で，各種の求心路遮断痛の治療において有効例が報告されている[2,10,11]．しかし，大脳皮質運動領刺激における電極の留置部位を決定する方法については，①局所麻酔下に手術を行い，術中の刺激によって誘発される motor twitch や muscle contraction を観察する，②全身麻酔下にグリッド電極を頭蓋内に留置し，術後に覚醒下で刺激の効果を確認する，③MRI 画像誘導装置を用いて中心溝や中心前回を同定し，解剖学的に留置部位を決定する，④誘発電位を用いて電極の留置部位を決定する，⑤これらの方法を複数組み合わせる方法，などが報告されている．誘発電位を用いる方法としては，脳表から直接に somatosensory evoked potential（SEP）を記録し，N 20 の phase reversal を用いて中心溝を同定する方法，大脳皮質刺激による筋電図反応ならびに下行性の脊髄誘発電位を記録する方法がある．

われわれは術中の運動機能をモニタリングする方法として，corticospinal motor evoked potential（corticospinal MEP）を臨床応用してきた[12,13]．corticospinal MEP の D-wave は皮質下の pyramidal neuron が直接に刺激された反応であるので，大脳皮質各部位の刺激によって誘発される D-wave の振幅を比較することによって，最適の刺激部位を決定することができる．

(2) D-wave と VAS の変化

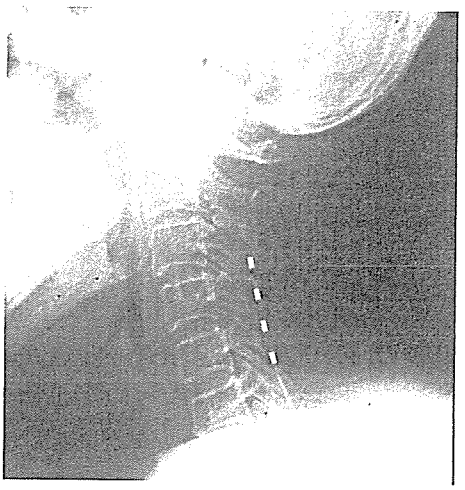
corticospinal MEP の記録電極としては，メドトロニック社製 Quad 電極を用いる．患者を腹臥位として，X 線透視下に経皮的に脊髄硬膜外腔に刺入し，電極の先端部を C 2 レベルに留置する．

D-wave を用いて刺激部位を決定する方法の意義を検討する目的で，D-wave の振幅と除痛効果について以下の方法で検討した．通常の全身麻酔薬を用いて非動化の状態で開頭し，MRI 画像誘導装置を用いて決定した中心溝をまたぐように，直径 5 mm の円板電極が 5 mm 間隔で存在し，5×4 列が 1 シートとなった 20 極のグリッド電極を硬膜外腔に固定し，それぞれの刺激点を用いた monopolar anodal stimulation を行い，D-wave を記録した．刺激強度は 30 mA，刺激幅 0.2 msec，2 Hz で 16 回加算平均した．band pass は 5 Hz-5 KHz で，記録は 4 カ所ある記録点の中から隣接する記録部位を用いた双極導出とした．D-wave 記録後にグリッド電極をそのまま留置して閉頭し，手術を終了した．翌日以降に覚醒状態で，グリッド電極を用いて monopolar anodal stimulation を行った．25 Hz で 0.2 msec の刺激幅とし，10～20 mA の範囲で刺激強度を漸増し，途中で muscle contraction を認めた場合には，それ以上の強刺激は中止した．visual analogue scale（VAS）を用いてそれぞれの刺激部位で記録された D-wave の振幅と VAS の変化を比較した．

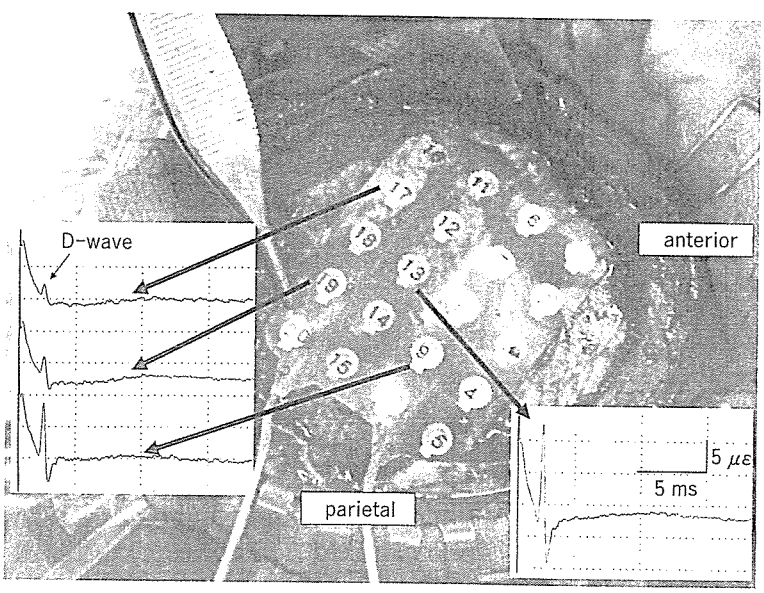
30 mA の monopolar anodal stimulation を用いたことから，通常の双極刺激で D-wave を誘発する範囲よりも広い範囲で D-wave が誘発された．D-wave の振幅と VAS の減少率を比較すると，D-wave が高振幅で記録された部位の刺激が有効であった．また，相関の有意性の検定を行うと，D-wave の振幅と VAS の減少率に有

意の相関を認めた（R＝0.828，p＜0.001：Pearson's correlation coefficient）．

大脳皮質運動領刺激における電極の留置部位を決定するには corticospinal MEP の D-wave を指標とするのが有効であることが，グリッド電極を用いた monopolar anodal stimulation で明らかとなった（図⓫）．



図⓫-A　経皮的に脊髄硬膜外腔に挿入した記録電極（quad electrode）．



図⓫-B　中心溝をまたいで開頭し，硬膜上にグリッド電極を置き，単極刺激で各刺激点を刺激（30 mA）し，corticospinal MEP の D-wave を記録した．術後の覚醒下での刺激で，D-wave の振幅と VAS の減少率に相関関係を認めた．

(3) 手 術 法

メドトロニック社製の慢性植込み型刺激装置では，単極刺激を選択した場合には刺激装置本体部分が陽極，電極部位が陰極の設定のみが可能であるため，単極刺激を用いると刺激装置本体の存在する部位の muscle response を誘発するので，双極刺激を選択する必要がある．実際の手術ではメドトロニック社の RESUME 電極で最大の極間距離（4 cm）を用いて双極刺激を行い，硬膜上を移動しながら D-wave が最大の振幅で記録される部位を決定して電極を留置している．

D-wave を用いる刺激部位の決定では，① D-wave を誘発するために使用した電極をそのまま慢性留置電極として使用できる，②皮質下の pyramidal neuron が刺激された反応そのものをモニターできるので，最適の刺激部位ならびに電極の留置方法を選択できる，③通常の全身麻酔で一期的な手術が可能である，などの利点がある．画像誘導装置を用いて中心前回に刺激電極を留置する方法では，電極が motor cortex 上に留置されても，実際に motor cortex がどの程度刺激されているかを確定することはできない．また，硬膜を開いて中心溝を確認して電極を留置することを推奨する報告もあるが，この方法でも実際にどのように刺激されているかを評価するのは困難である．一方，corticospinal MEP を用いる方法では，硬膜の上からでも最適の部位を決定することができるので，最も優れた方法であると考える．また，誘発筋電図を記録して電極の留置部位を決定する方法も有用であるが，α-motoneuron の興奮性によって変化するため，確実な方法とするには困難がある．D-wave の振幅と VSA の減少率に有意の相関を認めた事実は，最適の電極留置部位を決定するための有用な手段を提供するのみならず，大脳皮質刺激による除痛効果の発現機序を考える上で重要な事実と考える．

ま と め

多彩な薬理学的背景を有する中枢性疼痛に対しては，各種の方法を組み合わせた治療が必要となる症例が数多く存在する．また，情動の激しい変動や心因性の反応を呈する症例が多く認められることから，抗うつ薬，抗不安薬，抗てんかん薬の投与などに習熟する必要がある．難治性の疼痛が多い中枢痛の治療については，抗うつ薬，抗不安薬，抗てんかん薬の投与に加えて，大脳皮質運動領刺激，ケタミンの点滴投与などの治療を併用する必要のある症例も少なくない．

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Chapter 18

Cortical processing of noxious information in humans: a magnetoencephalographic study

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1. Introduction

Recent functional imaging studies in humans have provided evidence that multiple regions of the brain are involved in pain perception, including the primary (SI) and secondary (SII) somatosensory cortices, insula and anterior cingulate cortex (for review, see Bushnell et al., 1999; Schnitzler and Ploner, 2000). In support of the involvement of these regions in pain perception, neurophysiological studies in monkeys have demonstrated nociceptive neurons in SI (Biedenbach et al., 1979; Kenshalo and Isensee, 1983), SII (Robinson and Burton, 1980; Dong et al., 1994) and the insula (Robinson and Burton, 1980; Dostrovsky and Craig, 1996; Zhang et al., 1999). However, the precise temporal sequence of cortical activation is not well understood, especially in humans.

In this study, we sought to clarify the timing of multiple cortical activities following noxious stimulation using magnetoencephalography (MEG). MEG has an advantage over imaging modalities in that it can provide temporal information about an activity in addition to its location.

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2. Methods

The experiment was performed on 12 healthy male volunteers, aged 28–42 (mean 33.8 ± 4.3) years. The study was approved in advance by the Ethical Committee of the National Institute for Physiological Sciences and written consent was obtained from all subjects.

2.1. Noxious stimulation

For noxious stimuli, we used intra-epidermal electrical stimulation, a method that we recently developed (Inui et al., 2002a). A pushpin-type needle electrode with a needle tip 0.2 mm in length was used. By pressing the electrode plate gently against the skin, the needle tip was inserted adjacent to the nerve endings of the thin myelinated fibers in the epidermis and superficial part of the dermis. A surface electrode, 1.0 cm in diameter, was placed on the skin at a distance of 4 cm from the needle electrode as the anode. The electric stimulus was a current constant square wave

pulse delivered at random intervals of 0.1–0.3 Hz. The stimulus duration was 0.5 ms. The current intensity (0.19 ± 0.07 mA) was the level producing a definite pain sensation in each subject, which was determined prior to the experiment. The stimulated site was the dorsum of the left hand between the first and second metacarpal bones. By using this method, we could selectively stimulate cutaneous Aδ fibers (Inui et al., 2002a, b).

2.2. *SEF recording and analysis*

The somatosensory evoked magnetic fields (SEFs) were measured using dual 37-channel axial-type first-order biomagnetometers (Magnes, Biomagnetic Technologies, San Diego, CA), as described elsewhere (Kakigi et al., 2000). The magnetic fields were recorded with a 0.1–200 Hz filter at a sampling rate of 2083 Hz and then filtered at low pass, 100 Hz. The analysis window was 100 ms pre- to 400 ms post-stimulus. A hundred responses were collected and averaged.

Since several cortical activities overlapped temporally following painful stimulation (Watanabe et al., 1998), we used a multiple source model instead of a single equivalent current dipole (ECD) model. We used a brain electric source analysis (BESA) software package (NeuroScan, Inc, McLean, VA, USA) to analyze theoretical multiple source generators. The goodness of fit (GOF) indicated the percentage of data that can be explained by the model. We used the GOF value to determine whether the model was appropriate. To identify the best location of a source, movements were made in steps of 0.5–2.0 mm and the GOF was calculated at each location. We repeated this procedure until the largest GOF was obtained.

3. Results

A consistent magnetic field (termed 1M) was identified following epidermal stimulation (ES) in the hemisphere contralateral to the stimulated side (contralateral hemisphere) in all 12 subjects and in the hemisphere ipsilateral to the stimulated side (ipsilateral hemisphere) in 11 subjects (Fig. 1). Its peak latency was 149.0 ± 11.1 ms for the contralateral hemisphere

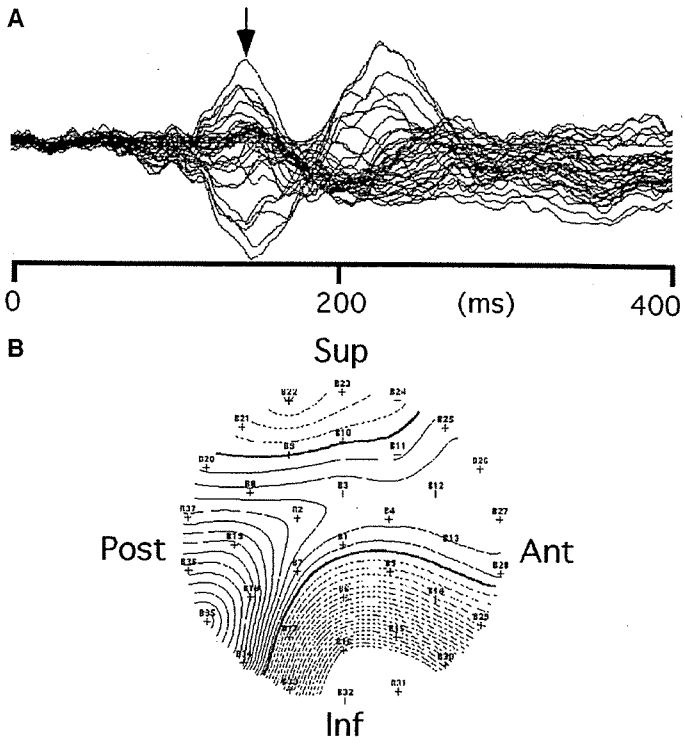

Fig. 1. Evoked magnetic fields following painful stimulation of the dorsum of the left hand. (A) Superimposed waveforms recorded from 37 channels in the hemisphere contralateral to the stimulation following epidermal stimulation in subject 1. (B) Isocontour map at the peak latency (shown by an arrow in (A)) of 1M. Note the complicated topography indicating multiple sources.

and 166.4 ± 13.1 ms for the ipsilateral hemisphere (1M (I)). The latency difference between the hemispheres was 17.4 ms and significant ($p < 0.0001$). The topography at the peak of 1M (Fig. 1B) often indicated the presence of multiple source activities at this latency point.

3.1. *Procedure of BESA analysis*

First, a latency range of about 10–160 ms was chosen as the period of ES evoked magnetic fields because one or two later activities emerged around the peak latency of 1M, as described below. We started the analysis with one source (source 0) placed around the Sylvian fissure since this area has been reported as a major source responsible for 1M evoked by noxious stimulation (Kakigi et al., 1995). As shown in Fig. 2A, the most effective source was usually the upper bank

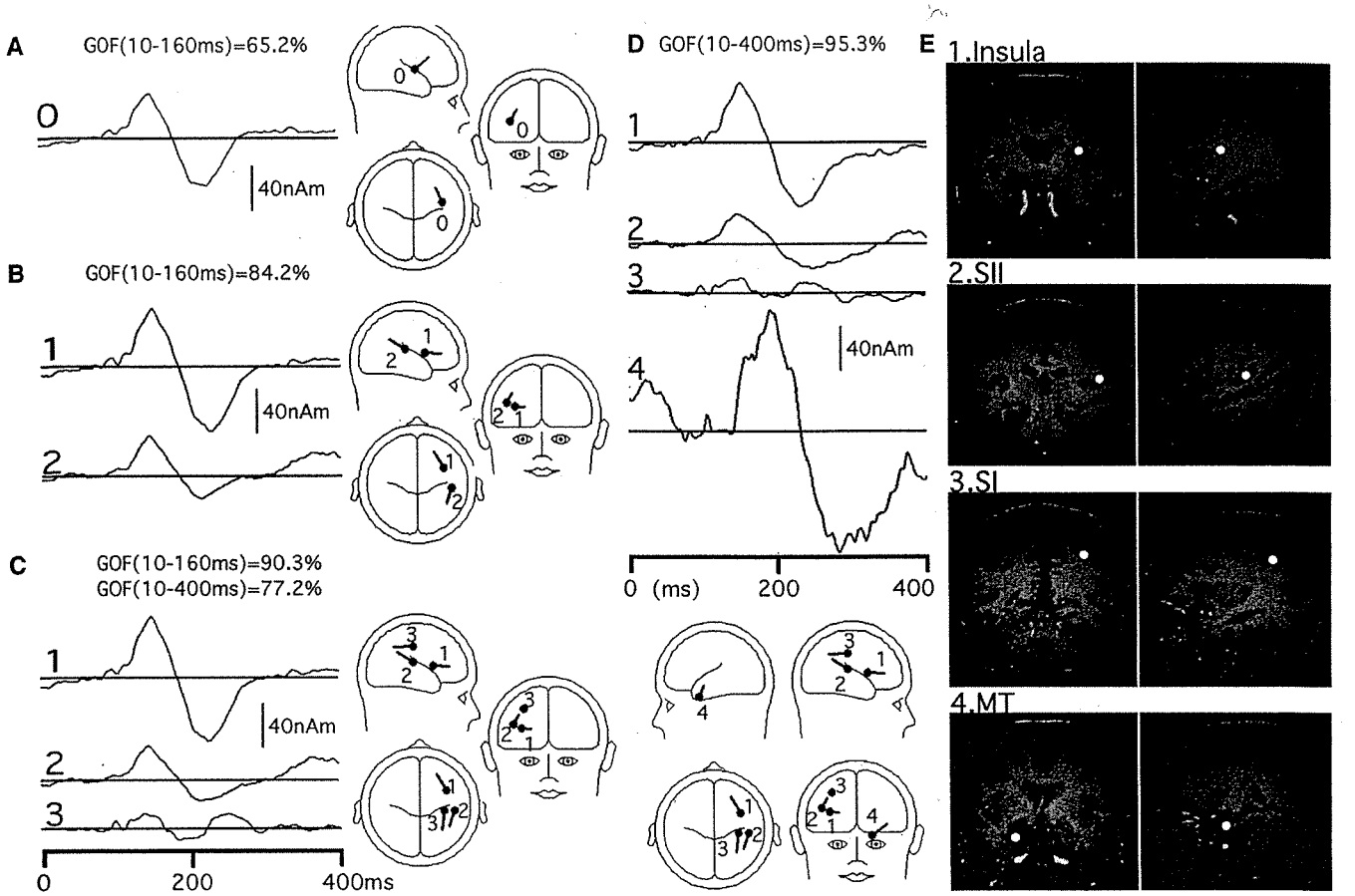

Fig. 2. Procedures for multiple source analysis. Brain electric source analysis (BESA) for epidermal stimulation (ES) evoked magnetic fields recorded from the hemisphere contralateral to the stimulation in subject 1. Traces show temporal profiles of source strength in each step of analysis. Bars in schematic drawings of the source location indicate directions of upward deflection of the waveform. (A)–(D) Results for the one-, two-, three-, and four-source model, respectively. (E) Location of source generators overlaid on MRI scans. Sources 1–4 correspond to the insular cortex, secondary somatosensory cortex (SII), primary somatosensory cortex (SI) and amygdala/hippocampal formations(medial temporal (MT) area), respectively. GOF – goodness of fit. (Adopted from Inui et al., 2003.)

or bottom of the Sylvian fissure, supporting previous reports including our own. However, this source could not explain the magnetic fields during the analysis period (mean GOF = 65.2%) as expected from the complicated topography of 1M in Fig. 1. We therefore then tested a pair of sources placed around the Sylvian fissure that explained the magnetic field most effectively. In most cases, one source (source 2) was located in the upper bank of the Sylvian fissure and the other (source 1) near the insular circular sulcus (Fig. 2B). When the GOF did not exceed 90% with the two-source model, we placed one more source (source 3) around the central sulcus (Fig. 2C) since recent MEG studies have revealed that 1M contains an activity originating from SI (Ploner et al., 1999; Kanda et al., 2000; Inui et al., 2002b). The two- or three-source model provided a GOF value of more than 90% in all subjects, and the location and orientation of the sources were fixed. The period of analysis was then expanded to 10–400 ms (whole recording), and one or two sources were added, if necessary, to obtain a GOF larger than 90% (Fig. 2D). We placed sources in the medial temporal (MT) area, around the amygdalar nuclei or hippocampal formation and at the cingulate cortex because both areas were considered to contribute to pain perception (Talbot et al., 1991; Watanabe et al., 1998). After this process, a three- to five-source model was obtained in each subject and

TABLE 1

PEAK LATENCIES OF CORTICAL RESPONSES (in ms)

	SI		Insula	SII	MT		Cingulate
	Early	Late			Early	Late	
Contralateral	93.9	160.8	147.8	152.2	184.0	289.7	208.5
Ipsilateral			164.5	170.5	196.5	313.3	206.5

the results were used for further analysis. The actual location of the sources was confirmed by overlaying on MR images (Fig. 2E).

In all subjects, SII and insular sources were identified in the contralateral hemisphere. The peak latency was 152.2 and 147.8 ms, respectively (Table 1), and corresponded approximately to that of 1M (149.0 ms). These sources were therefore considered major components of 1M. Activity in the contralateral SI was identified in all subjects. The time course of SI activity was complicated compared with the insula and SII activities, i.e. SI activity consisted of 1–3 brief components followed by a relatively long component (Fig. 3). However, the first early SI component was very small in amplitude and was identified in only three subjects. We therefore used the second brief component (early SI, $n = 9$) and the later component (late SI, $n = 12$) for analysis. The peak latency of the early SI component was 93.9 ms, which slightly preceded the onset of SII activity (98.3 ms) but was slightly delayed compared to the onset of insula activity (90.9 ms). The peak latency of the late SI component was 160.8 ms; therefore, the late SI activity also contributed to 1M production.

From the recordings obtained from the ipsilateral hemisphere, insula and SII activity was identified in ten subjects. The peak latency of SII (170.5 ms) and the insula (164.5 ms) approximately corresponded to that of 1M (I) (166.4 ms), indicating that these activities were major components of 1M (I). The peak latency of the ipsilateral SII activity was 18.7 ms later than the contralateral SII activity ($p = 0.001$). Similarly, the ipsilateral insular activity peaked 16.5 ms later than the contralateral response ($p = 0.0016$).

For magnetic fields later than 1M, a source in the MT area was necessary in eleven out of twelve subjects. Activity in the ipsilateral hemisphere was identified in eleven subjects, but in only three subjects in the contralateral hemisphere. The activity in this area always consisted of two peaks in opposite directions. The onset latency of this activity (ipsilateral hemisphere) was 155.6 ± 16.7 ms, near the peak latency of insula and SII activity. As another source of magnetic fields later than 1M, the cingulate cortex was identified in five subjects, the contralateral hemisphere in three, the ipsilateral hemisphere in one, and both hemispheres in one. This ECD always pointed laterally and the vector of superior–inferior orientation was very small (Fig. 3). The onset and peak latencies were almost identical for the first component of the MT source (Table 1). ECDs for this activity were localized to the anterior part of the cingulate cortex (Fig. 3).

4. Discussion

Results in experimental animals (Biedenbach et al., 1979; Kenshalo and Isensee, 1983) and human imaging studies (Bushnell et al., 1999) clearly indicate that SI is involved in nociception. In this study, early SI activity clearly showed a shorter response latency than other source activities. Only a few MEG studies have shown SI activation following painful stimulation. Ploner et al. (1999) demonstrated the simultaneous activation of SI and SII by painful laser stimulation for the first time, indicating a parallel thalamocortical distribution of nociceptive information, which was confirmed later by Kanda et al. (2000) and Inui et al. (2002b). Anatomical data from experimental animals

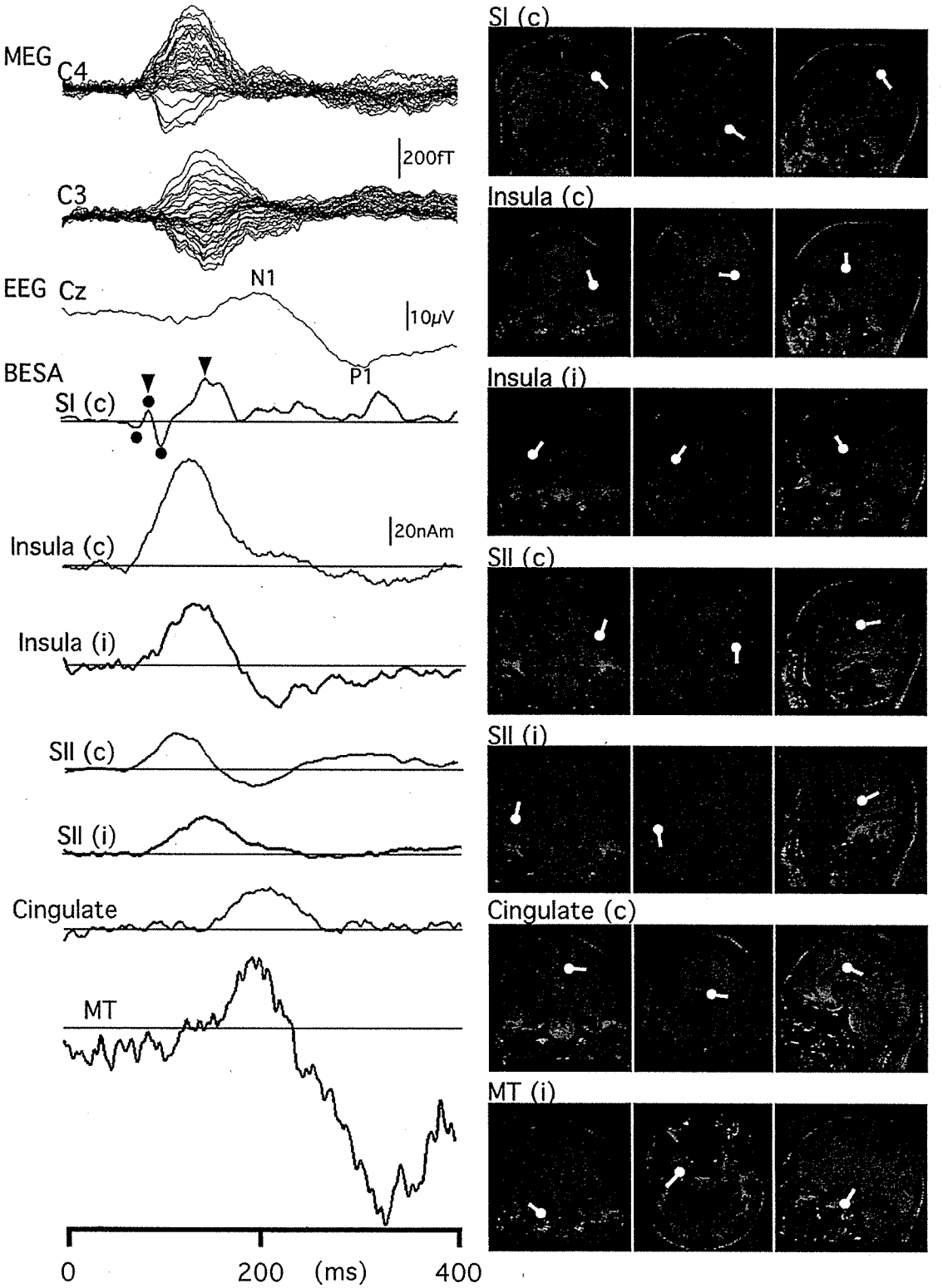

Fig. 3. Temporal profile of cortical activities following painful epidermal stimulation. Cortical responses to epidermal stimulation in subject 2. The upper three traces are superimposed waveforms recorded from 37 channels in both hemispheres. The lower seven traces are temporal profiles of each source strength. Filled circles indicate a group of early SI activities. Arrowheads indicate the peak latency of early and late SI activity analyzed in this study. Right: locations of source generators overlaid on MRI scans. (Adopted from Inui et al., 2003.)

also supported the parallel thalamocortical distribution of nociceptive information (Kenshalo et al., 1980; Friedman and Murray, 1986). However, the SI activity mentioned above corresponded to our late SI activity, i.e. MEG studies observed late SI activity but did not identify early components. Previous studies probably failed to identify early SI activities because laser stimulation takes a relatively long time to activate nociceptors because of temperature conduction and this causes latency jittering of the response. Since early SI activities consisted of several brief components oriented in opposite directions, 10–20 ms of latency jittering easily canceled out these activities after averaging the trials. Our method, in contrast, uses electrical stimulation and therefore provides constant responses in terms of latency.

ES activated the anterior/mid-part of the insular cortex. The anterior location of pain-related activation in the insula was consistent with most functional imaging studies (for review, see Schnitzler and Ploner, 2000). Unitary recordings in monkeys have provided evidence of nociceptive neurons in the insula (Robinson and Burton, 1980; Dostrovsky and Craig, 1996). The failure to detect insular activities in previous MEG studies is probably due to the similar time course and the proximity of insular and SII activity. As the insula is located deeper than SII and recorded magnetic fields from the insula are weaker than those from SII, insula activity may be buried in those from SII when we analyze data using a single dipole model.

Our results showed that noxious cutaneous stimuli produced SII activation as consistently demonstrated by brain imaging studies. The latency of the SII response coincided with the results of previous MEG studies (Kakigi et al., 1995; Ploner et al., 1999). While this study could not clarify whether there is hierarchical activation in SI and SII in pain processing, our data showing sequential activation in these areas favor a serial mode rather than a parallel mode of pain processing in SI and SII. This notion is consistent with anatomical findings in monkeys that SI receives projections from the lateral thalamic nuclei and, in turn, sends fibers to SII.

For middle–late components of ES evoked magnetic responses, we found anterior cingulate cortex activity in five subjects, in which recent imaging studies have consistently found pain-related activity (for review, see Schnitzler and Ploner, 2000). We identified the MT, including the amygdala nuclei and hippocampus as another source of activity for middle–late ES evoked responses. Since limbic structure activity emerged later than SI, SII and insular activity, and since corresponding pain-related vertex potentials were modulated by arousal and attentional levels in previous studies, these limbic structures are considered involved in the attentional and emotional aspect of nociception.

4.1. Temporal sequence of cortical activity

Our findings that neither onset nor peak latencies differed between SII and the insula indicated parallel processing. Our data showing that ES evoked SII activity appeared 7.4 ms later than insular activity also indicated an origin other than SII (Friedman et al., 1986) for insula activation, including the thalamus (Friedman and Murray, 1986) and SI (Mufson and Mesulam, 1982). As activation in the anterior/mid-insula is related to noxious stimuli in imaging studies, it seems possible that the insula receives input from modality-specific neurons in the thalamus. For example, Craig et al. (1994) demonstrated a very high concentration (97%) of pain- and thermo-specific neurons in the posterior part of the ventral medial thalamic nucleus (VMpo), which has dense lamina I spinothalamic tract terminations. VMpo projects to the insula (Craig et al., 1994) and the dorsal anterior region of the insula in monkeys contains a concentrated number of nociceptive-specific neurons (Dostrovsky and Craig, 1996).

The insula has been shown to project to limbic structures including the amygdaloid complex (Mesulam and Mufson, 1982; Friedman et al., 1986) and cingulate cortex (Vogt and Pandya, 1987). Our results revealed that onset latencies of MT and the cingulate cortex approximately corresponded to the peak latencies of insular activity, so it is possible that both MT and the cingulate cortex were driven by the insula. As the anterior insula sends fibers directly to the amygdaloid complex and the hippocampal formation indirectly via the perirhinal cortex (Friedman et al., 1986), this cortico-limbic pathway may play a role in pain recognition or

emotional reactions to noxious events (LeDoux, 1995). Our results therefore suggested two parallel pathways of pain processing, one through the lateral thalamic nuclei, SI, and SII serially and another through the medial thalamic nuclei, insula, and limbic structures serially. These two distinct pathways seem to correspond to the classic dichotomy of pain processing, the lateral and medial systems, which are involved in discriminative and emotional aspects of pain, respectively.

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Inner Experience of Pain: Imagination of Pain While Viewing Images Showing Painful Events Forms Subjective Pain Representation in Human Brain

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Pain is an unpleasant sensation, and at the same time, it is always subjective and affective. Ten healthy subjects viewed 3 counterbalanced blocks of images from the International Affective Picture System: images showing painful events and those evoking emotions of fear and rest. They were instructed to imagine pain in their own body while viewing each image showing a painful event (the imagination of pain). Using functional magnetic resonance imaging, we compared cerebral hemodynamic responses during the imagination of pain with those to emotions of fear and rest. The results show that the imagination of pain is associated with increased activity in several brain regions involved in the pain-related neural network, notably the anterior cingulate cortex (ACC), right anterior insula, cerebellum, posterior parietal cortex, and secondary somatosensory cortex region, whereas increased activity in the ACC and amygdala is associated with the viewing of images evoking fear. Our results indicate that the imagination of pain even without physical injury engages the cortical representations of the pain-related neural network more specifically than emotions of fear and rest; it also engages the common representation (i.e., in ACC) between the imagination of pain and the emotion of fear.

Keywords: brain, emotion, fMRI, IAPS (International Affective Picture System), pain, SII (secondary somatosensory cortex)

Introduction

Pain is an unpleasant sensation, but at the same time, it is always subjective and emotional (Fields 1999). Individuals learn of "pain" through experiences related to injury in their life, and they are able to imagine pain from their past experiences even without physical injury.

Recently, from the viewpoint of "empathy," some neuroimaging studies on pain processing have revealed a partial neural overlap between the experience of pain in self and the observation of pain in others (i.e., empathy for other's pain) (Singer and others 2004; Botvinick and others 2005; Jackson and others 2005). Although the actual experience of pain and the empathic feeling of the pain of other individuals involve similar brain regions such as the anterior cingulate cortex (ACC) and anterior insula, activations of the secondary somatosensory cortex (SII) and dorsal ACC were specifically attributable to receiving actual pain and were not detected from the observation of pain in others (Singer and others 2004). However, changing perspective taking, Jackson and others (2006) clearly differentiated the cerebral representation between the imagination of pain (i.e., a self-oriented aversive response that induces both empathy and distress) and imagining how others would feel pain (i.e., empathy for other's pain), showing that the imagination of pain activates the pain-related neural network (pain matrix) extensively including the SII, dorsal ACC (Brodmann Area [BA] 24), and insula. Furthermore, in a study of patients with phantom limb pain using a hypnotic suggestion that the missing limb was in a painful position, Willoch and others (2000) found a similar activation in the pain matrix including the SII, ACC, and insula in the absence of any noxious stimulation.

The aim of our functional magnetic resonance imaging (fMRI) study is to investigate the hemodynamic changes stemming from the inner experience of pain (imagination of pain) perceived from viewing images showing painful events in an intact body, in comparison with those stemming from another aversive emotion, that is, fear and rest emotion elicited by the International Affective Picture System (IAPS) (Lang and others 2005). This picture system includes images of several different emotional scenes; it is possible to use these images to elicit specific emotions. In a number of neuroimaging studies using the IAPS, various emotions, such as happiness, sadness (Lang and others 1998), and disgust (Schienle and others 2002), the anticipation of painful stimulation and aversive situations (Simmons and others 2004), the anticipation of aversion (Nitschke and others 2006), and their neural mechanisms have been shown. We focused on the emotions of pain and fear because these emotions have common features. Pain and fear belong to the category "negative affect," which is associated with the withdrawal from the emotion elicitor serving to protect the organism from being harmed and are also part of different warning systems dealing with different types of threat.

Materials and Methods

Subjects

Ten healthy, right-handed volunteers (10 males; mean age 26.3 ± 4.7 years [range 22–37 years]) participated in the fMRI study. The subjects were all fMRI-experienced males. The subjects had no history of head injury, learning disability, or psychiatric illness, including substance abuse/dependence or taking regular medications. All the subjects gave their written informed consent after the explanation of the experimental protocol, as approved by the local Institutional Review Board.

Task Design

The stimulus materials consisted of 45 images belonging to 3 emotional categories: images showing painful events (pain condition), images evoking fear (fear condition), and images evoking rest (rest condition) (15 each). Trials were blocked by the emotional categories. The block order was counterbalanced. In each block, 5 images of the same emotional category were presented for every 6 s (a 5-s presentation with a 1-s interstimulus interval). One run consisted of nine 30-s blocks and lasted 270 s. All the subjects performed 2 runs. Each pain, fear, and rest image was presented twice in the experiment. The stimuli were displayed through a shielded liquid crystal display panel mounted on the head coil.

The images were taken from the IAPS of Lang and others (2005), which includes images that have already been rated as representative examples on different emotional dimensions: mainly valence and arousal

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

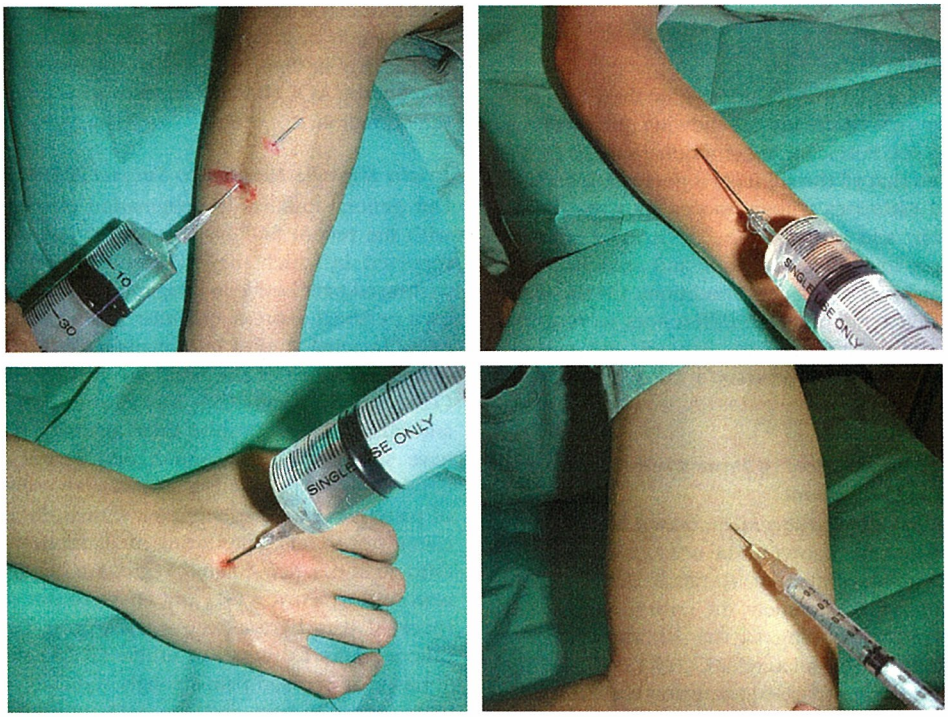

Figure 1. Sample painful images. We used 15 images for each condition (pain, fear, and rest conditions). In addition to the "images showing painful events" taken from IAPS (Lang and others 2005), we used 8 pictures made by the authors in the pain condition to fill up the deficit of images showing painful 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

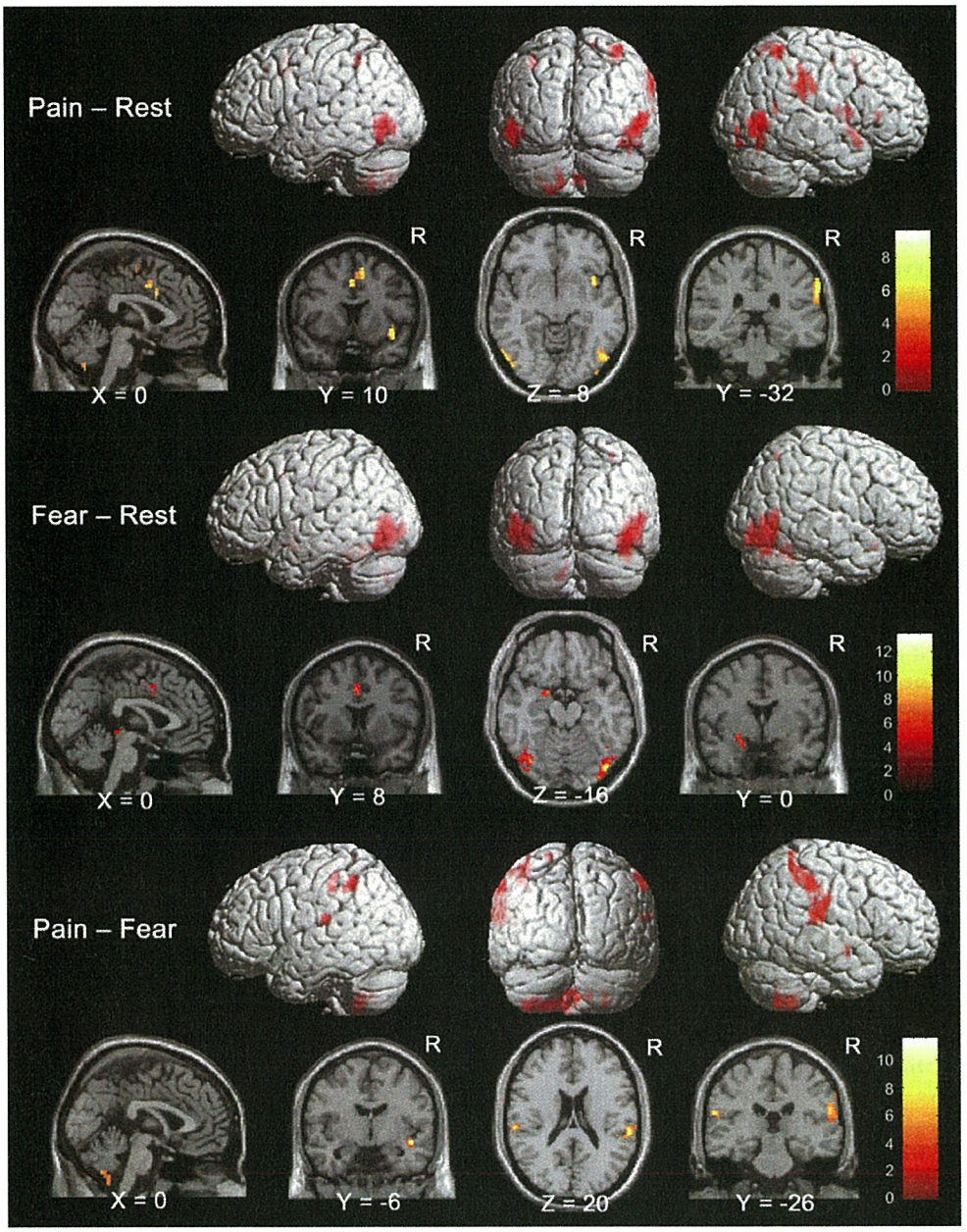

Figure 2. Brain activations in each contrast. Activated brain areas in each contrast: pain – rest, fear – rest, and pain – fear conditions. Pain – rest and pain – fear contrasts revealed activations in the SII region and PPC areas and in the affective components of the pain matrix such as the ACC, anterior 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

AUTHOR PROOF

Early cortical activities evoked by noxious stimulation in humans

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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.

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