

Social context and perceived agency affects empathy for pain: An event-related fMRI investigation

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ABSTRACT

Studying of the impact of social context on the perception of pain in others is important for understanding the role of intentionality in interpersonal sensitivity, empathy, and implicit moral reasoning. Here we used an event-related fMRI with pain and social context (i.e., the number of individuals in the stimuli) as the two factors to investigate how different social contexts and resulting perceived agency modulate the neural response to the perception of pain in others. Twenty-six healthy participants were scanned while presented with short dynamic visual stimuli depicting painful situations accidentally caused by or intentionally caused by another individual. The main effect of perception of pain was associated with signal increase in the aMCC, insula, somatosensory cortex, SMA and PAG. Importantly, perceiving the presence of another individual led to specific hemodynamic increase in regions involved in representing social interaction and emotion regulation including the temporoparietal junction, medial prefrontal cortex, inferior frontal gyrus, and orbitofrontal cortex. Furthermore, the functional connectivity pattern between the left amygdala and other brain areas was modulated by the perceived agency. Our study demonstrates that the social context in which pain occurs modulate the brain response to other's pain. This modulation may reflect successful adaptation to potential danger present in a social interaction. Our results contribute to a better understanding of the neural mechanisms underpinning implicit moral reasoning that concern actions that can harm other people.

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Introduction

By virtue of its aversiveness, pain promotes the organism's health and integrity, to the extent that congenital absence of pain on injury significantly shortens human life (Williams, 2002). This aversive ability promotes protective or recuperative visceromotor and behavioral responses. Pain serves evolved protective functions not only by warning the suffering person, but also by impelling expressive behaviors that attract the attention of others (Craig, 2004). Since pain can be an indicator of a potentially life-threatening situation, successful adaptation to the physical and social environment is critical to the organism's survival. Furthermore, pain is not only experienced by the self, it can be perceived in others. Through watching the negative consequences of other people's behavior, individuals learn to avoid situations that are potentially hazardous and likely to injure themselves, without having to experience them. Thus, the social context in which pain occurs is likely to influence the cognitive appraisal and neural mechanism underpinning its perception in the observer.

The perception of pain in others can be used as a window to investigate the neurophysiological mechanisms that underpin the experience of empathy, i.e., the capacity to share and appreciate others

emotional and affective states in relation to oneself (Decety, 2007; Goubert et al., 2009; Jackson et al., 2005). Empathy may be regarded as a proximate factor motivating prosocial behaviors and is crucial in the development of moral reasoning (Decety and Meyer, 2008). Interestingly, a growing number of functional magnetic resonance imaging (fMRI) studies have demonstrated that the perception of another individual in a painful situation is associated with specific activation in regions that belong to the pain matrix (Derbyshire, 2000; Price, 2000; Rainville, 2002), particularly areas coding for the motivational-affective dimension of pain (Botvinick et al., 2005; Cheng et al., 2007; Gu and Han, 2007; Jackson et al., 2005, 2006a,b; Lamm et al., 2007ab; Moriguchi et al., 2007; Morrison et al., 2004, 2007; Ogino et al., 2007; Saarela et al., 2007; Singer et al., 2004; Zaki et al., 2007). This neural network includes the supplementary motor area (SMA), cerebellum, dorsal anterior cingulate cortex (ACC), the anterior midcingulate cortex (aMCC), and anterior insula (AI). In addition, studies using different modalities of neuroimaging including transcranial magnetic stimulation (Avenanti et al., 2005), somatosensory-evoked potentials (Bufalari et al., 2007), functional MRI (Cheng et al., 2007; Lamm et al., 2007b; Moriguchi et al., 2007), and magnetoencephalography (Cheng et al., 2008) also indicated that areas processing the sensory dimension of pain (the somatosensory cortex and posterior insula) are also activated by the mere visual perception of pain in others. Altogether, there is strong evidence that both the affective and the sensory dimensions of the pain matrix are

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involved in empathy for pain. It is worth mentioning that activation of these regions (insula, SMA, ACC and PAG) may reflect a general aversive response which is not specific to nociception.

Previous work documented that a restricted number of neural regions are critically engaged in the evaluation of risk in the environment and in the regulation of adaptive behaviors to cope with it. For example, functional MRI studies indicated that the fusiform gyrus (FG), amygdala, periaqueductal gray (PAG) and superior temporal sulcus (STS) are involved in detecting features such as movements, vocalizations, and faces, which contribute to an individual being perceived as safe or trustworthy (Adolphs, 2002; Winston et al., 2002). The amygdala is known to play a pivotal role in appraisal of actual and potential threats in the environment, which are usually associated with fear-related behaviors (Pessoa et al., 2002; LeDoux, 2000; Phelps et al., 2001).

Furthermore, another area of research indicates that the medial prefrontal cortex (mPFC), particularly the anterior paracingulate cortex (PCC) is implicated in understanding the mental states of an agent involved in social interaction, regardless of whether this interaction is observed or imagined (e.g., Walter et al., 2005). Those studies have also demonstrated that the PCC, the orbitofrontal cortex (OFC) and temporoparietal junction (TPJ) contribute to the attribution of intentions, emotions and beliefs to oneself and others (see Amodio and Frith (2006) for a review). Interestingly this circuit is also critically involved in moral reasoning (e.g., Moll et al., 2007; Young and Koenigs, 2007).

While there are many studies on the perception of pain in others, the impact of social and cognitive circumstances on the experience of empathy for pain has, despite its importance, been less explored. It has been shown, however, that social support modulates the neural activity in brain areas involved in the perception of threat. For instance, Coan et al., (2006) conducted an fMRI study in which the female participants were threatened with electric shock while either their husbands or an unknown man held their hand. Results indicated that, while hand-holding by both the husband and stranger resulted in reduced neural responses in areas associated with physiological arousal due to threat (aMCC), support from the husband also regulated neural response associated with emotion regulation (right dorsolateral prefrontal cortex, caudate) and emotion-related homeostasis (superior colliculus).

In the current study we were interested in the opposite effect of social interaction: how the neural processing in the pain matrix is modulated by the perception of painful situations when the pain is intentionally inflicted by another individual in comparison with pain accidentally caused by oneself. Since pain is the result of a type of social interaction in the former situation, its recognition is likely to involve not only the perception of pain but also the cognitive evaluation of the social interaction. This is important for two reasons. First, pain has an evolutionary importance in signaling a potential threat, which requires the nervous system to swiftly evaluate risk in the environment. Second, once the risk is assessed it is then necessary to initiate appropriate behaviors to the potentially dangerous environment, such as fighting, fleeing, or freezing (Porges, 2003). In addition, the perception of human agency plays a critical role in moral reasoning. This perceptual understanding is crucial in how behavior is evaluated and how people are held accountable for their actions (Sokol et al., 2004).

The goal of the study was to compare patterns of brain activation while individuals observed painful situations occurring by accident and painful situations intentionally caused by another individual. We predicted that both situations would be associated with signal increase in the pain matrix. We also expected that painful situations caused by another individual would additionally recruit neural systems subserving mentalizing and emotion regulation. Specifically, we predicted the amygdala, medial prefrontal cortex and posterior temporal cortex to play an important role in this modulation.

Materials and methods

Subjects

Twenty-six right-handed healthy volunteers who were paid for their time (14 female, mean = 24.4 years, SD = 5.75 years) participated in the study. Right-handedness was assessed with the Edinburgh Handedness Inventory (Oldfield, 1971). After a complete and detailed description of the study, written informed consent was obtained from each participant. The study was approved by the University of Chicago Institutional Review Board and conducted in accordance with the Declaration of Helsinki. Participants were also requested to complete the emotion contagion questionnaire (EC) (Doherty, 1997) that assesses one's susceptibility to other's emotions.

Stimuli preparation and validation

The task consisted of the successive presentation of animated visual images of hands and feet depicting painful and non-painful situations. Furthermore, these situations involved either an individual whose pain was caused by accident or an individual whose pain was inflicted on purpose by another person. A series of 144 stimuli were created and validated for this study. Validation of the material was conducted with a group of 222 participants (110, females) who were shown these dynamic stimuli and asked to estimate how painful these situations were and whether they believed that the pain was caused intentionally (Estabrook, 2007). Each animation consisted of three digital color pictures, which were edited to the same size (600 × 480 pixels). The durations of the first, second and third pictures were 1000 ms, 400 ms and 1000 ms respectively. These animated stimuli contained scenes of various types of painful and non-painful everyday situations (Fig. 1).

Each animation displayed one or two persons whose right hands or right feet are visible but not their faces. When presented, the two people are easily distinguishable from one another in clothing or shoe type. These 144 stimuli belong to four categories (36 stimuli in each category) including:

1. One person is in a painful situation caused by accident, e.g., an individual dropping a heavy bowl on her hand (PCS).
2. One person is involved in a non-painful situation, e.g., opening a door (NPS).
3. One person is in a painful situation caused by another individual, e.g., stepping purposely on someone's toe (PCO).
4. The two individuals are present and moving, but there is no pain (NPO).

Scanning session

The participants were scanned while the stimuli were displayed on a gray background, randomly interspersed with null events. The E-prime software (Psychology Software Tools, Inc. Pittsburgh, PA, USA) and a back-projection system were used for the stimuli presentation. Each stimulus was presented for 2.4 s with jittered inter-stimulus intervals (ISI), during which a black fixation cross was presented against the gray background. During null events, the fixation cross remained on screen. To avoid confounding motor-related activation in the ACC and SMA, no overt response was required. Instead, the subjects were asked to watch the stimuli very carefully. There were three runs in each participants and the order of the stimuli presentation was pseudorandomized across them.

After the scanning session, the participants were presented with the same stimuli that they saw in the scanner and asked to rate how painful each situation was using a computer-based visual analogue scale (VAS) ranging from "no pain" (i.e., score = 0) to "very painful" (i.e., score = 100).

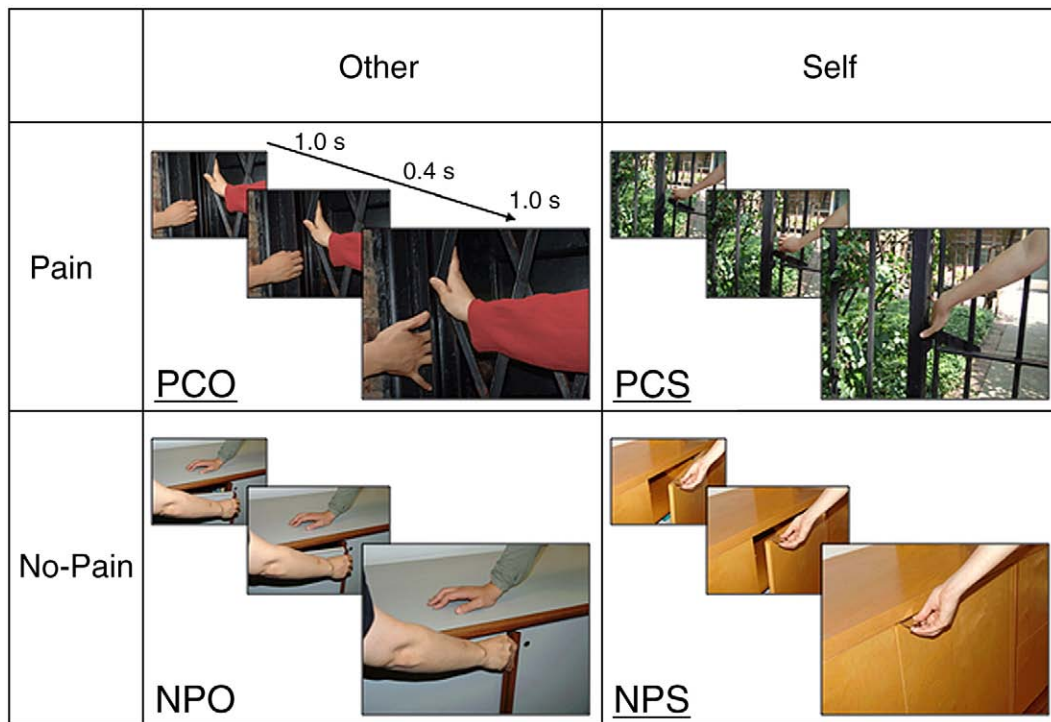


Fig. 1. Examples of the visual stimuli used for each category. Each dynamic stimulus consists of three pictures of the same size. The durations of the first, second, and third picture are 1.0 s, 0.4 s, and 1.0 s, respectively. PCO, pain caused by another individual; PCS, pain caused by self; NPO, no pain with another individual; NPS, no pain with self.

Image acquisition

Magnetic resonance imaging was performed on a GE 3 T magnet (Horizon LX). Functional images were obtained using T2*-weighted gradient echo spiral-in/out pulse sequence (Glover and Law, 2001). Thirty-eight interleaved coronal slices of 5 mm slice thickness without spatial gap were obtained for 184 repetitions (including 4 discarded acquisitions at the onset of each of three runs) using the following parameters: TR = 2400 ms, TE = 26 ms, flip angle = 81°, FOV = 24 cm, matrix = 64 × 64, and in-plane resolution = 3.75 × 3.75 mm. The spiral-in/out sequence was shown to be effective in recovering blood oxygenation level-dependent (BOLD) signal in frontal regions important to this study (Preston et al., 2004). An axial T1-weighted 3D magnetization-prepared rapid acquisition gradient echo (MP-RAGE) anatomical scan was also acquired for 3D localization (TR = 8 ms, TE = 3.2 ms, flip angle = 6°, FOV = 24 cm, matrix = 256 × 192, slice thickness = 1.5 mm, 124 slices).

Image processing and analysis

Image processing was carried out with SPM5 (Wellcome Department of Imaging Neuroscience, London, UK), implemented in MATLAB 7.0 (Mathworks Inc. Sherborn, MA). Preprocessing included slice-timing correction, correction for head motion, normalization to the EPI template provided in SPM5, and smoothing using a 6-mm full-width half-maximum isotropic Gaussian kernel. A conventional two-stage random-effects approach was adopted using SPM5; A voxel-by-voxel multiple regression analysis of expected signal changes for each of the four conditions and the null event, which were constructed using the canonical hemodynamic response function provided by SPM5, was applied to the preprocessed images for each subject. Applying linear contrasts to the obtained parameter estimates, effects of interest were then tested across all the subjects.

The main effect of pain (pain vs. no pain) was computed by contrasting the PCO and PCS trials with the NPO and NPS trials to

identify brain regions involved in the perception of pain irrespective of the social context (i.e., the number of people present in the stimuli). The main effect of the social context (self vs. self and other) was calculated by comparing PCO and NPO trials with the PCS and NPS trials to identify brain regions involved in processing the presence of a second individual. Regions showing an interaction between pain and social context in the sense of an increased activation in the PCO compared to any other stimulus categories were assumed to be specifically associated with the processing of pain caused by another person.

To extract regions showing a significant main effect of pain, contrast (PCO + PCS) – (NPO + NPS) (i.e., pain > no pain) and (NPO + NPS) – (PCO + PCS) (i.e., no pain > pain) were tested; To extract regions showing a significant main effect of the social context, (PCO + NPO) – (PCS + NPS) (i.e., self and other > self) and (PCS + NPS) – (PCO + NPO) (i.e., self > self and other) were tested. To extract regions showing a significant interaction between factors pain and social context, in a way that activation is selective to PCO trials, the contrast (PCO – PCS) – (NPO – NPS) was tested, and masked with PCO – PCS and PCO – NPO. The masks were applied at $p < 0.001$ without correction for multiple comparisons. Results were thresholded at $p < 0.05$ using the false discovery rate (FDR) to correct for multiple comparisons. Activations were overlaid on a representative high-resolution structural T1-weighted image from a single subject from the SPM5 canonical image set, co-registered to Montreal Neurological Institute (MNI) space. For better illustration of the activation in the temporal cortex, we also used an inflated brain atlas (PALS-B12 human atlas) that is provided by Carret software (<http://brainmap.wustl.edu/caret.html>; Van Essen et al., 2001).

To further clarify the characteristics of the activated clusters, specific regions of interest (ROIs) were computed with the MarsBaR toolbox in SPM5. ROIs were defined as a 6-mm spherical region centered on the peak coordinate found in each area showing a significant main effect of pain or social context. Estimates of percentage signal change were displayed for each of these ROIs across trial categories.

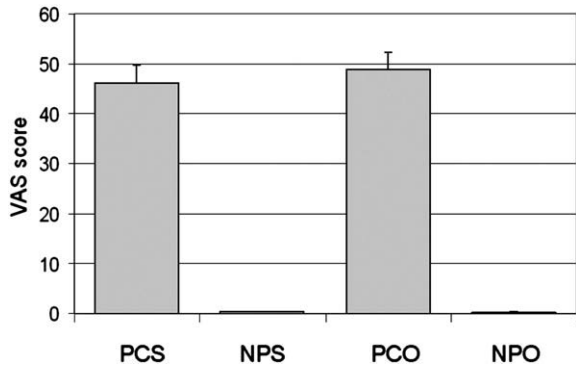


Fig. 2. The VAS means ± standard errors for pain ratings shown for each of the four trial categories.

Correlation analyses with EC and pain ratings

In order to assess the relationship between each individual's personality trait and brain activity, random effects of correlation analyses were performed with the results from the EC dispositional measure. Scores on the EC were correlated with parameter estimates of the contrast PCO>null. Correlation analyses were also conducted to determine the regions whose hemodynamic responses varied with the participants pain ratings. Each individual's averaged scores for PCO

on the VAS ratings was correlated with parameter estimates of the contrast PCO>null. A significance threshold of $p < 0.005$ (uncorrected) was selected for these analyses. To avoid an abundance of false positives associated with the multitude of analyses, significant correlations were only interpreted if they were located in a priori defined regions of the pain matrix (Derbyshire, 2000).

Functional MRI connectivity analysis

To investigate the context-dependent contributions of left amygdala activity during pain trials, a psycho-physiological interaction (PPI) (Friston et al., 1997) analysis was performed. A PPI means that the contribution of one area to another changes significantly with the experimental or psychological context. The contribution could be seen as the modulation of responses evoked by a stimulus (in our case, the social context in which the pain occurred). In other words, the PPI analysis reveals which areas show activation patterns covarying with left amygdala activity depending on whether the pain was caused by another individual (PCO) or caused by oneself (PCS). Thus, the PPI analysis consists of a design matrix with three regressors: 1) the "psychological variable" representing the cognitive process of interest (PCO vs. PCS), 2) the "physiological variable" representing the neural response in a given brain region (here the left amygdala), and 3) the interaction term of 1) and 2). The psychological variable used was a vector depending on the social context (1 for PCO, -1 for PCS) con-

Table 1
Regions showing a significant main effect of pain.

Brain regions	Lat	MNI coordinates			t-Score	k
		x	y	z		
Pain > no pain						
Superior frontal gyrus	L	-24	-8	62	4.63	52
Precentral gyrus	R	28	-10	56	4.41	28
Supplementary motor area*	R	8	14	60	6.56	2815
Supplementary motor area*	L	-12	10	54	5.84	
Superior medial gyrus*	L	-4	44	44	5.74	
Superior medial gyrus*	L	-4	34	38	5.63	
Superior medial gyrus*	R	8	54	40	4.03	
Middle frontal gyrus**	L	-30	28	42	4.77	
Inferior frontal gyrus**	L	-44	32	6	8.59	4856
Inferior frontal gyrus***	R	38	28	-18	6.73	2020
Superior parietal lobule†	L	-24	-46	66	5.86	
Superior parietal lobule††	R	18	-52	72	6.30	1319
Inferior parietal lobule‡	L	-40	-46	54	7.36	3011
Postcentral gyrus††	R	36	-46	66	5.60	
Postcentral gyrus††	R	52	-18	34	4.88	
Supramarginal gyrus†	L	-58	-24	36	6.81	
Supramarginal gyrus††	R	60	-30	34	4.95	
Middle temporal gyrus	L	-52	-70	4	6.38	
Inferior temporal gyrus†††	R	50	-72	-10	8.06	1527
Middle occipital gyrus	L	-34	-92	0	6.56	1428
Middle occipital gyrus†††	R	36	-88	2	5.05	
Calcarine gyrus	M	0	-84	0	3.13	12
Anterior insula**	L	-26	22	8	5.04	
Anterior insula***	R	40	24	0	3.52	
Middle insula**	L	-38	-2	14	7.23	
Middle insula	R	38	0	12	4.36	27
Posterior insula**	L	-40	-4	-6	4.31	
Anterior cingulate cortex*	L	-8	36	22	4.12	
Middle cingulate cortex	L	-6	2	32	4.91	257
Temporal pole***	R	40	10	-20	5.28	
Thalamus	L	-8	-14	8	4.16	446
Thalamus	R	8	-12	10	3.63	23
Cerebellum	L	-26	-74	-32	3.89	38
Cerebellum	L	-18	-74	-48	4.99	88
Cerebellum	R	20	-82	-19	4.18	119
Cerebellum	R	16	-76	-50	5.25	71
Periaqueductal gray	M	-2	-28	-20	3.89	19
No pain > pain						
No significant activation						

Stereotactic coordinates and t values are provided for local voxel maxima in the regions showing a significant main effect of pain. ($p < 0.05$, FDR corrected). Coordinates are defined in Montreal Neurologic Institute (MNI) stereotactic space in millimeters: $x > 0$ is right of the midsagittal plane, $y > 0$ is anterior to the anterior commissure and $z > 0$ is superior to anterior commissure-posterior commissure plane. L = left hemisphere; R = right hemisphere, M = medial activation. Regions marked with */**/***/†/††/††† are in the same cluster. k = cluster size.

volved with the HRF. To obtain data for the physiological variable, we extracted the individual time series from a 6-mm spherical region centered on the coordinates of subject-specific activations in the left amygdala. The contrast $\{(PCO - null) + (PCS - null)\}$ was used for this ROI definition. Three subjects did not show any activation within the left amygdala and did not enter into the analysis. Of the remaining 23 subjects the PPI analyses were then carried out for each subject involving the creation of a design matrix with the interaction term, the psychological factor, and the physiological factor as regressors. Subject-specific contrast images using the contrast $[1\ 0\ 0]$, where the first column represents the interaction term, were then entered into a random-effects group analysis. Results were thresholded at $p < 0.005$ (uncorrected).

Results

Behavioral data

A repeated-measure 2×2 ANOVA indicated that participants' pain ratings were significantly higher for the painful situations intentionally caused by another individual (PCO: $48.9 \pm SE\ 3.54$) than for the painful situations accidentally caused by oneself (PCS: $46.1 \pm SE\ 3.58$). There was a significant main effect for pain, $F(1, 25) = 183.43$, $p < 0.0001$. There was also a significant main effect of social context, $F(1, 25) = 5.849$, $p = 0.023$. A significant interaction was found between pain and social context, $F(1, 25) = 7.152$, $p = 0.013$. This result indicates that the participants' subjective evaluations were modulated by the social context in which the pain occurred (see Fig. 2). The pain ratings for no-pain trials were scored very low and there was no significant difference between NPS and NPO (NPS: $0.37 \pm SE\ 0.13$; NPO: $0.26 \pm SE\ 0.15$) ($p = 0.53$).

Functional imaging data

1. Main effect of pain: areas showing a significant main effect of pain are listed in Table 1 and illustrated in Fig. 3. Significant activation associated with the perception of painful situations relative to non-painful situations was detected in the insula, thalamus, aMCC, dACC, PAG, somatosensory cortex, and SMA. Additional signal change was also observed bilaterally in the visual cortex, inferior frontal gyrus, middle temporal gyrus (V5/MT) and cerebellum.
2. Main effect of social context: areas showing a significant increase with respect to the presence of a second individual are listed in Table 2 and illustrated in Fig. 4. Significant hemodynamic activity was found in the amygdala, right temporal pole, right TPJ, posterior STS, and PCC (including the medial aspect of the orbito-frontal and prefrontal cortices). Additional activations were observed bilaterally in precuneus, lingual gyrus, insula, and middle temporal gyrus (V5/MT).
3. Interaction: a significant interaction of pain and social context with greater activation in the PCO trials was observed in the left inferior prefrontal cortex only (MNI coordinate: $x = -54$, $y = 28$, $z = -2$; t -Score = 4.05) (Fig. 5).
4. ROI analysis: a 2×2 ANOVA was performed on each ROI, with pain and social context as the two factors. Significant main effect of pain was found on ROIs in the aMCC $[-6, 2, 32]$, right insula (Rt. Ins) $[40, 24, 0]$ and primary somatosensory cortex (SI) $[-40, -46, 54]$: aMCC: $F(1, 25) = 21.905$, $p < 0.001$; Rt. Ins: $F(1, 25) = 27.715$, $p < 0.001$; Lt. SI: $F(1, 25) = 50.756$, $p < 0.001$ (Fig. 3). Significant main effect of social context was found on ROIs in right posterior part of STS (pSTS) $[62, -42, 12]$, right

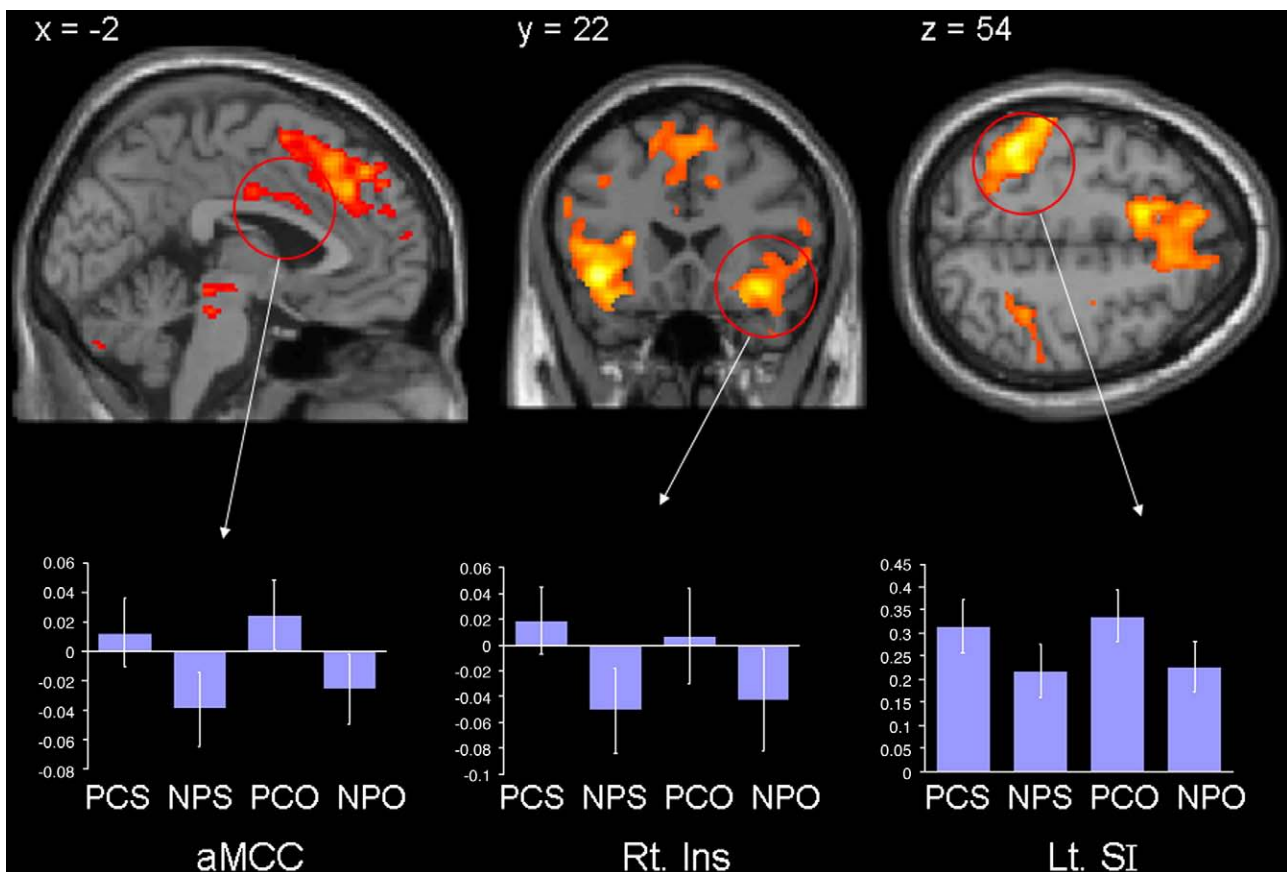


Fig. 3. Brain areas showing significantly greater hemodynamic increase in pain trials than in no-pain trials. Activation profiles in parameter estimate are also shown for ROIs in the aMCC $[-6, 2, 32]$, right insula (Rt. Ins) $[40, 24, 0]$ and primary somatosensory cortex (SI) $[-40, -46, 54]$ as measured with MarsBaR (mean \pm standard errors). A 2×2 ANOVA was performed for each ROI. There was a significant main effect for pain in each ROI. (aMCC: $F(1, 25) = 21.905$, $p < 0.001$; Rt. Ins: $F(1, 25) = 27.715$, $p < 0.001$; Lt. SI: $F(1, 25) = 50.756$, $p < 0.001$).

Table 2
Regions showing a significant main effect of social context.

Brain regions	Lat	MNI coordinates			t-Score	k
		x	y	z		
Self + Other > Self						
Middle frontal gyrus*	L	−32	20	50	4.01	
Middle frontal gyrus	R	28	18	52	3.86	79
Superior medial gyrus	M	−2	60	32	3.88	47
Superior medial gyrus	M	0	60	18	3.60	21
Superior medial gyrus	M	−2	66	4	4.24	46
Mid orbital gyrus	M	2	54	−8	3.11	27
Inferior frontal gyrus	L	−42	32	−14	4.18	78
Precuneus*	M	0	−60	58	10.05	
Superior occipital gyrus*	R	16	−94	28	8.58	
Linual gyrus*	L	−12	−80	−10	9.42	
Linual gyrus*	L	−8	−78	−8	8.80	
Middle occipital gyrus*	L	−42	−74	10	10.45	
Middle occipital gyrus*	R	48	−76	2	8.76	
Middle temporal gyrus*	R	48	−70	12	11.19	27828
Superior temporal cortex*	R	62	−42	12	6.86	
Middle temporal gyrus**	R	58	−2	−24	4.58	212
Temporal pole**	R	54	8	−24	3.05	
Amygdala	L	−20	−6	−26	5.71	40
Amygdala	R	28	−4	−24	3.07	13
Insula	L	−36	6	−9	3.74	37
Insula	R	44	14	−12	3.32	19
Cerebellum*	M	8	−78	−24	4.19	
Periaqueductal gray	M	0	−32	−22	4.49	69
Self > Self + Other	No significant activation					

Stereotactic coordinates and *t* values are provided for local voxel maxima in the regions showing a significant main social context. ($p < 0.05$, FDR corrected). Coordinates are defined in Montreal Neurologic Institute (MNI) stereotactic space in millimeters: $x > 0$ is right of the midsagittal plane, $y > 0$ is anterior to the anterior commissure and $z > 0$ is superior to anterior commissure–posterior commissure plane. L = left hemisphere; R = right hemisphere, M = medial activation. Regions marked with * or ** are in the same cluster. *k* = cluster size.

temporal pole (TP) [54, 8, −24], medial prefrontal cortex (mPFC) [−2, 60, 32], and left amygdala (Amy) [−20, −6, −26]: Rt.pSTS: $F(1, 25) = 43.755$, $p < 0.001$; Rt.TP: $F(1, 25) = 9.895$, $p = 0.004$; mPFC: $F(1, 25) = 16.023$, $p < 0.001$; Lt. Amy: $F(1, 25) = 28.454$, $p < 0.001$ (Fig. 4). A significant interaction of pain and social context was found on the ROI in the left inferior frontal cortex [−54, 28, −2]: $F(1, 25) = 16.277$, $p < 0.001$. On this ROI, there was a significant main effect for pain: $F(1, 25) = 15.023$, $p = 0.001$. And there was also a main effect of social context: $F(1, 25) = 3.902$, $p < 0.059$ (Fig. 5).

- PPI analysis: PPI analysis was performed to examine the functional connectivity between the amygdala and other brain areas during painful trials (see Table 3 and Fig. 6). Regions in the medial orbital cortex, left superior frontal cortex, and precuneus showed stronger covariation with the left amygdala during PCO trials than during PCS trials, indicating a stronger connectivity between the left amygdala and these areas. On the other hand, ACC, SMA, and right anterior insula showed stronger covariation with the left amygdala during PCS trials than during PCO trials. The left amygdala was selected because of its significant signal increase (5.71, FDR corrected).
- Correlation analysis: scores from the emotional contagion scale (EC) significantly correlated with the activity in the regions involved in processing the affective dimension of pain processing, namely the left AI and aMCC, as well as motor preparation (SMA). Hemodynamic change in the left amygdala, ACC and bilateral anterior insula showed significant correlation with the pain ratings during PCS and PCO trials (Table 4 and Fig. 7).

Discussion

Perception of pain caused by another individual

Though the participants did not engage any explicit discrimination task, significant activation was detected in the amygdala, along with the left IFG, right pSTS/TPJ, right TP, and mPFC during trials that involved the presence of two people. In addition, a significant

interaction with greater activation during PCO trials was observed in the left IFG, which is equivalent to the anterior part of Broca's area, suggesting a special role of this region in the perception of painful situations intentionally inflicted by another individual. Furthermore, the functional connectivity pattern between the left amygdala and other brain areas was modulated by the social context.

It is noteworthy that even the mere presence of another individual elicits the activation in the regions that are known to be associated with social cognition (e.g., Iacoboni et al., 2004). The STS region plays an important role in social perception via its involvement in interpreting the actions and social intentions of other people from an analysis of biological–motion cues (Allison, Puce and McCarthy, 2000). Social perception refers to the initial stages of evaluating the social communicative intentions of others by analysis of eye-gaze direction, facial expressions, body movements, and other types of biological motion. Electrophysiological recordings in monkey (e.g., Jellema et al., 2000) as well as functional neuroimaging studies (e.g., Blakemore et al., 2003; Decety and Stevens, 2008; Saxe et al., 2004) have documented that areas of the STS/TPJ are involved in the representation of intentional action, which is crucial in determining whether an environment is safe. The STS, via its connections with the amygdala and the orbitofrontal cortex, is crucially implicated in the evaluation and interpretation of social cues in both human and nonhuman primates (e.g., Puce and Perrett, 2003). As illustrated in Fig. 4, signal change in the right posterior STS/TPJ was driven by the presence of two individuals in the dynamic stimuli. This region is known to be sensitive to the detection of intentionality in the by means of perceptual analysis of biological motion and sensitivity to the intentionality and appropriateness of an action in a given context (e.g., Pelphrey et al., 2004). Another complementary interpretation for the pSTS activation is along the role of this region, especially in the right hemisphere, as part of a system specialized for the detection of behaviorally relevant stimuli, particularly when they are salient (Corbetta and Shulman, 2002). This interpretation fits well with what the stimuli conveyed in the PCO and NPO situations since the mere presence of two individuals (interacting or not) likely enhances sensitivity to potential goals and intentions of agents in the environment.

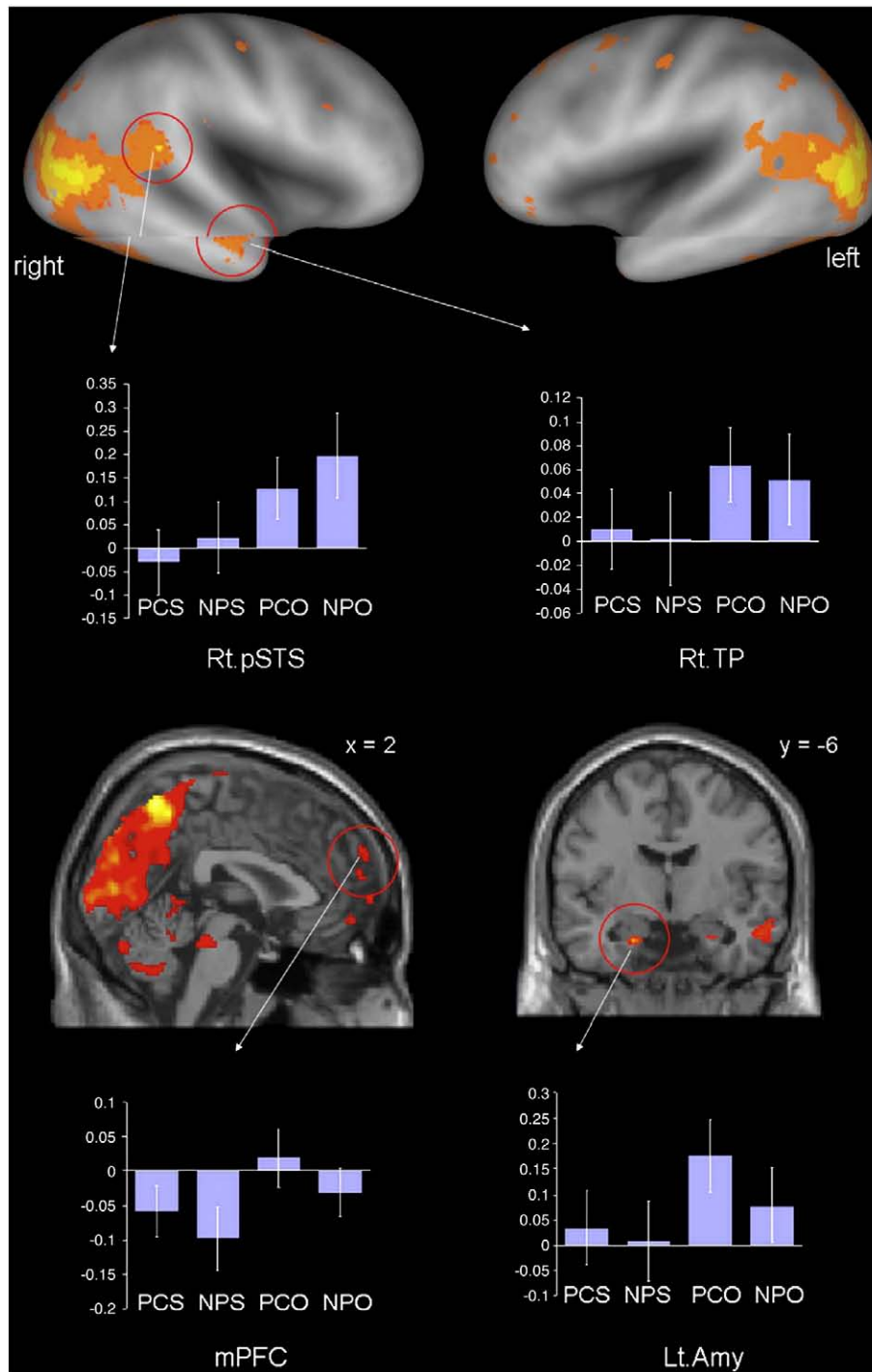


Fig. 4. Main effect of social context. Regions showing a significant main effect of social context (i.e., areas showing greater activation in self and other trials than in self trials). Activation profiles in parameter estimate are also shown for ROIs in right posterior part of STS (pSTS) [62, -42, 12], right temporal pole (TP) [54, 8, -24], medial prefrontal cortex (mPFC) [-2, 60, 32], and left amygdala (Amy) [-20, -6, -26]. A 2×2 ANOVA was performed for each ROI. There was a significant main effect for social context in each ROI. (Rt. pSTS: $F(1, 25) = 43.755$, $p < 0.001$; Rt.TP: $F(1, 25) = 9.895$, $p = 0.004$; mPFC: $F(1, 25) = 16.023$, $p < 0.001$; Lt. Amy: $F(1, 25) = 28.454$, $p < 0.001$).

Connectivity between the temporal cortex and the amygdala suggests a top-down control in the processing of social cues that could actively inhibit the expression of defensive strategies. The amygdala is a well-known brain structure engaged by emotionally salient stimuli, both positive and negative. Here signal increased in the amygdala during both NPO and PCO conditions (i.e., involving two individuals). Countless studies have consistently documented that the amygdala plays a critical role in fear-related behaviors, such as the evaluation of actual or potential threats (LeDoux, 2000). Both patient and functional neuroimaging studies also suggest that the

amygdala is critical for evaluating facial expressions of fear, which can be cues to the threat of physical attack (Adolphs et al., 1994; Breiter et al., 1996). Furthermore, previous research indicates that the amygdala response to fearful faces occurs automatically and is not reduced in response to unattended faces (Anderson et al., 2003). The signal in the amygdala was stronger when participants watched pain intentionally inflicted by another individual than when observing pain caused by accident. The former situation is certainly more arousing and this is consistent with a general role of the amygdala in processing relevant stimuli (Norris et al., 2004). In the

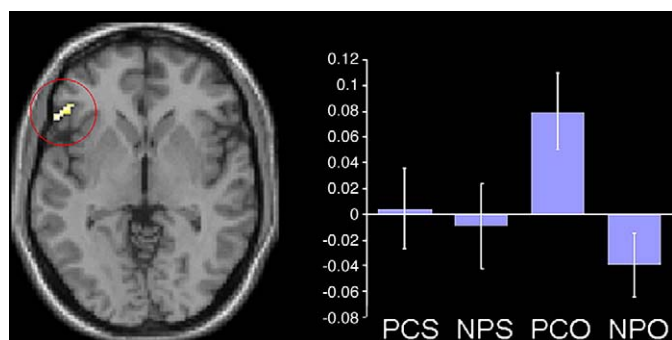


Fig. 5. Interaction effect. Cluster in the left inferior frontal gyrus [$-54, 28, -2$] showing a significant interaction of pain and social context with greater activation in PCO trials. A 2×2 ANOVA was performed for this ROI. There was a significant main effect for pain: $F(1, 25) = 15.023, p = 0.001$. There was also a main effect of social context: $F(1, 25) = 3.902, p < 0.059$. A significant interaction was found between pain and social context: $F(1, 25) = 16.277, p < 0.001$.

context of these studies, the results from the PPI analysis are intriguing: the left amygdala was more strongly connected to aspects of the pain matrix (i.e., ACC, SMA and AI) during PCS trials compared to PCO trials. On the other hand, the left amygdala was more strongly connected to the mOFC during PCO trials compared to PCS trials. A recent functional MRI study demonstrated a significant increase of connectivity between mOFC and left amygdala in response to social threat (Coccaro et al., 2007). Taken together, our results suggest that the left amygdala processes perception of pain as a threat during PCS trials, while during PCO trials the amygdala processes the perception of an individual hurting another as a more relevant threat. The selective connectivity seen in these situations could reflect a key aspect in successful adaptation to the environment. The mOFC plays a critical role in decision making especially in incompletely specified situations, in which uncertainty or unpredictability cause subjects to make choices on the basis of partial information (Elliott et al., 2000). Further, the mOFC is also implicated in monitoring associations between stimuli, responses, and outcomes under changing circumstances (Amodio and Frith, 2006). According to neuroanatomical and neurophysiological research with animals, defensive behaviors towards perceived risk are also mediated by the

well-defined connections between the amygdala and the PAG (Porges, 2003).

The activation of the above neural network can also be discussed in relation to the assessment of another individual's action and intention which involves two different, yet interacting neurophysiological systems, i.e., the mirror-neuron system and theory of mind, subserved by specific and distinct neural circuits (Blakemore and Decety, 2001; Sommerville and Decety, 2006). Interestingly, in our study the interaction between pain and social context resulted in the specific activation of left inferior frontal gyrus. The role of this region in action understanding, based on mirror-neuron mechanism is well established (e.g., Iacoboni et al., 2005). Recent studies point out a role of the IFG in the perception of social interaction. For instance, one EEG study measured the *mu* rhythm in relation to the observation of actions performed by others, and found that it was modulated by the degree of social interaction, with the social interactive condition showing the most suppression (Oberman et al., 2007). Another functional MRI study demonstrated that the inferior frontal gyrus processes the intentionality of an observed action on the basis of the visual properties of the action, irrespective of whether the participants paid attention to the intention or not (De Lange et al., 2008). The authors also found that brain areas that are part of a "mentalizing" network (especially the medial prefrontal cortex) become active when participants reflect about the intentionality of an observed action, but they are largely insensitive to the visual properties of the observed action. A recent study reported that *mu* suppression was positively correlated with accuracy on the social-perceptual task but not in the social-cognitive task (Pineda and Hecht, 2009). In addition, a study using repetitive transcranial magnetic stimulation (rTMS) over left inferior frontal gyrus demonstrated that this region contributes to action understanding (Pobric et al., 2006). The authors also suggested that the left IFG is involved in tasks that require a detailed assessment and interpretation of a human action but not by tasks that require simple observation of human actions.

Another alternative hypothesis to account for the increased activity of the IFG during the observation of pain inflicted by another individual is that higher activity in this region was triggered by the presence of strong pain. Subjective data of pain ratings indicate that PCO trials were perceived as more painful than the PCA trials. Such an

Table 3

Task-related PPI analysis with the left amygdala as a seed.

Brain regions	Lat	MNI coordinates			t-Score	k
		x	y	z		
PCO>PCS						
Superior frontal gyrus	L	-20	42	46	3.45	101
Precuneus	M	2	-74	46	3.22	45
Medial orbital gyrus	L/M	-10	64	-8	3.14	85
PCS>PCO						
Supplementary motor area*	M	0	20	50	3.60	83
Supplementary motor area*	R	8	24	48	4.63	
Precentral gyrus	L	-40	-8	48	3.50	22
Precentral gyrus	R	44	-2	50	4.43	76
Anterior cingulate cortex	R/M	10	16	28	4.67	49
Middle frontal gyrus	R	36	52	14	5.14	257
Middle occipital gyrus	R	34	-80	32	4.98	79
Middle occipital gyrus	R	36	-84	10	3.44	37
Inferior occipital gyrus	L	-40	-84	-6	4.91	196
Inferior occipital gyrus	R	32	-86	-14	3.79	33
Inferior occipital gyrus	R	24	-94	-4	4.47	49
Linual gyrus	R	8	-64	-4	3.38	27
Linual gyrus	R	16	-92	-14	4.33	32
Fusiform	R	44	-42	-22	3.72	137
Fusiform	R	24	-78	-8	3.78	57
Anterior Insula	R	42	24	-6	3.94	209
Temporal pole	R	52	10	-12	4.07	44

MNI coordinates and t values are provided for local voxel maxima in the regions showing left amygdala coupling ($p < 0.005$, uncorrected). Regions marked with * are in the same cluster.

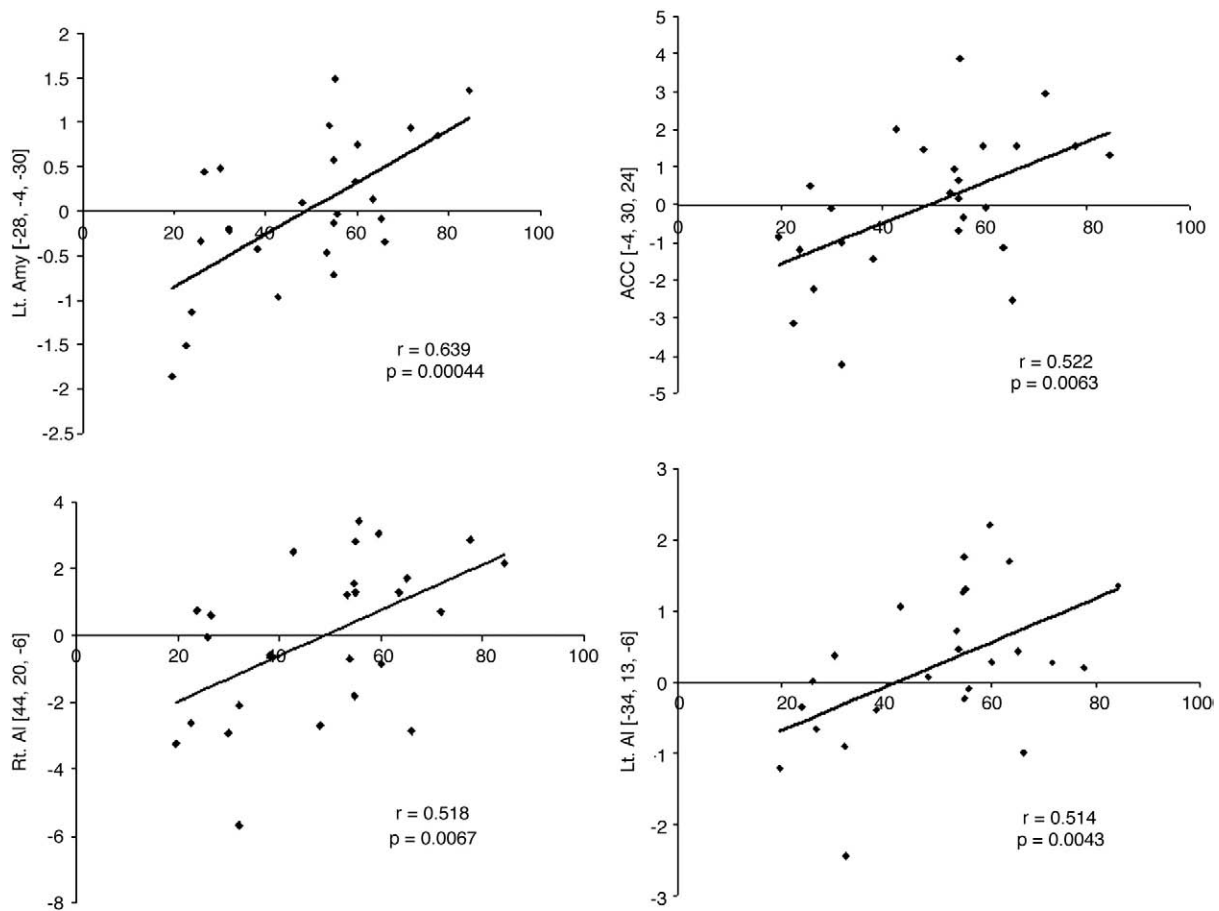


Fig. 6. Task-related PPI analysis with the left amygdala as a seed. Brain regions showing significant task-dependent (PCO>PCS or PCS>PCO) coupling with the left amygdala: (left) mOFC (right) SMA, ACC, right Ins. Results are superimposed on sagittal and coronal MRI sections.

interpretation supports the finding that motor resonance with others' pain is greater during the observation of strong painful stimuli (deep needle penetrations) than during observation of light painful stimuli (light pinpricks) as measured by TMS and motor-evoked potentials (Avenanti et al., 2006).

We cannot rule out, however, a language-like processing during the perception of pain caused by the other. This reasoning is in line with previous linguistic studies suggesting that the anterior aspect of Broca's area is specifically involved in semantic processing (Bookheimer, 2002; Devlin et al., 2003).

Table 4

Regions showing significant correlation with hemodynamic response during PCS trials and PCO trials.

Analysis and brain region	Lat	MNI coordinates			t-Score	r	k
		x	y	z			
Emotion contagion score (during PCS trials)							
Supplementary motor area	R/M	4	14	54	4.19	0.651	312
Anterior insula	L	-34	22	-4	4.52	0.678	114
Anterior insula	L	32	24	-8	3.21	0.548	4
Pain ratings (during PCS trials)							
Anterior insula	L	-32	16	-8	3.53	0.584	13
Anterior insula*	R	40	20	-6	2.62	0.472	
Anterior cingulate cortex*	R/M	2	40	14	2.37	0.435	
Emotion contagion score (during PCO trials)							
Supplementary motor area	L/M	-6	8	60	4.11	0.651	17
Middle cingulate cortex	L/M	-10	14	40	4.92	0.709	28
Anterior insula	L	-36	22	-4	4.22	0.653	19
Pain ratings (during PCO trials)							
Anterior cingulate cortex	L/M	-4	30	24	3.00	0.522	6
Anterior insula	R	44	20	-6	2.97	0.518	9
Anterior insula	L	-34	14	-6	3.16	0.514	14
Amygdala	L	-28	-4	-30	4.07	0.639	12
Temporal pole**	R	46	10	-36	3.55	0.587	14
Middle frontal gyrus**	L	-42	40	24	5.54	0.749	283
Middle temporal gyrus**	L	-46	-70	12	5.11	0.722	257

Note. r Refers to the correlation coefficient.

* Regions whose voxels survived at $p < 0.05$, uncorrected.

** Regions that were not in our a priori hypothesis.

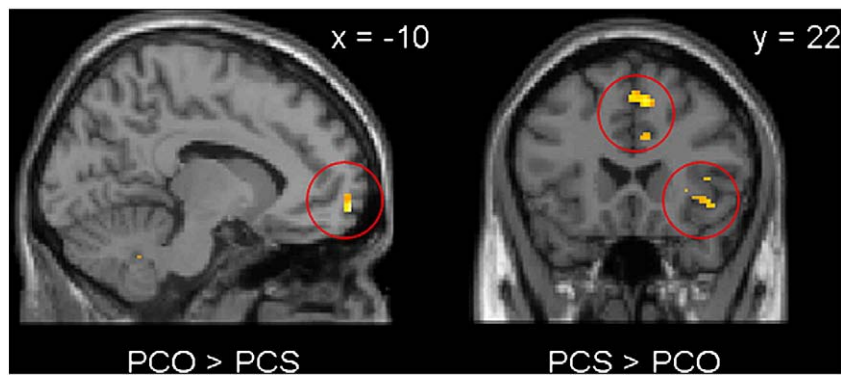


Fig. 7. Correlation with pain ratings. Activation level (parameter estimate) observed within clusters peaks in the left amygdala, ACC and bilaterally in the AI during PCO trials are significantly correlated with individual's averaged pain ratings for PCO trials. The lines represent the linear best fit; r refers to the correlation coefficient. MNI Coordinates (mm) of peak activation of each region are given in mm.

As for the more anterior region of the rostral mPFC, previous work has demonstrated that this region responds more strongly to emotional versus neutral stimuli (Moriguchi et al., 2006). In general, regions around the anterior PCC in the mPFC play a specific role in understanding the mental states of an agent involved in social interaction (Brunet et al., 2000; Walter et al., 2004). The medial prefrontal cortex/PCC contains spindle cells, large projection neurons found only in great apes and humans, which are thought to be involved in coordinating widely distributed neural activity involving emotion and cognition (Allman et al., 2001). The medial PFC region has been found to be reliably activated in conjunction with the TPJ by theory of mind tasks of various types and difficulties, from judging the emotion in another person's gaze to detection of intention in simple dynamic animations, attribution of intention to cartoons characters, story comprehension, and detection of social transgression and appreciation of humor (Gallagher and Frith, 2003). Indeed, we also found a significant activation in the right pSTS, extending to the TPJ in the main effect of perceived agency. Previous fMRI studies indicate that TPJ plays a distinct role in the detection of agency (Decety and Grèzes, 2006; Farrer et al., 2003; Ruby and Decety, 2001) and in the representation of intentional actions, including sensitivity to the contingent relation between the action and the local environmental context (Saxe et al., 2004; Pelphrey et al., 2004). Furthermore, it has recently been proposed that contribution of the right TPJ to social perception – as seen in theory of mind or empathy tasks – relies on low-level computational mechanisms involved in generating, testing, and correcting internal predictions about external sensory events (Decety and Lamm, 2007), and reorienting attention to salient events (Corbetta and Shulman, 2002). The results of the current study endorse this latter functional hypothesis of pSTS/TPJ: situations that involved the presence of two individuals require greater attentional demands, predictions about the agent's behavior, and appreciation of agent's intention to inflict the other.

Another region reliably associated with theory of mind tasks is the anterior part of the temporal pole (Gallagher et al., 2002; Olson et al., 2007; Walter et al., 2004). A study by Vollm et al. (2006) found that clusters of activation for a theory of mind task overlapped with those for an empathy task in the temporal pole (TP), suggesting that these regions function in the making of inferences about the mental state of others. Altogether these results support the idea that motor simulation (subserved by the mirror-neuron system) and mentalizing have complementary functions (Sommerville and Decety, 2006; De Lange et al., 2008; Uddin et al., 2007).

A final explanation, though quite speculative, for the activation seen in PCO trials is that viewing an individual intentionally harming another person may elicit a signal involved in judgments of moral wrongdoing. Recent social neuroscience work suggests that the

vmPFC/mOFC, anterior PCC, STS, amygdala, and anterior temporal lobes including TP play a crucial role in moral judgment (Moll et al., 2005, 2007). Particularly, the amygdala and vmPFC have frequently been identified in neuroimaging studies of moral reasoning (Moll et al., 2007; Greene et al., 2001; Luo et al., 2006). The amygdala is crucial for stimulus-reinforcement learning and thus enables the individual to learn the goodness and badness of objects and actions (Everitt et al., 2003; Davis and Whalen, 2001; Blair, 2007). As the relationship between the amygdala and the temporal cortex is reciprocal, this learning enables the amygdala to influence attention (Adolphs et al., 2005). In humans and other primates fear serves as a reinforcer, and thus fearful stimuli will be avoided. This type of stimulus-reinforcement learning depends on the amygdala too (Hooker et al., 2006). On the other hand, vmPFC is preferentially involved in representing social and emotional event knowledge, which is essential for the formation of social attitudes (Pietrini et al., 2000). Thus, it is worth noting that the neural regions associated with the presence of an agent harming the other belong to this moral judgment network. Furthermore, the TP, which has been shown to be involved in moral decisions (Moll et al., 2002; Heekeren et al., 2003), is strongly interconnected with both the amygdala and OFC, and the right TP in particular is suggested to be associated with the linking of high-level sensory representations with emotional responses and socially relevant memory (Olson et al., 2007). This suggestion is compatible with an fMRI study demonstrating that TP activation correlates with personal distress scores, a measure of how much one personally feels upset when viewing another's negative emotions (Moriguchi et al., 2006).

A growing body of empirical neuroscientific evidence suggests that perception and/or empathy for pain is not an all-or-none phenomenon but it is strongly influenced by interpersonal, intrapersonal and situational factors (Decety and Jackson, 2004; Decety and Lamm, 2006). A number of behavioral studies reported that seeing unpleasant pictures depicting disgust, fear, anger, or pain increase subjective pain intensity (Wunsch et al., 2003) and decrease pain tolerance (de Wied and Verbaten, 2001; Meagher et al., 2001). Some fMRI studies also demonstrated that attention (Gu and Han, 2007), cognitive appraisal (Lamm et al., 2007a), medical expertise (Cheng et al., 2007), and likeability of the person in pain (Singer et al., 2006) are significant factors that influence the participants' pain ratings as well as the neural response to the pain of others. Based on these previous studies, it is not surprising that additional neural/psychological modulation is at play when the painful situations involve a social interaction between two people. Interestingly, no significant difference of activation was found between PCO and PCS trials for the ROIs of the pain matrix. The main source psychological was related to the activation associated with the presence of two individuals in the stimuli.

Activation of the pain matrix

Our data support the results of earlier studies of pain empathy. Predictably, a significant main effect of pain was found in the insula, somatosensory cortex, ACC, thalamus, PAG and cerebellum. These regions have reliably been detected in functional neuroimaging studies of perception of pain in others. A significant positive correlation was found between the subjective pain ratings and the hemodynamic response in the anterior insula and ACC. This is consistent with previous fMRI studies, which demonstrated that participants' estimates of the intensity of observed pain were significantly correlated with the activation in the anterior insula and left ACC (Saarela et al., 2007; Jackson et al., 2005), as well as with participants' own percepts of pain intensity (Coghill et al., 1999). Furthermore, in our study the activation of left anterior insula was significantly correlated with the individual scores in EC. This finding is in line with a recent study which demonstrated that left anterior insula activation was linearly related to perceived unpleasantness, depending on individual differences in susceptibility to aversive stimuli (Benuzzi et al., 2008). As for the somatosensory cortex, however, results of previous fMRI studies are less consistent. Singer et al. (2004) reported that only the actual experience of pain activated the somatosensory cortex. In contrast, we found significant hemodynamic signal change in the somatosensory cortex in response to the observation of pain in others, as did other fMRI studies (Cheng et al., 2007; Jackson et al., 2006a,b; Lamm et al., 2007b; Moriguchi et al., 2007), and a recent magnetoencephalography study (Cheng et al., 2008). Another group, using somatosensory-evoked potentials (SEPs), found that viewing videos of pain increased the activation in the somatosensory cortex, and that the activity was correlated with the intensity of the pain (Bufalari et al., 2007). In our data, significant activation was also found in brain areas that do not belong to pain matrix (e.g., ventral premotor, medial prefrontal, bilateral occipital and temporal cortices) in the contrast of painful vs. non-painful trials. These activations are associated with the recognition of biological motion (and thus emotionally salient), as it has been demonstrated in a previous study using dynamic visual stimuli (Vaina et al., 2001).

Conclusion

Our results demonstrate the impact of social context on the neural response to the perception of pain in others. Regions showing significant effect of pain are consistent with previous fMRI studies of empathy for pain (Jackson et al., 2006a,b for a meta-analysis). Most interestingly however, empathy for pain was modulated by the social context in which the painful situations occurred. As a consequence of this modulation, participants' ratings of pain intentionally caused by another person were greater than ratings of pain that was accidentally caused by oneself, and hemodynamic signal increase was detected in the amygdala and left inferior frontal gyrus. The circuits involved in theory of mind and emotion regulation showed a significant main effect of social context, and modulation of functional connectivity was also observed depending on the social context. Stronger connectivity between the left amygdala and the ventromedial prefrontal cortex was found when participants perceived painful situations caused by another individual relative to situations where pain accidentally occurred. Altogether, these new findings contribute to better understanding of the neural underpinnings of perceived agency and its link with empathy, which play an important role in the building blocks of moral reasoning.

Certain limitations of this study are noteworthy. First we did not include a condition of social interaction between the two individuals with no pain. Therefore design cannot unequivocally disentangle the possibility that some results can be associated with both the perception of pain caused by another individual and because another individual was interacting but without painful outcome. However, this

interpretation limitation cannot detract from the fact that, when an interaction was taking place, it was always a negative one (i.e., an individual intentionally inflicting harm on another). It is thus possible, given we used an event-related design, that participants anticipated negative consequences and threat even when watching the situations with two agents with interaction.

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References

- Adolphs, R., 2002. Trust in the brain. *Nat. Neurosci.* 5, 192–193.
- Adolphs, R., Tranel, D., Damasio, H., Damasio, A., 1994. Impaired recognition of emotion in facial expressions following bilateral damage to the human amygdala. *Nature* 372, 669–672.
- Adolphs, R., Gosselin, F., Buchana, T.W., Tranel, D., Schyns, P., Damasio, A.R., 2005. A mechanism for impaired fear recognition after amygdala damage. *Nature* 433, 68–72.
- Allison, T., Puce, A., McCarthy, G., 2000. Social perception from visual cues: role of the STS region. *TICS* 4, 267–278.
- Allman, J.M., Hakeem, A., Erwin, J.M., Nimchinsky, E., Hof, P., 2001. The anterior cingulate cortex: the evolution of an interface between emotion and cognition. *Ann. N. Y. Acad. Sci.* 935, 107–117.
- Amodio, D.M., Frith, C.D., 2006. Meeting of minds: the medial frontal cortex and social cognition. *Nat. Rev., Neurosci.* 7, 268–277.
- Anderson, A.K., Christoff, K., Panitz, D., Rosa, E.D., Gabrieli, J.D.E., 2003. Neural correlates of the automatic processing of threat facial signals. *J. Neurosci.* 23, 5627–5633.
- Avenanti, A., Buetti, D., Galati, G., Aglioti, S.M., 2005. Transcranial magnetic stimulation highlights the sensorimotor side of empathy for pain. *Nat. Neurosci.* 8, 955–960.
- Avenanti, A., Minio-Paluello, I., Bufalari, I., Aglioti, S.M., 2006. Stimulus-driven modulation of motor-evoked potentials during observation of others' pain. *NeuroImage* 32, 316–324.
- Benuzzi, F., Lui, F., Duzzi, D., Nichelli, P.F., Porro, C.A., 2008. Does it look painful or disgusting? Ask your parietal and cingulate cortex. *J. Neurosci.* 28, 923–931.
- Blair, R.J.R., 2007. The amygdala and ventromedial prefrontal cortex in morality and psychopathy. *Trends. Cogn. Sci.* 11, 387–392.
- Blakemore, S., Decety, J., 2001. From the perception of action to the understanding of intention. *Nat. Rev., Neurosci.* 2, 561–567.
- Blakemore, S.-J., Boyer, P., Pachot-Clouard, M., Meltzoff, A., Segebarth, C., Decety, J., 2003. The detection of contingency and animacy from simple animations in the human brain. *Cereb. Cortex* 13, 837–844.
- Bookheimer, S., 2002. Functional MRI of language: new approach to understanding the cortical organization of semantic processing. *Annu. Rev. Neurosci.* 25, 151–188.
- Botvinick, M., Jha, A.P., Bylsma, L.M., Fabian, S.A., Solomon, P.E., Prkachin, K.M., 2005. Viewing facial expression of pain engages cortical areas involved in the direct experience of pain. *NeuroImage* 25, 312–319.
- Breiter, H.C., Etcoff, N.L., Whalen, P.J., Kennedy, W.A., Rauch, S.L., Buckner, R.L., Strauss, M.M., Hyman, S.E., Rosen, B.R., 1996. Response and habituation of the human amygdala during visual processing of facial expression. *Neuron* 17, 875–887.
- Brunet, E., Sarfati, Y., Hardy-Bayle, M.C., Decety, J., 2000. A PET investigation of attribution of intentions to others with a non-verbal task. *NeuroImage* 11, 157–166.
- Bufalari, I., Aprile, T., Avenanti, A., Russo, F.D., Aglioti, S.M., 2007. Empathy for pain and touch in the human somatosensory cortex. *Cereb. Cortex* 17, 2553–2561.
- Cheng, Y., Lin, C., Liu, H.L., Hsu, Y., Lim, K., Hung, D., Decety, J., 2007. Expertise modulates the perception of pain in others. *Curr. Biol.* 17, 1708–1713.
- Cheng, Y., Yang, C.Y., Lin, C.P., Lee, P.R., Decety, J., 2008. The perception of pain in others suppresses somatosensory oscillations: a magnetoencephalography study. *NeuroImage* 40, 1833–1840.
- Coan, J.A., Schaefer, H.S., Davidson, R.J., 2006. Lending a hand: social regulation of the neural response to threat. *Psychol. Sci.* 17, 1032–1039.
- Coccaro, E.F., McCloskey, M.S., Fitzgerald, D.A., Phan, K.L., 2007. Amygdala and orbitofrontal reactivity to social threat in individuals with impulsive aggression. *Biol. Psychiatry* 62, 168–178.
- Coghill, R.C., Sang, C.N., Maisog, J.M., Iadarola, M.J., 1999. Pain intensity processing within the human brain: a bilateral, distributed mechanism. *J. Neurophysiol.* 82, 1934–1943.
- Corbetta, M., Shulman, G.L., 2002. Control of goal-directed and stimulus-driven attention in the brain. *Nat. Neurosci., Rev.* 3, 201–215.
- Craig, K.D., 2004. Social communication of pain enhances protective functions. *Pain* 107, 5–6.
- Davis, M., Whalen, P.J., 2001. The amygdala: vigilance and emotion. *Mol. Psychiatry* 5, 13–34.
- Decety, J., 2007. A social cognitive neuroscience model of human empathy. In: Harmon-Jones, E., Winkielman, P. (Eds.), *Social Neuroscience: Integrating Biological and*

- Psychological Explanations of Social Behavior. In Guilford Publications, New York, pp. 246–270.
- Decety, J., Grèzes, J., 2006. The power of simulation: imagining one's own and other's behavior. *Brain Res.* 1079, 4–14.
- Decety, J., Jackson, P.L., 2004. The functional architecture of human empathy. *Behav. Cogn. Neurosci. Rev.* 3, 71–100.
- Decety, J., Lamm, C., 2006. Human empathy through the lens of social neuroscience. *Scientific World J.* 6, 1146–1163.
- Decety, J., Lamm, C., 2007. The role of the right temporoparietal junction in social interaction: how low-level computational processes contribute to meta-cognition. *Neuroscientist* 13, 580–593.
- Decety, J., Meyer, M., 2008. From emotion resonance to empathic understanding: a social developmental neuroscience account. *Dev. Psychopathol.* 20, 1053–1080.
- Decety, J., Stevens, J., 2008. Action representation and its role in social interaction. In: Markman, K.D., Klein, W.M.P., Suhr, J.A. (Eds.), *The Handbook of Imagination and Mental Simulation*. In Psychology Press, New York, pp. 3–20.
- De Lange, F.P., Spronk, M., Willems, R.M., Toni, I., Beckering, H., 2008. Complementary systems for understanding action intentions. *Curr. Biol.* 18, 454–457.
- Derbyshire, S.W.G., 2000. Exploring the pain neuromatrix. *Curr. Rev. Pain* 6, 467–477.
- Devlin, J.T., Matthews, P.M., Rushworth, M.F.S., 2003. Semantic processing in the left inferior prefrontal cortex: a combined functional magnetic resonance imaging and transcranial magnetic stimulation study. *J. Cogn. Neurosci.* 15, 71–84.
- de Wied, M., Verbaten, M.N., 2001. Affective pictures processing, attention, and pain tolerance. *Pain* 90, 163–172.
- Doherty, R.W., 1997. The emotional contagion scale: a measure of individual differences. *J. Nonverbal Behavior* 21, 131–154.
- Elliott, R., Dolan, R.J., Frith, C.D., 2000. Dissociable functions in the medial and lateral orbitofrontal cortex: evidence from human neuroimaging studies. *Cereb. Cortex* 10, 1047–1061.
- Estabrook, S., 2007. Does context modulate empathy for pain? Master of Art Thesis under direction of Dr. Jean Decety at the University of Chicago.
- Everitt, B.J., Cardinal, R.N., Parkinson, J.A., Robbins, T.W., 2003. Appetitive behavior: impact of amygdala-dependent mechanisms of emotional learning. *Ann. N. Y. Acad. Sci.* 985, 233–250.
- Farrer, C., Franck, N., Frith, C.D., Decety, J., Jeannerod, M., 2003. Modulating the experience of agency: a PET study. *NeuroImage* 18, 324–333.
- Friston, K.J., Buechel, C., Fink, G.R., Morris, J., Rolls, E., Dolan, R.J., 1997. Psychophysiological and modulatory interaction in neuroimaging. *NeuroImage* 6, 218–229.
- Gallagher, H.L., Frith, C.D., 2003. Functional imaging of theory of mind. *Trends Cogn. Sci.* 7, 77–83.
- Gallagher, H.L., Jack, A.I., Roepstorff, A., Frith, C.D., 2002. Imaging the intentional stance in a competitive game. *NeuroImage* 16, 814–821.
- Glover, G.H., Law, G.S., 2001. Spiral-in/out bold fMRI for increased SNR and reduced susceptibility artifacts. *Mag. Res. Med.* 46, 515–522.
- Goubert, L., Craig, K.D., Buysse, A., 2009. Perceiving others in pain: experimental and clinical evidence on the role of empathy. In: Decety, J., Ickes, W. (Eds.), *The Social Neuroscience of Empathy*. In MIT press, Cambridge, pp. 153–166.
- Greene, J.D., Sommerville, R.B., Nystrom, L.E., Darley, J.M., Cohen, J.D., 2001. An fMRI investigation of emotional engagement in moral judgment. *Science* 293, 1971–1972.
- Gu, X., Han, S., 2007. Attention and reality constraints on the neural processes of empathy for pain. *NeuroImage* 36, 256–267.
- Heekeren, H.R., Wartenburger, I., Schmidt, H., Schwindtowski, H.-P., Villringer, A., 2003. An fMRI study of simple ethical decision-making. *NeuroReport* 14, 1215–1219.
- Hooker, C.I., Germine, L.T., Knight, R.T., D'Esposito, M., 2006. Amygdala response to facial expressions reflects emotional learning. *J. Neurosci.* 26, 8915–8922.
- Iacoboni, M., Lieberman, M.D., Knowlton, B.J., Molnar-Szakacs, I., Moritz, M., Throop, C.J., Fiske, A.P., 2004. Watching social interactions produces dorsomedial prefrontal and medial parietal BOLD fMRI signal increases compared to a resting baseline. *NeuroImage* 21, 1167–1173.
- Iacoboni, M., Molnar-Szakacs, I., Gallese, V., Buccino, G., Mazziotta, J.C., Rizzolatti, G., 2005. Grasping the intentions of others with one's own mirror neuron system. *PLoS Biol.* 3, e79.
- Jackson, P.L., Meltzoff, A.N., Decety, J., 2005. How do we perceive the pain of others: a window into the neural processes involved in empathy. *NeuroImage* 24, 771–779.
- Jackson, P.L., Brunet, E., Meltzoff, A.N., Decety, J., 2006a. Empathy examined through the neural mechanisms involved in imagining how I feel versus how you feel pain: an event-related fMRI study. *Neuropsychologia* 44, 752–761.
- Jackson, P.L., Rainville, P., Decety, J., 2006b. To what extent do we share the pain of others? Insight from the neural bases of pain empathy. *Pain* 125, 5–9.
- Jellema, T., Baker, C.I., Wicker, B., Perrett, D.I., 2000. Neural representation for the perception of the intentionality of actions. *Brain Cogn.* 44, 280–302.
- Lamm, C., Batson, C.D., Decety, J., 2007a. The neural substrate of human empathy: effects of perspective-taking and cognitive appraisal. *J. Cogn. Neurosci.* 19, 42–58.
- Lamm, C., Nusbaum, H., Meltzoff, A.N., Decety, J., 2007b. What are you feeling? Using functional magnetic resonance imaging to assess the modulation of sensory and affective responses during empathy for pain. *PLoS ONE* 12, e1292.
- LeDoux, J.E., 2000. Emotion circuits in the brain. *Annu. Rev. Neurosci.* 23, 155–184.
- Luo, Q., Nakić, M., Wheatley, T., Richell, R., Martin, A., Blair, R.J.R., 2006. The neural basis of implicit moral attitude — an IAT study using event-related fMRI. *NeuroImage* 30, 1449–1457.
- Meagher, M.W., Arnau, R.C., Rhudy, J.L., 2001. Pain and emotion: effects of affective picture modulation. *Psychosomatic Med.* 63, 79–90.
- Moll, J., de Oliveira-Souza, R., Eslinger, P.J., Bramati, I.E., Mourão-Miranda, J., Andreiolo, P.A., Pessoa, L., 2002. The neural correlation of moral sensitivity: a functional magnetic resonance imaging investigation of basic and moral emotions. *J. Neurosci.* 22, 2730–2736.
- Moll, J., Zahn, R., de Oliveira-Souza, R., Krueger, F., Grafman, F., 2005. The neural basis of human moral cognition. *Nat. Rev. Neurosci.* 6, 799–809.
- Moll, J., de Oliveira-Souza, R., Garrido, G.J., Bramati, I.E., Caparelli-Daquer, E.M.A., Paiva, M.L., Zahn, R., Grafman, J., 2007. The self as a moral agent: linking the neural bases of social agency and moral sensitivity. *Soc. Neurosci.* 2, 336–352.
- Moriguchi, Y., Ohnishi, T., Lane, R.D., Maeda, M., Mori, T., Nemoto, K., Matsuda, H., Komaki, G., 2006. Impaired self-awareness and theory of mind: an fMRI study of mentalizing in alexithymia. *NeuroImage* 32, 1472–1482.
- Moriguchi, Y., Decety, J., Ohnishi, T., Maeda, M., Mori, T., Nemoto, K., Matsuda, H., Komaki, G., 2007. Empathy and judging other's pain: an fMRI study of alexithymia. *Cereb. Cortex* 17, 2223–2234.
- Morrison, I., Lloyd, D., di Pellegrino, G., Roberts, N., 2004. Vicarious response to pain in anterior cingulate cortex: is empathy a multisensory issue? *Cognitive Affective and Behavior. Neurosci.* 4, 270–278.
- Morrison, I., Peelen, M.V., Downing, P.E., 2007. The sight of others' pain modulates motor processing in human cingulate cortex. *Cereb. Cortex* 17, 2214–2222.
- Norris, C.J., Chen, E.E., Zhu, D.C., Small, S., Cacioppo, J.T., 2004. The interaction of social and emotional processes in the Brain. *J. Cogn. Neurosci.* 10, 1818–1829.
- Oberman, L.M., Pineda, J.A., Ramachandran, V.S., 2007. The human mirror neuron system: a link between action observation and social skills. *SCAN* 2, 62–66.
- Ogino, Y., Nemoto, H., Inui, K., Saito, S., Kakigi, R., Goto, F., 2007. Inner experience of pain: imagination of pain while viewing images showing painful events forms subjective pain representation in human brain. *Cereb. Cortex* 17, 1139–1146.
- Oldfield, R.C., 1971. The assessment and analysis of handedness: the Edinburgh inventory. *Neuropsychologia* 9, 97–113.
- Olson, I.R., Plotzker, A., Ezzyat, Y., 2007. The enigmatic temporal pole: a review of findings on social emotional processing. *Brain* 130, 1718–1731.
- Pelphrey, K.A., Morris, J.P., McCarthy, G.M., 2004. Grasping the intentions of others: the perceived intentionality of an action influences activity in the superior temporal sulcus during social perception. *J. Cogn. Neurosci.* 16, 1706–1716.
- Pessoa, L., McKenna, M., Gutierrez, E., Ungerleider, L.G., 2002. Neural processing of emotional faces requires attention. *Proc. Natl. Acad. Sci.* 99, 11458–11463.
- Phelps, E.A., O'Connor, K.J., Gatenby, J.C., Gore, J.C., Grillon, C., Davis, M., 2001. Activation of the left amygdala to a cognitive representation of fear. *Nat. Neurosci.* 4, 437–441.
- Pietrini, P., Guazzelli, G., Basso, G., Jaffe, K., Grafman, J., 2000. Neural correlates of imaginal aggressive behavior assessed by positron emission tomography in healthy subjects. *Am. J. Psychiatry* 157, 1772–1781.
- Pineda, J.A., Hecht, E., 2009. Mirroring and mu rhythm involvement in social cognition: are there dissociable subcomponents of theory of mind. *Biol. Psychol.* 80, 306–314.
- Pobric, G., Hamilton, A.F., de, C., 2006. Action understanding requires the left inferior frontal cortex. *Curr. Biol.* 16, 524–529.
- Porges, S.W., 2003. Social engagement and attachment: a phylogenetic perspective. *Ann. N. Y. Acad. Sci.* 1008, 31–47.
- Preston, A.R., Thomason, M.E., Ochsner, K.N., Cooper, J.C., Glover, G.H., 2004. Comparison of spiral-in/out and spiral-out BOLD fMRI at 1.5 and 3 T. *NeuroImage* 21, 301–391.
- Price, D.D., 2000. Psychological and neural mechanisms of the affective dimension of pain. *Science* 288, 1769–1772.
- Puce, A., Perrett, D., 2003. Electrophysiology and brain imaging of biological motion. *Phil. Trans. R. Soc. Lond. B.* 358, 435–445.
- Rainville, P., 2002. Brain mechanisms of pain affect and pain modulation. *Curr. Opin. Neurobiol.* 12, 195–204.
- Ruby, P., Decety, J., 2001. Effect of the subjective perspective taking during simulation of action: a PET investigation of agency. *Nat. Neurosci.* 4, 546–550.
- Saarela, M.V., Hlushchuk, Y., Williams, A.C. de C., Schürmann, M., Kalso, E., Hari, R., 2007. The compassionate brain: human detect intensity of pain from another's face. *Cereb. Cortex* 17, 230–237.
- Saxe, R., Xiao, D.-K., Kovacs, G., Perrett, D.I., Kanwisher, N., 2004. A region of right posterior superior temporal sulcus responds to observed intentional actions. *Neuropsychologia* 42, 1435–1446.
- Singer, T., Seymour, B., O'Doherty, J., Kaube, H., Dolan, R.J., Frith, C.D., 2004. Empathy for pain involves the affective but not sensory components of pain. *Science* 303, 1157–1162.
- Singer, T., Seymour, B., O'Doherty, J.P., Stephan, K.E., Dolan, R.J., Frith, C.D., 2006. Empathic neural responses are modulated by the perceived fairness of others. *Nature* 439, 466–469.
- Sokol, B.W., Chandler, M.J., Jones, C., 2004. From mechanical to autonomous agency: the relationship between children's moral judgments and their developing theories of mind. *New Dir. Child and Adolesc. Dev.* 103, 19–36.
- Sommerville, J.A., Decety, J., 2006. Weaving the fabric of social interaction: articulating developmental psychology and cognitive neuroscience in the domain of motor cognition. *Psychon. Bull. Rev.* 13, 179–200.
- Uddin, L.Q., Iacoboni, M., Lange, C., Keenan, J.P., 2007. The self and social cognition: the role of cortical midline structures and mirror neurons. *Trends Cogn. Sci.* 11, 153–157.
- Vaina, L.M., Solomon, J., Chowdhury, S., Sinha, P., Belliveau, J.W., 2001. Functional neuroanatomy of biological motion perception in humans. *Proc. Natl. Acad. Sci.* 98, 11656–11661.
- Van Essen, D.C., Dickson, J., Harwell, J., Hanlon, D., Anderson, C.H., Drury, H.A., 2001. An integrated software system for surface-based analyses of cerebral cortex. *J. Am. Med. Inform. Assoc.* 41, 1359–1378.
- Vollm, B.A., Taylor, A.N.W., Richardson, P., Rhiannon, C., Stirling, J., McKie, S., Deakin, J.F.W., Elliott, R., 2006. Neuronal correlates of theory of mind and empathy: a

- functional magnetic resonance imaging study in a nonverbal task. *NeuroImage* 29, 90–98.
- Walter, H., Adenzato, M., Ciaramidaro, A., Enrici, I., Pia, L., Bara, B.G., 2004. Understanding intentions in social interaction: the role of the anterior paracingulate cortex. *J. Cogn. Neurosci.* 16, 1854–1863.
- Walter, H., Abler, B., Ciaramidaro, A., Erk, S., 2005. Motivating forces of human actions. Neuroimaging reward and social interaction. *Brain Res. Bull.* 67, 368–381.
- Williams, A.C., 2002. Facial expression of pain: an evolutionary account. *Behav. Brain Sci.* 25, 439–488.
- Winston, J.S., Strange, B.A., O'Doherty, J., Dolan, R.J., 2002. Automatic and intentional brain responses during evaluation of trustworthiness of faces. *Nat. Neurosci.* 5, 277–283.
- Wunsch, A., Philippot, P., Plaghki, L., 2003. Affective associative learning modifies the sensory perception of nociceptive stimuli without participant's awareness. *Pain* 102, 27–38.
- Young, L., Koenigs, M., 2007. Investigating emotion in moral cognition: a review of evidence from functional neuroimaging and neuropsychology. *Br. Med. Bull.* 84, 69–79.
- Zaki, J., Ochsner, K.N., Hanelin, J., Wager, T.D., Mackey, S.C., 2007. Different circuits for different pain: patterns of functional connectivity reveal distinct networks for processing pain in self and others. *Soc. Neurosci.* 2, 276–291.