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Virtual needle pain stimuli activates cortical representation of emotions in normal volunteers

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ABSTRACT

Psychological factors are known to play an extremely important role in the maintenance and development of chronic pain conditions. However, it is unclear how such factors relate to the central neural processing of nociceptive transmission in healthy individuals. To investigate this issue, the activation of the brain was studied in 30 healthy volunteers responding to virtual pain stimuli by fMRI. In the first series of the study (non-preconditioned study), 15 participants were shown a digital video demonstrating an injection needle puncturing the right palm. In the second series of the study (pre-conditioned study), same-task paradigms were used for another 15 participants. Prior to the fMRI session, real needle punctuate stimuli were applied to the right palm of participants for pre-conditioning. fMRI analysis revealed that bilateral activations in anterior insula (BA45), parietal operculum (S2: BA40), premotor area, medial globus pallidus, inferior occipital gyrus (BA18), left temporal association cortex, right fusiform gyrus, right parietal association cortex and cerebellum occurred due to the task in the preconditioned group. On the other hand, right parietal operculum (S2: BA40), premotor area, parietal association cortex, left inferior frontal gyrus and bilateral temporal association cortex were activated in the non-preconditioned group. In addition, activation of anterior insula, inferior frontal gyrus, precentral gyrus and cerebellum significantly increased in the preconditioned group compared with the non-preconditioned group. These results suggest that the virtual needle puncture task caused memory retrieval of unpleasant experiences which is possibly related to empathy for pain, resulting in the activation of specific brain areas.

Psychological factors are known to affect the subjective experience of pain. Pain catastrophizing is a maladaptive response to pain characterised by an experience of heightened pain intensity [17], increased disability [16] and difficulty disengaging from pain [22]. Indeed, this is an example of a psychological concern that can have an effect on the experience of pain, especially in chronic pain situations. In the previous functional MRI (fMRI) study, we attempted to investigate whether the anticipation of painful stimuli can cause the activation of cortical areas responsible for pain and emotions in chronic neuropathic pain patients. Interestingly, unusual discomfort appeared in these pain subjects when they watched a video demonstrating a hand undergoing painful stimulus. Activation was observed in the anterior cingulate cortex (ACC) and medial prefrontal cortex (MPFC) which are known to be pain-related and/or emotion-related areas [20]. A similar attention model of pain catastrophizing is also supported by neuroimaging data in subjects with chronic pain (fibromyalgia), showing a correlation between catastrophizing scores and activity in the dorsolateral prefrontal cortex (DLPF), rostral ACC, and MPFC [6]; cortical regions implicated in pain vigilance, attention and awareness [2–4,21]. These results suggest that pain-related neuronal activities might reflect the development and maintenance of chronic pain syndromes. Although the degree of pain each individual experiences is different, similar pain-related distress and emotions may exist (fear of injection, bee stings, etc.) even in healthy persons. However, it is still unclear how such factors relate to the central neural processing of nociceptive transmission in healthy individuals.

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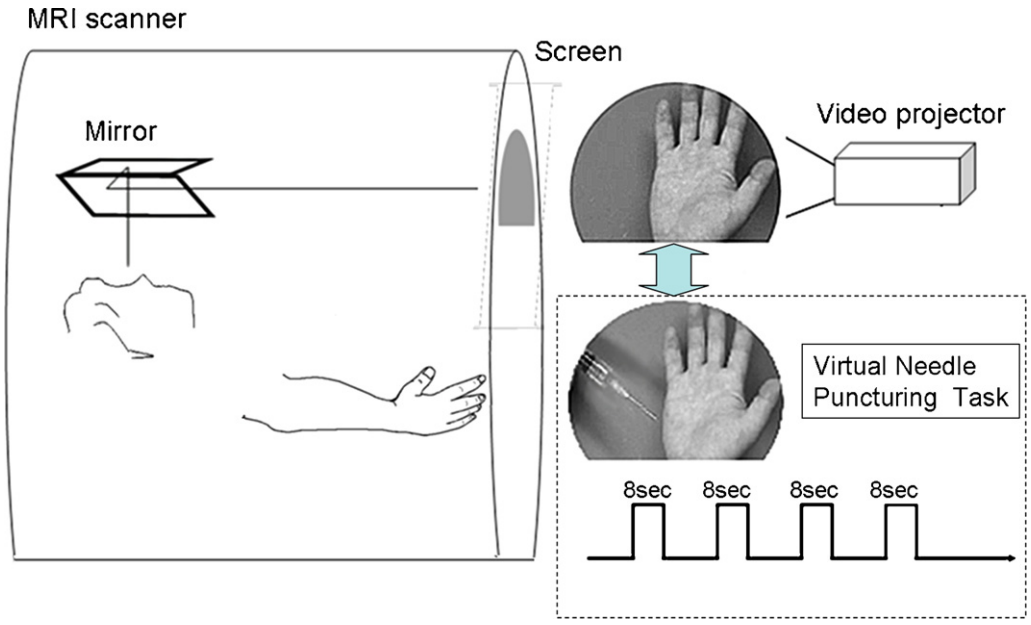

Fig. 1. Experimental design. Subjects enrolled in the experiment were shown a digital video clip demonstrating a virtual needle punctuate stimulus of the palm.

Pain and the fear of injection are closely associated in medical settings, even in healthy human beings. According to previous reports, approximately 10% of individuals report an excessive fear of needles that causes significant avoidance, distress and/or impairment in medical settings [7,11].

Recently, functional neuroimaging techniques have been recognised as informative tools for detection of neurological activation in the brain in response to various neuronal tasks. The blood oxygenation level-dependent contrast (BOLD-fMRI) is considered to be the main tool for mapping studies of the human brain [1]. Pain-related brain activations have been reported in various studies. According to early volunteer studies performed with normal volunteers, primary and secondary cortices, insula, ACC, thalamus, motor cortex, and other areas all responded to real noxious stimuli and are regarded as pain-related areas. However, no study to date has used fMRI to examine the functional anatomy of the brain in relation to virtual needle puncture by means of visual stimuli. Thus, the aim of this study is to investigate whether anticipation of painful stimuli by virtual needle puncture task can cause the activation of cortical areas responsible for pain and emotions in normal volunteers. We also aimed to determine whether a real, painful event for preconditioning could alter cerebral activations and emotions by the same functional task.

Activation of the brain was studied in 30 normal right-handed individuals (16 males and 14 females). The mean age of the subject group was 29, ranging from 22 to 34 years. All participants were interviewed by a psychologist to analyse mental status and if any abnormal findings were present, the subject was excluded from this study. No participants had a past history of brain vascular diseases or head trauma. After these processes, participants were informed of the purposes of the study and gave written consent. Prior to commencing the fMRI scanning sessions, plane T2-weighted whole brain MR images were taken to check for non-symptomatic brain lesions.

We used virtual visual stimuli to evoke unpleasant feelings resulting from needle puncture and to provoke pain anticipation in the cortex of normal volunteers. The experiment was designed to reproduce sensations evoked by expectation of pain. At the time of the fMRI session, tasks were applied in a fixed block design. All participants were exposed to the virtual visual stimuli, that is to say they were shown a digital video clip demonstrating a needle puncturing the ulnar side of the right palm (Fig. 1). Before and between the tasks, participants enrolled in the study were shown a static right hand (palm) on a screen that served as the baseline stimulus (control condition). The distance between the eyes and the screen was 125 cm. The hand projected on the screen was 16.2 cm wide and 25 cm high and subtended a visual angle of $7.4 \times 11.3^\circ$ (Fig. 1). The tasks were applied four times in each series and each task lasted 8 s (see details of paradigms in Fig. 1). Prior to fMRI scanning, the actual needle was shown to familiarize participants with the feelings evoked by the shown stimuli and one or two gentle pricks were applied to the ulnar side of the right palm of participants in one subgroup (group P: $n = 15$; nine males and six females, mean age 26.9 years old) 10 min prior to task for preconditioning. Participants were advised to stabilise their right hand with palms facing upwards as the video images were shown on screen during the fMRI scanning. In contrast, this preconditioning was not applied to group N ($n = 15$ {seven males and eight females, mean age 27.3 years old}). After fMRI scanning, subjects were interviewed. Feelings evoked by tasks, such as discomfort or anxiety, were classified and recorded in accordance with diagnostic criteria of specific phobia and anxieties.

Images of the entire brain were acquired using GE Co. apparatus, SIGNA 1.5 Teslar; blood oxygenation level-dependent (BOLD); T2-weighted multislice gradient echo-planar imaging (EPI) sequence (TE = 40 ms, TR = 4000 ms, flip angle = 90°); slice width = 7 mm; gap = 1 mm; 17 axial slices. Images of the subjects were taken in the supine position, in the standard manner with foam pads placed under the lower half of the head, and fixed to minimize artifact due to movement. During the imaging process, they were instructed to observe the video on screen. Noise generated by the MRI apparatus was suppressed with earplugs. Respiratory conditions and O_2 saturation were monitored during the session. The study was performed in adherence with the guidelines of the Kochi Medical School Ethics Committee. All subjects were informed of the study purposes and provided written consent to participate.

Results were analysed on a Unix workstation using SPM2 (statistic parametric mapping) software (Wellcome Department of Cognitive Neurology: Institute of Neurology, London: http://www.fil.ion.ucl.ac.uk/spm). The acquired images were realigned, spatially normalized with a standard EPI template and

Table 1
Talairach coordinates and Brodmann's areas for regions of statistically significant activation ($p < 0.001$ at voxel level, uncorrected threshold) in response to virtual video stimulation in volunteers with (group P) and without preconditioning (group N)

Anatomical region	Side	Coordinate	Brodmann area	*Z* score
Group P				
Anterior insula	Lt	−38, 22, 4	Area 45	4.88
	Rt	30, 28, 6	Area 45	3.97
Parietal operculum (S2)	Lt	−54, −26, 26	Area 40	3.77
	Rt	66, −26, 26	Area 40	3.91
Premotor area	Lt	−50, 6, 44	Area 6	5.13
	Rt	48, 4, 46	Area 6	4.33
Medial globus pallidus	Lt	−10, −2, −2	–	3.58
	Rt	12, −2, −4	–	3.77
Temporal association cortex	Lt	−48, −72, −12	Area 19	4.68
Fusiform gyrus	Rt	56, −62, −12	Area 37	4.23
Parietal association cortex	Rt	40, −46, 62	Area 5	4.44
Inferior occipital gyrus	Lt	−30, −90, −12	Area 18	3.92
Cerebellum	Lt	−36, −47, −34	–	3.87
	Rt	40, −64, −34	–	3.75
Group N				
Parietal operculum (S2)	Rt	52, −26, 30	Area 40	4.35
Premotor area	Rt	46, 4, 44	Area 6	3.81
Inferior frontal gyrus	Lt	−48, 8, 20	–	3.74
Temporal association cortex	Lt	−40, −58, 4	Area 37	3.57
	Rt	48, −76, 10	Area 39	3.48
Parietal association cortex	Rt	32, −52, 58	Area 7	4.19

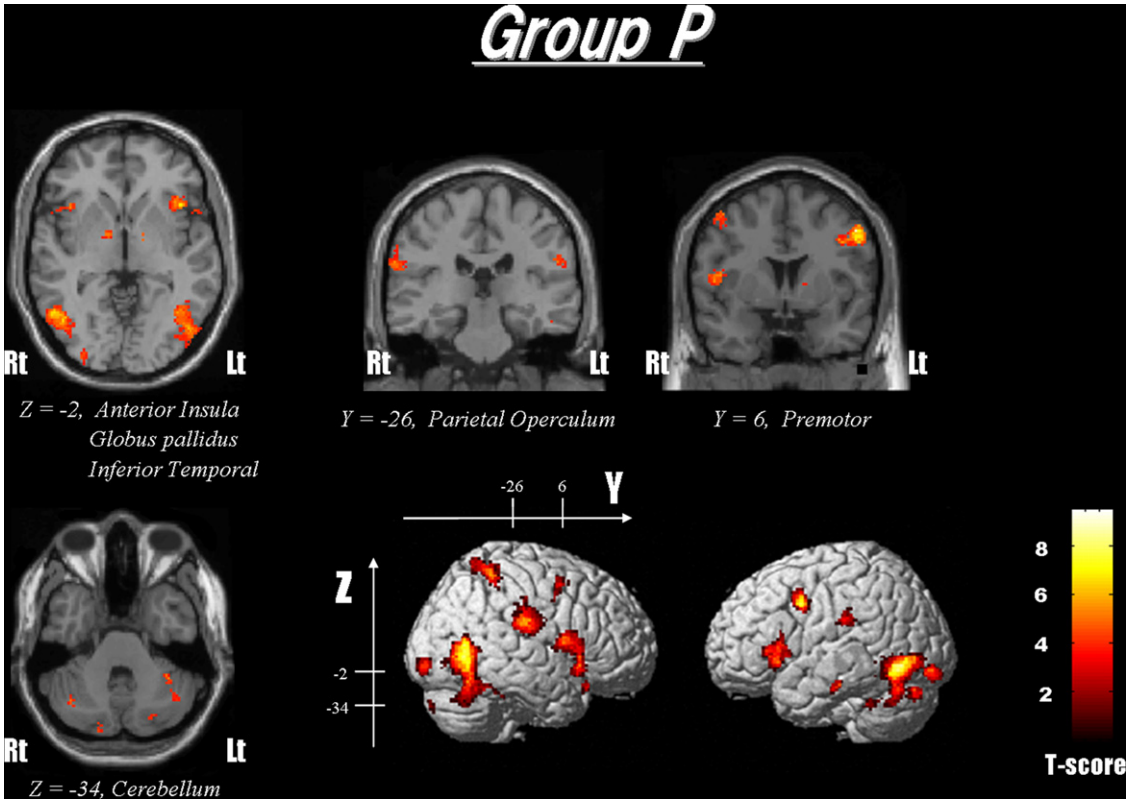

Fig. 2. Areas of cortical activation in preconditioned volunteers (group P) in response to virtual visual needle puncture task detected by fMRI ($p < 0.001$, *Z* score > 3.5, uncorrected threshold). Participants showed activation of bilateral anterior insula (BA 45), parietal operculum (S2: BA40), premotor area (BA6), medial globus pallidus, inferior occipital gyrus (BA18) and left temporal association cortex, right fusiform gyrus, right parietal association cortex and cerebellum.

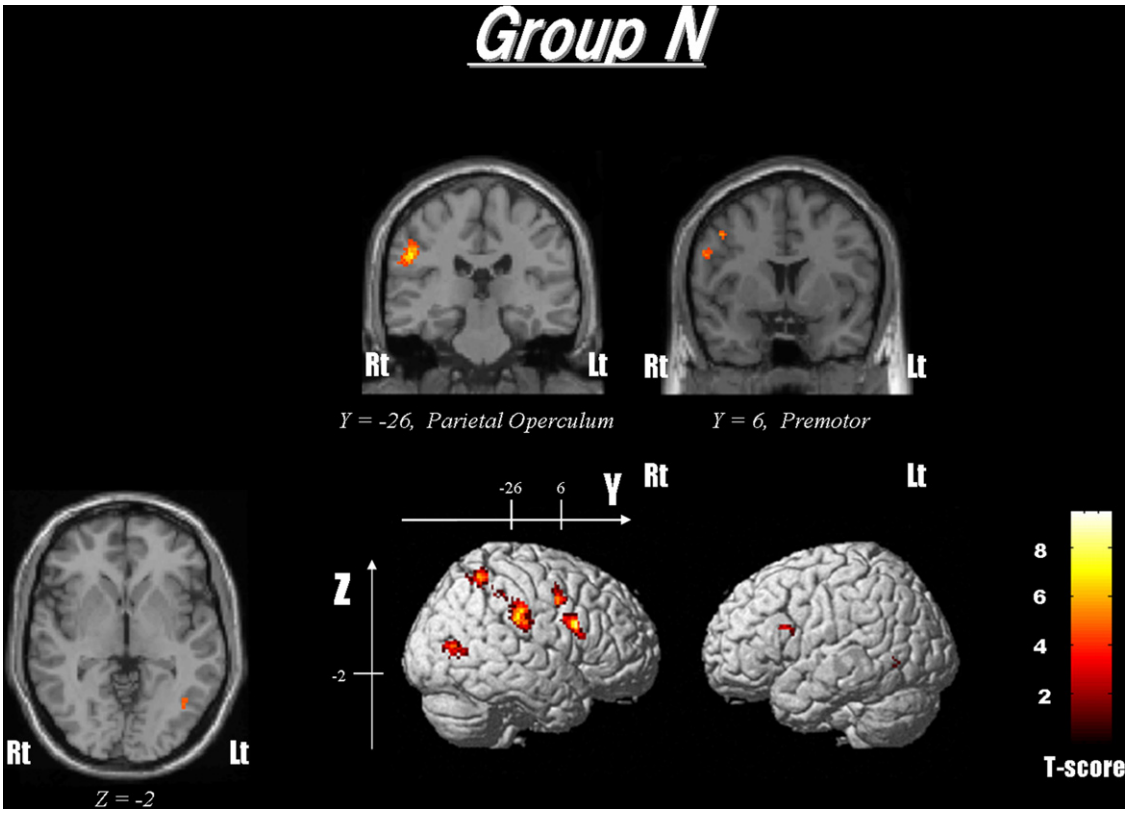

Fig. 3. Areas of cortical activation in non-preconditioned volunteers (group N) in response to virtual visual needle puncture task detected by fMRI ($p < 0.001$, Z score > 3.5, uncorrected threshold). Participants showed activation of right parietal operculum (S2), premotor area (BA6), parietal association cortex, left inferior frontal gyrus, and bilateral temporal association cortex.

finally smoothed with an isotropic Gaussian kernel of 8 mm FWHM (full width at half maximum). Significance was assessed using the delayed box-car reference convolved with a haemodynamic response (HR) function. Linear contrasts in the results between different conditions indicated the activated areas, by creating a spatially distributed map of the t-statistic (SPM $\{t\}$). The thresholds of activation were set at $p < 0.001$ for the voxel level of activation to detect brain activations with regard to the virtual puncture task. The atlas of Talairach and Tournoux was used to anatomically localize the foci of significant activations [18]. To detect the neural substrates related to the preconditioning effect, brain activation between Group P and N was statistically compared ($p < 0.001$, Z score > 3.0, uncorrected threshold).

All participants experienced some emotional event during the session and recognised that the hand and needle appearing on the screen were not real. Despite this, all subjects belonging to group P reported an unpleasant emotional experience following the needle puncture video task stimuli. However, signs or symptoms listed under diagnosis of specific phobia and anxieties (such as actual sweating of the palms, body shivers, chest discomfort and apparent desire to escape) were not detected. In contrast, no group N participant reported having any such emotional experiences. In addition, monitored O_2 saturations of all participants were not altered during the fMRI scanning.

In response to the virtual needle puncture task in Group P, bilateral activations were detected in the anterior insula (BA45), parietal operculum (S2: BA40), premotor area (BA6), medial globus pallidus, inferior occipital gyrus (BA18) and cerebellum. In addition, ipsilateral activations of left temporal association cortex, right fusiform gyrus and right parietal association cortex were also observed during the task (Table 1, Fig. 2). On the other hand, the right parietal operculum (S2: BA40), right premotor area (BA6), right parietal association cortex, left inferior frontal gyrus and bilateral temporal association cortex were all activated in Group N, respectively (Table 1, Fig. 3).

In the bilateral anterior insula and cerebellum, Group P responses significantly increased compared with Group N (uncorrected threshold, $P < 0.001$) (Table 2, Fig. 4).

Our results demonstrate that the virtual needle puncture task evokes types of unpleasant feelings and brain activation in normal participants. According to the International Association for the Study of Pain, *pain* is defined as, "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage". As this definition suggests, both real pain stimuli and virtual pain experiences such as the virtual needle puncture task used in our study may play an important role in pain recognition and interpretation in the brain. Recent fMRI studies in humans have documented real pain-related activation in the limbic sites, such as anterior cingulate cortex, rostral insula, and in the primary sensory regions, S1 and S2 [13,19]. It is not easy to compare the results because viewing of dynamic video task and static picture are known to evoke partially different cortical

Table 2
Talairach coordinates of significant activity for the contrast Group P as compared to Group N

Anatomical region	Side	Coordinate	Z score
Anterior insula	Rt	40, 4, 11	3.33
	Lt	−38, 30, 2	3.57
Cerebellum	Lt	−24, 77, −18	3.72

$p < 0.001$ at voxel level, uncorrected threshold.

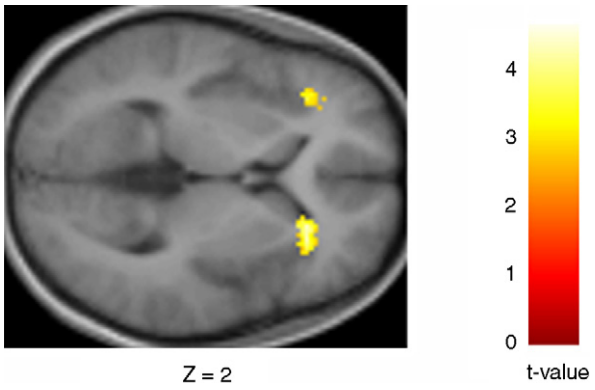

Fig. 4. Statistically increased activity of bilateral insula was observed in Group P compared with Group N. ($P < 0.001$, uncorrected threshold).

activations [14]. Ogino et al. reported that activations of anterior insula, ACC, cerebellum, posterior parietal cortex, and secondary somatosensory cortex regions were detected when subjects viewed pain-related static pictures but ACC, cerebellum, occipitotemporal cortices and amygdala were activated by fearful pictures in normal participants [12]. From this related research, one could speculate that similar activations would be detected in the present study. However, ACC activations were not detected under the present methodological conditions. In their review, Wicker et al. reported that activation of ACC was known to increase in a resting state (loss of attention to subject) rather than in a state of attention [23]. Therefore, one possible explanation why our results failed to reveal ACC activity is that our control conditions enhanced ACC activity to a level nearly equaling needle puncture conditions, making it difficult to measure the level of activation.

For this project, we tried to determine whether Group P and Group N participants reacted differently to the same video images shown to both groups by observing which parts of the brain were activated. Koyama et al. reported that the expectation of a heat-pain experience can provoke patterns resembling cortical activation (ACC, S2, etc.) from a real heat pain experience [9]. These results suggest that previous pain experiences may strongly affect pain anticipation and its related brain activations. In other words, a neurophysiological mechanism of memory retrieval is an important factor when explaining brain activations observed in our virtual needle puncture task. In previous studies, retrieval of old memories, including the retrieval of fear and/or pain conditions, caused activations in the inferior frontal gyrus. Activation in the frontoparietal network was also suggested. Although activations of globus pallidus, an area known to have a role in learning, working memory [10], were detected in Group P, activation of this area could not be detected by subtraction analysis.

Anterior insula activation is in accordance with previous findings on phobias in related neuroimaging studies [15] and patients suffering from other anxiety disorders and pain. On this occasion, as both groups had watched the same needle puncture task video and had recognised the task as one involving pain, we surmised that the neurological areas that were activated in the brain in both of these groups must therefore be the areas that can visually recognize painful experiences. As mentioned earlier, Group P participants reported having an unpleasant emotional experience. Considering that all participants recognized the hand on the task video as not their own, we believe that this unpleasant emotional experience they underwent involved empathy for pain [8].

As for activations in the premotor area, Ehrsson et al. reported that this area is associated with ownership of the hand and motor coordination [5]. Despite the fact that all Group P participants recognized the hand appearing in the video as not their own nor attempted hand withdrawal during video stimuli, the possibility of ownership of the hand and subconscious self-control affecting the results can not be ruled out.

Finding the differences between normal participants and chronic pain patients following virtual pain-provoked brain activation is an important issue for understanding the development of pathological pain conditions. Our present study clearly shows that the virtual needle puncture task can provoke emotional experiences in normal volunteers. Even in preconditioned participants however, severe anticipations were not elicited in present study. Therefore, it is difficult to conclude from our study that pain catastrophe or pathological pain was observed in clinical settings and hence it is necessary to undertake a comparative study in future between normal volunteers and needle phobic patients in order to determine the underlying neuropathological mechanisms.

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