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ScienceDirect
Behavioural Brain Research 181 (2007) 218–223
BEHAVIOURAL BRAIN RESEARCH
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Research report

Neural substrates underlying evaluation of pain in actions depicted in words

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Received 5 February 2007; received in revised form 7 April 2007; accepted 15 April 2007
Available online 20 April 2007

Abstract

Previous research has shown that evaluation of pain shown in pictures is mediated by a cortical circuit consisting of the primary and secondary somatosensory cortex (SI and SII), the anterior cingulate cortex (ACC), and the insula. SI and SII subserve the sensory-discriminative component of pain processing whereas ACC and the insula mediate the affective-motivational aspect of pain processing. The current work investigated the neural correlates of evaluation of pain depicted in words. Subjects were scanned using functional magnetic resonance imaging (fMRI) while reading words or phrases depicting painful or neutral actions. Subjects were asked to rate pain intensity of the painful actions depicted in words or counting the number of Chinese characters in the words. Relative to the counting task, rating pain intensity induced activations in SII, the insula, the right middle frontal gyrus, the left superior temporal sulcus and the left middle occipital gyrus. Our results suggest that both the sensory-discriminative and affective-motivational components of the pain matrix are engaged in the processing of pain depicted in words.

Keywords: Anterior cingulate; fMRI; Insula; Pain; Reading

1. Introduction

It is well documented that pain processing is mediated by a neural network consisting of both cortical and subcortical structures. The cortical structures of the pain matrix includes the primary and secondary somatosensory cortex (SI and SII), the anterior cingulate cortex (ACC), the insula and prefrontal regions, whereas the subcortical components of the pain matrix includes the thalamus, amygdala and hippocampus, etc. [1,2]. Nociceptive specific neurons in SI and SII respond only to noxious stimuli [3–5] and their receptive fields are organized in a somatotopic pattern (particularly in the post-central gurys) [6]. Neuroimaging studies also showed evidence that painful stimulation induced increased hemodynamic responses in SI and SII [7] or resulted in positive covariation between the activity in SI and other brain regions that are known to be involved in pain processing [8]. These findings suggest that SI and SII play an important role in the sensory-discriminative component of pain processing. Recent neuroimaging studies show that while the activity of ACC and the insula can be increased by noxious stimuli [9,10], illusions evoked by non-noxious stimuli [11] and perception of others in pain [12–15] also induce activation in ACC and the insula. In addition, the magnitude of ACC activity is correlated with subjective pain-related unpleasantness [9]. These results indicate that ACC and the insula subserve the affective-motivational component of pain processing.

Most of the previous studies of pain processing employed noxious stimuli such as thermal or mechanical stimulation. However, people often encounter 'painful' information when noxious stimuli are absent. For example, words or phrases such as "prick" and "hit by a car" are used in novels or newspapers to describe painful situations. To date, we know little about whether the same brain circuits underlying pain processing can also be activated by pain evaluation depicted in words. In particular, it is unclear if both the sensory-discriminative and the affective-motivational components of the pain matrix are involved in evaluation of pain depicted in words. Osaka et al. found that ACC can be activated when subjects were asked to form unpleasant mental images

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doi:10.1016/j.bbr.2007.04.008

of affective pain corresponding to onomatopoeia words suggestive of subjective pain presented auditorily [16]. The current study extended the previous work by assessing whether evaluation of pain described in words or short phrases presented visually induces activation of the pain matrix. One possibility is that reading words or phrases depicting painful actions is similar to watching painful pictures in generating empathic responses mediated by the pain matrix. Alternatively, words or phrases cannot produce painful situations as vivid as those illustrated in pictures and, thus, cannot activate the neural circuit underlying empathy for pain. We addressed these issues by recording heomodynamic responses from human adults using functional magnetic resonance (fMRI). Brain activity linked to rating pain intensity of actions described in Chinese words or phrases presented visually was contrasted with reading words or phrases describing neutral actions so as to identify whether the somatosensory cortex and other brain areas such as ACC and insula are involved in evaluation of pain depicted in words. We also compared the tasks of counting the number of Chinese characters in painful and neutral words to assess the necessity of the rating task in activation of the pain matrix.

2. Method

2.1. Subjects

Ten healthy subjects (3 males and 7 females) aged between 20 and 27 years (mean ± S.D. = 21.6 ± 2.01) participated in this study as paid volunteers. All subjects had no neurological or psychiatric history. All were right-handed, had normal or corrected-to-normal vision, and were naïve to the purpose of this study. Informed consent was obtained from all participants prior to scanning. This study was approved by the local ethic committee from the Department of Psychology at Peking University.

2.2. Stimuli and procedure

The stimuli were presented through an LCD projector onto a rear projection screen located at a subject's head. The screen was viewed with an angled mirror positioned on the head-coil. Visual stimuli consisted of 40 Chinese words or phrases describing actions. Half of the actions were pain inducing (e.g., "prick", "hit by a car") whereas the others were neutral (e.g., "walk", "watch TV"). These items were first evaluated by 27 independent subjects to verify that they indeed depicted painful and neutral actions (the mean ratings for painful and neutral items were 6.47 and 0.48, respectively, on a 9 point scale where 8 = very painful, 0 = no pain, $t = 33.11$; $p < 0.001$). Half of the words or phrases were composed of two Chinese characters and the others were composed of three Chinese characters. Each character subtended a visual angle of 1.5° × 1.5° at a viewing distance of 90 cm.

A box-car design was used in the current study. Each subject participated in two fMRI sessions. Each session contains three blocks of trials that varied in stimuli and task: (1) rating pain intensity of painful actions; (2) counting the number of Chinese characters in painful words or phrases and (3) counting the number of Chinese characters in neutral words or phrases. Thus, there were two blocks of trials for each stimulus condition. The contrast between tasks 1 and 3 identified neural substrates involved in word-induced pain, whereas the contrast between tasks 2 and 3 examined whether the rating task was necessary for word-induced pain to occur. Each block started with the presentation of instructions for 3 s, which defined the task (i.e., rating pain intensity or counting the number of Chinese characters) for each block of trials. There were 20 trials in each block of trials. Each trial began with the presentation of a blank screen for 500 ms, which was then overlapped by a stimulus display with a duration of 2500 ms. The stimulus display was followed by words for 2000 ms showing two options ("mildly painful/extremely painful" for the rating task or "two character/three characters" for the counting task), while subjects had to make judgments by a button press with the right index or the middle finger. A fixation cross was presented for 7 s at the end of each block of trials. The order of the three tasks was counterbalanced across subjects. The items in each block of trials were presented in a random order.

2.3. fMRI data acquisition

Scanning was performed on a 3T Siemens Trio system using a standard head-coil at Beijing MRI Center for Brain Research. Thirty-two transversal slices of functional images that covered the whole brain were acquired using a gradient-echo echo-planar pulse sequence (64 × 64 × 32 matrix with 3.4 mm × 3.4 mm × 4.4 mm spatial resolution, TR = 2000 ms, TE = 30 ms, FOV = 220 mm, flip angle = 90°). Anatomical images were obtained using a standard 3D T1-weighted sequence (256 × 256 × 176 matrix with 0.938 mm × 0.938 mm × 1.3 mm spatial resolution, TR = 1600 ms, TE = 3.93 ms). Subjects' heads were immobilized during the scanning sessions using pieces of foam.

2.4. fMRI data analysis

SPM2 (the Wellcome Department of Cognitive Neurology, UK) was used for data processing and analysis. The functional images were realigned to the first scan to correct for the head movement between scans. The anatomical image was co-registered with the mean functional image produced during the process of realignment. All images were normalized to a 2 mm × 2 mm × 2 mm Montreal Neurological Institute (MNI) template in Talairach space [17] using bilinear interpolation. Functional images were spatially smoothed using a Gaussian filter with a full-width at half maximum (FWHM) parameter set to 8 mm. The image data were modeled using a box-car function. Contrasts were calculated between rating and counting painful words, between rating painful words and counting neutral words, and between counting painful and neutral words. Statistical effects were first assessed in individual subjects using a fixed effect analysis. Random effect analyses were then conducted based on statistical parameter maps from each individual subject to allow population inference. A one-sample *t*-test was applied to determine group activation for each effect. Significant activation was identified at the voxel level of $p < 0.0001$ (uncorrected) and at the cluster level for values exceeding a p value of 0.05 (corrected for multiple comparisons). The SPM coordinates for a standard brain from MNI template were converted to Talairach coordinates using a nonlinear transform method. We also conducted a region-of-interest (ROI) analysis, using the parameter estimate of signal intensity at each activated cluster, to compare brain activations in different conditions. The ROIs were centered at the peak voxel of each activated cluster in the conjunction analysis of the contrasts between rating painful stimuli and counting neutral stimuli and between rating and counting painful stimuli. The parameter estimate of voxels in spheres with a radius of 6 mm that centered at the peak voxels were calculated, using MarsBaR, by contrasting the sessions of rating or counting tasks and the null sessions with the presentation of only the fixation. The contrast values representing BOLD signal changes related to the rating and counting tasks were then subjected to a repeated measure analysis of variance (ANOVA).

3. Results

3.1. Behavioral performance

There was no significant difference between the percentages of painful words rated as mildly painful and extremely painful (46.5 ± 10.42% versus 53.5 ± 10.42%, $t(9) = 1.062$; $p > 0.05$) in the pain rating task. Error rates for judging the number of Chinese characters in the words were below 1.0%.

3.2. fMRI results

Relative to the task of counting neutral words, rating painful words revealed significant activations in the right anterior insula,

Table 1
Brain activations in the contrasts between rating painful words and counting painful or neutral words

Brain region	BA	x	y	z	Z-value	Voxel no.
pr-nc						
R insula		34	10	1	4.90	147
R MFG	9	46	23	25	4.39	444
L IFG	45/46	−38	33	8	4.27	151
L STG	22/42	−42	−32	20	5.13	1123
L SII	4/3	−57	−12	26	4.57	363
L MOG	18	−28	−74	4	3.99	139
R Putamen		22	−7	6	3.58	146
pr-pc						
R insula		38	−9	8	4.67	456
R MFG	9	46	21	23	3.63	115
L STS	22/42	−46	−44	8	4.23	111
L SMA/MI	6	−16	−21	42	4.46	345
L MI	4	−50	−14	32	3.89	97
R SII	2	48	−16	23	4.71	456
L SII	2	−61	−15	17	4.25	110
L MOG	17/18	−28	−73	9	4.89	247
pc-nc						
No activation						

pr: Rating painful words; pc: counting painful words; nc: counting neutral words; BA: Brodmann area; R: right hemisphere; L: left hemisphere; MOG: middle occipital gyrus; MFG: middle frontal gyrus; IFG: inferior frontal gyrus; STG: superior temporal gyrus; MI: primary motor cortex; SMA: supplementary motor area and SII: secondary somatosensory cortex. Voxels survived an uncorrected p value of 0.0001, cluster size > 20; $p < 0.05$ corrected.

the frontal gyrus bilaterally, the left superior temporal sulcus, the left SII, the left middle occipital gyrus and the right putamen (Table 1). Similarly, the contrast between pain rating and counting of painful words showed activations in the right anterior insula, the right middle frontal gyrus, the left superior temporal sulcus, SII bilaterally, the left motor area and the left middle occipital gyrus, (Table 1). We also conducted a contrast between counting of painful words and neutral words. However, no significant activation was found in any brain area in this comparison.

To identify the brain activation that was related to pain rating and independent of the pain contents of the stimuli used in the control task, we conducted a conjunction analysis of the contrasts between rating painful stimuli and counting neutral stimuli and between rating and counting painful stimuli. This revealed activation in the right anterior insula, the right middle frontal gyrus, the left superior temporal sulcus, SII bilaterally and the left middle occipital gyrus (Table 2; Fig. 1).

The parameter estimates of signal intensity obtained in the ROI analysis were subjected to ANOVAs with condition (rating painful words, counting painful words and counting neutral words) as an independent variable. The main effect of condition was significant at all the clusters identified in the conjunction analysis ($F(2, 18) = 16.94$–34.85; $p < 0.01$). Post hoc analysis confirmed that the signal changes were larger in the rating task than in the other two tasks ($p < 0.01$; Fig. 1) where the signal changes did not differ between the latter two conditions ($p > 0.05$).

Table 2
Brain activations shown in the conjunction analysis

Brain region	BA	x	y	z	Z-value	Voxel no.
Conjunction of "pr-nc" and "pr-pc"						
R insula		34	10	2	4.49	177
R MFG	9	46	23	23	4.49	131
L STS	22/42	−44	−44	10	4.50	91
L SII	3	−50	−14	32	4.66	157
R SII	2	48	−16	23	5.15	143
L MOG	18	−28	−74	4	4.94	89

pr: rating painful words; pc: counting painful words; nc: counting neutral words; BA: Brodmann area; R: right hemisphere; L: left hemisphere; MOG: middle occipital gyrus; MFG: middle frontal gyrus; IFG: inferior frontal gyrus; STG: superior temporal gyrus; MI: primary motor cortex; SMA: supplementary motor area and SII: secondary somatosensory cortex. "pr-pc" Was inclusively masked with "pr-nc" at an uncorrected p value of 0.05, voxels survived an uncorrected p value of 0.0001, cluster size > 20; $p < 0.05$ corrected.

4. Dicsussion

This study examined to what extent the pain matrix can be activated by evaluation of pain intensity of actions described in words or short phrases presented visually. In particular, we investigated whether the neural correlates of pain evaluation of painful actions depicted in words are different from those induced by perception of painful pictures [12–15]. We found, by recording heomodynamic responses using fMRI, that rating pain intensity of actions depicted in words or short phrases was associated with increased activations in the cortical structures including SII, the right anterior insula, the right middle frontal gyrus, the left superior temporal sulcus and the left middle occipital gyrus. Because the contrasts between rating painful words and counting painful or neutral words showed similar activations, the frequency or familiarity of the words and phrases used in this study contributed little to the fMRI results.

Our findings provide evidence that the sensory-discriminative component of the pain matrix (e.g., SII) was engaged in the evaluation of pain intensity of painful actions depicted in words or phrases. These results are consistent with recent fMRI observations that rating pain intensity of body parts shown in painful pictures induced activation in SII when the pain was perceived from the self-perspective [15,18]. Recent TMS studies also found that viewing video clips showing painful stimuli delivered to others increased the amplitudes of somatosensory-evoked potentials [19] but decreased the amplitudes of motor-evoked potentials [20,21]. Our results complement these findings by showing that rating pain intensity of actions depicted in words can also lead to increased somatosensory activity. These results together indicate that the somatosensory activity can be modulated by watching or thinking of painful actions when no noxious stimulation is applied to the subjects. SII receives input from the subcortical structures such as thalamus and brainstem [1] and is involved in the intensive and qualitative aspect of pain processing [2]. However, in the current study, as no painful sensory stimulation was applied to the subjects, the SII activation was unlikely to be induced by bottom-up painful sensory stimulation. One possible account is that somatosensory activity was modulated by the input from other brain areas. It is likely that

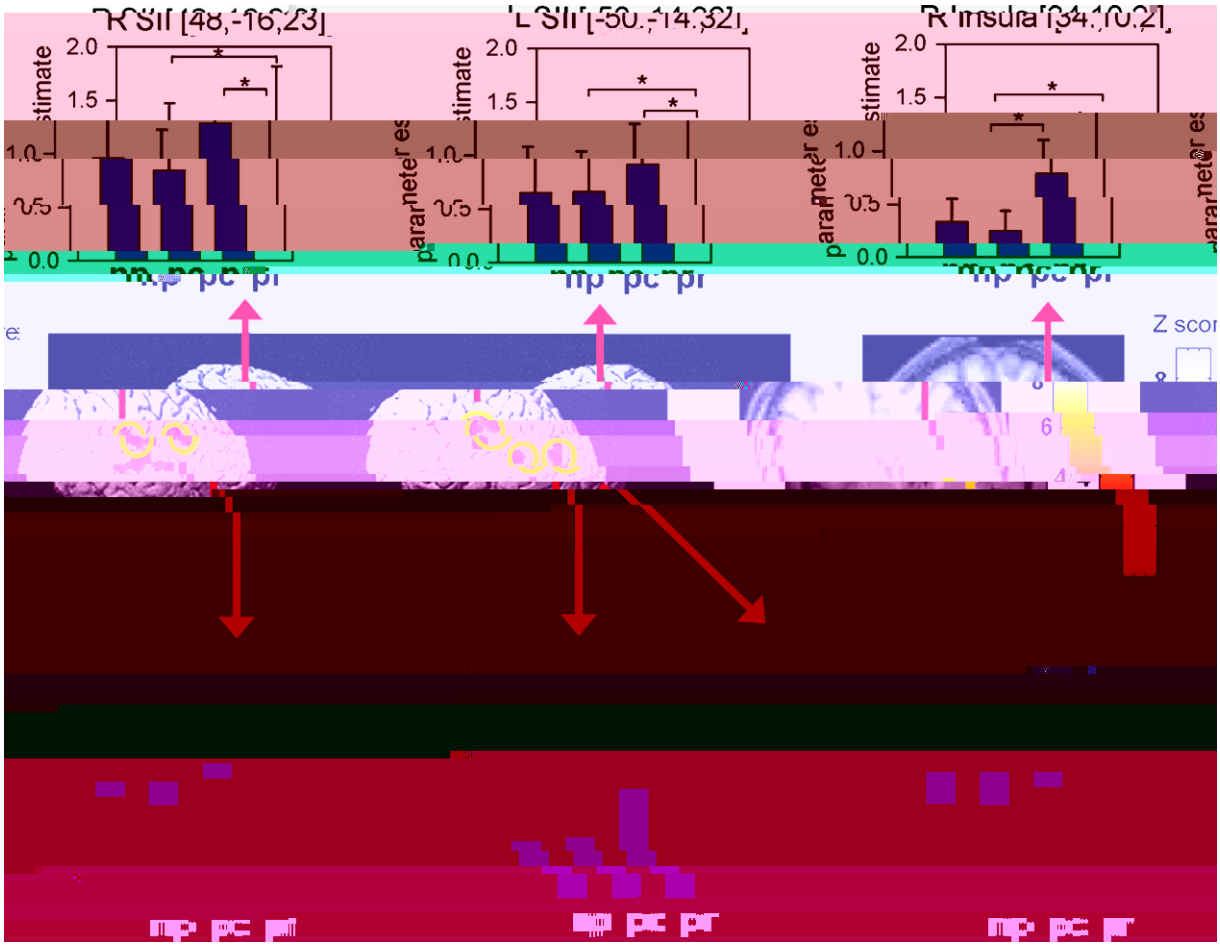

Fig. 1. Brain activations shown in the conjunction analysis of the contrasts between rating painful stimuli and counting neutral stimuli and between rating and counting painful stimuli. The results of ROI analysis are shown for each activated cluster. Asterisk (*) indicates significant difference ($p < 0.05$) in parameter estimate of signal intensity between the two conditions.

reading words or phrases depicting actions may activate the mirror neuron system [22], which in turn exerted modulation of the somatosensory activity. However, such influence would be comparable for painful and non-painful actions. Alternatively, the painful stimuli induced increased activity in the emotional system (whereas the neutral stimuli did not), which in turn exerted modulation of the somatosensory activity. The late account can interpret why the painful stimuli induced increased somatosensory activity relative to the neutral stimuli, though this analysis needs to be further confirmed.

The insula has been repeatedly reported to activate together with SII to respond to various kind of painful stimuli. Similarly, we also found increased activity in the insula related to evaluation of pain intensity of painful actions depicted in words or short phrases. Although the functional role of SII/insula with regard to pain processing remains unidentified, some researchers suggest that SII/insula are involved in pain discrimination [23]. It is possible that SII and insula function with each other to augment the discrimination of pain intensity of the painful actions depicted in words. Alternatively, although no nociceptive stimuli were applied to the participants, rating pain intensity of painful actions described in words could initially induce the cognitive and emotional processing of pain in the brain areas such as the insula and the frontal cortex [24]. The feedback from these brain areas then led to the modulation of the SII activity. In line with this analysis, our fMRI results showed increased activation in the right insula and middle frontal gyrus related to the task of rating pain intensity. The insula can be activated by noxious stimuli [25,26] and has been demonstrated to be engaged in coding of the unpleasantness of tonic pain [27]. Watching others in pain also activates the insula [12–15], suggesting that the insula mediates empathy for pain of other individuals. The frontal activation has been observed when subjects imitate others' emotion [28] and has been suggested to play an important role in regulation of pain distress and negative affect [29]. In the current study, rating pain intensity of painful actions described in words or short phrases might first provoked high-level emotional processing of pain, which in turn induced activation of the somatosensory cortex (e.g., SII in the present study). Similar top-down modulation of the activity of the somatosensory cortex was reported in other studies. For example, Porro et al. [30,31] found that while the insula and prefrontal cortex show increased activation during anticipation of noxious stimuli, SI and the motor cortex are also activated by anticipation of pain before nociceptive stimuli

are applied. Taken together, these findings suggest that noxious stimuli are not necessary to activate the sensory-discriminative component of the pain matrix.

Interestingly, rating pain intensity of painful actions depicted in words failed to activate ACC. ACC is a critical part of the pain matrix underlying pain experience [8] and its activity is correlated with subjective unpleasantness induced by pain [7,32]. ACC is also involved in imagination of one's own pain [33] and empathic responses to others' pain [12–15,34]. Most of the previous studies using thermal or electrical stimuli found increased activation in both the insula and ACC associated with pain processing [1,2]. It appears that the processing of pain induced by rating pain intensity of actions depicted in words is essentially different from the processing of pain induced by noxious stimuli and the processing of imagined pain. Evaluation of pain of actions described in visually presented words is also different from pain evaluation of onomatopoeia words suggestive of subjective pain presented auditorily [16] in that the latter also activated ACC. One possibility is that painful actions depicted in words or phrases were not as vivid as those illustrated in pictures or sound and, thus, failed to activate ACC. Alternatively, the neutral actions depicted in words used in the control task might tap into ACC processing to a certain degree. However, these interpretations need to be confirmed in future work. In any case, the absence of ACC activation in the present study suggests that the task of evaluation of pain in actions described in word or short phrases did not engender emotional responses such as unpleasantness as strong as that induced by thermal and

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