Neuron
Case Study

Can We Share a Pain We Never Felt? Neural Correlates of Empathy in Patients with Congenital Insensitivity to Pain

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DOI 10.1016/j.neuron.2008.11.023

SUMMARY

Theories of empathy differ regarding the relative contributions of automatic resonance and perspective taking in understanding others' emotions. Patients with the rare syndrome of congenital insensitivity to pain cannot rely on "mirror matching" (i.e., resonance) mechanisms to understand the pain of others. Nevertheless, they showed normal fMRI responses to observed pain in anterior mid-cingulate cortex and anterior insula, two key regions of the so-called "shared circuits" for self and other pain. In these patients (but not in healthy controls), empathy trait predicted ventromedial prefrontal responses to somatosensory representations of others' pain and posterior cingulate responses to emotional representations of others' pain. These findings underline the major role of midline structures in emotional perspective taking and understanding someone else's feeling despite the lack of any previous personal experience of it—an empathic challenge frequently raised during human social interactions.

INTRODUCTION

Recent brain imaging studies have shown overlapping activation patterns when subjects feel their own emotions and observe the same emotions in others (Wicker et al., 2003; Singer et al., 2004; Morrison et al., 2004; Botvinick et al., 2005; Jabbi et al., 2007; Lamm et al., 2007; Ochsner et al., 2008). The theory of "embodied simulation" postulates that such overlap reflects an automatic resonance to others' affective states, allowing implicit affect sharing and empathy (Gallese et al., 2004; Gallese, 2007; Keysers and Gazzola, 2006). In addition to this "mirror matching" mechanism, higher-level inferential processes, referred to as perspective taking, provide a means for understanding others' emotions in a more reflective way (Decety and Jackson, 2004; Beer and Ochsner, 2006; Mitchell, 2006). Accordingly, it has been hypothesized that an observer lacking the specific representation of a given feeling might hardly be able to directly empathize with someone experiencing this feeling and would necessarily have to engage in a perspective-taking posture to understand the other's state (Singer, 2006).

Patients with congenital insensitivity to pain (CIP) offer a unique opportunity for us to test this model of empathy; we can explore how the lack of self-pain representation might influence the perception of others' pain. In a previous behavioral study (Danziger et al., 2006), we found that CIP patients globally underestimated the pain of others when emotional cues were lacking, and that their pain judgments, in contrast with those of control subjects, were strongly related to interindividual differences in empathy trait. Here, we used event-related functional magnetic resonance imaging (fMRI) to study the neural correlates of empathy for pain in a group of 13 CIP patients and a control group of 13 healthy subjects. Participants were scanned while observing body parts in painful situations (Experiment 1) or facial expressions of pain (Experiment 2), and were instructed to imagine how the person in the picture feels. We anticipated that CIP patients, deprived as they are of the depicted pain experiences, would show decreased activation in regions supposedly involved in automatic resonance to others' pain, including the anterior insula (AI) and anterior mid-cingulate cortex (aMCC) (Singer et al., 2004; Keysers and Gazzola, 2006). In addition, we predicted that the patients' effort to build a representation of others' pain might engage brain areas known to be involved in emotional perspective taking, especially midline structures such as medial prefrontal and posterior cingulate cortices (Ochsner et al., 2005; Amodio and Frith, 2006; Saxe, 2006; Olsson and Ochsner, 2008). Such engagement of neural processes supporting emotional inference was expected to

depend both on the presence or absence of emotional cues during the task and on the empathic abilities of the observer.

RESULTS

Dispositional and Behavioral Measures

CIP patients and control subjects did not differ significantly in terms of self-rated empathy, as assessed by both the Balanced Emotional Empathy Scale (BEES) (Mehrabian, 1997) and the four subscales of the Interpersonal Reactivity Index (IRI) (Davis, 1983). Self-rated anxiety and depression did not differ between the two groups (Table 1).

In agreement with previous results (Danziger et al., 2006), pain intensity ratings of pictures depicting body parts in painful situations (Experiment 1) were lower in CIP patients, while the propensity to infer pain from facial expressions (Experiment 2) did not differ between the two groups. Arousal scores for pictures showing painful situations (Experiment 1) did not differ between CIP patients and control subjects.

fMRI Responses to Others' Pain

Experiment 1: fMRI Responses to Viewing Body Parts in Painful Situations

The observation of body parts in painful situations (contrasted with nonpainful situations) resulted in a similar brain activity pattern in CIP patients and control subjects. In each group, the activated regions corresponded to the neural network observed in previous studies on the perception of others' pain (for review, see Jackson et al., 2006), including bilateral AI, aMCC, and bilateral posterior parietal cortices (Figure 1A; Table 2).

No brain area was found to be differently activated between the two groups in the [Painful − Nonpainful] contrast, even when the significance threshold was lowered to $p < 0.001$ uncorrected at the voxel level. On the other hand, between-group comparison of the [Painful − Baseline] contrast revealed significantly lower activation of visual occipito-temporal cortices bilaterally in the CIP group as compared with those of the control group (Table S1 available online).

No correlation was found between brain activity and ratings of pain intensity in either group. In the control group, bilateral caudate, aMCC, and left AI activities were significantly correlated with the arousal score (Table 3), while no correlation with the arousal score was found in the CIP group. Analysis of group x covariate interactions showed a significantly greater correlation coefficient between left caudate and aMCC activities and the arousal score in the control group as compared with that of the CIP group (Table 3).

Experiment 2: fMRI Responses to Viewing Facial Expressions of Pain

Viewing facial expressions of pain (contrasted with neutral facial expressions) evoked a significant activation in left insula/inferior frontal gyrus in both groups (Figure 1B; Table 4). A significant activation of the mid-cingulate cortex was found in the control group only.

Between-group comparison of the [Painful − Nonpainful] contrast showed significantly less activity in occipito-temporal and posterior parietal regions in the CIP group, and between-group comparison of the [Painful − Baseline] contrast showed significantly less activity in occipital and posterior parietal regions in the CIP group (Table S2). Whatever the contrast, activity in the insula and mid-cingulate cortex did not differ significantly between the two groups, even when the significance threshold was lowered to $p < 0.001$ uncorrected at the voxel level.

No correlation was found in either group between brain responses to facial expressions of pain and ratings of pain intensity.

Correlations between Brain Responses to Others' Pain and Empathy Trait

Experiment 1: Pictures of Body Parts in Painful Situations

In the control group, right precuneus and inferior parietal lobule activities were correlated with the BEES score, but not with any of the IRI scores. In the CIP group, by contrast, the functional activity of the ventromedial prefrontal cortex (vmPFC), including pregenual anterior cingulate cortex (pgACC), was significantly correlated with both the BEES score and the Empathic Concern score of the IRI, two distinct measures of emotional empathy (Table 5; Figure 2A). Inclusion of anxiety and depression scores as covariates in the analysis did not alter the significance level of these correlations (data not shown). Analysis of group x covariate interactions showed a significantly higher correlation coefficient between pgACC activity and the BEES score in the CIP group as compared with that of the control group (Table 5).

Experiment 2: Facial Expressions of Pain

In the control group, no significant correlation was found between brain responses to facial expressions of pain and BEES or Empathic Concern scores. In the CIP group, by contrast, ventral posterior cingulate cortex (vPCC) activity was significantly correlated with both of these emotional empathy scores (Table 5; Figure 2B). Inclusion of anxiety and depression scores as covariates in the analysis did not alter the significance level of these correlations (data not shown). Analysis of group x covariate interactions showed a trend toward a higher correlation coefficient between vPCC activity and the BEES score in the CIP group as compared with that of the control group (Table 5).

DISCUSSION

Similarities and Differences in Brain Activation Patterns between CIP Patients and Control Subjects

Although CIP patients cannot refer to their own experience of pain to understand how the pain of others feels, they showed normal responses to observed pain in AI and aMCC, two key regions consistently activated by both self and other pain in healthy subjects (Singer et al., 2004; Morrison et al., 2004; Botvinick et al., 2005; Lamm et al., 2007; Ochsner et al., 2008). Indeed, no group differences were seen in AI and aMCC, whether others' pain was represented from a somatosensory perspective (body parts in painful situations) or from an emotional perspective (facial expressions of pain). These findings challenge the frequently advanced hypothesis that activity in these regions during observed pain corresponds to the automatic engagement of the observer's own pain circuits through a mirror matching

Table 1. Dispositional and Behavioral Measures in Control and CIP Groups

		CIP Group (n = 13)	Control Group (n = 13)	p
Dispositional measures	Balanced Emotional Empathy Score (BEES)	48.7 ± 29.9	44.5 ± 22.0	0.7
	Interpersonal Reactivity Index (IRI)[a]			
	Empathic Concern score	21.1 ± 5.0	21.7 ± 3.8	0.8
	Perspective Taking score	14.9 ± 4.3	17.3 ± 2.3	0.3*
	Fantasy score	17.5 ± 5.4	14.8 ± 4.7	0.2
	Personal Distress score	9.5 ± 4.9	10.7 ± 5.1	0.5
	Anxiety score (Zung)	41.1 ± 6.9	37.3 ± 5.5	0.2
	Depression score (QD2A)	1.4 ± 2.5	0.3 ± 0.6	0.4*
Experiment 1	Pain score for pictures with painful situations	69.8 ± 19.5[c]	83.7 ± 14.1[c]	0.048[c]
	Pain score for pictures with nonpainful situations	1.7 ± 3.3	3.1 ± 4.0	0.4
	Arousal score for pictures with painful situations[a]	105.6 ± 43.6	118.7 ± 28.4	0.4
	Arousal score for pictures with nonpainful situations[a]	0	0	1
Experiment 2	Pain score for facial expressions of pain[b]	56.7 ± 12.6	62.2 ± 13.3	0.3
	Pain score for neutral facial expressions[b]	7.7 ± 7.2	5.8 ± 6.2	0.5

Note: p values are given for Student's t tests, except for Mann-Whitney U-test (performed because of the nonhomogeneity of variances between groups), marked by an (*).
[a] Obtained in all except one control subject.
[b] Obtained in all except one CIP patient.
[c] Significant ($p < 0.05$) difference between CIP and control groups.

mechanism. Rather than specifically reflecting shared representations of pain, AI and aMCC responses to others' pain may relate to the processing of the emotional significance of aversive stimuli in general. A number of studies using a vast variety of emotional stimuli unrelated to pain have shown similar AI and aMCC activations in healthy volunteers (e.g., Morris et al., 1998; Phillips et al., 1997; Phan et al., 2004; Britton et al., 2006; Benuzzi et al., 2008). Moreover, a recent study suggests that, far from being automatic, such coding of the affective quality of the pain experienced by another person requires an explicit focus on others' pain, as demonstrated by the disappearance of aMCC and AI responses to viewing body parts in painful situations when attention is withdrawn from the pain aspect of the stimuli (Gu and Han, 2007).

Interestingly, the finding of a significant correlation between AI and aMCC (as well as caudate) activities and arousal score in control subjects, but not in CIP patients, suggests that the engagement of these regions during observed pain may be related to different qualities of emotional processing in the two groups. In control subjects, insular and aMCC activation could reflect the generation and/or monitoring of arousal and autonomic changes contributing to the unpleasantness of watching others' pain (Critchley et al., 2000; Ochsner et al., 2008), while less-embodied and more cognitive processes might be at work in CIP patients. One possibility is that despite their lack of sensory experiences of pain, CIP patients may have learned to respond empathetically to others' pain through association mechanisms. Given the involvement of AI and aMCC during both physical pain and the pain of social exclusion (Eisenberger et al., 2003) or grief (Gündel et al., 2003), one might hypothesize, for example, that CIP patients' previous experiences of psychological distress allows them to understand what it means to feel pain (Panksepp, 2003; Danziger and Willer, 2005). The lack of significant correlations between AI and aMCC activities and the arousal score in the CIP group suggests that such *analogical* understanding of others' pain may not be associated with the kind of embodiment observed in healthy subjects, however.

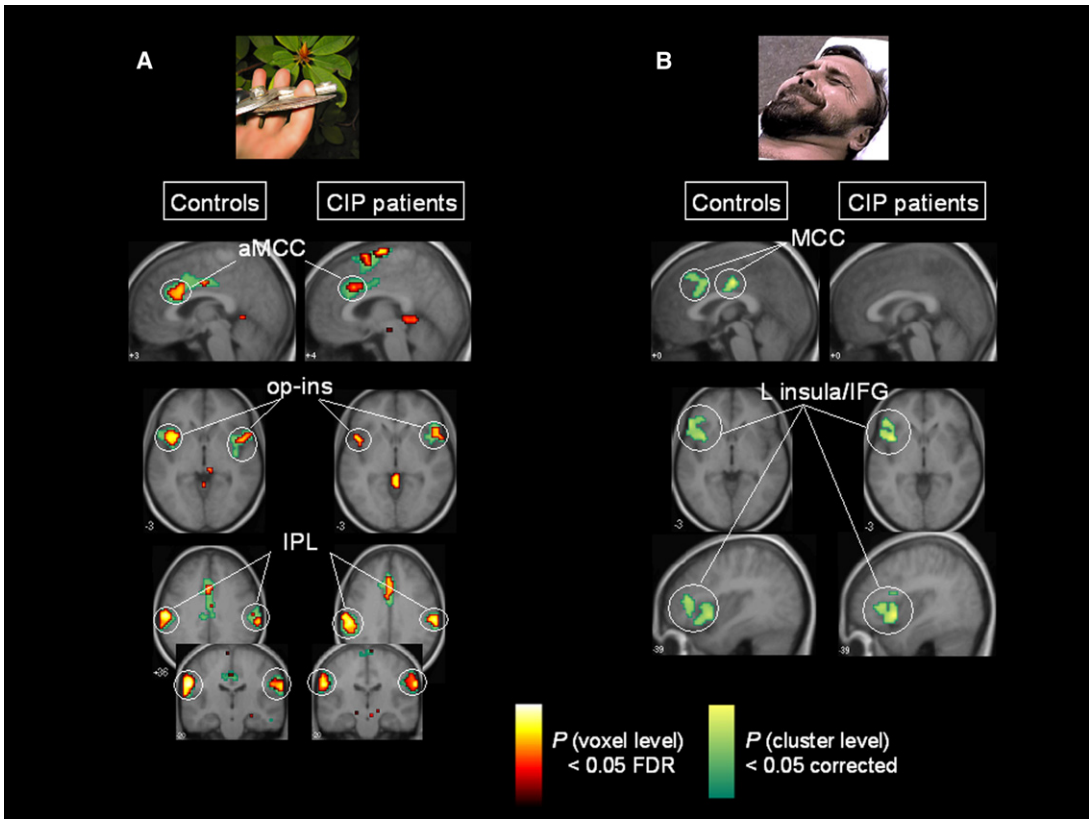

Figure 1. Brain Responses to Others' Pain in CIP Patients and Control Subjects

(A) Viewing pictures of body parts in painful situations contrasted with viewing nonpainful situations (Experiment 1). In both control subjects and CIP patients, a significant increase of BOLD signal was observed in particular in bilateral operculo-insular (op-ins) cortices, anterior mid-cingulate cortex (aMCC), and bilateral inferior parietal lobule (IPL). (B) Viewing facial expressions of pain contrasted with viewing neutral facial expressions (Experiment 2). A significant increase of BOLD signal was observed in the left (L) insula and inferior frontal gyrus (IFG) in both groups. The activation of the mid-cingulate cortex was observed in the control group but did not reach significance in the CIP group.

In agreement with this assumption, CIP patients, compared with control subjects, exhibited reduced occipito-temporal responses to the sight of others' pain, whether represented from a somatosensory or emotional perspective. In healthy subjects, both valence and arousal are known to contribute to stronger occipito-temporal activation in response to visual stimuli (Lang et al., 1998, 1999; Taylor et al., 2000; Pessoa et al., 2002; Mourão-Miranda et al., 2003). The lesser occipito-temporal activation observed in CIP patients might therefore be associated with reduced emotional salience of pictures with painful content and could indicate impaired immediate affective resonance to others' pain. As a matter of fact, although we did not find any significant between-group difference in arousal scores in the present study, CIP patients did report reduced aversive emotional responses to videos of injury in our previous behavioral study (Danziger et al., 2006). Because increased occipito-temporal response to emotional stimuli may result from the modulatory influence of the amygdala (Vuilleumier et al., 2004), lesser amygdala activation would have been expected in the CIP group. However, no amygdala response was found in either group because of Blood Oxygenation Level-Dependent (BOLD) signal loss due to bone artifact (Preston et al., 2004).

Differential Contribution of Empathy in CIP Patients and Control Subjects to the Neural Processing of Others' Pain

Whatever the mode of representation of others' pain, CIP patients showed on average no significant activation in brain regions known to be involved in perspective taking, namely the medial prefrontal cortex (mPFC), the posterior cingulate cortex (PCC), the right temporo-parietal junction (TPJ), and adjacent superior temporal sulcus (See Saxe, 2006 for review). However, regression analyses revealed task-specific correlation patterns between emotional empathy scores and activity in mPFC and PCC. In the CIP group (but not in the control group), emotional empathy scores strongly predicted both ventromedial prefrontal responses to pictures of body parts in painful situations and vPCC responses to facial expressions of pain. A number of studies have underlined the role of these midline structures in processes supporting judgments about the emotional states of others (i.e., emotional perspective taking) (Völlm et al., 2006; Ochsner et al., 2004; Amodio and Frith, 2006; Saxe, 2006; Olsson and Ochsner, 2008). The mPFC—particularly its ventral part (vmPFC)—help integrate information about the internal state of the body with higher-level

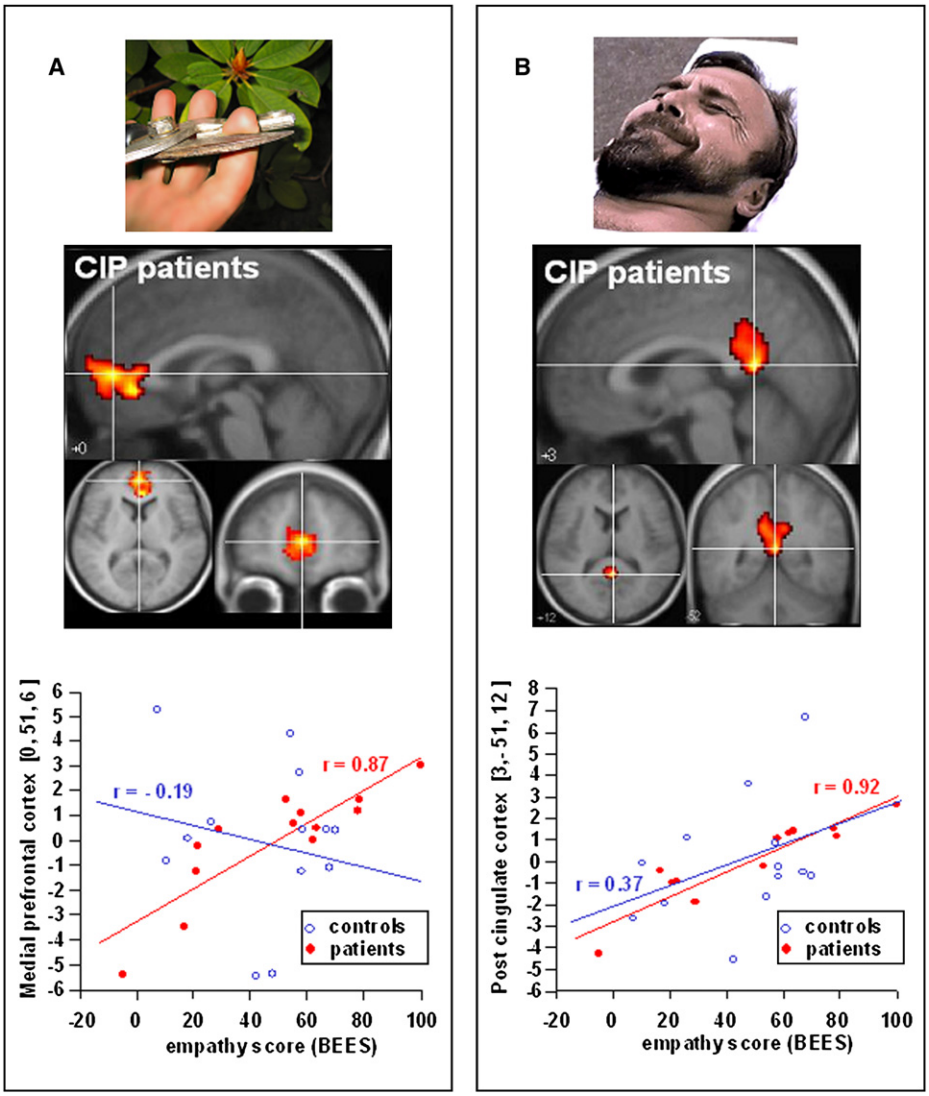

Figure 2. Correlations between Empathy Trait and the Hemodynamic Responses to Others' Pain in CIP Patients and Control Subjects

(A) Correlation between empathy trait and the hemodynamic responses to pictures of body parts in painful situations (Experiment 1). In the CIP group (but not in the control group), ventromedial prefrontal responses (parameter estimates, ordinate) are strongly and positively correlated with the Balanced Emotional Empathy Scale (BEES) score (abcissa). (B) Correlation between empathy trait and the hemodynamic responses to facial expressions of pain (Experiment 2). In the CIP group (but not in the control group), ventral posterior cingulate cortex responses (parameter estimates, ordinate) are strongly and positively correlated with the BEES score (abcissa). Note: in both experiments, similar correlations were found with the Empathic Concern score of the IRI.

mental state knowledge needed to categorize one's own as well as others' emotions (Amodio and Frith, 2006; Olsson and Ochsner, 2008). Patients with lesions in this region exhibit markedly reduced social emotions, including empathetic concern (Shamay-Tsoory et al., 2004; Lough et al., 2006; Koenigs et al., 2007), and show a selective impairment of affective (as compared to cognitive) theory of mind (Shamay-Tsoory et al., 2006; Shamay-Tsoory and Aharon-Peretz, 2007). Interestingly, a recent functional connectivity study showed increased interaction between mPFC activity and the aMCC and AI during pain perception in others, as compared with self-pain experience (Zaki et al., 2007). The posterior cingulate also has been associated with emotional evaluation and perspective taking (Gallagher et al., 2000; Maddock et al., 2003; Wicker et al., 2003; Völlm et al., 2006). Its contribution to emotional processing is believed to depend more specifically on its ventral part, which is connected with the subgenual anterior cingulate cortex (Vogt et al., 2006). Altogether, the correlation patterns between vmPFC or vPCC activity and emotional empathy trait suggest that CIP patients may particularly rely on their empathic abilities to imagine the pain of others. This interpretation is in agreement with previous results showing that empathy trait strongly predicted CIP patients' (but not control subjects') estimations of others' pain from both injury scenes and facial expressions of pain (Danziger et al., 2006).

Table 2. Brain Areas Activated While Viewing Pictures Depicting Body Parts in Painful Situations (Contrasted with Nonpainful Situations) in CIP and Control Groups (Experiment 1)

	CIP Group				Control Group			
	Coordinates				Coordinates			
Region of activation	x	y	z	T-score	x	y	z	T-score
L medial frontal gyrus					−12	42	21	4.57*
L superior frontal gyrus					−21	51	24	4.37*
R superior frontal gyrus	12	18	63	3.94*				
ant mid-cingulate cortex	0	15	36	3.86*	0	21	24	4.03*
R ant insula	39	15	6	3.75*	36	6	6	3.77*
L ant insula	−48	9	−3	3.86*	−48	9	6	4.47*
R post insula					42	−9	−6	4.10*
L mid-insula					−39	0	9	4.44*
R superior temporal gyrus	60	12	0	4.70*	57	6	6	4.81*
L superior temporal gyrus	−57	12	0	4.18*	−60	12	3	4.83*
R inferior parietal lobule	66	−30	39	7.31**	66	−30	39	6.85**
L inferior parietal lobule	−48	−48	60	4.51*	−57	−30	30	6.37**
R post-central gyrus	66	−24	27	5.90**	69	−21	30	6.58**
L post-central gyrus	−63	−27	42	5.67**	−63	−18	30	6.03**
R superior parietal lobule	27	−51	72	4.28*	24	−57	72	3.96*
L superior parietal lobule	−27	−51	66	3.90*				
L middle occipital gyrus	−54	−69	−9	5.12**				
cuneus	0	−96	3	3.83*				
cerebellum	0	−48	−6	5.94**	0	−48	−6	4.04*
L thalamus	−3	−33	3	4.23*				
R thalamus					6	−30	0	5.21**
R caudate					21	−36	12	4.01*

Coordinates (mm) are in MNI space. R, right; L, left; ant, anterior; post, posterior; *p < 0.05, FDR corrected; **p < 0.01, FDR corrected.

How can we explain the differential empathy-related engagement of vmPFC and vPCC in CIP patients during observation of body parts in painful situations and facial expressions of pain, respectively? One possible reason could be that the level of abstraction regarding others' pain differed between the two tasks. Previous work in healthy subjects has provided evidence of pain somatic resonance mechanisms, in which basic sensory aspects of someone else's painful experience are automatically mapped onto the observers' motor and somatosensory systems (Avenanti et al., 2005; Cheng et al., 2008). In the absence of functional somatic resonance mechanisms shaped by previous pain experiences, imagining the pain of others from pictures of body parts, i.e., from a somatosensory perspective, might represent a complex mental state attribution (MSA) task, as compared with the more stimulus-driven emotional inferences triggered by facial pain expressions. At the behavioral level, such difference in task complexity could account for the lower accuracy of CIP patients in estimating others' pain from scenarios where body parts are shown in painful situations, as compared with making estimations from facial expressions of pain. Previous works suggest that the vPCC could support simple first-order sensory aspects of MSA in emotion, whereas abstract representations of others' emotions might depend on more anterior regions such as the vmPFC (Amodio and Frith, 2006; Olsson and Ochsner, 2008). Our finding of task-specific correlation patterns involving either vPCC or vmPFC fits well with this model of functional-anatomical organization.

We previously showed that the ability of CIP patients to fully acknowledge the pain of others strongly depended on their empathic capacities (Danziger et al., 2006). The present data suggest that this contribution of empathy to the perception of others' pain mainly relies on the engagement of anterior (vmPFC) and posterior (vPCC) midline structures, which may in part compensate for the patients' lack of automatic resonance mechanisms. Our findings thus underline the major role of these midline regions in emotional perspective taking and in understanding someone else's feeling despite the absence of any previous personal experience of it—an empathic challenge frequently raised during human social interactions.

EXPERIMENTAL PROCEDURES

Subjects

CIP is a rare clinical syndrome characterized by dramatic impairment of pain sensation since birth, caused by a hereditary neuropathy (Nagasako et al., 2003) or channelopathy (Cox et al., 2006) involving small-caliber sensory nerve fibers. Thirteen patients from eight families (seven females; age: 32 ± 12 years [mean ± SD]; education: 13 ± 3 years) with established diagnoses of diffuse CIP were recruited after full clinical and neurophysiological assessment (Danziger et al., 2006), together with 13 healthy gender-, age-, and educational-matched control subjects (seven females; age: 33 ± 9 years; education: 13 ± 2 years). The participants had no history of learning disability or psychiatric illness, including substance abuse/dependence or intake of regular medications, and all of them had normal or corrected-to-normal vision for both the behavioral and the fMRI experiments. All patients had a typical history of painless injuries (burns, wounds, bone fractures) from early childhood. They showed a complete lack of discomfort, grimacing, or withdrawal reaction to prolonged pin-pricks, strong pressure, soft tissue pinching, and noxious thermal stimuli (0 and 50°C) applied to the proximal and distal parts of the four limbs and to the face. Other abnormalities included decreased perception of warm and cold (seven cases), altered touch and proprioception (one case), mild autonomic dysfunction (four cases), anosmia (five cases), and ageusia (one case).

All patients and control subjects gave informed written consent and the study was approved by the local Ethics Committee (CHU St-Etienne, France) and conducted in accordance with the Declaration of Helsinki. Participants received monetary compensation for their participation.

Measures of Empathic Ability, Anxiety, and Depression

The empathy trait of participants was measured using two self-administered questionnaires translated to French: the 30 item BEES (Mehrabian, 1997)

Table 3. Viewing Pictures of Body Parts in Painful Situations (Experiment 1) and Correlations with the Arousal Score

		Coordinates				
	Region of Activation	x	y	z	T-score	k
Control group	L caudate	−18	−6	21	7.07§	491**
	R caudate	27	24	18	8.05§	330**
	L ant insula/inferior frontal gyrus	−42	12	21	5.43§	197*
	L ant insula	−45	9	−6	5.43§	
	L ant insula	−36	12	5	5.24§	
	L ant mid-cingulate cortex	−6	9	39	5.32§	250*
	R ant mid-cingulate cortex	9	18	30	4.69§	
	R ant mid-cingulate cortex	9	15	39	4.31§	
Control > CIP	L caudate	−18	−6	21	5.53§	119
	L ant mid-cingulate cortex	−6	9	39	3.92§	106

Note: no significant correlation was found in the CIP group. Coordinates (mm) are in MNI space. R, right; L, left; ant, anterior; post, posterior; k, voxels number in the cluster. Probabilities at the cluster level are corrected for multiple comparisons: **$p < 0.001$; *$p < 0.01$; and at the voxel level, uncorrected, §$p < 0.001$.

and the 28-item IRI (Davis, 1983). The BEES assesses the capacity to vicariously experience another's emotion. The IRI consists of four scales, each measuring a distinct component of empathy: empathic concern (feeling emotional concern for others); perspective taking (the ability to take cognitively the perspective of another); fantasy (emotional identification with characters in books, films, etc.); and personal distress (tendency to become anxious when witnessing others' suffering or need for help).

Participants' level of anxiety was assessed using the Zung self-rating anxiety scale (Zung, 1971). This self-reporting 20 item scale is designed to quantify anxiety-associated symptoms. The scale is based on symptom frequency and includes 15 items worded toward increasing anxiety levels and 5 items worded toward decreasing anxiety levels, with each item being measured on a four-point Likert scale.

Participants also completed the QD2A Depression Questionnaire, a 13-item French self-questionnaire on depressive symptoms from which a total depression score was computed (Pichot et al., 1984).

Picture Stimuli

Twelve of the thirteen CIP patients had previously participated in a behavioral study 1 year before (Danziger et al., 2006). In this previous study we used a different set of pictures. Consequently, all photographs and video clips shown in the present experiments were shown to the participants for the first time.

Pictures of Body Parts (Experiment 1)

In Experiment 1, a series of digital color pictures showing right hands and right feet in painful and nonpainful situations (40 each) were used. These included 60 pictures previously developed and validated by Jackson et al. (2005) which were used with their permission, to which 20 home-made pictures were added. Pictures were shot from angles that promoted first-person perspective (i.e., no mental rotation of the limb required for the observer). All situations depicted familiar events that can happen in everyday life. Various types of nociceptive stimulations (pinch, blow, pressure, prick, cut, heat) were represented. For each painful situation, a nonpainful situation, which involved the same setting without any nociceptive component, was also obtained. All pictures were edited to the same size (600 × 450 pixels). Scrambled images were obtained for each picture and used as baseline.

Video Clips of Facial Expressions (Experiment 2)

In Experiment 2, videotaped recordings of facial expressions showing expressions of pain or neutral expressions were used. These consisted of 78 video clips (39 pain clips and 39 neutral clips) of 21 separate individuals (10 women) with current complaints of shoulder pain undergoing motion exercises involving active or passive movements of the affected limb, previously developed and validated by Botvinick et al. (2005) and kindly provided by K.M. Prkachin. Videotaped recordings of facial expressions of pain displayed one of the three facial movements which have consistently been associated with pain: brow lowering, orbit tightening, and raising of the upper lip. All selected pain expressions contained at least one of these actions coded 3 or greater in the Facial Action Coding System (FACS; Ekman and Friesen, 1978). For each selected excerpt, a control clip showing a neutral facial expression was sampled from the same participant. Care was taken to ensure that the control clips were as close as possible to the pain clips in terms of features such as orientation of the face to the camera, luminance, and duration. The average duration of clips was 1.10 s (SD = 0.50).

Table 4. Brain Areas Activated while Viewing Facial Expressions of Pain (Contrasted with Neutral Expressions) in CIP and Control Groups (Experiment 2)

	CIP Group					Control Group				
	Coordinates					Coordinates				
Region of activation	x	y	z	T-score	k	x	y	z	T-score	k
L insula	−39	12	−6	4.15§	355*	−39	12	−6	3.98§	745**
L frontal opercule	−45	21	6	3.90§		−45	15	6	4.42§	
L inferior frontal gyrus	−51	39	3	3.75§		−54	27	3	4.31§	
post mid-cingulate cortex						0	−15	39	4.93§	276*
L post mid-cingulate cortex						−12	0	33	4.39§	
L ant mid-cingulate cortex						−3	18	39	3.37	

Coordinates (mm) are in MNI space. R, right; L, left; ant, anterior; post, posterior; k, voxels number in the cluster. Probabilities at the cluster level are corrected for multiple comparisons: **$p < 0.001$; *$p < 0.01$; and at the voxel level, uncorrected, §$p < 0.001$.

Table 5. Correlations between Brain Responses to Observed Pain and Empathy Trait

			BEES					EC				
			Coordinates					Coordinates				
		Region of Activation	x	y	z	T-score	k	x	y	z	T-score	k
Body parts in painful situations (Experiment 1)	CIP group	R pregenual anterior cingulate cortex	6	33	9	7.56§	398**	3	36	−6	5.23§	195*
		pregenual anterior cingulate cortex	0	36	−6	6.52§		6	33	9	4.68§	
		ventromedial prefrontal cortex	0	51	6	5.81§		0	48	3	4.35§	
	CIP > control	pregenual anterior cingulate cortex	0	39	−6	3.93§	145	0	39	−9	3.52$	21
		L pregenual anterior cingulate cortex	−3	30	9	3.77§						
Facial expressions of pain (Experiment 2)	CIP group	R posterior cingulate cortex	3	−51	12	7.72§	276**	3	−51	9	5.90§	336**
		R posterior cingulate cortex	6	−42	21	4.90§		6	−48	33	4.61§	
		L precuneus	−9	−51	33	4.88§		−3	−66	42	4.12$	
	CIP > control	R posterior cingulate cortex						3	−45	36	2.58	5
		L posterior cingulate cortex	−6	−51	27	3.08$	12	−3	−48	30	2.64	

BEES, Balanced Emotional Empathy Scale; EC, Empathic Concern subscale of the Interpersonal Reactivity Index (IRI). Correlations with empathy trait were considered only when brain activity was significantly correlated with both the BEES score and at least one of the four scores of the IRI; following this criteria, significant correlations between brain activity and empathy trait were found only in the CIP group, not in the control group. Coordinates (mm) are in MNI space. R, right; L, left; k, voxels number in the cluster. Probabilities at the cluster level are corrected for multiple comparisons: **$p < 0.001$; *$p < 0.05$; and at the voxel level, uncorrected, §$p < 0.001$, $p < 0.005$.

Scanning Method and Procedure

Subjects were told that the aim of the study was to investigate brain activity elicited by viewing pictures either related or unrelated to pain. They were instructed to look attentively at all pictures and try to imagine how the person in the picture feels. After a structural scan, pictures were projected on a screen (60 × 40 cm) that was 2.5 m in front of the subjects and that could be seen by means of mirrors placed on the headcoil.

Experiment 1 used an event-related paradigm and consisted of two sessions of 212 scans (9 min 40 s each). Each session consisted of 40 trials (20 pictures with painful content, 20 pictures without painful content) delivered in a random order with no more than 4 consecutive stimuli of the same category and presented for 2 s. Between trials, subjects fixated a red cross on the center of the field of view superimposed onto the previous, now-scrambled image. Experiment 2 used a very similar event-related paradigm and consisted of two sessions of 194 scans (8 min 40 s each). Each session consisted of 38 trials (19 video clips with a facial expression of pain, 19 video clips with a neutral expression) delivered in a random order with no more than 4 consecutive stimuli of the same category. Between trials, subjects fixated a red cross on the center of the field of view. Due to equipment failure, fMRI data of Experiment 2 were obtained from only 12 of the 13 CIP patients. In both experiments, interstimulus interval was jittered (mean = 12 s, minimum/maximum = 4/25 s). Each trial began with a brief (500 ms) change of the cross color (from red to green) as a visual warning cue. No picture or video clip was presented more than once throughout the whole experiments. The order of the four fMRI sessions was randomized and counterbalanced across participants.

After scanning, 40 pictures of body parts (20 painful, 20 nonpainful), which were representative of the 80 pictures used in the scanner in terms of pain location, pain intensity, and type of nociceptive stimulation, as well as 40 video clips of facial expressions (20 pain expressions, 20 neutral expressions), were presented again on a computer screen and participants were asked to rate the intensity of the pain they thought the person in the picture would feel with a 7-point Likert-type pain scale (indifferent: 0; painless discomfort: 1; slight pain: 2; moderate pain: 3; strong pain: 4; very strong pain: 5; extreme pain: 6). Participants were also asked to rate their arousal on a scale from 0 (no arousal) to 10 (maximal arousal) for each picture of body parts. The algebraic sums of the pain and arousal ratings of the 20 pictures/video clips with painful content and the ratings of the 20 pictures/video clips without painful content were computed for each subject.

Data Acquisition and Analyses

Imaging was conducted on a 1.5 Tesla MR scanner (Symphony Maestro Class, Siemens Medical Systems, Erlangen, Germany). BOLD images were recorded using a single-shot echo planar imaging sequence (repetition time, 2710 ms; echo time, 60 ms; flip angle, 90°; field of view, 256 mm; imaging matrix, 64 × 64; 28 axial slices, 4 mm thick). An anatomical image was also acquired for each participant (MPRAGE, TI/TR/TE: 920/1780/4.33 ms, field of view, 256 mm; matrix, 256 × 256; voxel size: 1 × 1 × 1 mm). fMRI data were analyzed using Statistical Parametric Mapping (SPM2, Wellcome Department of Imaging Neuroscience, London, UK) implemented in MATLAB. Three initial brain volumes of each run were discarded from the analyses to eliminate nonequilibrium effects of magnetization. The functional images were then corrected for slice time acquisition and for head movements (parameters were for all subjects less than 3 mm or 3°). The anatomical image was coregistered with the mean realigned image and then normalized to the standard T1 Montreal Neurological Institute (MNI) template. The normalizing parameters were applied to the functional images, which were resampled to 3 mm of isotropic voxel size and spatially smoothed using an isotropic Gaussian kernel of 8 mm full-width half-maximum. High-pass filtering (cutoff period of 128 s) was applied to reduce the effect of slow signal drifts and the serial correlation was compensated by "prewhitening" the data with a first-order autoregressive model. For each experiment, statistical analyses at the first level were calculated using an event-related design, with two types of events (nonpainful or painful) and two runs. Events were modeled using a canonical hemodynamic response function (HRF) and its time derivatives (Hopfinger et al., 2000). The models also included six covariates per run to capture residual movement-related artifacts. Following the single-subject analyses, we performed random-effect analyses (Friston et al., 1998) at the group level using the individual contrast estimates. Three contrasts were performed for each subject: P [Painful – Baseline], N [Nonpainful – Baseline], and PvsN [Painful – Nonpainful]

modeled by the HRF only. Activations were overlaid onto the mean anatomical image of each group, and anatomical labeling of activations was performed with the use of the AAL software (Anatomical Automatic Labeling, CYCERON, Caen, France) (Tzourio-Mazoyer et al., 2002).

For each experiment, two ANOVA analyses with two groups and sphericity correction were performed using P or PvsN contrast estimates images for both groups in order to (1) estimate the main effects of P or PvsN for each group; and (2) compare the P or PvsN effects between groups. In addition, regression analyses were computed in each group to explore whether individual differences in activity induced by viewing body parts (Experiment 1) or facial expressions (Experiment 2) with painful content ([Painful – Baseline] contrast) covaried with individual differences in pain and arousal ratings or in empathy scores. Anxiety and depression scores were successively included in the analysis as covariates to test whether correlations between empathy scores and brain activity would remain unchanged. Finally, analysis of group x covariate interactions was performed , using the "multi-subjects: covariates only" option of the SPM PET designs with the scores of each group as the two covariates, to assess between-group comparison of the correlation between either arousal or empathy scores and brain activity induced by observed pain.

Each analysis yielded an SPM of the *t*-statistic (SPM [*t*]), subsequently transformed to the unit normal distribution (SPM[*Z*]). Results were reported at $p < 0.05$ corrected for multiple comparisons either at the cluster level (voxel level set to $p < 0.01$) or at the voxel level (False Detection Rate) (FDR). To reduce the risk of false negatives, a more lenient height threshold ($p < 0.001$ uncorrected for multiple comparisons) was applied when no significant difference between groups was observed. On the other hand, to avoid an abundance of false positives associated with the multitude of regression analyses, correlations with empathy trait were considered only when brain activity was significantly correlated with both the BEES score and at least one of the four subscale scores of the IRI.

SUPPLEMENTAL DATA

The supplemental data for this article include two supplemental Tables and can be found at http://www.neuron.org/supplemental/S0896-6273(08)01016-7.

ACKNOWLEDGMENTS

This work was supported by Institut UPSA de la Douleur. We thank R. Gaillard, L. Naccache, J.J. Benoliel, L. Garcia-Larrea, and L. Cohen for comments on an earlier version of the manuscript; K.M. Prkachin, who provided us with selected videotaped recordings of facial expressions; and Anne Renardet, who kindly edited this material.

Accepted: November 24, 2008
Published: January 28, 2009

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