

Attention and reality constraints on the neural processes of empathy for pain

Xiaosi Gu^a and Shihui Han^{a,b,*}

^aDepartment of Psychology, Peking University, Beijing 100871, PR China

^bFunctional Imaging Center, Academy for Advanced Interdisciplinary Studies, Peking University, Beijing 100871, PR China

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Recent brain imaging studies have shown that the neural substrates underlying the ability to infer and share the feeling of pain of other individuals overlap with the pain matrix that mediates the process of one's own pain. While there has been evidence that the neural activity mediating pain experience is influenced by top-down attention, it remains unclear whether the neural substrates of empathy for pain are modulated by top-down controlled mechanisms. The current work investigated whether the neural correlates of empathic processes of pain are altered by task demand and prior knowledge of stimulus reality. Subjects were scanned using functional magnetic resonance imaging (fMRI) while watching pictures or cartoons of hands that were in painful or neutral situations. Subjects were asked either to evaluate pain intensity supposedly felt by the model or to count the number of hands in the stimulus displays. Relative to counting neutral stimuli, rating pain intensity of painful pictures and cartoons induced increased activation in ACC/paracingulate and the right middle frontal gyrus. Rating pain intensity also activated the inferior frontal cortex bilaterally and the right insula/putamen for pictures but activated the left parietal cortex, the postcentral gyrus, and the occipito-temporal cortex for cartoons. However, the neural activities related to pain rating were eliminated when subjects counted the number of hands in the painful stimuli. In addition, the ACC activity associated with empathy for pain was stronger for the pictures than for the cartoons. Our findings indicate that the involvement of the neural substrates underlying pain-related empathy is constrained by top-down attention and contextual reality of stimuli.

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Introduction

Perception of humans not only involves understanding of other individuals' emotional experiences but also generates a similar emotional state in oneself. The ability to infer and share emotional

or sensory experiences of another, referred to as empathy, develops in the early years of age (Ungerer et al., 1990; Thompson, 1987) and plays an important role in successful interaction with others in a social context. Researchers assume that empathy involves at least two psychological mechanisms. The cognitive process of empathy acts to take "the perspective of the other person" and to "keep track of the origins of self- and other feeling" (Decety and Jackson, 2004). The affective processes of empathy involve emotional responses arising from perception and understanding of others' emotional states (Feshback, 1975; also see Decety and Jackson, 2004 for review).

Several neuropsychological studies found that focal lesions of the orbitofrontal cortex impaired empathic processing (Eslinger, 1998; Stuss et al., 2001). Recent brain imaging research has shown evidence that a neural network is engaged in the cognitive and affective processes involved in empathy. For example, watching others telling sad stories (Decety and Chaminade, 2003) or watching cartoons describing emotional stories (Völlm et al., 2006) induced significant activation in the emotion-related system consisting of the frontal lobe, the temporal poles, and the amygdala. Similar brain areas were also activated by imitation of others' emotions (Carr et al., 2003). Watching emotional facial expression of disgust or pain expression induced increased activity in the anterior insula and the anterior cingulate cortex (ACC) (Wicker et al., 2003; Saarela et al., 2007) and even in the amygdala (Botvinick et al., 2005). Empathic judgments in a verbal task also activated the frontal/orbitofrontal cortex and the anterior middle temporal cortex (Farrow et al., 2001). Recent transcranial magnetic stimulation (TMS) study even showed evidence that observing others being pricked reduced amplitudes of motor-evoked potentials (Avenanti et al., 2005, 2006), suggesting the involvement of sensorimotor cortex in empathic processing. Taken together, these neuroimaging findings suggest that experience of one's own emotion and empathic responses to others' emotion may share common neural mechanisms.

However, other neuroimaging research has found evidence for differential neural substrates underlying affective process of empathy and sensory processing of the same type of emotion. Singer et al. (2004) recorded blood oxygen level-dependent (BOLD)

* Corresponding author. Department of Psychology, Peking University, 5 Yiheyuan Road, Beijing 100871, PR China. Fax: +1 86 10 6276 1081.

E-mail address: shan@pku.edu.cn (S. Han).

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signal using functional magnetic resonance imaging (fMRI) from volunteers who either experienced painful stimuli themselves or watched signals indicating their loved one in receipt of pain stimuli. They found that experiencing painful stimuli gave rise to increased activity of a pain matrix including the sensorimotor cortex, the secondary somatosensory cortex, ACC, the insula, the cerebellum, and the subcortical structures such as the thalamus and brainstem. Observation of others in pain, however, mainly activated the insular and the rostral part of ACC. In addition, the activity in ACC and the left insula showed significant covariation with subjective differences in empathy. Other recent work observed empathy-related activity in ACC regardless of the modality of stimulation (tactile vs. visual stimulation; Morrison et al., 2004) and body parts where pain stimulation was applied (hand vs. foot; Jackson et al., 2005, 2006a). These results demonstrate that experience of pain stimulation and pain-related empathic responses share only a part of the pain matrix. Empathizing with pain of others mainly involves the affective process that is mediated by ACC and the insula.

Most of the aforementioned studies examining the neural mechanisms of empathy employed contrasts between emotional (or painful) stimuli and neutral stimuli. These comparisons reflect both the effect of automatic representation of an emotional state and the effect of controlled intentional processing of emotional experiences of other individuals. Lanzetta and Englis (1989) found that subjects expecting cooperation showed greater electromyographic (EMG) responses to displays of distress than displays of pleasure whereas those expecting competition showed weaker EMG responses to displays of distress as compared with displays of pleasure. Singer et al. (2006) recently reported that pain-related empathic responses in the insula were larger to confederates who played fairly than unfairly. These findings suggest that the neural correlates of empathy are modulated by social relations between individuals. However, to date there has been no research assessing to what extent the neural activities linked to empathy are modulated by top-down controlled processes such as attention. This is an important issue because it helps to clarify whether understanding and sharing of the emotional state of another is a controlled and effortful processing. Some researchers argued that empathy is based on an unconscious and automatic simulation of the subjectivity of others (Gallese, 2001; Gallese and Goldman, 1998). In contrast, others proposed that “empathy is not a simple resonance of affect between the self and other” (Decety and

Jackson, 2004). It has been shown that pain experience can be reduced when attention is distracted away from noxious stimuli (Melzack and Casey, 1968; Good et al., 1999) and neural activity of the pain matrix is decreased when subjects perform cognitively demanding tasks that withdraw attention from noxious stimuli (Bantick et al., 2002; Brooks et al., 2002; Longe et al., 2001; Petrovic et al., 2000). Nevertheless, so far it remains poorly understood to what extent pain-related empathic responses rely on top-down controlled mechanisms such as attention. Avenanti et al. (2006) recently found that the activity of the sensorimotor cortex associated with empathic processing was comparable when task instructions emphasized either the first- or third-person perspective during empathy, suggesting that the sensorimotor component of empathy for pain may not be modulated by task demand. However, to date, there has been no research examining the attentional effects on the cognitive and affective components of empathetic processing of pain.

Given the neuroimaging findings of attentional modulation of pain experience, we proposed that the neural processes involved in the affective component of empathic understanding of pain of others are also modulated by top-down attention. To assess this hypothesis, we used pictures that were shot from the first-person perspective and showed situations such as a hand trapped in a door or being cut by scissors, similar to those used in the study of Jackson et al. (2005). These painful stimuli were matched with neutral ones showing hands in similar situations but not being hurt, as illustrated in Fig. 1. Jackson et al. (2005, 2006a) found that rating the intensity of the mechanical pain of the hand owners activated a network consisting of ACC and the insula. Their recent meta-analysis study (Jackson et al., 2006b) even suggests distinct functional roles of the subregions of the insula in pain processing, namely, the rostral region plays a key role in perception of pain in others whereas the caudal part in self pain. In the current study, we first replicated the task used in the work of Jackson et al. by asking subjects to judge pain intensity of the hand owner while counting hand numbers in neutral stimuli was used as a baseline. Because the contrast of rating painful vs. counting neutral stimuli identified neural activities underlying both effects of attention demand and stimulus properties, we designed another task to isolate these two effects. We asked subjects to count the number of hands (one vs. two) in the pictures. This task was associated with the hands in the stimuli but was unrelated to the feeling of pain. The contrast of

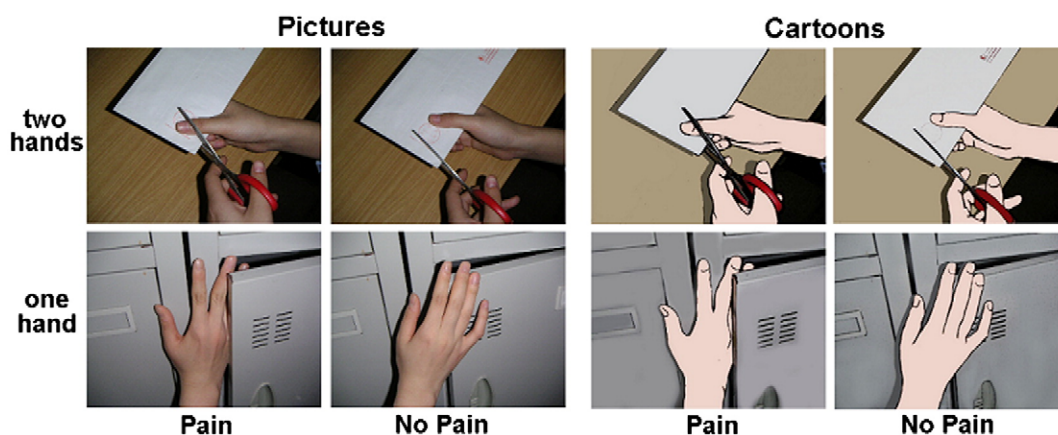


Fig. 1. Illustration of the stimulus displays used in the current study. Left=pictures; Right=cartoons.

rating vs. counting painful stimuli should remove the effect of stimulus properties and reflect mainly the contribution of attention because the stimuli were identical in the two conditions. Similarly, the contrast of counting painful vs. neutral stimuli should remove the effect of attention and give prominence to the contribution of stimulus properties because the task demand was the same in the two conditions.

The current study also investigated if the normal function of the neural network underpinning empathy was constrained by the contextual reality of stimuli. A recent fMRI study using cartoons depicting emotional social contexts found empathy-related activity in ACC, paracingulate, and the amygdala (Völlm et al., 2006). Inferring mental states such as beliefs and intentions (i.e., building a theory of mind of others) from cartoons also generates activity of the theory-of-mind-related network including the medial prefrontal cortex and the temporo-parietal junction (Castelli et al., 2000; Gallagher et al., 2000). These results suggest that cartoons that simulate a real social context can induce understanding of emotional and mental states of others. However, because of the lack of direct comparisons between neural correlates associated with empathic responses to real and virtual stimuli, it remains an unresolved issue whether similar neural mechanisms are involved in the representation of others' emotional states in a real or virtual social context. Han et al. (2005) has shown evidence for distinct neural substrates for the perception of real and virtual visual worlds. In particular, watching movie clips depicting social interactions between humans automatically induced increased activity in the brain areas mediating theory-of-mind ability (e.g., the medial prefrontal cortex). In contrast, these brain regions were not activated when watching cartoon clips describing similar situations. Instead, the posterior parietal cortex bilaterally was activated. Perani et al. (2000) also found that perception of real hand actions activated a visual spatial network including the posterior parietal cortex whereas only the occipital cortex was engaged in observation of virtual-reality hand actions. To uncover the reality constraint on the neural substrates of empathy for pain, we made a set of cartoons derived from the picture stimuli (see Fig. 1). The cartoons were similar to the picture stimuli in presentation of painful and neutral situations but lacked the colors and textures that were necessary for representation of visual reality. We hypothesized that, relative to those pictures, pain-related empathic responses to cartoons would be weakened or eliminated because of the lack of stimulus reality. The results from cartoons would lead a better understanding of the nature of human empathy.

Methods

Subjects

Twelve healthy subjects (7 males and 5 females) aged between 20 to 24 years (mean \pm SD: 21.9 \pm 1.24) participated in the 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 not color blind. Informed consent was obtained from all participants prior to scanning. This study was approved by a local ethics committee.

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 digital color pictures showing one hand or two hands in painful and neutral situations (20 each). The pictures were shot from the first-person perspective and described accidents that may happen in everyday life, as illustrated in Fig. 1. Painful pictures included situations such as a hand trapped in a door or cut by scissors. There was one hand in 8 painful pictures and two hands in 12 painful pictures. The right hand was involved in the painful situations in half of the painful stimuli, and the left hand was involved in the painful situations in other painful stimuli. Each painful picture was matched with a neutral picture which showed one or two hands in situations that, although similar in contexts, did not imply any pain. The pictures were transformed into a set of cartoons using "filter \rightarrow artistic \rightarrow poster edge" tool of the software "Photoshop". Each picture was 28 \times 21.6 cm (width \times height), subtending a visual angle of 17.6 $^\circ$ \times 13.6 $^\circ$ at a viewing distance of 90 cm.

A boxcar design was used. Each subject participated in four fMRI sessions. Each session contained six blocks of trials that varied in stimuli and task: (1) rating pain intensity of hands in painful pictures; (2) counting the number of hands in painful pictures; (3) counting the number of hands in neutral pictures; (4) rating pain intensity of hands in painful cartoons; (5) counting the number of hands in painful cartoons; and (6) counting the number of hands in neutral cartoons. In the pain judgment tasks, subjects were clearly instructed to judge the pain intensity felt by the person depicted in the pictures. 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 hands) for each block of trials. There were 10 trials in each block. Each trial began with the presentation of a blank screen for 500 ms, which was then overlapped by a stimulus displayed for 2500 ms. Because of the limitation of the response keys, a pain judgment task rather than analogic measures was used in the current study. The stimulus display was followed by words for 2000 ms showing two options ("mildly painful/extremely painful" for the rating task or "one hand/two hands" for the counting task), during which time subjects had to make judgments by a button press with the right index or middle finger. A fixation cross was presented for 7 s at the end of each block of trials. The order of stimulus conditions was counterbalanced across subjects using the Latin-square design.

fMRI data acquisition and analysis

Scanning was performed on a 3 T 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 \times 64 \times 32 matrix with 3.4 \times 3.4 \times 4.4-mm spatial resolution, TR=2000 ms, TE=30 ms, FOV=220 mm, flip angle=90 $^\circ$). Anatomical images were obtained using a standard 3D T1-weighted sequence (256 \times 256 \times 176 matrix with 0.938 \times 0.938 \times 1.3-mm spatial resolution, TR=1600 ms, TE=3.93 ms). Subjects' heads were immobilized during the scanning sessions using pieces of foam.

SPM99 (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 \times 2 \times 2 mm³ Montreal

Neurological Institute (MNI) template in Talairach space (Talairach and Tournoux, 1998) 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 boxcar function. Contrasts were defined separately for the pictures and cartoons to reveal empathy-related activity and to examine the effect of top-down attention. These included the comparisons between rating painful stimuli and counting neutral stimuli, between counting painful stimuli and counting neutral stimuli, and between rating painful stimuli and counting painful stimuli. 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. Analyses of the conjunction of, and interaction between the following two contrasts were conducted to assess the common and distinct brain areas activated in the two conditions: rating painful pictures vs. counting neutral pictures and rating painful cartoons vs. counting neutral cartoons. The conjunction and interaction analysis was performed in each subject using the contrast 1 1 -1 -1 (corresponding to rating painful picture, rating painful cartoons, counting neutral pictures, counting neutral cartoons) and 1 -1 -1 1 (corresponding to rating painful picture, counting neutral pictures, rating painful cartoons, counting neutral cartoons), respectively. A random effect analysis was then conducted based on the fixed effect analysis from each subject to reveal the significance at the group level. Significant activation was identified 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 (<http://www.mrc-cbu.cam.ac.uk/Imaging/mnispace.html>).

After having identified the involvement of the ACC and insula in empathy for pain, we performed a psychophysiological interaction (PPI) analysis (Friston et al., 1997) to identify brain regions that showed significantly stronger covariation with the ACC and insula during rating painful stimuli than counting painful or neutral stimuli. The coordinates of the peak voxels from the random effect analysis comparing rating painful stimuli vs. counting painful or neutral stimuli were used to serve a landmark for the individual seed voxels. An ROI of a sphere with a diameter of 5 mm was searched around the peak voxel in ACC or insula.

The time series of each ROI were then extracted, and PPI regressor was calculated as the element-by-element product of the mean-corrected activity of this ROI and a vector coding for the differential task effect of rating painful stimuli versus counting painful or neutral stimuli. The PPI regressors reflected the interaction between psychological variable (rating painful stimuli versus counting painful or neutral stimuli) and the activation time course of the ACC or insula. The individual contrast images reflecting the effects of the PPI on other brain areas were subsequently subject to a one-sample *t*-test. The results of the group analysis identified brain regions that showed increased activity to rating painful stimuli when the activity in the ACC or insula was high. The threshold at the voxel level was set to $p < 0.05$ (corrected for multiple comparisons) for the identification of brain areas that showed significant functional connectivity with the ROI.

Result

Behavioral results

Recording of the behavioral performance during scanning showed that the mean percentage of painful stimuli rated as mildly painful did not differ between pictures (51.3%) and cartoons (49.0%) ($t(11)=1.167$, $p < 0.268$), suggesting that subjective perception of pain intensity did not differ significantly between pictures and cartoons. Error rates for judging the number of hands in the stimuli were below 2.0% for both pictures and cartoons.

After the scanning procedure, subjects were further required to rate the pain intensity supposedly felt by the hand-owner in the stimuli using a Faces Pain Scale-Revised (FPSR) (Hicks et al., 2001). The mean ratings were 3.7 ± 1.23 and 4.1 ± 0.83 for the pictures and cartoons, respectively (on a 6-point scale where 1=no pain, 6=very much pain, $t(11)=1.448$, $p=0.176$). The same scale was also used to evaluate subjects' unpleasant feelings when they watched the pictures and cartoons. The mean ratings were 3.9 ± 1.20 and 4.0 ± 0.76 for the pictures and cartoons, respectively ($t(11)=0.352$, $p=0.732$).

fMRI results

Pictures

Similar to Jackson et al. (2005), we first made a contrast between rating painful pictures and counting neutral pictures to

Table 1
Brain activations associated with rating painful stimuli vs. counting neutral stimuli

Brain region	Pictures						Cartoons					
	BA	x	y	z	Z-value	Voxel no.	BA	x	y	z	Z-value	Voxel no.
ACC	32	-6	23	30	4.07	404	32	10	30	30	3.50	186
Paracingulate	8	-4	20	45	3.76	263	8	-2	22	50	3.62	240
Right MFG	46	42	36	17	4.10	363	9/46	53	32	17	3.94	431
Left IFG	46	-46	45	1	4.10	483						
Right insula/IFG	47	38	23	-3	4.03	286						
Right putamen		17	19	-1	3.72	95						
Left OG/ITG							19/37	-51	-68	2	4.27	829
Left IPL							40	-46	-43	37	4.24	630
Left SPL							7	-22	-66	49	3.80	224
Left postcentral gyrus							2	-61	-23	40	4.17	467

ACC: anterior cingulate; MFG: middle frontal gyrus; IFG: inferior frontal gyrus; OG: occipital gyrus; ITG: inferior temporal gyrus; IPL: inferior parietal lobe; SPL: superior parietal lobe.

identify neural substrates involved in empathic processing. This contrast showed increased activation in ACC, the paracingulate cortex, the right middle frontal gyrus, the right anterior insula with an extension into the inferior frontal cortex, the left inferior frontal cortex, and the right putamen (see Table 1 and Fig. 2a). The locus of the activation in ACC and the insula was consistent with those observed in the previous studies (Singer et al., 2004; Jackson et al., 2005).

However, rating of painful pictures was different from counting of neutral pictures in both task demand and stimulus properties. To clarify which factor dominated in generating the increased neural activity observed in the above contrast, we made the second contrast between counting painful pictures and counting neutral

pictures, which dissociated the contribution of stimulus difference in producing empathy-related neural activity. Surprisingly, this contrast did not show significant activation in any brain areas (even using a more liberal threshold of $p < 0.005$, uncorrected), suggesting that watching painful pictures did not automatically induce enhanced neural activity in the brain areas mediating empathic responses to pain. Relative to rating painful pictures, counting painful pictures required subjects to focus attention on the number of hands and, to a certain degree, to ignore the feeling of pain of the hand owner.

To identify the role of task demand (i.e., pain rating) in producing neural responses related to empathy, we made another contrast between rating and counting painful pictures. Because

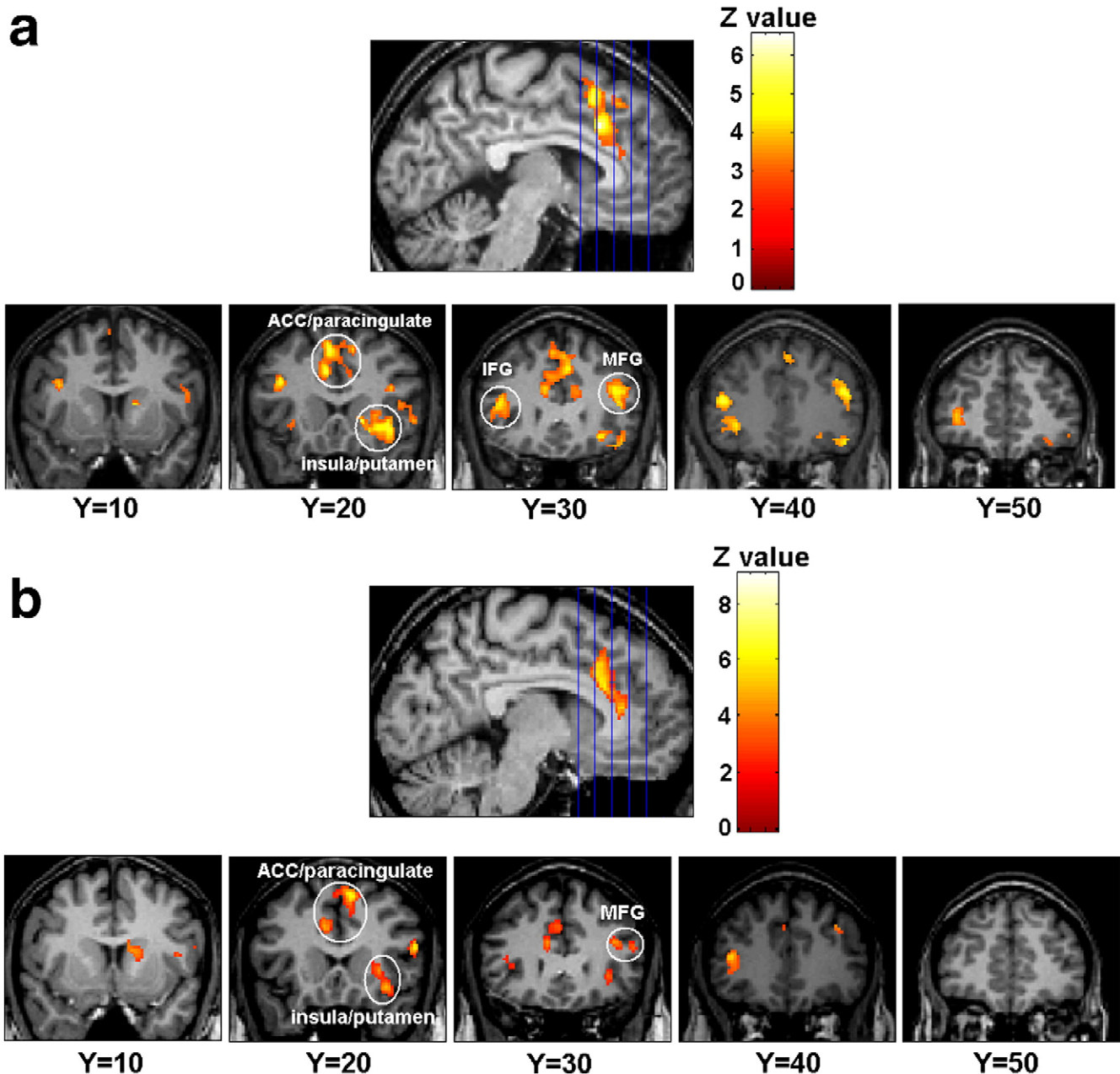


Fig. 2. (a) Brain activations shown in the contrast between rating painful pictures and counting neutral pictures. (b) Brain activations shown in the contrast between rating and counting painful pictures. IFG=inferior frontal gyrus; MFG=middle frontal gyrus.

Table 2
Brain activations shown in the contrast between rating and counting painful stimuli

Brain region	Pictures						Cartoons					
	BA	x	y	z	Z-value	Voxel no.	BA	x	y	z	Z-value	Voxel no.
ACC	32	−6	26	24	3.74	364	32	−2	38	22	3.72	376
Paracingulate	8	6	18	54	4.12	173	8	−4	28	54	3.89	283
Right MFG	9	38	38	29	4.17	110						
Right insula/IFG	47	36	19	−9	3.52	205						
Right putamen		18	8	11	3.54	428						
Left OG/ITG							19/37	−46	−51	−8	5.00	420
Left postcentral gyrus							1/2	−61	−23	38	4.82	292

ACC: anterior cingulate; IFG: inferior frontal gyrus; OG: occipital gyrus; ITG: inferior temporal gyrus.

the stimuli were identical in the two conditions, this contrast identified task-dependent neural activity. Increased activation was observed in the ACC/paracingulate cortex, the right inferior frontal cortex and the anterior insula, the right middle frontal cortex, and the right putamen (see Table 2 and Fig. 2b). These activations were associated with top-down attention to pain of others rather than automatic empathic responses induced by the stimuli.

Cartoons

Significant activation was observed in ACC, the paracingulate cortex, the right middle frontal cortex in the contrast between rating painful cartoons and counting neutral cartoons. Increased activation was also seen in the inferior and superior parietal cortex, lateral occipito-temporal cortex, and the postcentral gyrus (see Table 1 and Fig. 3a). The parietal and occipito-temporal activation was evident only in the left hemisphere. These posterior activations were not observed for the picture stimuli.

Similar to the results of picture stimuli, counting painful cartoons did not show any activation relative to counting neutral cartoons (even using a more liberal threshold of $p < 0.005$, uncorrected), suggesting that empathic responses did not take place automatically for the painful stimuli when attention was drawn away from the painful aspects of the cartoons stimuli. However, the contrast between rating painful cartoons and counting painful cartoons showed increased activity in ACC, the paracingulate, the left occipito-temporal junction, and the left postcentral gyrus (see Table 2 and Fig. 3b), suggesting the involvement of these areas in the task of rating pain intensity.

Conjunction analysis

We used a conjunction analysis of the contrasts between rating painful stimuli and counting neutral stimuli to identify the neural substrates shared by empathic responses to pictures and cartoons. The conjunction analysis showed increased activation in the ACC/paracingulate (centered at $-4/22/45$, BA 8/32, $Z=3.83$, voxel number=34, $p < 0.05$, corrected) and the right middle frontal gyrus (centered at $48/34/17$, BA 46, $Z=3.35$, voxel number=27, $p < 0.05$, corrected) that were common for both pictures and cartoons. The conjunction analysis of the contrasts between rating painful stimuli and counting painful stimuli revealed activation in the ACC/paracingulate (centered at $8/29/44$ BA 8/32, $Z=3.95$, voxel number=353, $p < 0.05$, corrected) and the left inferior frontal gyrus (centered at $-36/37/2$, BA 45/46, $Z=4.52$, voxel number=1062, $p < 0.05$, corrected) that were common for both pictures and cartoons.

Interaction analysis

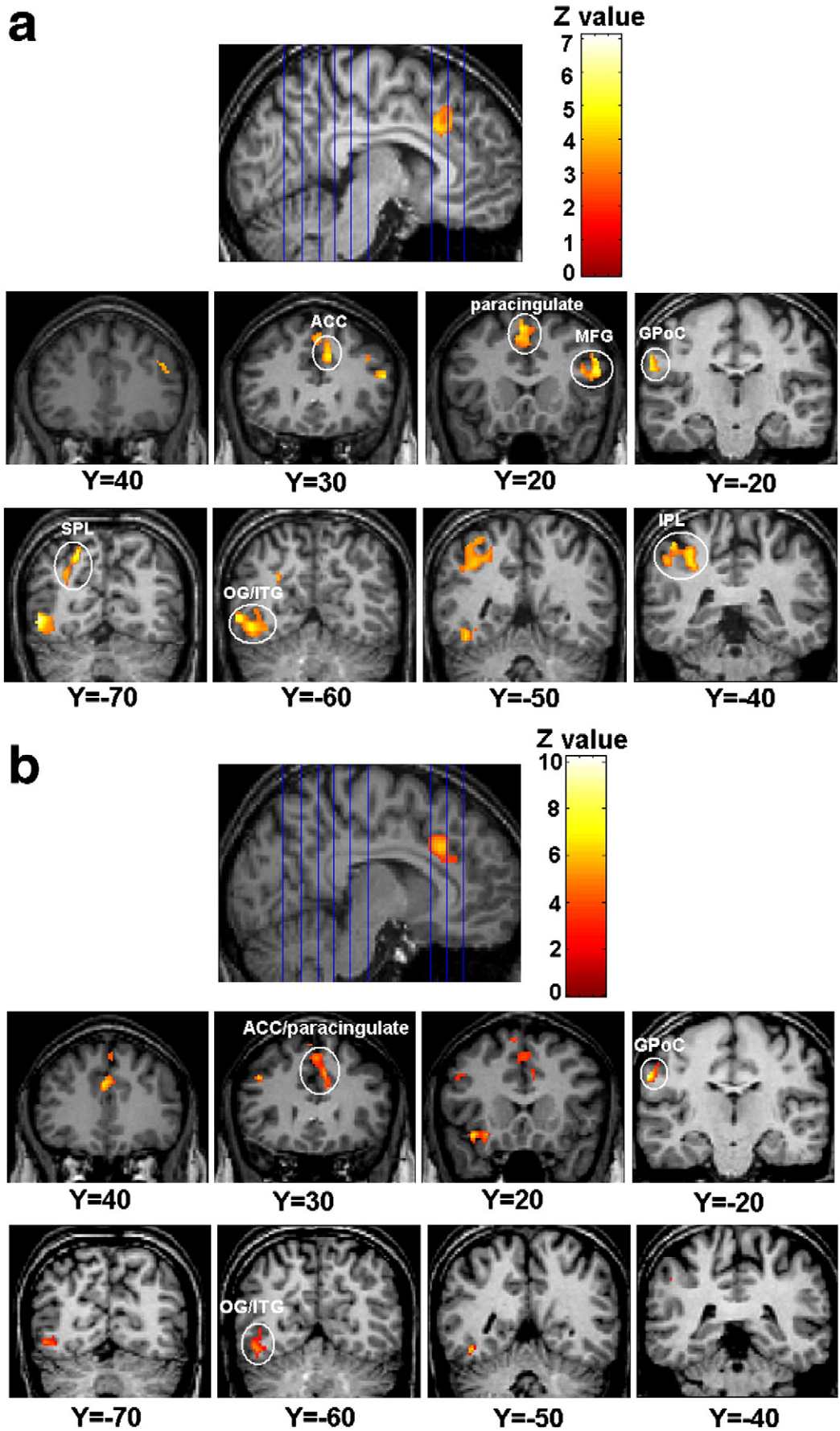
To uncover the differential activity related to empathizing with pain of others shown in picture and cartoons, an interaction analysis was made to compare the two contrasts (rating painful pictures vs. counting neutral pictures and rating painful cartoons vs. counting neutral cartoons). This revealed stronger increased activation in ACC (centered at $-8/34/20$, BA 32, $Z=3.75$, voxel number=33, $p < 0.05$, corrected) for painful pictures than for painful cartoons. The reverse comparison, however, did not show any significant activation. Interaction analysis was also conducted to compare the two contrasts (rating painful pictures and rating painful cartoons vs. counting painful pictures and counting painful cartoons). However, these did not reveal any brain activation at the threshold $p < 0.05$ (corrected).

PPI analysis

PPI analysis was performed to examine the functional connectivity between the ACC or insula and other brain areas during rating painful pictures. The PPI analysis identified the left inferior frontal cortex (BA 45/46, centered at $-42/28/13$, $Z=3.93$, $p < 0.05$ corrected) that showed stronger covariation with the ACC during rating painful pictures than during counting neutral pictures (see Fig. 4), suggesting stronger functional connectivity between the ACC and the left inferior frontal cortex. However, similar PPI analysis did not find reliable functional connectivity between the ACC or insula and other brain areas when comparing rating vs. counting painful pictures and comparing counting painful vs. neutral pictures. PPI analysis of the fMRI data for cartoons did not show any brain areas that showed covariation with the ACC.

Discussion

The current work investigated the modulation of neural correlates of empathy for pain by top-down attention and the prior knowledge of stimulus reality. Similar to the prior study (Jackson et al., 2005, 2006a), we identified neural correlates of pain-related empathic responses by contrasting painful and neutral stimuli. Top-down attention to pain of another was manipulated by asking subjects either to rate pain intensity felt by the model or to count the number of hands in the stimulus displays. The rating task required attention to painful aspects of the hands in the stimuli whereas the counting task withdrew attention from the painful aspects of the stimuli. The stimulus reality was degraded by presenting subjects with cartoons showing hands in similar painful situations.



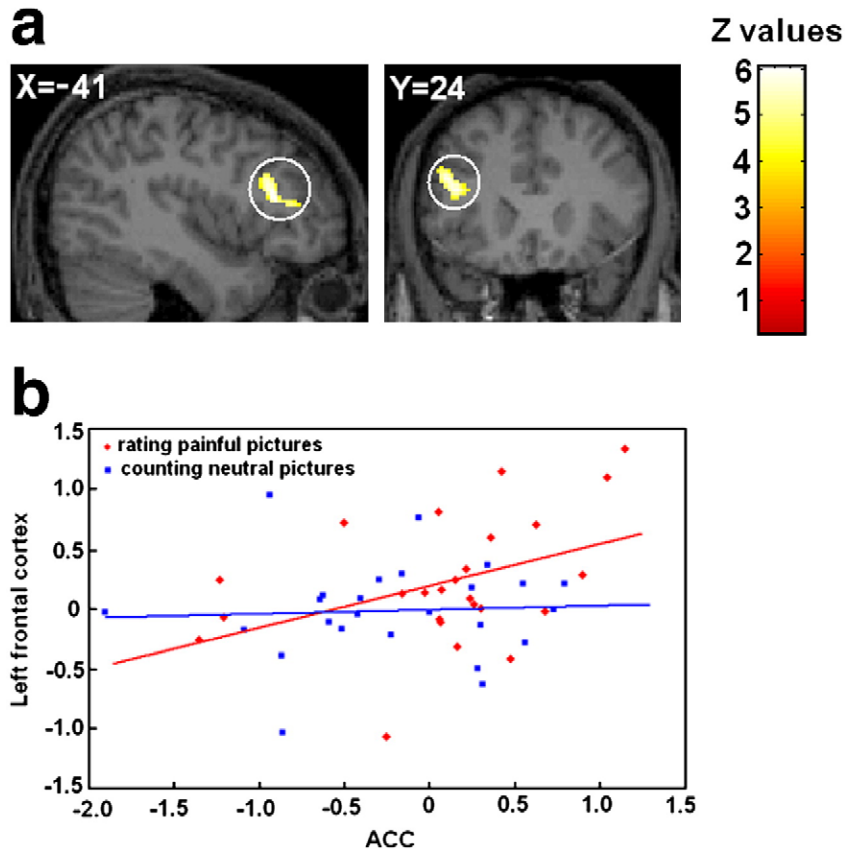


Fig. 4. (a) Illustration of the left inferior frontal cortex which showed significantly stronger covariation with the ACC during rating painful pictures than counting neutral pictures. (b) Profiles for a representative subject during rating of painful pictures and counting neutral pictures. The activities of the left inferior frontal cortex and the ACC were correlated during rating painful pictures but not counting neutral pictures.

The contrast between rating painful pictures and counting neutral stimuli revealed increased activations in ACC/paracingulate and the right insula. The right insula activation extended into the right inferior frontal cortex and the putamen. ACC/paracingulate and the insula are a part of the neural network underlying pain experience (Treede et al., 1999; Davis, 2000) and have been shown to be involved in empathy for pain in the studies using either visual stimuli showing hands in painful situations (Jackson et al., 2005, 2006a; Morrison et al., 2004) or visual symbols indexing the pain of other individuals (Singer et al., 2004). The ACC activity is associated with the affective dimension of one's own pain experience (Rainville et al., 1997) and is also correlated with ratings of others' pain (Jackson et al., 2005) and individual differences in empathy for pain (Singer et al., 2004). It has been suggested that ACC and the anterior insula underpin subjective unpleasantness of processing negative emotions such as pain (Bantick et al., 2002; Rainville et al., 1997) and disgust (Wicker et al., 2003). ACC and insula activations observed in the current experiment indicate that rating pain intensity of potentially painful situations in the pictures shot from the first-person perspective induced subjects' affective responses. We also found that rating pain intensity of

painful pictures activated the right middle frontal cortex and the left inferior frontal cortex. This is in agreement with the observation of Jackson et al. (2005). In addition, our PPI analysis showed stronger covariation of the left inferior frontal cortex and the ACC when rating painful pictures than when counting neutral pictures. Such functional connectivity between the ACC and the frontal cortex has been reported in the previous work (Koski and Paus, 2000). The results of our PPI analysis imply that the frontal cortex may play a key role in top-down modulation of the ACC activity. However, the enhanced functional connectivity was absent in the contrast of rating vs. counting painful pictures and in the contrast of counting painful vs. neutral pictures, suggesting that both top-down attention and emotional cues in the stimuli were necessary for enhanced functional connectivity between ACC and the inferior frontal cortex. The frontal activation was also observed in other studies of empathy using tasks of judging emotional states of others (Farrow et al., 2001) and imitating others' emotion (Carr et al., 2003), and has been implied in regulation of pain distress and negative affect (Petrovic et al., 2002). In the current study, relative to the counting task, rating painful stimuli might also encourage stronger attention to implied

Fig. 3. (a) Brain activations shown in the contrast between rating painful cartoons and counting neutral cartoons. (b) Brain activations shown in the contrast between rating and counting painful cartoons. ACC=anterior cingulate cortex; MFG=middle frontal gyrus; GPoC=postcentral gyrus; IPL=inferior parietal lobe; SPL=superior parietal lobe; OG=occipital gyrus; ITG=inferior temporal gyrus.

actions which were about to happen in the painful stimuli and thus induced the frontal activations. Our results support the proposal that both affective responses and emotion regulation are activated when watching others in painful situations. Increased activity in putamen has been observed when subjects endure painful stimuli (Downar et al., 2003) and is associated with negative emotions such as disgust (Calder et al., 2000). It appears that the putamen is involved in the processing of similar negative emotion both when experiencing painful stimuli and when watching others in pain.

Similar to the previous neuroimaging studies (Jackson et al., 2005; Morrison et al., 2004; Singer et al., 2004), the current work did not find evidence for the involvement of the sensorimotor cortex in empathizing others' pain. However, recent TMS studies showed evidence for the modulation of activity of the sensorimotor cortex by watching others in pain (Avenanti et al., 2005, 2006). It has been speculated that the difference in sensitivity to the activity of the sensorimotor cortex between fMRI and TMS or the difference in the stimuli or the mental attitudes of the participants between the studies may contribute to the differential findings regarding the involvement of the sensorimotor cortex in empathy for pain (Singer and Frith, 2005). However, recent fMRI studies found that, besides the ACC, insula, and the inferior frontal gyrus, watching provoked pain faces elicited prominent activation in the supplementary motor area (SMA) (Saarela et al., 2007). Rating pain intensity of painful actions depicted in words also activated both the insula and sensorimotor cortex (e.g., SII) (Gu and Han, submitted for publication). These results suggest that fMRI signals can be equally sensitive to activities in the insula, SMA, and sensorimotor cortex. Given the recent finding of Jackson et al. (2006a,b) stating that rating the level of pain shown in pictures of hands or feet in painful situations induced activation in SII when the pain was perceived from the self-perspective but not when from the other's perspective, it may be hypothesized that to assess pain intensity from the first-person perspective is necessary for the sensorimotor cortex to be involved in empathy for pain. In agreement with this hypothesis, Ogino et al. (in press) recently found that imagination of pain in one's own body induced strong activation in SII. Similar to Jackson et al. (2005), we analyzed the correlation between percent signal changes and scale reports of pain intensity felt by the model and of subjective unpleasantness when watching the stimuli. However, we did not find significant correlation between fMRI signals and the subjective reports, possibly because the subjective reports were obtained after the scanning procedure and thus were loosely linked to the neural activity obtained during the scanning procedure.

An important finding of the current work was that the activity of the neural network involved in empathic processing depended strongly upon the top-down controlled mechanisms. The neural network consisting of ACC, the insula, and the frontal cortex showed increased activity when subjects were asked to evaluate pain intensity of the hand owner. However, the activities of the entire network were eliminated when subjects were required to count the number of hands in the identical stimuli. The counting task did not draw subjects' attention away from the hands in the stimuli, but withdrew attention only from the painful aspect of the hands. According to the proposal that empathy is mediated by an unconscious and automatic simulation of others' emotional state (Gallese, 2001; Gallese and Goldman, 1998), one would expect that stimulus displays showing hands in a painful situation generate similar neural responses in the ACC and insula irrespective of the

task demand. Our fMRI findings, however, suggest that perception of others' body parts in potentially painful situation does not spontaneously elicit recognition of the emotional state of the body owner and produce empathic responses. Singer et al. (2004) found pain-related empathic responses in ACC and the insula when subjects were not asked to make explicit judgments of pain intensity of others. However, subjects had a strong social connection with the persons applied with painful stimuli (i.e., their loved ones) in their experiment. Because empathic activity is modulated by social relations between individuals (Singer et al., 2006), participants in the experiment of Singer et al. (2004) might pay attention to their loved ones even though no explicit tasks were assigned to their partners' pain. The current fMRI results are in agreement with a perception-action model of empathy (Preston and de Waal, 2002). According to this model, empathy consists of two stages of processing. Attention is required to represent the emotional state of other individuals at the first stage. Once the representation of others' emotional state is accomplished, activation of these representations automatically generates the associated autonomic and somatic responses. Our fMRI results indicate that recognition of others' emotional state is not a purely automatic and effortless process. Recognition of others' pain requires not only attention to others' body parts but attention to the painful aspect of the body parts as well. Once recognition of others' pain fails, the brain areas underlying pain-related affect responses cannot be activated. As our fMRI data showed that withdrawing attention from the pain aspect of stimuli (by performing a counting task) eliminated the neural activities in the ACC, insula, and the lateral frontal cortex, it may be proposed that both cognitive and affective components of empathy for pain were weakened by attenuation of attention demand in perception of others in pain.

A recent work found that passively viewing short video sequences showing faces expressing moderate pain could activate the ACC and insula (Botvinick et al., 2005). Subjects may be more sensitive to others' pain shown in face than other body parts. Alternatively, the task of passively viewing may automatically engage attention to pain of others and activate the brain areas related to empathy. Our fMRI results that the neural activities associated with the affective components of empathy for pain were modulated by attentional demand are different from the observations of Avenanti et al. (2006) stating that the sensorimotor activity linked to empathy for pain was not affected by task instructions. It is likely that different mechanisms are engaged in mediating attentional modulation of empathy for pain at different stages of processing.

Previous studies of attentional modulation of pain perception usually asked subjects to perform an attention demanding visual task while painful thermal or cold stimuli were applied to body parts (Bantick et al., 2002; Petrovic et al., 2000). Because the stimuli used in the cognitive tasks and the painful stimuli were presented to different modalities (e.g., visual vs. tactile), such attentional modulation was essentially cross-modal (i.e., attention was drawn from one modality to another modality). The effect of attentional modulation was to decrease the activity of brain areas in the pain matrix (such as ACC and the insula) and to increase the activity of orbitofrontal cortex (Bantick et al., 2002; Petrovic et al., 2000). In contrast to these studies, the attentional modulation of pain-related empathic responses in the current study was essentially within-modal. Subjects' attention was drawn from one aspect to the other of the same visual stimuli. Moreover, the counting task was not as difficult as

those used in the prior studies of attentional modulation of pain experience (e.g., the Stroop task used by Bantick et al., 2002 and a perceptual maze test used by Petrovic et al., 2000). However, such attentional shift eliminated rather than decreased the neural activity of ACC and the insula mediating empathy for pain of others. It seems that the neural correlates of empathy for pain are more sensitive to attentional modulation than those underlying pain experience induced by noxious stimuli. We found that the contrast between rating and counting painful stimuli showed activation in similar brain structures as the contrast between rating painful pictures and counting neutral stimuli (except that the left inferior frontal activation was observed in the latter contrast). These results indicate that the rating task was necessary for generating affective empathic responses to pain of other individuals.

Similar to the results of the pictures, increased activation was identified in the ACC/paracingulate and the right middle frontal gyrus in association with rating pain intensity of painful cartoons relative to counting neutral ones. Conjunction analysis confirmed that these areas were common for rating both painful cartoons and painful pictures, indicating that these brain areas are engaged in cognitive evaluation of pain of another regardless of whether the reality of the potential pain situations shown in the stimuli was degraded. However, unlike the brain activation observed for the painful pictures, rating pain intensity of hands in the cartoons failed to activate the right insula and putamen, which are associated with negative emotions such as disgust induced by facial expression (Calder et al., 2000; Surguladze et al., 2003; Wicker et al., 2003) or noxious stimuli applied to hands (Bantick et al., 2002; Downar et al., 2003; Rainville et al., 1997). The absence of insula and putamen activation for the painful cartoons suggest that rating painful cartoons with degenerated reality did not invoke negative emotions as strong as that associated with rating the painful pictures. In contrast, the analysis of the interaction showed stronger ACC activation when watching the painful pictures than when watching the painful cartoons. Although previous neuroimaging studies showed that requiring subjects to carry out mental state reasoning on static cartoon pictures (Gallagher et al., 2000) or moving shapes (Castelli et al., 2000) could induce activations in brain regions related to theory-of-mind, our results suggest that the affective responses to others in painful situation were suppressed when watching cartoons than when watching pictures. Thus subjects' prior knowledge of the virtual reality of the stimuli reduced empathetic responses to others' pain. Because activation of the ACC is associated with emotional motivation and activation of the insula is associated with subjective emotional feelings (Craig, 2002), it may be speculated that the knowledge of stimulus reality produces stronger influence on subjective emotional feelings than emotional motivations induced by painful stimuli. According to Goubert et al. (2005), empathy depends upon both bottom-up (e.g., features of incoming stimuli) and top-down (features of observers' knowledge) process. The cartoons used in the current study were different from the pictures in color and texture. The lack of visual features made the cartoons less vivid and animated than the pictures, and subjects knew in advance that what they saw in the cartoons were unanimated. Thus both the bottom-up process (the lack of visual features) and the top-down process (the prior knowledge of virtual reality about the cartoons) may contribute to the neural activity that distinguished empathy for pain of hands in the painful pictures and cartoons.

One may notice that the subjective ratings of others' pain did not differ between painful pictures and cartoons in the current study. This appears to conflict with the differential ACC and insula activations between the two types of stimuli. One possibility is that the subjective reports were obtained after the scanning procedure (because of the limitation of response buttons used inside the scanner, we could not ask subjects to perform rating task using a 6-point scale) and thus did not reflect subjective feelings about the stimuli inside the scanner. Alternatively, as subjective ratings basically reflect cognitive evaluations, the different patterns of activations in ACC and insula between pictures and cartoons could not simply be attributed to the difference in cognitive evaluations. Instead, the differential activations in the brain areas may reflect other aspects of empathy for pain such as subjective feelings and affective motivations.

It is not surprising that rating painful cartoons also activated the posterior parietal lobes and occipito-temporal cortex. The region in the lateral occipito-temporal cortex is particularly involved in the processing of human body (Downing et al., 2001; Bartels and Zeki, 2004). The posterior parietal cortex is activated during perception of hand actions (Perani et al., 2000). Han et al. (2005) found that watching cartoons (but not movie clips) depicting humans induced activation in the posterior parietal cortex, suggesting that perception of virtual visual world shown in cartoons is characterized with attention to actions. In the current study, painful cartoons elicited weaker negative emotions (indexed by the absence of the insula and putamen activation and weaker ACC activation) relative to painful pictures because of degenerated stimulus reality. On the other hand, as a result of weak affective responses to painful cartoons, subjects might pay more attention to the visual details and actions shown in the cartoons than to the emotional states of the hand owners. Relative to the pictures, virtual reality of the painful cartoons could result in strong self–other distinction even although the pictures were shot from the first-person perspective and thus induced activation in the postcentral gyrus. This is consistent with the role of this brain area in perspective – taking with social emotions (Ruby and Decety, 2004). Similar to the results of the picture stimuli, no increased neural activity was observed related to counting painful cartoons relative to counting neutral cartoons, indicating that the brain activation linked to rating the painful cartoons was eliminated when subjects' attention was withdrawn from the painful aspect of the stimuli.

In summary, our fMRI results confirm the hypothesis that human empathic responses are subject to constraints of top-down attention and the prior knowledge of contextual reality of stimuli. We showed evidence that the engagement of ACC/paracingulate, the insula, and the frontal cortex in empathic responses to pain of another takes place only when subjects pay attention to the pain aspect of the stimuli. Without such explicit focus on others' pain, these brain regions do not automatically respond to produce empathic responses. In addition, the neural activity related to empathy for pain can be weakened in ACC and eliminated in the insula and putamen when the reality of painful situation is degenerated. We suggest that both cognitive and affective processes involved in empathy for pain are modulated by top-down controlled mechanisms and the prior knowledge of stimulus reality. However, it should be noted that, because of the low temporal resolution of fMRI results, our findings reflected only the modulation of the final output of the processing of empathy for pain and cannot distinguish between the effects on the automatic and intentional processes during empathy that may be characterized with difference time courses.

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