cycle, in the normal physiological range, influence cortical processing of noxious stimuli. The current study investigated the influence of the cardiac cycle, as an index of pulsatile variations in blood pressure, on the cortical processing of nociception. The study used thulium-evoked laser stimulation, that exclusively activates nociceptive nerve fibers, to evoke pain-related late brain potentials [22,29]. Based on previous findings that the nociceptive flexion reflex is attenuated during systole, it was hypothesised that the N2–P2 amplitude, an objective index of the degree of induced pain [6], would be smaller during systole than diastole.

2. Methods

2.1. Participants

Ten healthy male normotensive volunteers, with a mean age of 33 years (SD = 6), mean height of 171 cm (SD = 4), mean weight of 65 kg (SD = 6), mean systolic blood pressure of 120 mmHg (SD = 11), mean diastolic blood pressure of 77 mmHg (SD = 9) and mean heart rate of 63 bpm (SD = 11), participated in the study. All participants were free from neurologic and psychiatric diseases and psychiatric and analgesic medications. Participants were asked to refrain from alcohol, caffeine and smoking for at least 12 h prior to testing. The study was approved by the Ethics Committee at National Institute for Physiological Sciences, Okazaki; all volunteers gave informed consent to participate.

2.2. Laser stimulation

A thulium:YAG laser stimulator (Carl Baasel Lasertech, Starnberg, Germany) was used to produce noxious stimuli. Laser pulses (1 ms in duration, 2000 nm in wavelength, and 3 mm in spot diameter) were delivered to the dorsum of the right hand at an interval of between 15 and 20 s. The irradiated points were moved slightly for each stimulus to avoid tissue damage and habituation of the receptors. At the start of the session, 10–20 laser stimuli were delivered to determine the stimulus intensity required to produce a painful sensation. After each stimulus, the participants rated the stimulus using a visual analogue scale (VAS), with anchors of 0 (no painful sensation) and 100 (imaginary intolerable pain sensation). A stimulus intensity ($M = 158$, SD = 9 mJ), rated as approximately 50 on the VAS, was used to examine pain-related evoked potentials (see below). At this laser intensity, all subjects rated the stimulus as a pricking pain sensation. Trained subjects can discriminate the first and second pain sensations, however, no subjects in this study reported a sensation other than pricking.

2.3. Laser evoked potential recording

The laser evoked potentials were recorded with an Ag/AgCl disk electrode placed over Cz (vertex), referred to the linked earlobes (A1 + A2) of the International 10/20 System. A pair of electrodes placed on the supra- and infra-orbit of the right eye was used for recording an electro-oculogram. An electrocardiogram was recorded using a pair of disk electrodes placed on each forearm. The impedance of all electrodes was kept below 5 kΩ. The electroencephalographic signals were recorded with a 0.1 to 100 Hz bandpass filter and digitized at a sampling rate of 1000 Hz. The period of analysis was 800 ms before to 600 ms after stimulus onset; the pre-stimulus period was used as the DC baseline. Individual trials containing artifacts due to eye blinks were rejected before averaging.

2.4. Procedure

Each subject was seated in an armchair in a quiet, electrically shielded, and temperature controlled (24 to 26 °C) room. Laboratory systolic blood pressure (mmHg), diastolic blood pressure (mmHg), and heart rate (bpm) were measured three times using a mercury sphygmomanometer and a brachial cuff attached to the participant's upper left arm. The experimental session consisted of 5 blocks of 12 trials. Each block was separated by a 10-min rest period. During the experiment, a fixation point (a white circle 2 cm in diameter) was displayed on a screen 1.5 m in front of the subjects from 10 to 15 s before until 2 s after each stimulus. Subjects were instructed to look at the fixation point when it was displayed. Two seconds after the onset of each stimulus, the fixation point disappeared and 'VAS' was displayed for 3 s, during which subjects rated the perceived sensation. Then the fixation point appeared again to prepare the next stimulus. The participants were instructed to rate the perceived pricking sensation associated with each laser stimulation by marking a 100 mm VAS.

2.5. Data reduction and analysis

The R-wave latency relative to stimulus onset (ms) and peak-to-peak amplitude (μV) of the N2–P2 component were measured in each trial. The peak of N2 and P2 was determined during a latency period of 180–240 and 280–400 ms, respectively, for each trial. To show the variability of N2/P2 components in each trial, the waveforms of 12 consecutive trials in a representative participant are depicted in Fig. 1. In addition, the amplitudes of each N2 and P2 component were measured, using a DC offset, from the prestimulus baseline of −100 ms to the peak negativity and positivity, respectively. Trials were then sorted into one of eight 100 ms wide intervals (each interval is labeled by its midpoint), whose minimum and maximum indicated the timing of the noxious stimulation after the R-wave: 0–99 ms (R + 50 ms), 100–199 ms (R + 150 ms), 200–299 ms (R + 250 ms), 300–399 ms (R + 350 ms), 400–499 ms (R + 450 ms), 500–599 ms (R + 550 ms), 600–699 ms (R + 650 ms) and 700–800 ms (R + 750 ms). The mean (SD) number of trials per R-wave to stimulation interval was 5.0 (1.6), 5.3 (2.8), 6.3 (2.8), 5.4 (2.8), 5.4 (1.8), 6.2 (1.9), 5.4 (2.9), 6.4 (2.2) for R-wave intervals R + 50 to R + 750 ms, respectively. All participants provided data for every R-wave to stimulation interval. Data were lost (25% of total number of trials) on trials with blink artifacts and trials when the R-wave occurred more than 800 ms before the onset of noxious stimulation. The mean N2, P2 and N2–P2 peak-to-peak amplitudes (μV) and pain ratings were calculated for each R-wave to stimulation interval. Repeated measures analyses of variance (ANOVAs) with R-wave to stimulation interval (i.e., R + 50,

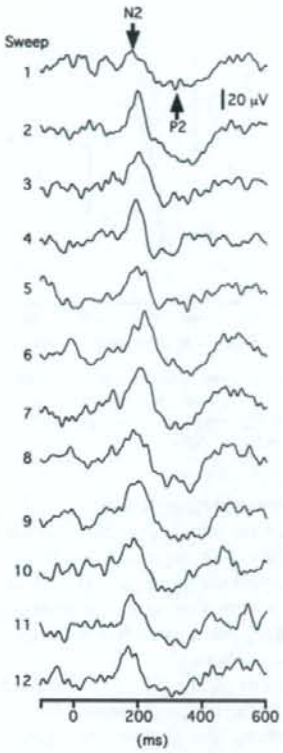

Fig. 1. Pain-related evoked potential waveforms of 12 consecutive trials, depicting N2 and P2, in a representative participant.

R + 150, R + 250, R + 350, R + 450, R + 550, R + 650, R + 750 ms) as a within-subjects factor were performed on the N2, P2 and N2–P2 amplitudes and pain ratings. ANOVAs were corrected for the assumption of independence of data points using the Huynh–Feldt correction (ε). Eta-squared (η^2), a measure of effect size, is also reported. A significance level of .05 was adopted. Significant results were followed by LSD post hoc tests. The data were analyzed using Statistica'99.

3. Results

3.1. N2–P2 peak-to-peak amplitudes

A repeated measures ANOVA (8 Intervals) revealed significant variations in the N2–P2 amplitude across the cardiac cycle, $\varepsilon = .74$, $F(7, 63) = 3.15$, $p = .02$, $\eta^2 = .26$, which were characterized by a quadratic trend, $F(1, 9) = 29.83$, $p = .0005$, $\eta^2 = .77$ (see Fig. 2). Post hoc comparisons confirmed that the N2–P2 amplitudes elicited by stimulation at R + 250, R + 350 and R + 450 ms were smaller than those elicited at R + 50, R + 150 and R + 750 ms. For illustrative purposes, the grand mean waveforms, averaged for the early (R + 50, R + 150 ms), middle (R + 250, R + 350, R + 450 ms) and late (R + 550, R + 650, R + 750 ms) phases of the cardiac cycle, are presented in Fig. 3, where it can be seen that the amplitudes were smaller mid-cycle compared to early and late cycle.

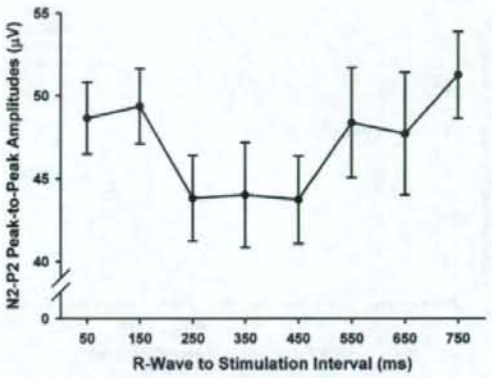

Fig. 2. Mean (SE) N2–P2 peak-to-peak amplitudes as a function of phase of the cardiac cycle. A repeated measures ANOVA revealed significant variations in the N2–P2 amplitude across the cardiac cycle ($p = .02$). Post hocs comparisons confirmed that N2–P2 amplitudes elicited by stimulation at R + 250, R + 350 and R + 450 ms were smaller than those elicited at R + 50, R + 150 and R + 750 ms. $N = 10$, Trials = 45. SE = SD ÷ $\sqrt{N}$.

3.2. N2 amplitudes

A repeated measures ANOVA (8 Intervals) revealed significant variations in the N2 amplitude across the cardiac cycle, $\varepsilon = .99$, $F(7, 63) = 4.13$, $p = .001$, $\eta^2 = .31$, which were characterized by a quadratic trend, $F(1, 9) = 25.43$, $p = < .001$, $\eta^2 = .74$ (see Fig. 4). Post hoc comparisons confirmed that the N2 amplitudes elicited by stimulation at R + 250 ms were smaller than those elicited at R + 50, R + 150, R + 650 and R + 750 ms. Stimulation at R + 350 ms produced smaller N2 amplitudes than R + 150, R + 650 and R + 750 ms. Finally, stimulation at R + 450 ms produced smaller N2 amplitudes than R + 650 and R + 750 ms.

3.3. P2 amplitudes

A repeated measures ANOVA (8 Intervals) did not reveal significant variations in the P2 amplitude across the cardiac cycle, $\varepsilon = .84$, $F(7, 63) = 0.73$, $p = .63$, $\eta^2 = .07$ (see Fig. 5).

3.4. Pain ratings

A repeated measures ANOVA (8 Intervals) revealed no significant differences in pain ratings across the cardiac cycle, $\varepsilon = .64$, $F(7, 63) = 1.10$, $p = .37$, $\eta^2 = .11$ (see Fig. 6).

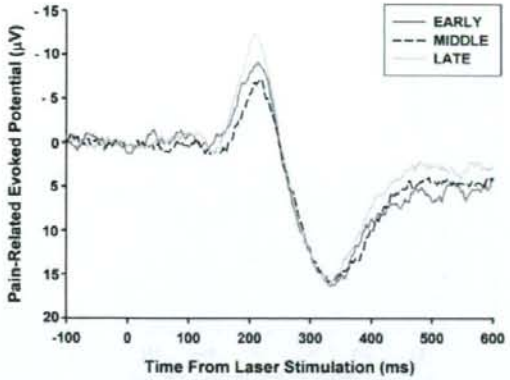

Fig. 3. Grand average pain-related evoked potentials waveforms grouped into early (R + 50 to R + 150 ms), middle (R + 250 to R + 450 ms), and late (R + 550 to R + 750 ms) phases of the cardiac cycle. $N = 10$, Trials = 45.

4. Discussion

The present study found significant variations across the cardiac cycle in the amplitude of the N2–P2 pain-related components of the evoked potential elicited by noxious laser stimulation. The N2–P2 amplitude difference is believed to be an objective index of the degree of induced pain [6]. Indeed, positive relationships have been found between the intensity of noxious laser stimuli, the amplitude of the N2–P2, and the magnitude of pain sensation [7]. The observation of smaller amplitude N2–P2 waveforms during the middle of the cardiac cycle indicates that pain-related cortical responses were attenuated during systole compared to diastole. Accordingly, these data support the hypothesis that stimulation of the arterial baroreceptors by natural changes in blood pressure during the cardiac cycle has a dampening effect on the nociceptive system.

In the present study, we only recorded the N2–P2 components of the evoked potential from one electrode at Cz. Therefore, the data cannot reveal the precise mechanisms of N2–P2 modulation across the cardiac cycle. However, the grand-averaged waveform (see Fig. 3) suggests that the cardiac cycle effect was larger for N2 than P2. Indeed, separate analyses of the N2

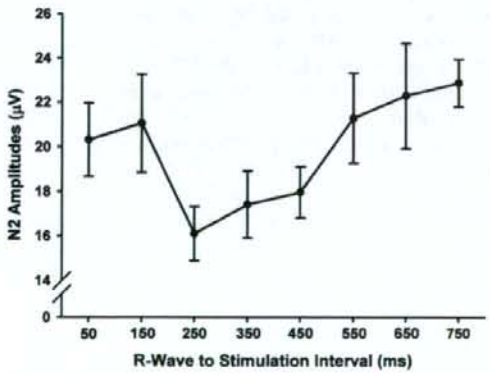

Fig. 4. Mean (SE) N2 amplitudes as a function of phase of the cardiac cycle. A repeated measures ANOVA revealed significant variations in N2 amplitude across the cardiac cycle, ($p = .001$). Post hocs comparisons confirmed that N2 amplitudes elicited by stimulation at R + 250 ms were smaller than those elicited at R + 50, R + 150, R + 650 and R + 750 ms. Stimulation at R + 350 ms produced smaller N2 amplitudes than R + 150, R + 650 and R + 750 ms. Finally, stimulation at R + 450 ms produced smaller N2 amplitudes than R + 650 and R + 750 ms. $N = 10$, Trials = 45. SE = SD + $\sqrt{N}$.

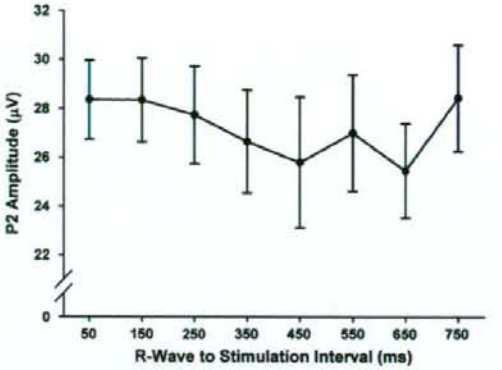

Fig. 5. Mean (SE) P2 amplitudes as a function of phase of the cardiac cycle. A repeated measures ANOVA did not reveal significant variations in the P2 amplitude across the cardiac cycle ($p = .63$). $N = 10$, Trials = 45. SE = SD + $\sqrt{N}$.

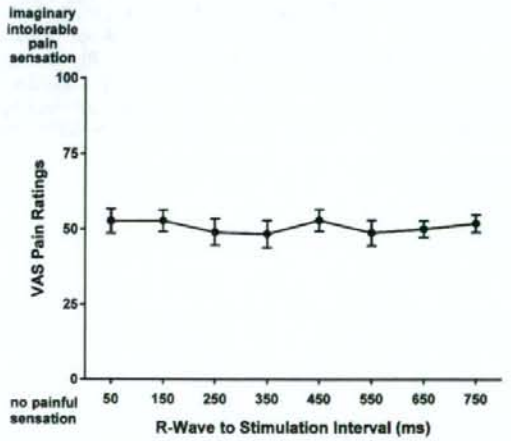

Fig. 6. Mean (SE) VAS pain ratings as a function of phase of the cardiac cycle. A repeated measures ANOVA revealed no significant differences in pain ratings across the cardiac cycle ($p = .37$). $N = 10$, Trials = 45. SE = SD + $\sqrt{N}$.

and P2 components revealed cardiac cycle time effects for N2 and not P2. The N2 and P2 components are generated mainly in the anterior cingulate cortex [8,43,46]. In addition to anterior cingulate cortex, the secondary somatosensory cortex or insula cortex contribute to shape the N2 component [8,31,43,46]. Therefore, our findings are compatible with the hypothesis that the target site of the interaction between N2 and P2 and baroreceptor output is the somatosensory or insula cortex. Further studies employing multi-channel recordings are required to test this hypothesis.

This is the first study, to our knowledge, to describe modulation of the pain-related evoked potential with natural variations in baroreceptor activation across the cardiac cycle. The current findings broadly agree with previous research which has reported reduced N2–P2 amplitudes elicited by intracutaneous stimulation of the finger during artificial stimulation of the baroreceptors using neck suction [3,28]. In addition, the current data are in line with reports of dampened lower limb nociceptive flexion reflex responding during systole compared to diastole [13–15,26]. The modulating effect of the cardiac cycle on the brain appears not to be exclusive to nociception. Auditory and visual perception vary with the phase of the cardiac cycle: sensitivity is generally lowest at the start of the cardiac cycle and increases as the cycle progresses [37,40]. Further, modulation of visual and auditory event-related potentials has been demonstrated during systole and diastole: the P1 component of the visual evoked potential [47] and the N1 component of the auditory evoked potential [38] were smaller during systole. Previous research has demonstrated that rhythmic oscillations of the EEG, most notably in the alpha range, were time locked to the carotid pressure wave [48]. Other research has examined the effects of artificial baroreceptor stimulation on the brain. A classic study in cats showed that mechanical stimulation of the carotid sinus baroreceptors had an inhibitory influence on cortical excitability [4]. Further, artificial baroreceptor stimulation in humans has been shown to cause a substantial reduction in slow cortical negative potentials, particularly the contingent negative variation, an index of cortical arousal [17,34,35]. Accordingly, the current cycle time effect for the pain-related evoked potential adds to a compelling body of evidence for a relationship between the cardiovascular system and the brain.

Pain was not modulated across the cardiac cycle in the current study. This is in line with previous studies which found no differences in pain reports for electrocutaneous stimuli delivered at various intervals after the R-wave of the electrocardiogram [13–15]. These findings contrast with the results of other studies that employed artificial baroreceptor manipulations. These studies reported that pain was lower during systole compared to diastole during neck suction [2], during repeated neck suction and compression [28,32], as well as during single neck suction and compression pulses [13]. These contradictory findings may be due to differences between natural and artificial baroreceptor stimulation studies in terms of the level of baroreceptor stimulation achieved.

The mechanism by which pain-related cortical processing is attenuated by the cardiac cycle has yet to be determined. However, it is reasonable to assume that these effects might be due to natural fluctuations in arterial baroreceptor activity across the cardiac cycle (see [15,16]). The integrated baroreceptor output of aortic baroreceptors located in the aortic arch and carotid sinus can be estimated to extend from 90 to 390 ms after the R-wave. The current study found that the N2–P2 amplitude was attenuated when noxious stimuli were delivered to the hand during the 200–299, 300–399 and 400–499 ms intervals after the R-wave. The onset latency of cortical activity in SI and SII, the proposed site of interaction, following noxious YAG laser stimulation to the hand has been recorded at 90–110 ms [30,49]. Thus, as N2–P2 was modulated from 200 ms after the R-wave, the earliest time the SII must be affected by baroreceptor activity is 290 ms after the R-wave. Accordingly, the observed pattern of modulation of the N2–P2 amplitude is compatible with the pattern of baroreceptor activation when a sensory transduction and processing delay of approximately 150 ms is included. This 150 ms delay may be explained by neural transmission times within the brainstem. For example, electrical stimulation of baroreceptor afferents in dogs and cats has been shown to cause inhibition of sympathetic activity with a latency of 150–200 ms, dependent on the recording site at the spinal level [10,36]. Allowing 10–15 ms for transmission of nerve impulses from carotid sinus and aortic arch to the nucleus of the solitary tract [42], and approximately 30 ms from the rostral ventrolateral medulla to sympathetic preganglionic neurons [25], this leaves 100–150 ms for transmission in the lower brainstem from the nucleus of the solitary tract to the rostral ventrolateral medulla [11]. This 100–150 ms transduction latency could perhaps explain the 150 ms delay between baroreceptor activation and attenuation of the N2–P2 amplitudes found in the current study. Further, there is substantial evidence suggesting that structures involved in the baroreflex pathway could also influence the pain system (for review, see [19]). For example, stimulation of the nucleus of the solitary tract induces antinociception [1] and the A5 cell group and locus coeruleus are sources of descending noradrenergic fibers that modulate spinal nociceptive transmission [27]. Furthermore, other evidence shows that pain areas are involved in baroreflex control. The periaqueductal grey matter, which produces analgesia when stimulated, can modulate the arterial baroreflex [21]. The nucleus raphe magnus in the rostral ventrolateral medulla, which plays a role in pain modulation, is involved in

the baroreflex pathway mentioned above, and also contains neurons that respond to noxious stimuli that show spontaneous fluctuations in phase with both natural variations and experimentally-induced changes in blood pressure [44,45]. Accordingly, this evidence demonstrates a close integration of areas involved in pain modulation and cardiovascular regulation.

The current study should be interpreted in light of some possible limitations. Neither blood pressure nor vessel diameter was measured during laser stimulation. Accordingly, the extent to which the pulse pressure wave distended the aortic arch and carotid sinus was not characterized, and therefore, the precise timing and magnitude of arterial baroreceptor stimulation is not known. Further, respiration was not measured in the current study and therefore the potential moderating effects of the phase of the respiratory cycle on the effects observed across the cardiac cycle were not determined. Given that baroreceptor function can vary between inspiration and expiration [12], research is needed to explore these putative effects. The sample size may be considered a potential weakness. However, many pain-related evoked potential studies tested similar numbers of participants. This study only tested men and therefore the generalizability of the cycle time effect for the N2–P2 amplitude needs to be determined in female participants. Accordingly, firm conclusions regarding the influence of baroreceptor activation on pain-related cortical processing should not be drawn until the current findings have been replicated by larger studies of mixed gender.

In conclusion, variations in the N2–P2 amplitudes across the cardiac cycle, with smaller amplitudes mid-cycle, indicated that cortical processing of nociception was attenuated during systole compared to diastole. These data support the hypothesis that arterial baroreceptors modulate the processing of nociception during each cardiac cycle.

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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

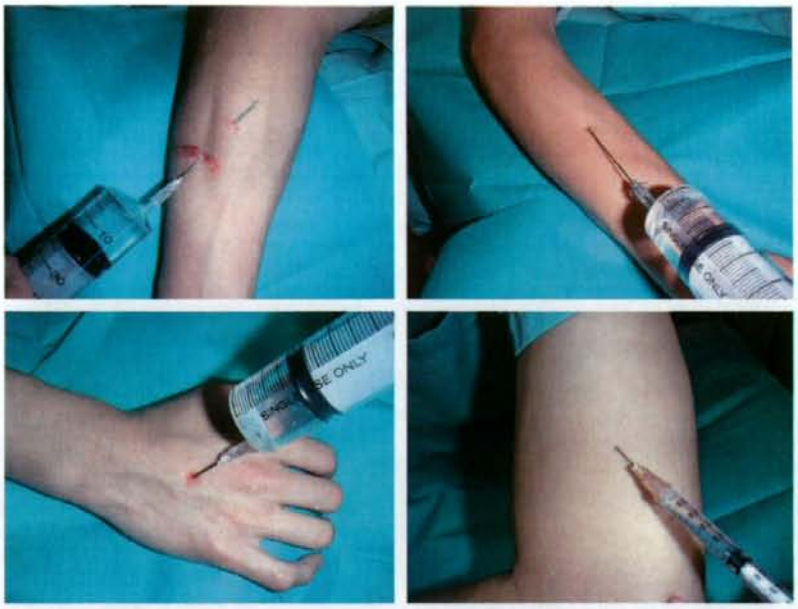

Figure 1. Sample painful images. We used 15 images for each condition (pain, fear, and rest conditions). In addition to the "images showing painful events" taken from IAPS (Lang and others 2005), we used 8 pictures made by the authors in the pain condition to fill up the deficit of images showing painful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

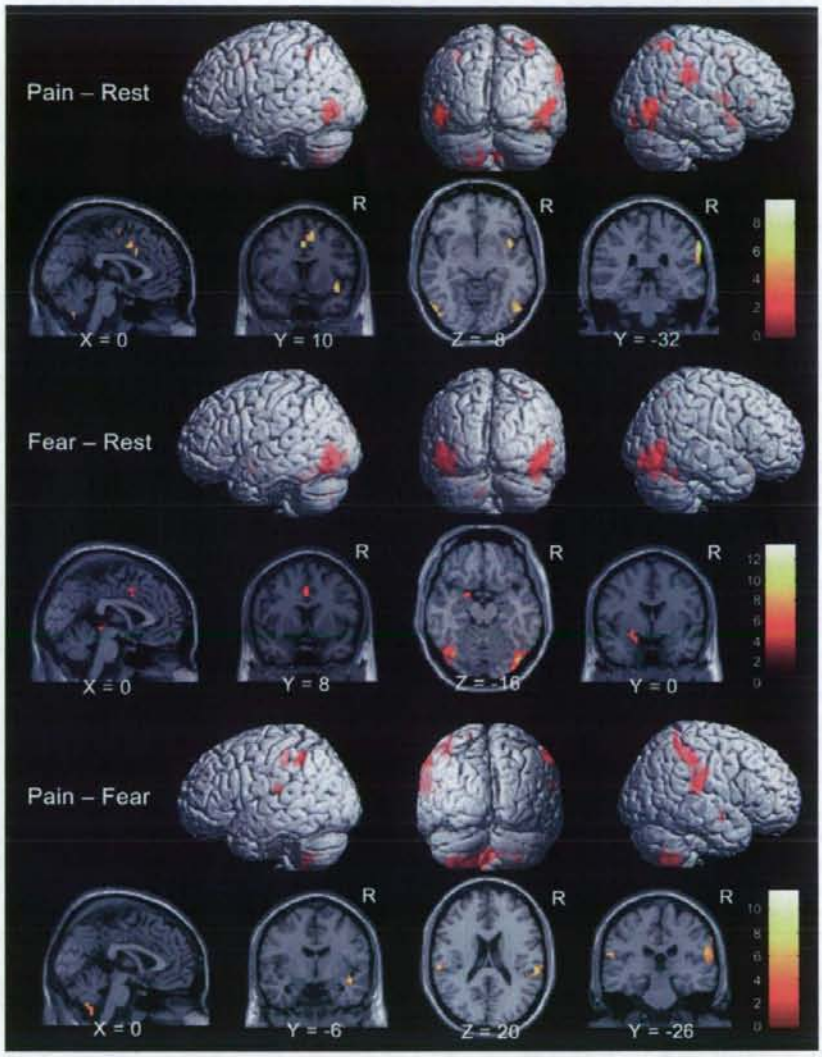

Figure 2. Brain activations in each contrast. Activated brain areas in each contrast: pain – rest, fear – rest, and pain – fear conditions. Pain – rest and pain – fear contrasts revealed activations in the SII region and PPC areas and in the affective components of the pain matrix such as the ACC, anterior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

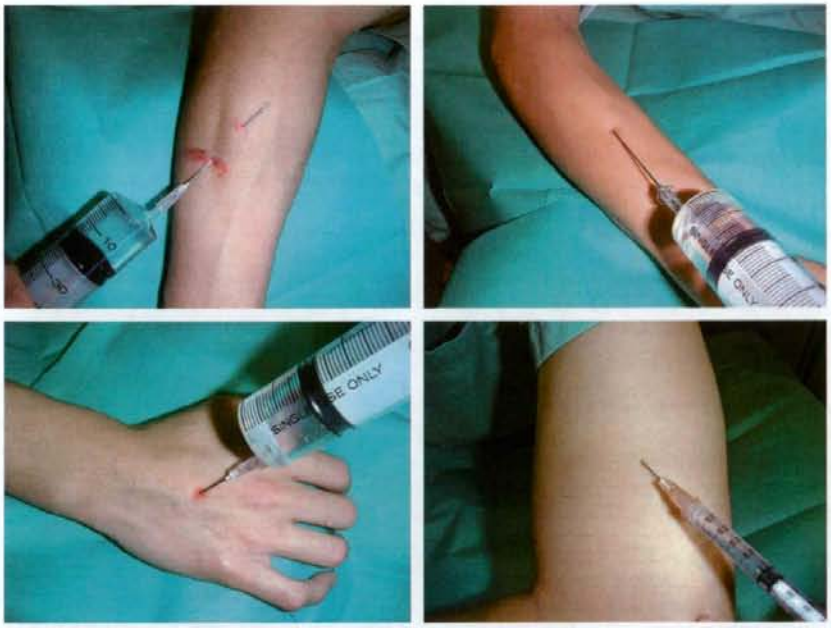

Figure 1. Sample painful images. We used 15 images for each condition (pain, fear, and rest conditions). In addition to the "images showing painful events" taken from IAPS (Lang and others 2005), we used 8 pictures made by the authors in the pain condition to fill up the deficit of images showing painful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

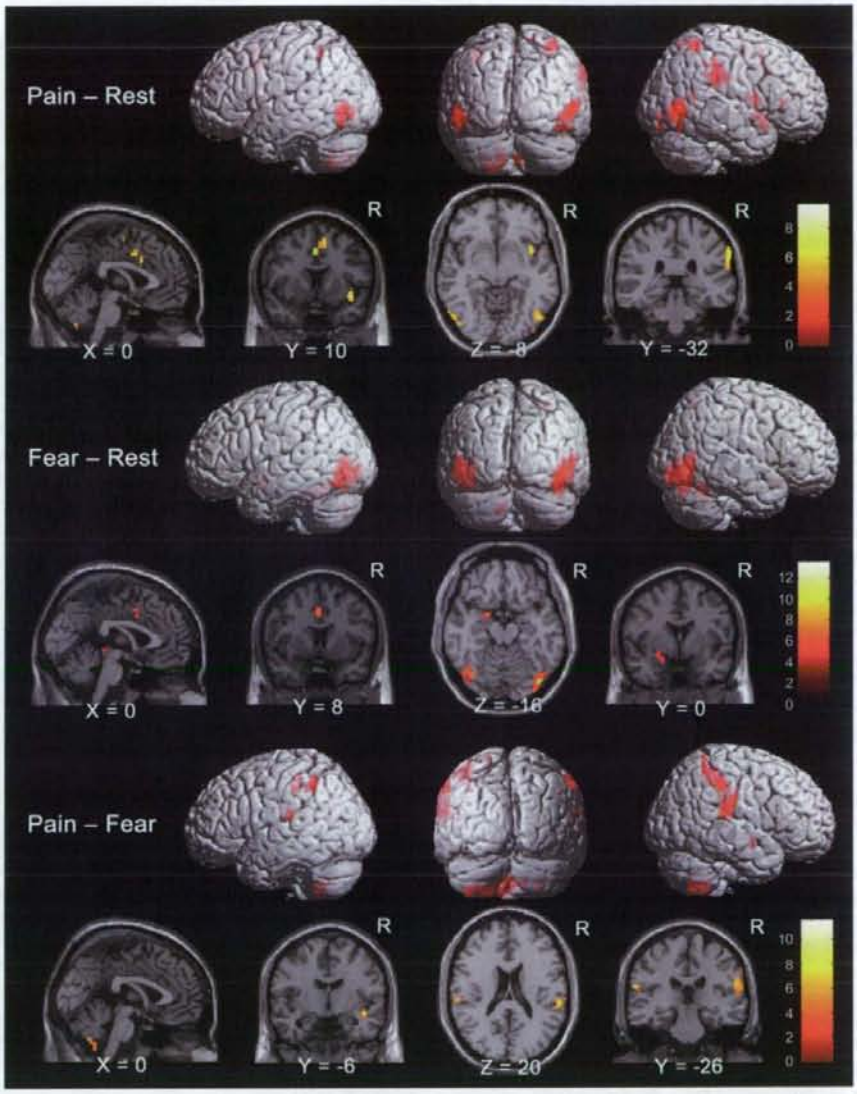

Figure 2. Brain activations in each contrast. Activated brain areas in each contrast: pain – rest, fear – rest, and pain – fear conditions. Pain – rest and pain – fear contrasts revealed activations in the SII region and PPC areas and in the affective components of the pain matrix such as the ACC, anterior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