traces in Fig. 1C). Such a procedure has been shown to improve S/N ratio of LEP components (Iannetti et al. 2005). Once trials to be included for L-AVE were determined, the original 0.1–100 Hz waveforms of the selected trials were then latency-corrected (Fig. 1E), so that the peak of the SOI matched on the time axis and averaged (Fig. 1F).

Data analysis

First, the source of the main components in C-AVE and L-AVE was estimated in order to know whether the quality of L-AVE was changed as compared with C-AVE. The equivalent current dipole (ECD), which best explains the measured data, was computed by using a least-squares search. A subset of 16–18 channels including the local signal maxima was used for the estimation of ECDs. These calculations gave the 3D location, orientation, and strength of the ECD in a spherical conductor model, which was based on each subject's MR images to show the source location. The goodness-of-fit (GOF) value of an ECD was calculated to indicate in percentage terms how much the dipole accounts for the measured field variance. Only ECDs explaining more than 85% of the field variance at selected periods of time were used for further analysis. Finally, all channels

ipsilateral parasylvian region (iParaS), respectively. This three-source model is compatible with previous laser-evoked MEG studies (Ploner et al. 1999; Kanda et al. 2000; Timmermann et al. 2001; Nakata et al. 2004). The location of each cortical activity is shown in Table 1. The location of each source in L-AVE did not differ significantly from that in C-AVE (Fig. 2C). The GOF for the cSI (94.7 ± 3.7) and cParaS (97.1 ± 2.7) sources was significantly larger in L-AVE than in C-AVE (91.1 ± 5.0 and 94.9 ± 4.6, respectively). The GOF for the iParaS showed no significant difference between C-AVE (95.8 ± 2.9) and L-AVE (94.6 ± 1.6) ($P = 0.25$). The onset and peak latency of the main deflection in the three cortical areas did not differ significantly between C-AVE and L-AVE (Table 2). In both C-AVE and L-AVE, the onset or peak latency for iParaS was significantly longer than that for cSI or cParaS. The onset latency did not differ between cSI and cParaS (Table 2). The time-varying source strength in each region is shown in Fig. 2B, D. The peak amplitude of the three main activities was significantly greater in L-AVE than in C-AVE (Table 3). ECD locations of these three regions showed no significant difference between C-AVE and L-AVE, indicating that the new method, L-AVE, was reliable.

In addition to the main activities, early deflections were identified in the contralateral parietal region and both temporal regions in both C-AVE and L-AVE (Fig. 2A). However, early deflections in C-AVE were very weak and usually did not meet our criteria for a significant deflection. By contrast, such deflections were identified more clearly in L-AVE. In C-AVE, significant early deflections were identified in four subjects for cSI, four subjects for cParaS, and three subjects for iParaS. After the L-AVE, significant early deflections were identified in seven subjects for cSI, in seven subjects for cParaS, and in five subjects for iParaS.

Table 1 The mean location of each source for C-AVE and L-AVE

	x (mm)	*y* (mm)	*z* (mm)
C-AVE			
cSI	27.8 ± 9.7	11.9 ± 18.3	107.4 ± 11.7
cParaS	52.2 ± 7.5	33.4 ± 6.5	64.0 ± 10.2
iParaS	−53.3 ± 4.4	21.3 ± 4.1	71.3 ± 8.1
L-AVE			
cSI	27.6 ± 12.3	14.0 ± 17.5	107.7 ± 11.3
cParaS	54.0 ± 9.7	31.6 ± 8.1	63.6 ± 7.0
iParaS	−53.0 ± 4.7	21.2 ± 5.0	72.1 ± 7.7
Early-cSI ($n = 3$)	30.0 ± 11.4	10.8 ± 19.3	110.7 ± 6.6
Early-cParaS ($n = 5$)	52.9 ± 9.4	24.1 ± 13.7	62.9 ± 5.4
Early-iParaS ($n = 4$)	−53.3 ± 5.3	13.6 ± 11.8	67.8 ± 10.2

The *x*-axis passed through the preauricular points, the positive direction pointing to the right. The positive *y*-axis traversed the nasion. The positive *z*-axis pointed up. The location of each source did not differ between C-AVE and L-AVE

Usually significant deflections at early latencies were detected in three distinct areas; the contralateral parietal region and both temporal regions, which were almost identical to the locations for the three main components in C-AVE (Fig. 3).

Figure 4 shows L-AVE waveforms of three channels respectively selected from the contralateral parietal region and bilateral temporal regions, in which the early and major deflections had the largest amplitude in all subjects (a) and ground-averaged waveforms (b). Figure 5 shows the waveform of the SOI and root mean square (RMS) of all subjects. For early deflections, a one-way ANOVA showed no significant difference in the onset and peak latencies among the three activities ($P = 0.48$), although the onset latency of cParaS tended to be shorter than that for cSI or iParaS (Table 2). The ECD of the early deflections could be estimated in three subjects for cSI, in five subjects for cParaS, and in four subjects for iParaS. In these samples, there was no consistent difference in the location of the source between the early and main activities (Table 1 and Fig. 6).

Discussion

In the present study, we found that three main activities originating from the contralateral SI and bilateral parasylvian regions and peaking at around 160–180 ms were responsible for laser-evoked magnetic fields. Both the locations and response latencies of the activities were consistent with previous MEG studies (Ploner et al. 1999; Kanda et al. 2000; Timmermann et al. 2001; Nakata et al. 2004), in which these activities have usually been considered the primary cortical response. However, in addition to these main activities, L-AVE in the present study revealed the presence of early activities in these three cortical areas peaking at 110–120 ms, indicating that the cortical processing of information on pain took place earlier than previously considered. Since the early component had an opposite direction to that of the main component, the early component is considered to be a discrete component but is not a part of the main component. The onset latencies (88–105 ms) of the early activities appear to be appropriate for the earliest cortical activity given a peripheral conduction velocity of 15 ms/s (Inui et al. 2002a, b) in A-delta fibers and 10–20 m/s in the spinal cord (Kakigi and Shibasaki 1991; Cruccu et al. 2000; Tsuji et al. 2006). Traveling at 15 m/s, it would take roughly 80 ms to move from the hand to the cortex (120 cm).

Methodological considerations

Before discussing the findings of L-AVE, we should consider the possibility that the early activities detected

Table 2 The onset and peak latency of early and main deflections in L-AVE and C-AVE (ms)

	L-AVE				C-AVE			
	Early deflection		Main deflection		Early deflection		Main deflection	
	Onset	Peak	Onset	Peak	Onset	Peak	Onset	Peak
cSI	104.7 ± 16.8	118.7 ± 19.0	136.7 ± 13.5*	169.3 ± 16.4	104.0 ± 16.1	114.3 ± 15.4	134.6 ± 16.1*	168.1 ± 17.8
cParaS	88.1 ± 20.4	109.0 ± 12.9	136.0 ± 11.8*	163.0 ± 11.8*	84.3 ± 13.0	98.3 ± 4.9	131.1 ± 11.2*	163.9 ± 14.3*
iParaS	94.0 ± 17.1	111.8 ± 11.6	152.1 ± 14.4	180.7 ± 13.3	89.0 ± 23.5	115.0 ± 11.1	153.0 ± 14.5	181.3 ± 13.3

The number of subjects who showed a significant early deflection was seven, seven, and five in L-AVE, and four, four and three in C-AVE for cSI, cParaS, and iParaS, respectively

cSI contralateral primary somatosensory cortex, *cParaS* and *iParaS* contralateral and ipsilateral parasylvian regions, respectively

* $P < 0.05$, compared with iParaS (Fisher's PLSD procedure)

Table 3 The peak amplitude of early and main deflections in L-AVE and C-AVE (nAm)

	L-AVE		C-AVE	
	Early deflection	Main deflection	Early deflection	Main deflection
cSI	−35.3 ± 9.8	93.7 ± 31.7*	−29.6 ± 3.2	70.4 ± 23.1
cParaS	51.6 ± 21.8	−139.8 ± 33.9*	38.2 ± 17.6	−89.5 ± 19.8
iParaS	43.4 ± 18.1	−107.2 ± 17.2*	40.9 ± 8.5	−83.3 ± 15.3

The number of subjects who showed a significant early deflection was seven, seven, and five in L-AVE, and four, four, and three in C-AVE for cSI, cParaS, and iParaS, respectively

cSI contralateral primary somatosensory cortex, *cParaS*and *iParaS* contralateral and ipsilateral parasylvian regions, respectively

* $P < 0.01$, compared with the main deflection in C-AVE (paired *t*-test)

with L-AVE were artificial. We could exclude this possibility based on the following. (1) In a few subjects, there were significant early deflections prior to the main deflections even in the C-AVE waveforms though they were low in amplitude as compared to the main deflections. (2) Although we used the peak latency of the main component for the adjusting, the L-AVE technique made both the early and main deflections clearer as compared to C-AVE. (3) Although we selected the sensors with the largest amplitude around the temporal area as SOIs and used them for adjusting the latency of each trial, the quality of the data from SI as well as the cParaS region was improved. Since the early activity was low in amplitude and had the opposite orientation to that of the main activity, we considered that it was easily cancelled out by the main activity in the C-AVE process.

Cortical activations in SI and the parasylvian regions

In C-AVE, main activities were found to originate from SI and the parasylvian regions, confirming previous findings (Ploner et al. 1999; Kanda et al. 2000; Timmermann et al. 2001; Inui et al. 2002b; Nakata et al. 2004). The peak latency of the activity, 160–180 ms, was consistent with results of previous MEG studies using laser stimulation (Ploner et al. 1999; Kanda et al. 2000; Timmermann et al. 2001; Nakata et al. 2004). In addition, the simultaneous activation of SI and cParaS and significantly later activation of iParaS were consistent with a recent MEG study (Ploner et al. 1999). The involvement of these cortical areas in pain processing has also been demonstrated in PET (Talbot et al. 1991; Casey et al. 1994) and fMRI studies (Gelnar et al. 1999; Apkarian et al. 2000).

However, only two papers have described the early activity prior to the main activity in SI (Inui et al. 2003a, b). The early activity identified in the contralateral SI area in the present study seems to correspond to that described by Inui et al. (2003a), who showed that the onset latency of the early SI activity (80 ms) following a noxious epidermal electrical stimulation was shorter by 29 ms than that for the main parasylvian activity (109 ms). Therefore, the temporal relationship between the early SI and the main parasylvian activities was very similar to the present results showing a latency delay of 31 ms. For the latter, the slightly longer onset latency (105 ms) of the early SI activity in the present study might be due to the temperature conduction time for laser stimulation.

As for the early activity in the parasylvian region, there are two studies that reported its presence. Valeriani et al. (2000) reported an early positive component (eP) in the contralateral parasylvian region with a peak latency of 83 ms that preceded the N1 negativity. Since they used a

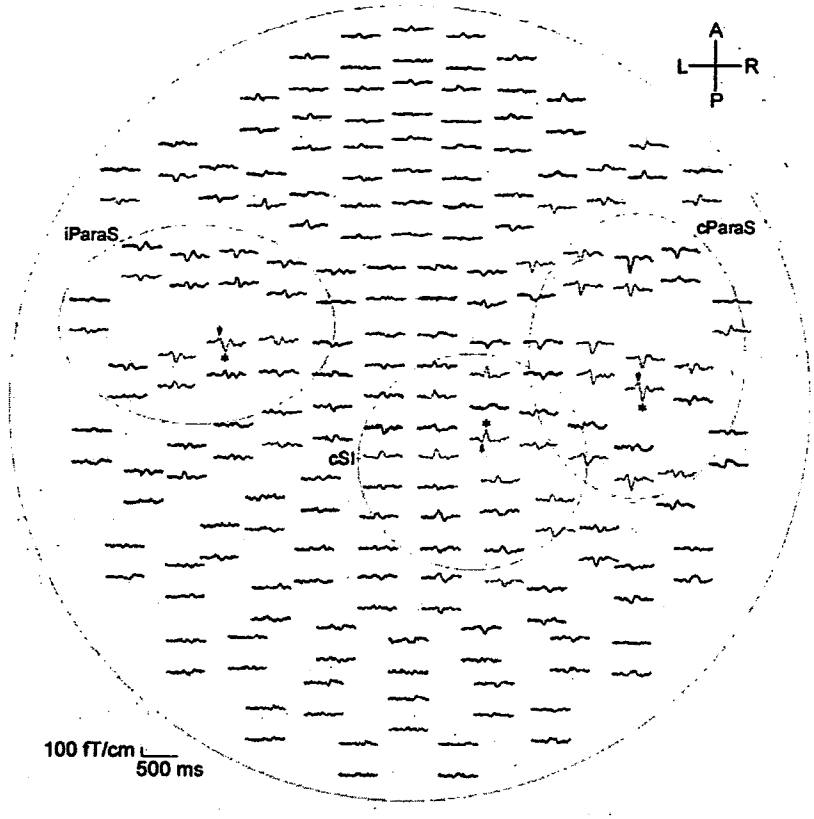


Fig. 3 Laser-evoked magnetic fields recorded from 204 planar coils in L-AVE in a single subject. The *waveform in grey* denotes that a significant early deflection prior to the main component is detected in this channel. *Arrows* and *asterisks* indicate the early and main deflection, respectively, with the largest amplitude in three areas around the contralateral parietal region and bilateral parasylvian regions. Significant early deflections are detected in the three cortical areas indicated by *circles*

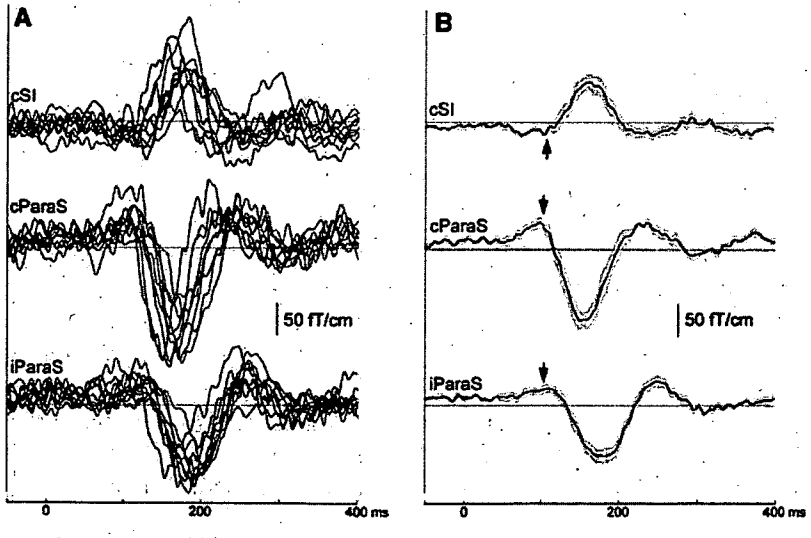


Fig. 4 **a** Superimposed waveforms of evoked magnetic fields of all subjects recorded form three channels, in which the main components showed the largest amplitude in the contralateral parietal region and bilateral temporal regions, respectively. **b** Group-averaged waveforms. *Shaded areas* depict ±SE. *Arrows* show the mean peak latency of the early responses

CO_2 laser and we used a YAG laser to elicit pain-related potentials, it is difficult to directly compare the early component between their study and the present study. However, the early deflection in the parasylvian region in the present study might correspond to the eP of Valeriani et al. (2000). In both studies, the early component preceding the N1 component had a small amplitude and an opposite orientation to that of the N1 component. In another study using intracranial recordings, Frot et al. (1999) demonstrated an early negative response at a latency of 135 ms in the parasylvian region, followed by a positive response peaking around 170 ms, which seems to correspond to the present early and main polarity-reversed activities.

As for the latency difference of the parasylvian activity between hemispheres, the 17-ms delay for the ipsilateral response of the main component in the present study was consistent with results of the intracranial recording study by Frot et al. (1999). In the study by Frot et al. (1999) a similar time

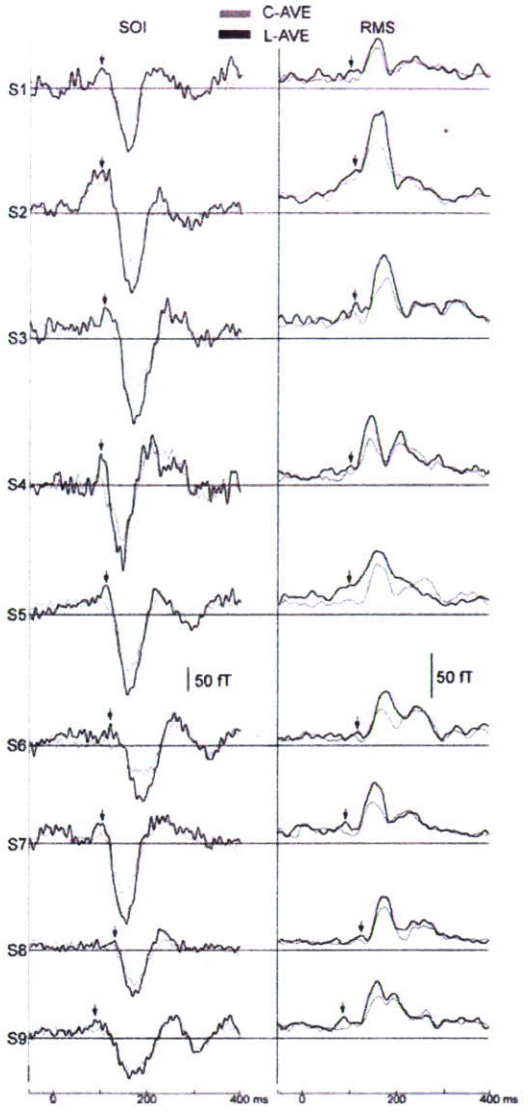


Fig. 5 The waveform of the SOI and RMS of nine subjects in C-AVE and L-AVE. *SOI* sensor of interest. *RMS* root mean square. *Arrows* indicate the early activity

lag was also found for the early component (15 ms). In the present study however, the latency of the early component did not differ significantly among the three cortical areas. This discrepancy was probably due to the low S/N ratio of the early component or the small sample of data in the present study.

The precise anatomical location of the early parasylvian activity was not clear like the main activity in this region. The location of nociceptive cortical areas around the sylvian fissure is still a matter of controversy. It has been difficult to determine whether the nociceptive area is situated within the classic SII (parietal operculum) or within an adjacent somatosensory area such as the frontoparietal operculum or insula. Many previous studies have shown that noxious stimuli activate at least one cortical area around the sylvian region other than SII. For example, fMRI (Bingel et al. 2003; Brooks et al. 2005; Iannetti et al. 2005) and intracranial EEG (Lenz et al. 2000; Frot and Mauguiere 2003) studies found activation in the posterior insula following noxious stimulation. Our previous studies also showed that activity from the insula may contribute to the major MEG signals evoked by noxious stimuli (Inui et al. 2003a; Wang et al. 2004). In the present study, the dipole was estimated to be located in the upper bank of the sylvian fissure in some cases but deeper around the circular sulcus in others. Therefore, we consider that activation in the sylvian region in this study may be a summation of activities from SII and adjacent areas. With regard to the early parasylvian activity, a reliable estimation of its source could not be obtained in some subjects because of the low S/N ratio. However, the sources of the early deflections were estimated to lie around the bilateral parasylvian region in the other subjects with a GOF of more than 85%. These findings suggested that the early components originated from similar regions to the main activities.

Temporal sequence of activation

The present results showing the simultaneous onset of the main SI and contralateral parasylvian activities are consistent with recent MEG studies (Ploner et al. 1999). These findings support the notion of a parallel mode of pain processing between the SI and parasylvian region. However, the temporal sequence of cortical activation should be reconsidered because of the presence of earlier activities. Our results suggested that early cortical processing of noxious information occurs earlier than previous neurophysiological studies

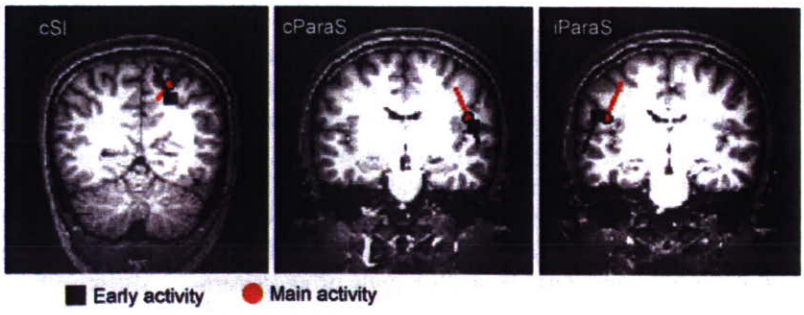


Fig. 6 Source locations of early and main activities in a representative subject. The locations were almost the same, but the dipole's direction was opposite

have estimated. As for the early component, our results did not find a significant difference in latency among the three cortical areas. However, this could be due to the small number of subjects, or due to the low S/N ratio of these activities. The slightly shorter latency of the contralateral parasylvian source compared to the other two sources might suggest the dominance of the contralateral parasylvian region in the early processing of noxious information.

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◆総　説

痛みの感情側面と痛覚認知

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要旨　痛みは不快な感覚であるが，同時に主観的な感情である．新しいニューロイメージングにより，痛みの感情と，それが痛覚認知に与える影響が科学的に明らかになってきた．本稿では，それらについて最近の私たちの研究成果を中心に紹介する．近年，侵害刺激に反応して活動する大脳皮質領域，いわゆる痛み関連脳領域が明らかとなったが，実際に痛み刺激が与えられなくても，痛みをイメージした時には類似の脳部位が活動するという仮説を実証するため，私たちは痛そうな写真（注射をされている写真など）を被験者に見せて，機能的MRI（fMRI）で脳活動を計測した．その結果，第二次体性感覚野，島，帯状回といった痛覚認知に関与する脳領域の血流が有意に上昇する事を発見した．また，瞑想中には痛みをまったく感じないというヨガの達人では，瞑想中に痛覚刺激を与えたときの脳磁図とfMRIの計測では，痛み関連脳領域の活動が著しく減弱していた．このように，痛みの感情により生じる脳活動は，痛み関連脳領域の主要活動を占めており，暗示や瞑想などにより，侵害刺激による痛み関連脳領域の活性化と抑制が起こり，痛覚認知が強く影響されていることが明らかとなった．

キーワード　痛み，感情，機能的MRI（fMRI），脳磁図

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I　はじめに

「心頭滅却すれば火もまた涼し」．これは織田信長が恵林寺を焼き討ちにしたとき，恵林寺快川禅師が火中に端座して，遒遥として死を受け入れつつ唱えた言葉と伝えられている．精神や心の状態が，痛みの感覚認知に大きな影響を与えることを示す有名な逸話である．また，スポーツなどに夢中になっていて怪我に気付かず，試合が終わった後に初めて痛みを感じるという現象は一般にもよく知られている．このように，心の状態，精神的状況によって，痛覚が修飾される機序が，ヒトの脳には存在するようである．本来，痛みは不快な感覚体験であるが，同時に感情体験でもある[1]．

近年，ポジトロン断層撮影（positron emission tomography：PET），機能的磁気共鳴画像（functional magnetic resonance imaging：fMRI）や脳磁図（magnetoencephalography：MEG）などの機能的脳画像法などにより，疼痛に関係する脳領域の活動の解明が急速に進歩し，これらの機能的脳画像診断法により，感覚体験と感情体験の密接な関係を示す知見が得られるようになっている．この総説では，機能的脳画像法を用いて得た著者らの成績を中心に，痛みの感情的側面とそれを修飾する機序の存在を示唆する最近の知見を紹介する．

II　痛み関連脳領域と痛覚伝導路

近年，侵害刺激に対して，第一次体性感覚野（primary somatosensory cortex），第二次体性感覚野（secondary somatosensory cortex），島，帯状回などの複数の大脳皮質領域が活性化されることが，機能的脳画像法により，明らかになった[2,3,4]．これらの痛覚受容に関与する複数の皮質領域は，順次あるいは同時に活動し，ネットワー

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クを形成しており，痛み関連脳領域（pain-related brain regions）あるいはペインマトリックス（pain matrix）と呼ばれている（本稿では，以降は「痛み関連脳領域」と統一して記載した）．

身体が侵害刺激を受けたとき，末梢神経，脊髄痛覚伝導路を通して，痛みの情報（侵害受容情報）が痛み関連脳領域に伝えられる．最近，Tsuji ら[5]は，ヒトの脊髄では2つの異なる経路が，それぞれ異なった伝導速度で侵害情報を伝えていること，またそれぞれの脊髄視床路が視床の異なる部位を通って痛み関連脳領域に情報を伝えていることを示した．これらの研究から痛覚伝達経路は大別して2つあり，侵害受容情報は脊髄後角レベルで2つの経路に分かれて処理されると考えられている（図1）[2]．1つの経路は脊髄後角の第I層に始まり，視床のVMpo（posterior part of the ventral medial）核を経由し，島や辺縁系に至る（lamina I-VMpo-Insula pathway）もので，もう1つの経路は脊髄後角の第V層に始まり，視床のVPL（ventral posterior lateral）核を経由し，第一次体性感覚野（SI）に至る（lamina V-VPL-SI pathway）ものである．これら2つの経路は通過する視床核の位置から，前者は内側系と，後者は外側系と呼ばれている．機能的には内側系経路は痛みの感情的側面や自律神経系に，外側系経路は痛みの判別的側面（痛みの強さや場所）に関与すると考えられている．

侵害受容情報が，脊髄レベルで，感情的痛覚認知システムと痛覚判別システムの異なった経路に分かれ，痛み関連脳領域に至ることが示唆されていることは興味深い．しかし，このような単純な二分で複雑な痛覚系が説明できるとは考えられず，これら2つの経路はそれぞれの役割を相互に補完的に果たしていると考えるのが妥当である[6,7]．

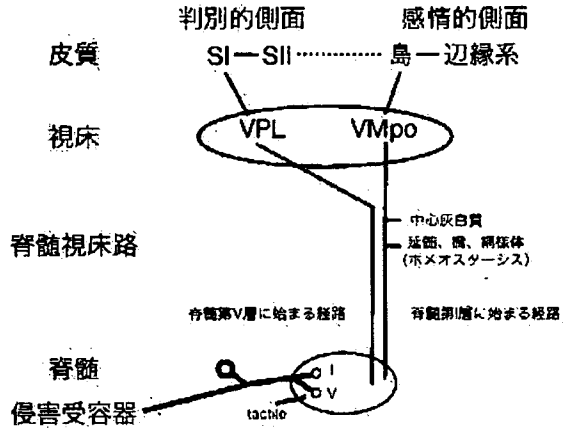

図1 痛覚伝達経路
機能的には外側系は痛みの判別的側面，内側系は痛みの感情的側面に関与すると考えられている．
SI：primary somatosensory cortex，SII：secondary somatosensory cortex，VPL：ventral posterior lateral 核，VMpo：posterior part of the ventral medial 核
（文献2より引用）

III "イメージされた痛み"，"心の痛み" と幻肢痛

痛みは，単なる感覚ではなく，恐怖，嫌悪，怒りなどと同じようにネガティブな感情体験である．従って，痛いという感情は，実際に痛み刺激が与えられなくても，身体的な痛みと類似の脳部位を活動させる可能性がある．例えば，われわれヒトには共感する能力が備わっており，配偶者，恋人や自分の子供のような近親者に痛みを与えられているのを見たとき，それを見ている自分も痛みを共感することができ，そのときの脳活動は前帯状回や島といった痛み関連脳領域の「感情面」の活動が活発になる[8]．一方，実際の痛みを加えられたときの脳活動は，後帯状回や第二次体性感覚野領域の活動が特異的にみられ，これらは他人の痛みを見た時には活動しない[8]．しかし，視点を少し変え，自分の痛みとして想像（痛みを想像）したときは，前帯状回や島に加えて，第二次体性感覚野領域の活動も現れることが示されている[9]．つまり，他人の痛みを「痛そう」と共感するだけでは，痛みの感情面に関する痛み関連脳領域しか活動しないが，自分の痛みとして想像した場合には，それらに加えて痛みの感覚的，判別的側面に関する痛み関連脳領域の活動が加わってくるのである．

著者らは，被験者に実際の痛み刺激は与えず，「痛そうな（痛みを連想させる）画像」を見せて自分の痛みとして想像させ，イメージされた痛みの脳活動をfMRIを用いて計測し，対照感情として「怖そうな（恐怖感情を起こさせる）画像」と「落ち着く風景画（安静感情）」[10]を用いて，それぞれの恐怖感情と安静感情の脳活動を比較した[11]．「痛そうな画像」とは，注射をされているところや，針が刺さっている写真などを用いた[11]．その結果，被検者が自分に注射される痛みを想像したとき，前帯状回後部，島前部，第一次体性感覚野領域，後部頭頂葉，小脳部位の血流が有意に増加していた．これらは，実際に侵害刺激を末梢組織に与えた場合の痛み関連脳領域の活性化とほぼ同様の結果であった（図2）．

痛みの感情に伴う脳活動領域のうち，前帯状回は，恐怖，嫌悪，怒りなどの活性化される脳領域と共有してい

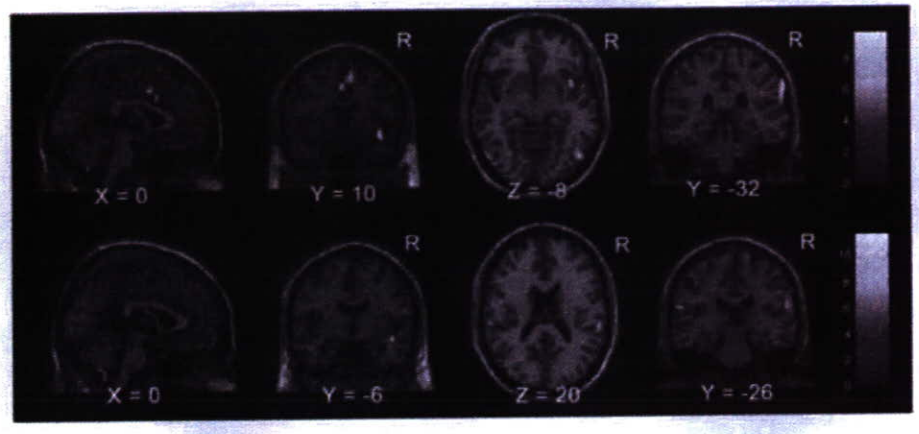

図2 「痛みを想像」したときの脳活動
上下段とも「痛みを想像」したときの脳活動を示している．前帯状回後部，島，第二次体性感覚野，後部頭頂葉の血流が有意に増加しており，あたかも実際の痛みを与えられたかのような脳活動を示した．
（文献9より引用）

る．しかし，痛みの感情に伴う脳活動領域は，島や第二次体性感覚野などと同時に活動するなど，明らかに恐怖などの他の感情に伴う脳活動とは異なる独特の様式を呈している．つまり，痛みの感情は，末梢からの侵害刺激（下位の末梢神経から上位の脳まで到達する感覚情報）がなくても，痛みを想像することにより特異的に痛み関連脳領域が活性化するということから，組織障害に起因を限定するものでない．また，その脳活動が痛み関連脳領域活動の主要を占めているとともに，痛みの持つ多面性（感覚，認知，感情等）を反映していると考えられた[11]．

近年，痛みの感情に伴う脳活動は，患者のうつ状態や，彼らの訴える主観的な痛みの程度と相関していることが明らかになってきた[12, 13]．さらには，仲間はずれやいじめなど社会的な疎外を受けているときには，実際に痛み刺激が与えられなくても，身体的な痛みと類似の痛み関連脳領域が活動する[14]．このような“心の痛み”も，痛み関連脳領域を共有していることが明らかになりつつある．うつ病や社会的疎外感は疼痛を増強させる因子である．fMRIや脳磁図などによる痛み関連脳領域活動の客観的評価による研究は，うつ病，社会的要素など精神的要素の強い痛みの治療法の客観的診断に有用かもしれない．

侵害刺激が存在しないのに痛みを感ずる特殊な疼痛として幻肢痛がある．Willoch ら[15]は，幻肢痛の患者では，幻肢が痛むときには，侵害刺激がないのにもかかわらず，第二次体性感覚野，前帯状回後部，島を含む痛み関連脳領域が活動していることを報告している．これは，健常者が侵害刺激を受けたときや，痛みを想像したときと同様の痛み関連脳領域の活動様式である．

IV　暗示・瞑想による痛覚認知の抑制

近年，暗示や瞑想が，痛覚認知に抑制的に働くことを示す機能的脳画像診断法による成績が報告されている．医師や看護師が患者に注射するときに，「痛くないから大丈夫ですよ」，「ちょっとチクッとしますよ」などと注射前にいうことがある．これは痛みが少ないと患者に暗示すると，痛みが強いと予想しているときに比べ，患者の痛みの感じ方が少ないであろうと経験的に感じているからである．Koyama ら[16]は，fMRIを用いた研究により，痛みを少ないと予想しているときには，主観的な痛みの強さと痛み関連脳領域の活動の両方が，実際の痛みよりも抑制されていることを，初めて科学的に証明した．また，Seymour ら[17]は痛みがなくなると予想できたときには扁桃体と中脳の活動が活発になることを報告し，暗示による自覚される痛みの強さの減弱が，扁桃体と中脳の活動に関係があることを示唆している．

インドのヨガの達人は，身体や舌に針を刺しても痛みを感じないという．最近，Kakigi ら[18]はインドで長期間ヨガの訓練を受け，瞑想中には痛みを感じないという日本人ヨガマスターの脳磁図とfMRIを記録した．脳磁図での背景脳磁場の周波数分析では，瞑想していない時に比し，瞑想中では10 Hz前後のアルファ波が著明に増強しており（**図3**），瞑想中には何らかの特殊な脳活動が起こっていることが明らかになった．少なくとも徐波成分は増強していなかったので，意識低下や催眠状態は考

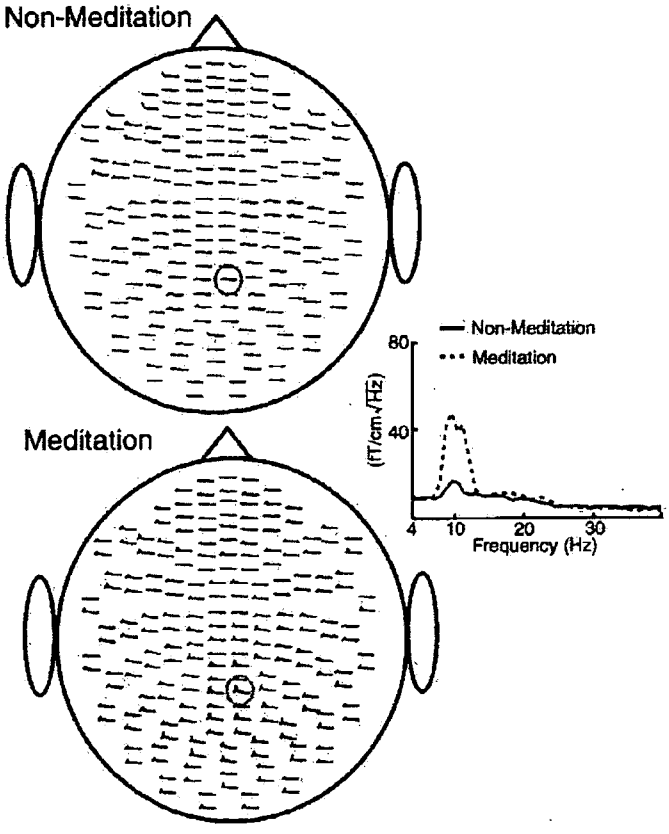

図3 ヨガマスターの瞑想時と非瞑想時の背景脳磁場の周波数解析
瞑想中では10Hz前後のアルファ波が著明に増強している.
(文献18より引用)

えがたい. 実際, 瞑想中であってもヨガマスターは通常と同様に会話が可能であった. 驚くべきことに, 瞑想中には炭酸ガスレーザー光線による痛覚刺激時に特異的に出現するはずの痛覚関連脳磁図がまったく記録されなかった. fMRIでは, 瞑想していない時には一般健常人と同様に, 痛覚刺激に対して, 両側半球の視床, 第二次体性感覚野, 島, 帯状回に血流が有意に増加していた. しかし, 瞑想中には上記の部位の血流は変化せず, 前頭葉, 頭頂葉, および中脳の血流が増加していた (図4). これらの結果から, このヨガマスターが瞑想中には本当に痛みを感じていないことが明らかになった. この機序は不明であるが, 中脳被蓋部は痛覚の下行性抑制路の重要な部位であり, この部位の血流増加は瞑想中の下行性抑制路の著明な活性化を示している可能性がある.

V 結 語

近年の機能的脳画像により, 侵害刺激に反応して活動する大脳皮質領域, いわゆる痛み関連脳領域が明らかになりつつあるが, これらの領域は, 侵害刺激だけではなく, 痛みのイメージ, うつ病などに伴う"心の痛み", や幻肢痛などでも活性化されることが明らかになっている. さらに, 暗示や瞑想などにより, 侵害刺激による痛み関連脳領域の活性化の抑制現象も確認されている. これらの機能的脳画像的診断法による新しい知見は, 痛みの診断や治療に有用な新しい視点を提供すると考えられる.

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