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Neural processing of sensory and emotional-communicative information associated with the perception of vicarious pain ☆

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ABSTRACT

The specific neural processes underlying vicarious pain perception are not fully understood. In this functional imaging study, 20 participants viewed pain-evoking or neutral images displaying either sensory or emotional-communicative information. The pain images displayed nociceptive agents applied to the hand or the foot (sensory information) or facial expressions of pain (emotional-communicative information) and were matched with their neutral counterparts. Combining pain-evoking and neutral images showed that body limbs elicited greater activity in sensory motor regions, whereas midline frontal and parietal cortices and the amygdala responded more strongly to faces. The pain-evoking images elicited greater activity than their neutral counterparts in the bilateral inferior frontal gyrus (IFG), the left inferior parietal lobule (IPL) and the bilateral extrastriate body area. However, greater pain-related activity was observed in the rostral IPL when images depicted a hand or foot compared to a facial expression of pain, suggesting a more specific involvement in the coding of somatomotor information. Posterior probability maps enabling Bayesian inferences further showed that the anterior IFG (BA 45 and 47) was the only region showing no intrinsic probability of activation by the neutral images, consistent with a role in the extraction of the meaning of pain-related visual cues. Finally, inter-individual empathy traits correlated with responses in the supracallosal mid/anterior cingulate cortex and the anterior insula when pain-evoking images of body limbs or facial expressions were presented, suggesting that these regions regulated the observer's affective-motivational response independent from the channels from which vicarious pain is perceived.

Introduction

An evolutionary perspective predicts that individuals who are capable of decoding pain in others benefit from information that serves both self-oriented (e.g., identifying environmental threats) and social purposes (e.g., social binding and altruism), giving them an advantage over competitors (Williams, 2002). Pain in others can be perceived and estimated through several channels that extend beyond verbal reports: it can be explicitly witnessed through viewing a noxious event, impending injury or tissue damage, or it can be signaled through non-verbal emotional/communicative pain behaviors, such as facial expression. While the first channel provides objective cues about the sensory component of the observed pain, the second one lacks such information and is considered more subjective and indirect as the observer has to interpret the meaning of communicative cues to infer the pain experienced by the expresser (for a review see Hadjistavropoulos et al. (2011)). In this study, we distinguished the difference between the influences of sensory and emotional-communicative information on the neural correlates of vicarious pain perception.

Several studies have shown that the vicarious affective-motivational response to pain involves the supracallosal mid/anterior cingulate cortex (mACC) and the anterior insula (AI), which are regions involved in self-pain, negative affect and/or motor preparation (Jackson et al., 2005; Jackson et al., 2006; Morrison et al., 2004; Singer et al., 2004). It is believed that such shared neural representations between an

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emotional state perceived in others and the corresponding state mapped in the observer is the core of the theoretical framework of empathy (Decety and Jackson, 2004). As such, self-related factors such as dispositional empathy (Jackson et al., 2005; Singer et al., 2004), expertise (Cheng et al., 2007; Decety et al., 2010), the affective link between individuals (Singer et al., 2006), perceived group membership (Hein et al., 2010) and racial bias (Avenanti et al., 2010; Xu et al., 2009) have been shown to modulate the vicarious pain response in the ACC and/or the AI. Besides the motivational/affective responses, the empathic neural response also involves a cognitive component that permits top-down influence (Lamm et al., 2007; Singer and Lamm, 2009) and perspective taking that are necessary for altruistic behaviors (de Vignemont and Singer, 2006; Decety and Jackson, 2004).

Animal studies have revealed that a population of neurons in the F5 (homologous to the inferior frontal gyrus (IFG)) and the PF (homologous to the inferior parietal lobule (IPL)) respond when a monkey generates a goal-oriented action or creates an internal representation of a motor act made by another agent (Cattaneo and Rizzolatti, 2009). It has been hypothesized that such internal representations permit the simulation of motor acts to rapidly understand the motor goal and intention that is observed in others. Accordingly, in humans, a fronto-parietal analog to this mirror neuron system is believed to permit an understanding of the action and the intention of others (Rizzolatti et al., 2001), learning by imitation and communication with others (Rizzolatti and Craighero, 2004), and participating in the decoding of another person's mind (Zaki et al., 2009). This system could represent one of the gateways that enable the resonance with other people's states and promote the shared representations (Hétu and Jackson, 2012). The presence of a vicarious pain response in the posterior IFG (BA 44) and IPL (BA 40) has been consistently reported when participants viewed a somatic representation of a painful agent as opposed to abstract cues signaling pain in others (for a review see Lamm et al. (2010)). Vicarious responses are also found in response to the observation of facial pain expressions in both the IFG and IPL, with stronger activation of the IFG when participants attend to the meaning of the expression to evaluate the other's pain, and stronger activation in the IPL when participants are asked to discriminate the facial movements composing the same expressions (Budell et al., 2010). The objective of this study was to clarify the relative implications of this fronto-parietal network in the processing of somatosensory cues compared with facial pain expressions.

In the present study, we sought to identify the differences in brain activity between decoding facial expressions communicating pain and explicitly witnessing pain through a noxious agent. First, we aimed to replicate the robust activation found in the putative human mirror neuron system when body limbs are observed (Grosbras and Paus, 2006; Kret et al., 2011; Peelen and Downing, 2007; van de Riet et al., 2009) and to contrast this effect to the activation expected from facial expressions in the amygdala and the medial prefrontal and posterior cingulate cortex which are thought to be involved in the attribution of intentions and feelings in others (Adolphs et al., 1994; Grosbras and Paus, 2006; Henson et al., 2003; Kret et al., 2011; van de Riet et al., 2009; Zaki et al., 2009). Second, consistent with the notion of sensorimotor resonance, we hypothesized that the IPL would be solicited more when others' pain states are inferred from sensory rather than emotive-communicative cues. This would be crucial to clarify how the brain creates the internal mapping of pain states observed in others. Third, based on our prior work showing that ventral-lateral frontal areas are associated with the explicit evaluation of pain in others (Budell et al., 2010), we used posterior probability maps to test the prediction that the anterior IFG would be solicited in sensory and facial pain-evoking conditions, but not by their neutral counterparts. Finally, we hypothesized that between-individual empathic traits of the participants would be positively correlated to activity in the mACC and the AI elicited by the pain-evoking images depicting either somatosensory or emotional-communicative information.

Methods

Participants

The participants were 20 healthy (10 female) volunteers between 21 and 53 years old (mean: 36; SD: 10) with no history of neurological or psychiatric disorders. None reported having chronic pain, and their scores on the Beck Depression Scale (Beck et al., 1996) were within normal ranges. All subjects gave written consent prior to the experiment, and the study was approved by the research ethics committee of the Institut Universitaire de Gériatrie de Montréal. Each participant filled a standard MRI safety form prior to the study, screening for previous surgeries, metal implants or pregnancy, to ensure his or her safety.

Assessment of empathy

The *Empathy Quotient* (EQ; (Baron-Cohen and Wheelwright, 2004)) and the *Interpersonal Reactivity Index* (IRI; (Davis, 1980)) were used to assess trait empathy. The EQ is a self-report questionnaire of 60 items that are summed to an overall score while the IRI is a 28 item questionnaire measuring 4 factors. For the purpose of the present study, only the empathic concern (EC), the perspective taking (PT) and the personal distress (PD) factors from the IRI were included in our analyses (as in our previous study (Vachon-Presseau et al., 2011)). Because the four scores of interest (EQ, EC, PT and PD) showed a high correlation, a principal component analysis was used for data reduction (Avenanti et al., 2009a; Vachon-Presseau et al., 2011). The 4 scores were loaded onto one factor, referred to as the global *empathy score*, which accounted for 47% of the variance and was positively correlated with the EQ ($r = .83$), the EC ($r = .65$), the PT ($r = .74$) and negatively correlated with the PD ($r = -.49$).

Visual stimuli

The 48 stimuli used in this study were static images displaying either a nociceptive agent applied to the right hand ($n = 8$) or the right foot ($n = 8$) that were presented from an allocentric perspective or a facial expression of pain ($n = 8$). No stimulus involved blood or actual tissue damage. Matching neutral images presenting the right hand ($n = 8$) or right foot ($n = 8$) in similar but innocuous situations, and neutral facial expressions by the same actor ($n = 8$), were included as a control condition for non-specific visual and attention processes. Fig. 1A illustrates examples of pain-evoking and neutral images from each category (similar to Jackson et al. (2005) for body limbs and identical to Simon et al. (2006) for facial expressions). We deliberately chose to use two categories of images representing the sensorimotor component of pain in order to test if brain activity generated by sensory information was specific to images of the hand or foot or generalized to body limbs. The importance of generalization is based on one of our previous studies, which showed that witnessing pain-evoking images of a hand or foot (generalized to body limbs), but not faces, facilitated the nociceptive withdrawal reflex of the lower limb in an observer (Vachon-Presseau et al., 2011).

Experimental procedure

In the present study, the experimental protocol included two functional scans of thermal pain administered to the leg of the participant and two functional scans where the participants observed images depicting pain-evoking experiences. Here, only the data regarding the impact of the sensory or emotional-communicative information on brain processing are presented. Other data regarding self-pain will be presented elsewhere. In the two functional scans, the participants were shown images and asked to determine if they depicted pain or neutral experiences. At the beginning of each trial, a fixation cross appeared for 3, 4 or 5 s on the screen, followed by a two-second

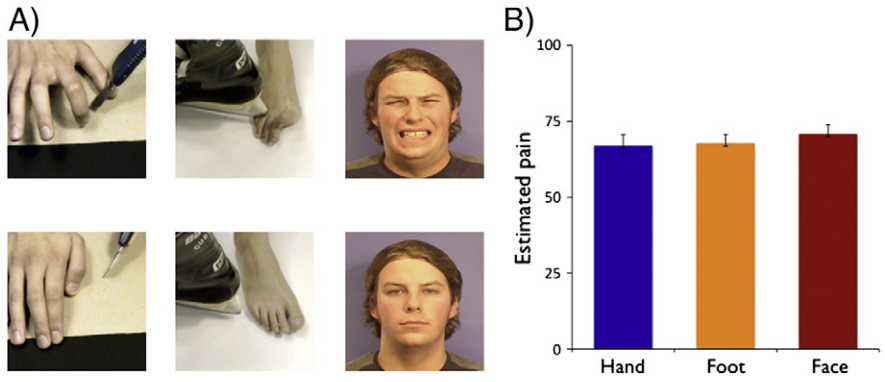

Fig. 1. A. Examples of pain-evoking and neutral images from each category. B. The estimated perceived pain scores (± standard error of the mean) are equivalent between categories.

image. At the image offset, participants were asked to indicate if the image was pain-evoking or neutral by using the index and middle finger keys of the response box on a computerized left/right decision task displayed for 3 s using E-Prime (Psychology Software Tools Inc.; http://www.pstnet.com). These instructions ensured that participants properly paid attention to the stimuli. Each trial ended with the fixation cross reappearing on the screen indicating that the next trial was beginning. The participants were instructed on how to perform the experimental task and were successful in a brief training session prior to entering the scanner. In the scanner, each of the 48 stimuli was shown six times for a total of 288 trials. The images were arranged in two series of 144 trials presented in two successive functional runs of 18 min. The order of stimuli was pseudo-randomized according to the category (foot, hand, or face) and the evoked pain (pain or neutral), as well as the sex of the model.

After the scanning session, the participants were asked to rate the pain perceived in the images presented in the experiment using a computerized visual-analog scale (VAS). The images were presented for 2 s while the scale was displayed for 12 s and labeled with the verbal anchor "neutral" at 0 (left extremity) and "extreme pain" at 100 (right extremity). This allowed us to verify that the estimated pain perceived in the images were comparable between the categories.

fMRI acquisition and analyses

Imaging was performed on a 3.0 T whole-body scanner (Siemens TRIO), using a 12-channel head coil, at the Centre de Recherche de l'Institut Universitaire de Gériatrie de Montréal (CRIUGM) in Montréal, QC, Canada. Blood oxygenation level-dependent (BOLD) signal was acquired using a standard T2*-weighted gradient-echo EPI sequence (TR = 3000 ms, TE = 30 ms; flip angle = 90°; FOV = 220 × 220 mm^2; matrix = 40 interleaved, axial slices per whole-brain volume at 3.4 mm thickness; in-plane resolution of 3.4 × 3.4 mm for isotropic voxels; 360 volumes). Structural images were acquired using a high-resolution, T1-weighted MPRAGE sequence (TR = 2.3 ms; TE = 2.99 ms; flip angle = 9°; FOV = 256 mm; matrix = 256 × 256; 1 × 1 × 1.2 mm voxels; 160 slices per whole-brain volume). All data preprocessing and analysis were performed using SPM 8 (Statistical Parametric Mapping, Version 8; Wellcome Department of Imaging Neuroscience, London, UK, http://www.fil.ion.ucl.ac.uk/spm/software/spm8/) executed in Matlab 7.8. (Mathworks, Sherborn, Massachusetts). Offline preprocessing of functional images included realignment of functional time series, co-registration of each subject's functional and anatomical data, spatial normalization to an EPI template conforming to the Montreal Neurological Institute space (2 × 2 × 2 mm), and spatial smoothing (8 mm FWHM Gaussian kernel).

The analysis of the fMRI data, based on a mixed effects model, was conducted in 2 serial steps, accounting for fixed and random effects. For each subject, changes in brain regional responses were estimated by a general linear model. Six trial types were modeled: 3 categories (hand, foot, or face) and 2 pain levels (pain-evoking image or neutral). Each type of trial was modeled as a delta function representing stimulus onset. The ensuing vector was convolved with the canonical hemodynamic response function and used as a regressor in the individual design matrix. Movement parameters estimated during realignment (translations in x, y, and z directions and rotations around x-, y-, and z-axes) and a constant vector were also included in the matrix as variables of no interest. A high-pass filter was implemented using a cut-off period of 128 s to remove the low-frequency drifts from the time series. Serial correlations in the fMRI signal were estimated using an autoregressive (order 1) plus white noise model and a restricted maximum likelihood (ReML) algorithm.

First, a contrast was performed between images of body limbs (hand and foot) and faces to detect differences between body and facial expressions irrespective of the pain content in the images. Second, a contrast between pain-evoking and neutral images was performed across all categories. Third, an interaction, [pain-evoking vs. neutral images] by [images of body limbs vs. facial expressions], was performed to determine if pain-evoked activity differed when perceived by sensory or emotional-communicative cues. To test if this effect was specific to each limb, the interactions, [pain-evoking vs. neutral images] by [images of hand vs. facial expressions] and [pain-evoking vs. neutral images] by [images of foot vs. facial expressions], were performed independently. These linear contrasts generated statistical parametric maps [SPM(T)]. These summary statistical images were then further spatially smoothed (Gaussian kernel 6 mm FWHM) and entered in a second-level analysis, corresponding to a random effects model and accounting for inter-subject variance. One-sample t-tests were run on the data of all the subjects. Finally, to assess the relationship between brain activity during pain processing and individual empathy, we regressed each individual's within-subject contrast images for pain-evoking images (body limbs and facial expressions) against their individual empathy score.

The resulting set of voxel values for each contrast constituted a map of the t statistic [SPM(T)], with the threshold at $p<0.001$ (uncorrected for multiple comparisons). Cluster-based statistics were used to define significant activations based on intensity and spatial extent. Clusters considered significant at the whole brain level based on the conservative family-wise error correction (FWE $p<.05$) were used for inferential statistics. Significant clusters were further explored to localize peaks of activation ($Z \geq 3.81$), as reported in the Tables. Additionally, regions of interest (ROI) were defined anatomically using the WFU PickAtlas software toolbox (Maldjian et al., 2003) and significant activation was assessed in these structures after family-wise error correction (FWE; $p<.05$) accounting for the volume of the ROIs. Based on our hypotheses, the IFG (BA 44, 45 and 47) and the IPL (BA 40) were targeted as ROIs for the interaction term [pain-evoking vs. neutral images] by [images of body limbs vs. facial expressions]. The ACC (BA 24) and the insula

were targets for the regression of the pain-evoking images against the individual empathy score. In this analysis, the insula did not survive FWE correction over the anatomically defined ROI. Because the anterior region of this structure (AI) is well documented for its association with empathy for pain, we used a less stringent threshold ($p<.005$ uncorrected) to detect activity in the AI over a small volume of interest (10 mm) centered on a peak previously shown to be associated with vicarious pain and empathy [x, y, z: 32, 18, 6 from Jackson et al. (2005)].

Finally, in the random-effects analyses, posterior probability maps (PPMs) enabling Bayesian inferences were generated (Friston and Penny, 2003). This type of analysis permitted the determination of the intrinsic probability of activation by the neutral images in the clusters of activity from the contrast [pain-evoking vs. neutral]. To test this, the PPM and effect size were computed for the pain-evoking and neutral images to verify which areas have a low probability of generating activations in the neutral condition. The target areas were determined using a 10-mm volume of interest around the activation peaks obtained with the contrast [pain-evoking vs. neutral]. This permitted us to statistically test if the activity in these regions was specific to the pain-evoking condition by showing a very low probability of activation when neutral images were presented.

Results

Behavioral results

The mean scores ($M \pm SD$) of pain perceived in the images were 65.4 ± 17.8 for the hand, 67.8 ± 11.2 for the foot, and 70.9 ± 13.6 for the face category in the pain-evoking images (Fig. 1B) while the neutral images yielded mean scores of <5.0 in each category. An ANOVA on the scores of the pain perceived revealed no significant differences between pain-evoking images of the three different categories ($p = 0.2$).

fMRI data: main effect of image category

The first analysis was performed to identify brain regions differentially activated by the images depicting body limbs and those depicting facial expressions irrespective of the pain content of the images (i.e., combining pain-evoking and neutral images). As illustrated in Fig. 2A and presented in Table 1A, the results revealed that the observation of body limbs, compared to facial expressions, elicited stronger activity in the fusiform gyrus (FG, BA 20/37), the parahippocampal gyrus (BA 36), the extrastriate body area (EBA, BA 37), the superior parietal lobule (BA 7), the rostral part of the IPL (BA 40), the pre-central gyrus (BA 4), the post central gyrus (BA 1/2/3), the middle occipital gyrus (BA 19) and the cerebellum. In contrast, as shown in Fig. 2B and Table 1B, more activity was evoked by images of facial expressions in the ACC (BA 32), the medial prefrontal cortex (BA 10), the posterior cingulate cortex (BA 31), the primary visual cortex (BA 17), the superior temporal sulcus (STS, BA 22) and the amygdala. These findings robustly replicated a whole body of literature showing that images depicting body limbs elicited stronger activity in sensorimotor regions, while facial expressions most strongly recruited the midline cortical structures and subcortical limbic structures.

fMRI data: The IFG was the only structure that exclusively responded to pain-evoking images

A contrast between pain-evoking and neutral images was first performed to identify regions more responsive to witnessing others' pain, regardless of the material used to induce this effect (hand, foot or facial expression). As illustrated in Fig. 2C and presented in Table 2, pain-evoking vs. neutral images yielded peaks of activation in the bilateral IFG (BA 45 and BA 47), the left rostral IPL (BA 40) and the left EBA (BA 37). Fig. 3 illustrates the mean activity estimates associated with each category of images in a sphere of interest (10 mm radius) around these peaks. From these, bilateral IFGs were

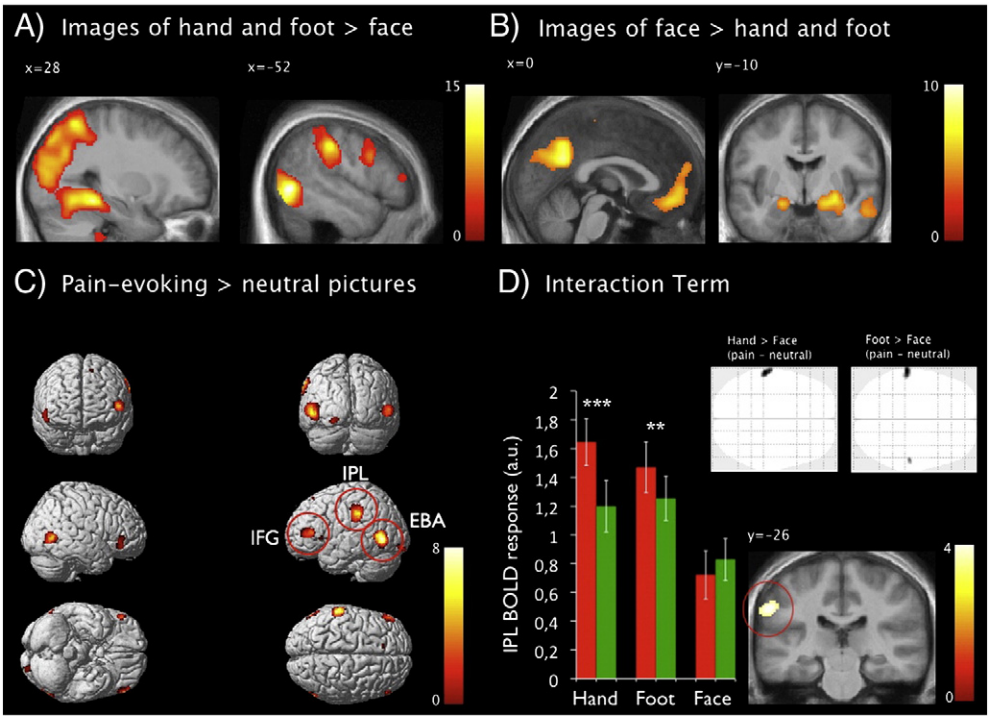

Fig. 2. A. Images depicting body limbs that produced stronger activity in sensory-motor regions compared with images depicting facial expressions. B. The contrast between regions activated by facial expressions compared to body limbs, such as the medial prefrontal cortex, the precuneus and the superior temporal sulcus involved in the theory of mind. C. Cerebral activity from pain-evoking vs. neutral images was observed in the inferior frontal gyrus (IFG), the left inferior parietal lobule (IPL), and the extrastriate body area (EBA). D. The rostral IPL responded more strongly to images of body limbs in pain than to images of facial pain expressions. Functional data are shown over the mean structural image of all participants on a 3D rendering of the brain to illustrate the location of peak activity ($p<.001$ uncorrected). The error bars represent the standard error of the mean. $^{**}p<.01$; $^{***}p<.001$.

Table 1
Clusters considered significant in the whole brain (FWE $p<.05$) when contrasting A. [body limbs vs. a facial expression] and B. [a facial expressions vs. body limbs].

k	Brain area	BA	MNI coordinates			Local peak z-value	p (FWE)
			x	y	z		
A. Cluster analysis corrected for the whole brain: hand and foot vs. face							
417	Pre-central gyrus	4	−50	8	30	4.89[a]	.083
947	Post central gyrus	1/2/3	62	−22	44	4.56	.003
	Inferior parietal lobule	40	58	−32	54	4.32	
			62	−36	38	3.93	
20,886	Inferior parietal lobule	40	−54	−28	40	6.19[a]	<.001
	Post central gyrus	1/2/3	−36	−36	44	5.26[a]	
	Parahippocampal gyrus	36	−26	−42	−12	6.65[a]	
			26	−42	−12	6.60[a]	
	Fusiform Gyrus	37	26	−58	−12	5.86[a]	
			−28	−46	−10	6.97[a]	
	Inferior temporal gyrus	20	−48	−46	−16	3.88	
	Superior parietal lobule	7	−26	−56	60	6.36[a]	
			26	−58	58	6.36[a]	
	EBA	37	−52	−66	0	6.97[a]	
			52	−62	−6	6.90[a]	
	Middle occipital gyrus	19	−34	−82	22	6.73[a]	
			38	−82	16	6.82[a]	
B. Cluster analysis corrected for the whole brain: face vs. hand and foot							
1425	Medial prefrontal cortex	10	6	58	18	4.18	<.001
	Anterior cingulate cortex	32	6	46	−10	4.48	
			−4	42	12	4.62	
658	Amygdala		28	−10	−10	4.93[a]	.016
1203	Superior temporal sulcus	21/22	54	−36	8	4.94[a]	.001
			46	−50	22	4.43	
1704	Posterior CC and precuneus	23/31	6	−54	28	5.77[a]	<.001
252	Primary visual cortex	17	12	−102	8	4.97[a]	.283

Montreal Neurological Institute (MNI)
[a] Significant at a peak level (FWE<.05).

the only brain regions responding to the pain-evoking images but not to the neutral images. The lack of activity during the presentation of neutral images is supported by the calculation of the posterior probability map (Friston and Penny, 2003), as inferred by Bayesian statistics, showing that the probability of activation of the IFG is very low when the image was neutral (left IFG: 2%; right IFG: 0%). This contrasts with the other pain-activated structures showing weaker but clearly significant responses to neutral images (left IPL: 100%; left EBA: 100%; right EBA: 100%). This result suggests that the IFG is specifically sensitive to the pain depicted in the images without being sensitive to other features present in the neutral image.

fMRI data: The IPL coded the sensory cues depicted in the pain-evoking images

The IPL coded the sensory cues depicted in the pain-evoking images.

The present study aimed to identify specific regions differently processing observed pain based on sensory or emotive-communicative cues. Fig. 2D illustrates that, as predicted, when testing the interaction between [pain-evoking images vs. neutral images] and [hand and foot vs. faces], the left rostral IPL (BA 40) was most strongly recruited when pain-evoking images depicted body limbs [x, y, z: −60, −26, 34; Z=3.59; FWE in ROI (BA 40) $p=.05$]. This effect could have been specific to images of the hand or foot. The analysis was therefore also performed independently with the contrasts [[pain-evoking hand vs. neutral hand] vs. [pain-evoking face vs. neutral face]] and [[pain-evoking foot vs. neutral foot] vs. [pain-evoking face vs. neutral face]]. As shown in the glass brain (Fig. 2D; uncorrected $p<.001$), both analyses resulted in increased brain activity limited to the rostral IPL (hand vs. face: x, y, z: −60, −26, 36; Z=3.40; and foot vs. face: x, y, z: −64, −26, 28; Z=3.54). This indicates that the IPL codes somatic information about pain in others. The same interaction term examining the effect of pain (pain-evoking vs. neutral) across hand vs. foot, foot vs. hand, face vs. hand, or face vs. foot, yielded no significant effect when corrected for the whole brain, a priori defined ROIs, or regions showing greater activity in response to pain-evoking images.

fMRI data: Trait empathy correlated with the activity in the ACC and the AI independently from the channels in which vicarious pain is perceived.

Trait empathy correlated with the activity in the ACC and the AI independent from the channels in which vicarious pain is perceived.

Table 2
Clusters considered significant when contrasting [pain-evoking vs. neutral pictures] and correcting for A. the whole brain (FWE $p<.05$), or B. ROIs delineating a bilateral IFG (FWE $p<.05$).

k	BRAIN AREA	BA	MNI COORDINATES			LOCAL PEAK z-value	p (FWE)
			x	y	z		
A. Cluster analysis corrected for the whole brain: pain-evoking pictures vs. neutral pictures							
727	Inferior parietal lobule	40	−62	−32	38	5.21[a]	.012
453	EBA	37	56	−66	0	4.38	.07[b]
967	EBA	37	−48	−68	−2	5.31[a]	.003
B. ROI correction: pain-evoking pictures vs. neutral pictures							
Inferior frontal gyrus pars orbitalis		47	52	34	−10	3.81	.034
Inferior frontal gyrus pars triangularis		45	−52	40	10	4.00	.007

[a] Significant at a peak level.
[b] Marginally significant at a cluster level.

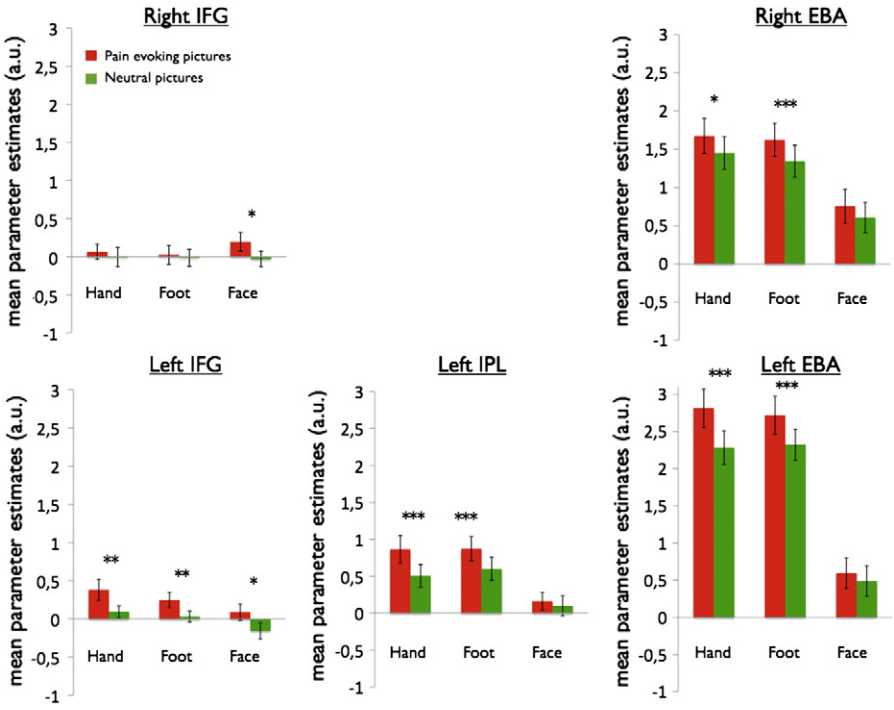

Fig. 3. The mean parameter estimates in the sphere of interest (10 mm radius) for each category of images in pain-evoking and neutral situations. The peaks were selected from the pain-evoking vs. neutral contrast images.

In this study, we also sought to determine if personality traits were differently associated with the neural correlates of empathy for vicarious pain depicted by sensory or emotive-communicative cues. For this purpose, we only used the brain signal during pain-evoking images because they elicited a very strong activity in the mACC and the AI, the two primary target areas in this analysis (mACC: x, y, z: −8, 8, 40; Z = 5.64; FWE $p < .001$; AI: x, y, z: −8, 8, 40; Z = 5.64; FWE $p < .001$). Fig. 4 shows that when corrected for an ROI targeting the supracallosal anterior and mid-cingulate cortex (BA 24), the brain activity elicited by pain-evoking images of the hand or foot was positively correlated with the empathy score (peak x, y, z: 4, 2, 36; Z = 3.58; FWE, $p = .03$). Similarly, using the same correction also revealed a positive correlation between the

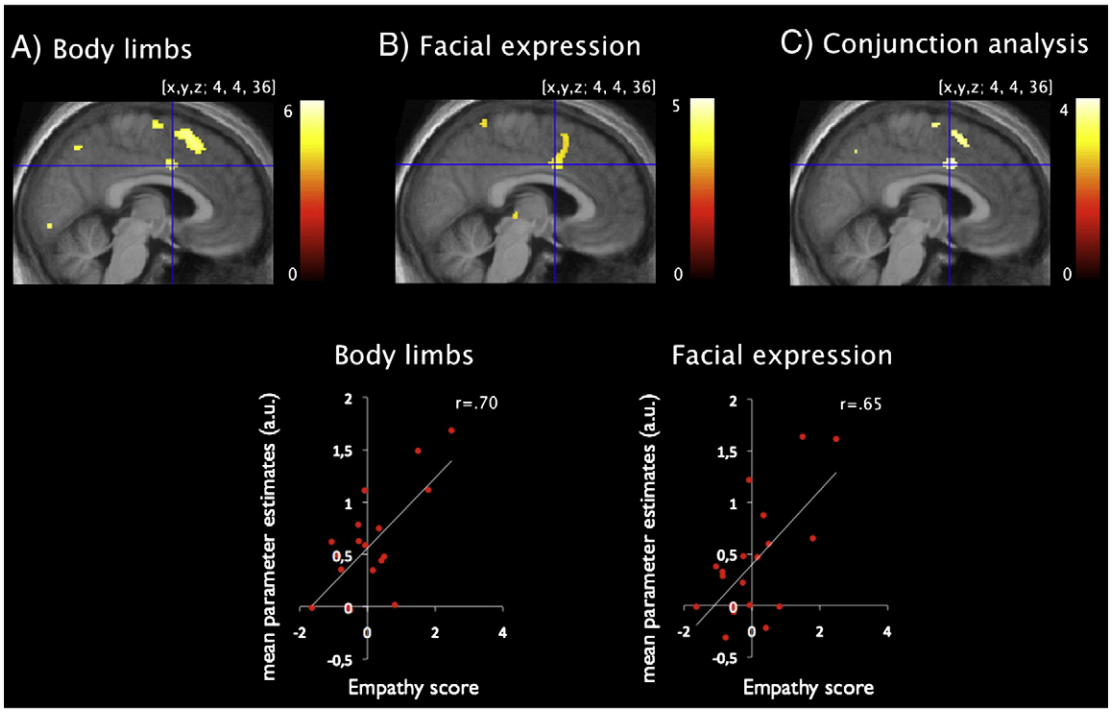

Fig. 4. The enhancement of vicarious pain responses by empathic traits of the observer was independent of the channel from which the vicarious pain was witnessed. Correlation between the subjects' empathy scores and the mean parameter estimates in anterior cingulate cortex with A. an image of a body limb in a pain-evoking situation and B. a facial pain expression. C. Conjunction analysis of A. and B. Functional data are shown over the mean structural image of all participants or a 3D rendering of the brain to illustrate the location of the peak ($p < .001$ uncorrected).

empathy scores and brain activity in the mACC when images of facial expressions were presented [peak x, y, z: −2, 6, 34; Z = 3.77; $p = .02$]. Hence, as shown by a conjunction analysis illustrated in Fig. 4C, these results suggest that trait empathy positively correlates with the level of activity within the mACC independent of cues depicting pain to the observer. Similarly, using a more liberal correction ($p < .005$ uncorrected), the conjunction analysis of brain activity elicited by pain-evoking images of body limbs or facial expressions marginally correlated with the anterior right insula [peak x, y, z: 4, 2, 36; Z = 2.64; svc FWE, $p = .07$]. Performing the same analysis on the brain activity elicited by the neutral images failed to show significant correlations to empathy in these ROIs. No additional cluster survived the FWE correction across the whole brain in the regression analysis of the sensory or emotive cue conditions or of pain-evoking or neutral images.

Discussion

In this study, we demonstrated that witnessing pain based on sensory or emotive-communicative cues influences the cerebral processing of the perception of pain in others. As expected, the results show that images of body limbs most strongly recruited sensorimotor areas, while facial expressions of pain rather more strongly activated the amygdala and cortical regions associated with socio-emotional processes. The results also revealed that the IFG, the IPL, and the EBA were sensitive to the pain evoked in the images. The novel findings of the current study were, first, that the bilateral anterior IFG was the only structure that uniquely responded to pain-evoking images, but not to their neutral counterparts, and second, that the rostral IPL very clearly coded more specifically for the pain depicted with sensory cues. These results complement those of a previous study suggesting that the IFG may be involved in understanding the meaning of the pain, while the IPL would be more sensitive to the sensorimotor cues conveying information about the pain (Budell et al., 2010). Finally, the results show that inter-individual differences in trait empathy correlated with the activity in the mACC and the AI (only at $p < .005$ in the AI) when observing pain-evoking images of body limbs or facial expressions.

Differences between body limbs and facial expressions

The results of the present study show that the ventral posterior IFG and the rostral IPL regions were recruited more by the observation of body limbs compared with the observation of facial expressions. These regions are located within the core mirror neuron system (Rizzolatti and Craighero, 2004), suggesting that attending to images of body limbs elicited greater sensory-somatic resonance than attending to facial expressions. In addition, the EBA, a region sensitive to biological motion (Downing et al., 2001), the FG and the parahippocampal gyrus also showed increased activity. It might seem surprising that body limbs elicited stronger activity than facial expressions in the FG, but these findings are consistent with previous reports, showing increased activity in the FG and the EBA when watching fearful and angry body postures compared to fearful and angry facial expressions (Kret et al., 2011; van de Riet et al., 2009). Similarly, a study looking at neutral hand movements compared with neutral facial expressions showed that the hand images generated stronger activity in the EBA and the FG, as well as the dorsal pre-motor area (Grosbras and Paus, 2006). Hence, it has recently been suggested that bodies that express emotions are processed holistically, similar to facial expressions, and share communicative features conveying information about social interaction (de Gelder et al., 2010).

That facial expressions most strongly activated the amygdala confirms its role in the communication of a potential threat to an observer by acting as a detector capable of enhancing the saliency of information with emotional significance to an observer (Anderson and Phelps, 2001). Our results also show increased activity in the medial prefrontal cortex and the precuneus when facial expressions were depicted compared to body limbs. These midline structures are commonly recruited in the default mode network serving self-referential thoughts (Buckner et al., 2008; Northoff et al., 2006; Raichle et al., 2001). The same midline structures are also involved in mentalizing, a cognitive strategy that uses a self-referential approach to understand others (Mitchell, 2009). The observation of facial expressions generated greater activation in this network, possibly because the social-emotional dimension is emphasized in these images in contrast to images explicitly depicting only nociceptive information. Facial expressions also yielded stronger activity in the STS, a region believed to be involved in the imitation of the action of others (Iacoboni et al., 2001; Molenberghs et al., 2010), communication abilities between individuals (Noordzij et al., 2009) and the attribution of emotional states to others (Frith and Frith, 2006). Together, these main effects robustly replicate previous findings and validate the current stimuli and experimental procedure in eliciting vicarious pain-related brain responses in expected regions.

Shared and unique activations to sensory and emotive-communicative pain cues

The main objective of the present study was to determine common and distinct networks involved in pain perception by sensory or emotive cues. We found that the IFG pars triangularis and orbitalis (BA 45 and BA 47), left IPL, and EBA showed increased activity when pain-evoking images were presented compared with their neutral counterparts. Fig. 2C illustrates that activity in the IFG was restricted to the pars triangularis (BA 45) and pars orbitalis (BA 47), without extending to the pars opercularis (BA 44). Recently, Budell et al. (2010) found that when participants were asked to evaluate the perceived pain or the motor component of identical dynamic facial expression of pain, the IFG (BA 45 and BA 47) was most strongly activated by the pain evaluation task. Although the peaks of activity found in the present report are somewhat anterior to those reported in previous studies, the combined results suggest that the activity in the IFG, outside of BA 44 (the equivalent of the monkey F5, where mirror neurons were found), specifically codes the pain evoked in the images. The posterior probability of activation for the neutral images was very low in the IFG but very high in the other brain regions. This supports the idea that the IFG could be involved in the extraction of meaning from the pain-evoking situation. Hence, the IFG is known to be part of a fronto-parietal network involved in detecting salient stimuli (Corbetta and Shulman, 2002) and might therefore underlie a stimulus-driven attention process. This is particularly relevant to our experimental design because we used a pain detection task.

We also found that pain perceived from sensory cues activated the rostral IPL (BA 40) more strongly than pain perceived from an emotive cue. It has been shown previously that the IPL (homologous to the PF in the monkey) contains mirror neurons (Rizzolatti and Craighero, 2004), is activated by the observation of others' actions and contains proprioceptive information allowing motor planning and imitation (Iacoboni et al., 2001). In the present study, this region responded most strongly to pain-evoking images when body limbs were depicted, suggesting that the IPL uses the sensory information depicted in the images to evaluate the presence and/or the amount of pain. This finding is consistent with our previous study showing that the IPL was more involved in the evaluation of motor rather than emotional aspects of facial expressions (Budell et al., 2010). Together, our findings point toward the IFG as the integrator of the meaning of a pain situation depicted in an image and the IPL as a coder of the somatic and motor-related information.

It is known that the IPL codes self-made motor acts and perceived movements in others with a specific goal (such as grasping). In the current study, witnessing sensory cues explicitly depicting a noxious agent threatening a body limb might have implied movement of withdrawal. This proposition is supported by recent studies showing that static images that implied movement recruit the putative mirror neuron system (Urgesi et al., 2006; Urgesi et al., 2010). It is therefore

likely that a top-down influence permits the anticipatory representation of the withdrawal of body limbs threatened by a noxious agent. This is particularly interesting because a previous study has shown that mirroring activity in the IPL is organized based on the type of movement being observed (dragging, dropping, grasping or pushing) regardless of the effectors (i.e., movement of the hand, the foot or the mouth) (Jastorff et al., 2010). This suggests that implied movement, rather than the body limb, would explain the neural activations in the IPL during pain observation.

Previous behavioral studies have shown that witnessing pain in others could modulate the motor response in an observer. For instance, pain observation slowed key-press responses and improved key-release reaction times (Morrison et al., 2007b). Interestingly, in a similar task, activity in the cingulate cortex paralleled fastest reaction times by showing increased activity during the pain-related modulation of overt motor responses (Morrison et al., 2007a). It is possible that activity in the putative mirror neuron system associated with pain perceived in body limbs primed the corresponding responses in the observer. Accordingly, we previously showed that the nociceptive withdrawal reflex induced by an electrical noxious shock was facilitated when images depicting body limbs (hand or foot), but not static facial pain expressions, were presented to an onlooker (Vachon-Presseau et al., 2011). The impact of vicarious pain on motor movement seems to engage a complex inhibitory and facilitatory network. Transcranial magnetic stimulation of the motor cortex inhibited the motor evoked potential of the hand while a participant observed a needle entering a congruent hand (same hand that is stimulated) and facilitated the MEP when entering the opposite hand (contralateral to the stimulated hand) (Avenanti et al., 2005; Avenanti et al., 2009b). Together, these studies revealed that pain observation can modulate pain-related responses that might be driven by different mechanisms involving the spinal cord (Vachon-Presseau et al., 2011), the cortical motor system (Avenanti et al., 2005; Costantini et al., 2008) and the cingulate cortex (Morrison et al., 2007a).

The affective-motivational response of the vicarious pain is independent from the channel of perceived pain

Several studies have shown that empathy for pain involves the mACC and the AI (e.g., (Jackson et al., 2005; Lamm et al., 2010; Lamm and Singer, 2010; Morrison et al., 2004; Singer et al., 2004)). It has been proposed that activity found in these regions might result either from a shared representation mechanism (Preston and de Waal, 2002), or from valence, arousal and withdrawal response priming induced by vicarious pain perception (Decety, 2010). The results of our conjunction analysis demonstrated that pain-evoking images of body limbs and facial expressions generated peaks of activity in the mACC and the AI that correlated with empathy traits in the observer. These peaks of activity are found almost at the same coordinates reported by Singer et al. (2004), who showed a positive correlation between activity in both the mACC and the AI with the empathy traits of the participant when a signal indicated that a painful electrical stimulation was administered to a loved one. Similar correlations were obtained in the cingulate cortex for the amount of pain perceived in others (Jackson et al., 2005; Saarela et al., 2007) and social distress personality traits during a social exclusion task (Eisenberger et al., 2003). Together these findings indicate that the channel by which vicarious pain is induced (communicative or sensory cues) have little influence on the vicarious response in brain regions underlying the motivational and affective components of pain perception. Accordingly, our results are consistent with the notion that the activity in these structures is involved in the regulation of behavior as a function of individual personality factors independent of the sub-channel from which vicarious pain is perceived. That such a relation was only found in the pain-evoking images, but not in the neutral ones, argues for the facilitation of brain activity by empathy only when arousal and feelings were elicited by the images in the observer.

Conclusion, future perspectives and limitations

This study stresses the influence of cues signaling vicarious pain on brain activity. These findings are important because they help understand how the brain extracts and processes information about the pain in others. This study demonstrates how the activation of separate input channels (sensory vs. emotional-communicative) converges on a core system underlying the representation of pain in others. Importantly, one limitation of most neuroimaging studies is the small sample size ($n<30$ participants) (Yarkoni et al., 2010). Here, a bigger sample could have yielded the most robust activations in the ACC and the AI that might have survived the FWE correction in the whole brain when comparing the pain-evoking with the neutral images. Further studies are needed to determine how the neural correlates of pain communication and perceived pain are affected in clinical conditions involving pain states or disorders of communication. These studies may elaborate a model that explains the effect of chronic pain on both the expressive and receptive components of pain communication and that helps in understanding the impact of pain cues on individuals exposed to high rates of vicarious pain such as health care professionals.

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