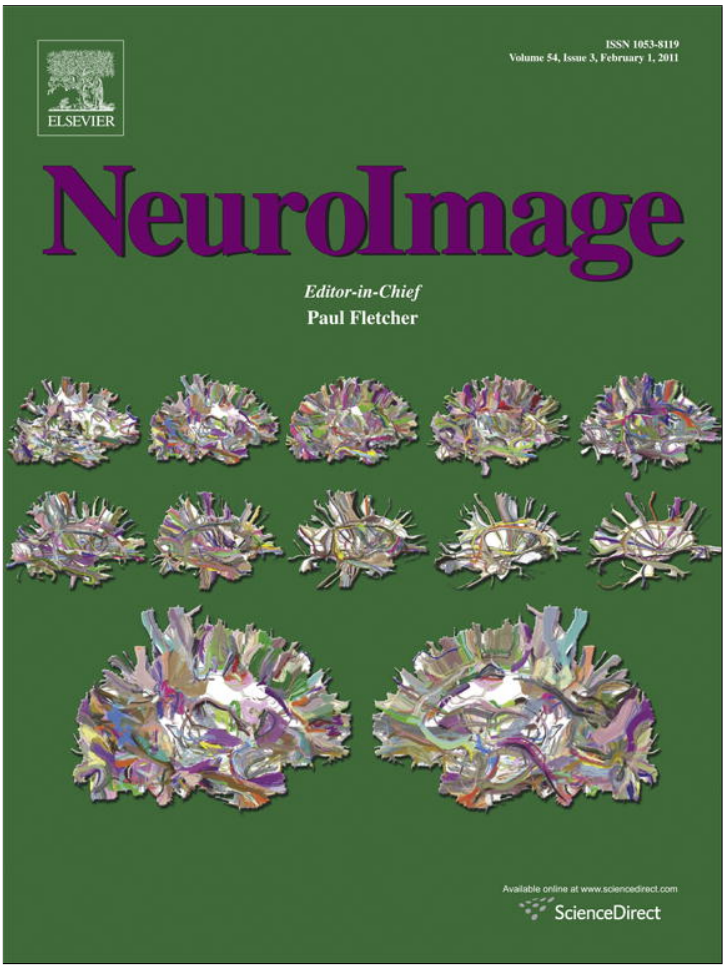

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Meta-analytic evidence for common and distinct neural networks associated with directly experienced pain and empathy for pain

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ABSTRACT

A growing body of evidence suggests that empathy for pain is underpinned by neural structures that are also involved in the direct experience of pain. In order to assess the consistency of this finding, an image-based meta-analysis of nine independent functional magnetic resonance imaging (fMRI) investigations and a coordinate-based meta-analysis of 32 studies that had investigated empathy for pain using fMRI were conducted. The results indicate that a core network consisting of bilateral anterior insular cortex and medial/anterior cingulate cortex is associated with empathy for pain. Activation in these areas overlaps with activation during directly experienced pain, and we link their involvement to representing global feeling states and the guidance of adaptive behavior for both self- and other-related experiences. Moreover, the image-based analysis demonstrates that depending on the type of experimental paradigm this core network was co-activated with distinct brain regions: While viewing pictures of body parts in painful situations recruited areas underpinning action understanding (inferior parietal/ventral premotor cortices) to a stronger extent, eliciting empathy by means of abstract visual information about the other's affective state more strongly engaged areas associated with inferring and representing mental states of self and other (precuneus, ventral medial prefrontal cortex, superior temporal cortex, and temporo-parietal junction). In addition, only the picture-based paradigms activated somatosensory areas, indicating that previous discrepancies concerning somatosensory activity during empathy for pain might have resulted from differences in experimental paradigms. We conclude that social neuroscience paradigms provide reliable and accurate insights into complex social phenomena such as empathy and that meta-analyses of previous studies are a valuable tool in this endeavor.

Introduction

In recent years considerable efforts have been made to unveil the neural mechanisms of human empathy. The majority of studies used functional magnetic resonance imaging (fMRI) and experimental paradigms in which participants were exposed to stimuli depicting or indicating that other people were in pain. The main insight derived from this research is that empathy for pain activates neural structures that are also involved in the direct experience of pain—such as the anterior insula and the medial/anterior cingulate cortex (Decety, 2010; Singer and Lamm, 2009, for recent reviews). This observation has been taken as evidence that "shared representations" between self and other lie at the core of the phenomena of empathy and affective sharing (see also Bastiaansen et al., 2009; Heberlein and Atkinson, 2009). A major shortcoming of existing reviews of the empathy literature is that they only verbally summarize published reports and therefore do not allow quantitative conclusions about the involved neural networks. In addition, the fact that previous studies mainly used two rather distinct types of empathy paradigms has not been taken into account either. In one type of paradigm, visual displays depicting limbs of target persons in painful situations were shown to participants (henceforth referred to as *picture-based* paradigms). Sensory-motor processes, including motor mimicry, might have strongly contributed to the neural responses elicited by this type of paradigm. Note though that mimicry and emotional contagion, which may result from mimicry, entail emotional responses without awareness of their extra-personal source, whereas the full-blown experience of empathy is characterized by self-other-awareness and clarity about the vicarious nature of the experienced emotion. However, many models of empathy assume an important role of mimicry and emotional contagion and regard these two phenomena as interacting (see Singer and Lamm, 2009, for clarification of terms, and Decety and Lamm, 2006; Preston and de Waal, 2002). In the

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second type of empathy for pain paradigm (labeled *cue-based* henceforth), target persons were seated next to the participants lying in the MRI scanner to create ongoing interaction and optimize ecological validity. Abstract visual symbols (cues) of different colors indicated whether the target person or the participant him/herself would receive electrical stimulation and whether this stimulation would be painful or not. In contrast to the picture-based paradigm this type of paradigm more extensively required top-down processing as neither explicit depictions of painful situations nor any sort of expression of pain was encountered by participants. These differences between paradigms are a valuable, but as of yet unexplored source of information in the quest for the neural mechanisms underpinning empathic responses. Detecting neural activation common to the two paradigms would unveil a neural network that is independent of the elicitation of empathy and therefore more specifically related to its core neural mechanisms. Moreover, the different types of paradigms allow investigating the repeatedly proposed existence of different neuro-functional pathways involved in empathic responses (de Vignemont and Singer, 2006; Decety and Jackson, 2004; Singer, 2006).

Using an image-based meta-analysis of nine fMRI studies of empathy for pain previously performed in our labs, we aimed to (1) identify common patterns of neural activation identified in those studies, and (2) to assess differences between activation patterns observed in picture-based and cue-based studies. Moreover, by investigating activation of somatosensory areas during the two paradigm types as well as during pain experienced in oneself, we addressed the controversy that some former results indicate the involvement of somatosensory and sensorimotor representations in empathy for pain, while others suggest that mainly the affective components of pain are shared between self and other (Singer and Lamm, 2009, for review). As it has been shown that image-based meta-analyses (IBMA) are more precise than coordinate-based analyses (Salimi-Khorshidi et al., 2009), our primary analyses were based on individual activation maps collected from nine different fMRI studies and a total of 168 participants (Bird et al., 2010; Hein et al., 2010; Jackson et al., 2005, 2006; Lamm et al., 2007, 2010; Singer et al., 2004, 2006, 2008). In order to assess the generalizability of these analyses, we also performed a coordinate-based meta-analysis of fMRI publications on empathy for pain identified via an exhaustive literature search.

Materials and methods

Image-based meta-analyses

Nine fMRI studies were included in the image-based meta-analyses: four picture-based studies, where empathy was elicited via the presentation of photographs displaying limbs in painful situations (e.g., a foot getting jammed in a door, or a hand undergoing a painful injection), and five cue-based studies, where electric pain stimuli were applied to either the dorsum of the hand of a target person sitting beside the MRI scanner (Other/Pain condition), or to the participant lying in the MRI scanner (Self/Pain condition). While the target person was present in the same room, the occurrence of a nociceptive stimulus could only be inferred from the color of a visual cue pointing either to one's own or the target person's hand. Neither movements of the hand, nor facial, vocal, or bodily expressions of pain could be observed. Note though that the picture-based paradigms did not contain any explicit displays of affect either (such as limb withdrawal or other protective responses such as muscle tightening), and that while only body parts were displayed, participants had been explicitly instructed as a means to induce empathy to imagine the pain of the persons whose limbs were seen. Table 1 provides a description of the nine studies, including the paradigm types, sample sizes, and the activation maps entering the meta-analyses (for details concerning the paradigms, see the original publications). MRI scans for all picture-based studies had been performed using a 3 Tesla Siemens Magnetom Allegra operated at the Lewis Center for Neuroimaging (University of Oregon, Eugene, OR, USA). Except for Jackson et al. (2005), event-related data analyses had been employed. Four of the five cue-based studies had been scanned on a 1.5 Tesla Siemens Magnetom Sonata, operated by the Wellcome Trust Centre for Neuroimaging, University College London, UK, and one cue-based study (Hein et al., 2010) was scanned on a 3 T Philips Achieva operated by The Institute for Biomedical Engineering, University and ETH Zurich, Switzerland. Event-related data analyses had been used in all of them. While the majority of participants for the picture-based studies had been recruited from an undergraduate student population, the cue-based studies included a larger proportion of subjects from local urban communities.

In total 168 contrast images ("activation maps"), all from different participants, were included in the image-based meta-analyses (picture-based: $N = 74$, 38 from female participants; cue-based: $N = 94$, 34 female). The mean age of the whole sample was 25.75 years, ranging from 18 to 63 years (only one participant was older than 41 years). Participants of the picture-based studies were significantly younger, reflecting the larger undergraduate student population investigated in these studies (M(picture-based) = 23.97; M(cue-based) = 27.15; $F(1,164) = 13.358$, $P < 0.001$). However, exploratory analyses of the whole sample indicated that age had no significant effects on brain activation.

Contrast images resulted from first-level general-linear-model based analyses of spatially preprocessed MRI images (correction for head movement, normalization to standard stereotactic space using the EPI template provided in SPM, spatial smoothing using a Gaussian kernel). Since the images differed in voxel resolution (2 mm or 3 mm) and spatial smoothing (6 to 10 mm FWHM), they were re-sliced to an isotropic voxel resolution of 3 mm, and if necessary subjected to 2nd-level smoothing yielding a uniform spatial smoothness of 10 mm FWHM for all images (Gaussian kernel). The original analyses had been performed using either SPM2 or SPM5, and analyses for the present paper were performed using SPM8 (Wellcome Trust Center for Neuroimaging; http://www.fil.ion.ucl.ac.uk/spm/).

The first-level contrast images were Other/Pain > Fixation, i.e., trials in which signal changes during witnessing another person's painful state (either cue-based or picture-based) were stronger than during a low-level visual baseline (fixation of a white cross on black background), and Other/No Pain > Fixation, i.e., activation during trials in which the target's affective state was non-painful. For the cue-based studies, we also analyzed the contrasts Self/Pain > Fixation and Self/No Pain > Fixation, i.e., trials in which the participant him/herself received painful or non-painful electric stimulation.

Contrast images were entered into a 2nd-level random effects ANOVA model implemented in SPM8. Using this ANOVA model, we calculated random effects contrasts for the cue-based and picture-based studies (i.e., Other/Pain > Other/No Pain: Cue-based and Other/Pain > Other/No Pain: Picture-based). Based on these contrasts, we assessed areas that were consistently or differentially activated by the two types of paradigms. *Consistent activation* was identified by performing a *conjunction* of the two contrasts (i.e., (Other/Pain > Other/No Pain: Cue-based) ∩ (Other/Pain > Other/No Pain: Picture-based); all conjunction hypotheses according to Nichols et al., 2005). Note that we preferred the more conservative conjunction analysis over calculating mean activation across all individual first-level contrast images as the latter might have been driven by strong activations in individual studies alone. *Activation differences* between the two types of paradigm were assessed by *difference contrasts*, i.e., (Other/Pain > Other/No Pain: Cue-based) > (Other/Pain > Other/No Pain: Picture-based), and vice versa. In order to compare empathy-related responses with the direct experience of pain, cue-based activation common to self pain and empathy for pain conditions was identified using a conjunction analysis (Self/Pain > Self/No Pain ∩ Other/Pain > Other/No Pain), and activation differences were

Table 1
The nine studies included in the image-based meta-analyses.

Study	Type	Conditions/Stimuli	Contrast	*N* (females)
1. Jackson et al., Neuroimage 2005	picture-based	Pictures of right hands/feet in painful vs. non-painful situations	Empathy for Pain>Fixation Empathy for No Pain>Fixation Average of trials showing hands and feet	15 (7)
2. Jackson et al., Neuropsychologia 2006	picture-based	Pictures of right hands/feet in painful vs. non-painful situations	Empathy for Pain>Fixation Empathy for No Pain>Fixation Average of "imagine self" and "imagine other" trials	18 (10)
3. Lamm et al., PLoS One 2007	picture-based	Pictures of needle injections into left hand vs. needle placed next to hand	Empathy for Pain>Fixation Empathy for No Pain>Fixation Only trials rated for intensity of pain, experiment I	18 (9)
4. Lamm et al., J Cogn Neurosci 2010	picture-based	Pictures of needle injections into left hand vs. hand touched by a Q-tip	Empathy for Pain>Fixation Empathy for No Pain>Fixation Only trials with "similar" target	23 (12)
5. Singer et al., Science 2004	cue-based	Painful and non-painful electric stimulation of self and other (right hand)	Pain>Fixation: Empathy, Self No Pain>Fixation: Empathy, Self	16 (16)
6. Singer et al., Nature 2006	cue-based	Painful and non-painful electric stimulation of self and other (right or left hand)	Pain>Fixation: Empathy, Self No Pain>Fixation: Empathy, Self Empathy: only trials with fair player	31 (15)
7. Singer et al., Emotion 2008	cue-based	Painful and non-painful electric stimulation of self and other (left hand)	Pain>Fixation: Empathy, Self No Pain>Fixation: Empathy, Self Only blocks after placebo administration	19 (0)
8. Bird et al., Brain 2010	cue-based	Painful and non-painful electric stimulation of self and other (left hand)	Pain>Fixation: Empathy, Self No Pain>Fixation: Empathy, Self Only healthy controls	12 (3)
9. Hein et al., Neuron 2010	cue-based	Painful and non-painful electric stimulation of self and other (right or left hand)	Pain>Fixation: Empathy, Self No Pain>Fixation: Empathy, Self Empathy: only trials with ingroup target	16 (0)

assessed using difference contrasts (Pain>No Pain: Self>Other, or Pain>No Pain: Other>Self). For the latter two analyses, a separate ANOVA model had been set up which only included contrasts from the cue-based studies (given there were no self pain conditions in the picture-based studies).

Gender differences were assessed by adding the between-subjects factor gender to the ANOVA models. SPMs were thresholded using $P = 0.05$, corrected for multiple comparisons at cluster-level using the Gaussian Random Fields approach (family-wise error correction FWE, cluster-defining threshold $P = 0.0001$, cluster size threshold (number of voxels k) = 50; note that no cluster-defining extent threshold is applicable for conjunction analyses). Potential violations of the sphericity assumption were accounted for by using restricted maximum likelihood estimation, as implemented in SPM8. Anatomical and cytoarchitectonic labeling of clusters were based on a combination of the Anatomy Toolbox (version 1.6, Eickhoff et al., 2005) and an anatomical atlas (Duvernoy, 1991).

In addition to whole-brain analyses, region of interest (ROI) analyses were performed to assess somatosensory responses in contralateral primary and secondary somatosensory cortex (S1 and S2) during the direct experience of pain, and during empathy for pain. ROIs were delineated in MNI space by a conjunction of voxels related to hand somatosensation (Eickhoff et al., 2008) with cytoarchitectonically defined areas known to be specifically related to nociception (Area 3 in S1, and posterior insula in S2; Craig, 2003b). Average beta estimates of all voxels in these ROIs were analyzed using repeated measures ANOVAs or paired *t*-tests, when testing for differences between Other/Pain vs. Other/No Pain, and one-sample *t*-tests, when testing whether activation of a particular condition was different from zero (all implemented in SPSS v. 16.0.1, SPSS Inc., Chicago, IL, USA).

Coordinate-based meta-analyses

In addition to the image-based meta-analyses, we performed a coordinate-based meta-analysis using the Activation Likelihood Estimation (ALE) approach (Eickhoff et al., 2009; Laird et al., 2009). Studies entering this analysis had investigated empathy for pain using fMRI, and were identified by a query of the PubMed database (http://www.pubmed.gov) with the search terms ("magnetic resonance imaging" OR "fMRI") AND ("empathy" OR "empathetic" OR "empathic"), performed on July 10 2010. In addition to this query, we used the list of references of the identified papers and the "related articles" function of the PubMed database to identify further relevant publications. In order to allow direct comparability between the image-based and coordinate-based analyses, only results specifically related to empathy for physical pain were included. Additional exclusion criteria were studies that did not report results in a coordinate-based format, papers reporting results already reported in another paper, studies investigating special populations such as children or clinical populations that were not comparable to the healthy controls investigated in the image-based meta-analysis (however, if a study had investigated special populations and separately reported results for healthy controls, results for the latter were included), or studies that did not report results separately for empathy for physical pain against baseline, in humans. An example of the latter case is the paper by Filippi et al. which only reports activation differences between seeing humans and animals in pain (Filippi et al., 2010), but no direct comparison with a neutral or no pain baseline. The resulting 32 papers contained a total of 617 foci for contrasts being equivalent to either Other/Pain>Other/No Pain, or Other/Pain>Baseline (usually fixation; see Appendix A). These foci were analyzed using the latest version of the GingerALE software (version 2.0.1, http://www.brainmap.org/ale/), which uses random-effects inference and an algorithm taking into account the sample size of each contrast (Eickhoff et al., 2009). The resulting ALE maps were thresholded at $P = 0.05$ (minimum volume criterion = 400 m^3, corresponding to 50 voxels at a resolution of 8 mm^3), corrected for multiple comparisons using the False Discovery Rate approach. All analyses were performed in MNI space, with coordinates reported in Talairach space having been converted to MNI space using the "Talairach to SPM" conversion function implemented in GingerALE.

Results

Common activation related to empathy for pain: image-based and coordinate-based analyses

The conjunction analysis testing for brain responses common to both types of paradigms (Other/Pain>Other/No Pain: Cue-based ∩ Picture-

Table 2
Significant clusters of the conjunctions Other/Pain>Other/No Pain: Cue-based ∩ Other/Pain>Other/No Pain: Picture-based, and Self/Pain>Self/No Pain ∩ Other/Pain>Other/No Pain (Cue-based). Coordinates and *z*-values pertain to peak coordinates of identified clusters, thresholded at $P=0.05$ (cluster-size correction for multiple comparison, cluster-defining threshold $P=0.0001$; $^*P=0.055$).

Cluster size	*z*-value	*x*	*y*	*z*	Anatomical areas
Cue-based ∩ Picture-based					
165	5.42	−45	15	0	Anterior insula, extending to inferior frontal gyrus (pars opercularis)
50	5.10	6	18	30	Medial/anterior cingulate cortex
32	4.85	−9	−24	3	Thalamus, extending to dorsal midbrain
145	4.77	24	18	6	Putamen/anterior insula, extending to inferior frontal gyrus (pars opercularis and pars triangularis)
Self/Pain>Self/No Pain ∩ Other/Pain>Other/No Pain (Cue-based)					
118	5.12	6	18	30	Medial/anterior cingulate cortex
66	4.98	−45	15	−6	Anterior Insula, extending to inferior frontal gyrus (pars orbitalis)
39	4.15	9	−45	54	Precuneus/paracentral lobule
21*	4.40	−33	3	−18	Anterior insula (ventral)
21*	4.20	39	12	15	Anterior insula (dorsal)

based) revealed significant clusters in a cortical region at the border of anterior medial cingulate cortex and posterior anterior cingulate cortex (aMCC/pACC; classified and labeled based on Vogt, 2005), in bilateral AI/fronto-insular cortex (AI and adjacent inferior frontal gyrus/ventral frontal operculum, cytoarchitectonic Area 44 in the left and Areas 44 and 45 in the right hemisphere), and in the left thalamus (Table 2; Fig. 1).

The coordinate-based analysis yielded comparable results as the image-based meta-analysis, in particular with respect to activation in aMCC/pACC, and bilateral anterior insular cortex (Table 3, Fig. 2), where clusters identified by both analyses were highly similar both with respect to location and extent. Additional clusters were revealed in the middle insular cortex, in the amygdala, as well as in supramarginal gyrus, pre- and postcentral gyrus, pars opercularis of inferior frontal gyrus, and dorsal premotor cortex. However, when taking into account how many out of the 32 studies contributed to a significant cluster according to the activation likelihood estimation algorithm, only aMCC, and bilateral AI were consistently activated across studies (see discussion, and Table 3). Note also that a separate coordinate-based analysis without the coordinates of the nine studies included in the image-based meta-analysis revealed virtually the same clusters.

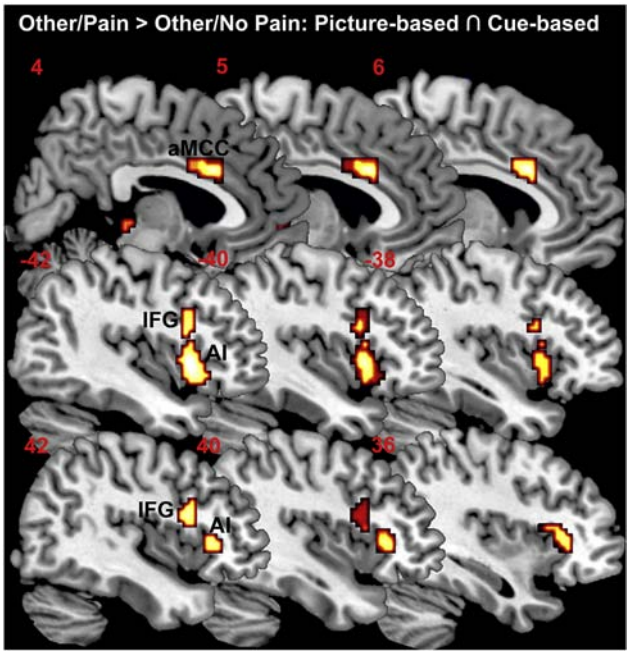

Fig. 1. Common activation (conjunction) for the picture-based and cue-based paradigms. Shown are clusters in anterior medial cingulate cortex (aMCC), anterior insular cortex (AI), and inferior frontal gyrus (IFG). Activation is displayed on a high-resolution structural MRI scan in MNI stereotactic space (neurological orientation, red labels: MNI coordinates, negative values = left hemisphere, threshold $P=0.05$, FWE-corrected on cluster-level, $P=0.0001$ voxel selection threshold).

Distinct activation for the two types of paradigms

The contrast Other/Pain>Other/No Pain: Picture-based>Cue-based showed that activation in the picture-based studies was higher in bilateral inferior parietal cortex (IPC, supramarginal gyrus and intraparietal sulcus, extending into postcentral gyrus/primary somatosensory cortex), bilateral inferior frontal gyrus (IFG, pars opercularis; Area 44), dorsal medial prefrontal cortex (encompassing pre-supplementary motor area, cingulate motor area, dorsal lateral pre-motor areas/frontal eye fields), bilateral dorso-lateral prefrontal cortex, and AI (Fig. 3, Table 4). In AI, clusters during both paradigms were very similar in the left hemisphere, whereas in the right hemisphere stronger activation during the picture-based studies was predominantly observed in ventral parts of AI.

The reverse comparison (Other/Pain>Other/No Pain: Cue-based>Picture-based) indicated stronger responses in posterior and frontal "midline structures" as well as in bilateral medial and superior temporal cortex for the cue-based studies. Activation in posterior medial cortex encompassed large parts of an anatomical area labeled as "posteriomedial cortex" (Parvizi et al., 2006), which includes the precuneus, dorsal posterior cingulate cortex, and adjacent medial superior parietal

Table 3
Significant clusters of the coordinate-based meta-analysis of 32 studies (thresholded at $P=0.05$, corrected for multiple comparisons using false discovery rate; x/y/z = MNI coordinates). Count = number of studies contributing to the cluster.

x	*y*	*z*	Anatomical areas	Count
−2	23	40	Medial cingulate cortex	28
−40	22	0	Anterior insula/fronto-insular cortex	24
39	23	−4	Anterior insula/fronto-insular cortex	20
59	−25	38	Inferior parietal cortex, supramarginal gyrus	10
−57	−25	38	Inferior parietal cortex, supramarginal gyrus	11
15	−2	6	Globus pallidus	9
52	−64	−11	Inferior temporal gyrus	6
−47	−67	−8	Inferior occipital gyrus	7
−39	−46	56	Left postcentral gyrus	4
−18	3	3	Globus pallidus	5
−1	−26	−11	Periaqueductal gray	4
−21	−9	−15	Amygdala	2
−37	−2	60	Precentral gyrus/dorso-lateral premotor cortex	4
42	−7	−7	Mid-insular cortex	4
60	14	24	Inferior frontal gyrus, pars opercularis	3
36	13	−18	Anterior insular cortex/temporal pole	3
−10	−12	3	Thalamus	4
23	−3	−17	Amygdala	2
48	8	36	Precentral gyrus/lateral premotor cortex	3

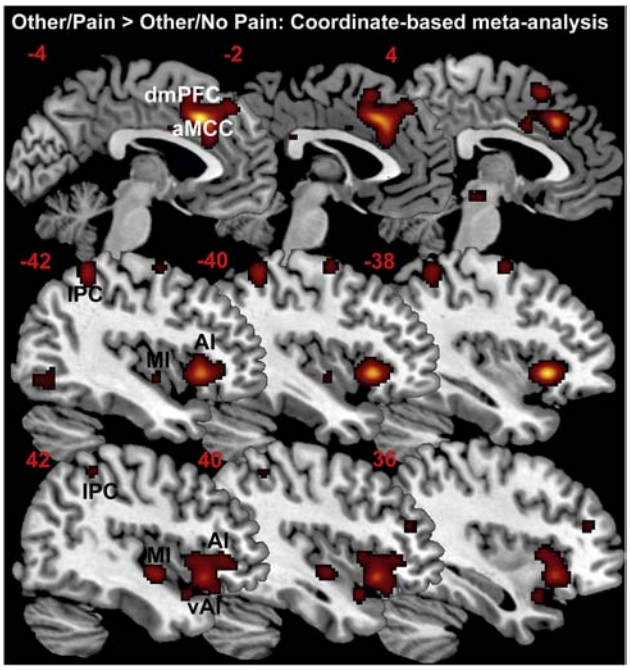

Fig. 2. Significant clusters from the coordinate-based meta-analysis, in dorso-medial prefrontal cortex (dmPFC), aMCC, inferior parietal cortex (IPC), AI, and middle anterior insula (MI; threshold $P = 0.05$, FDR-corrected, other specifications as in Fig. 1).

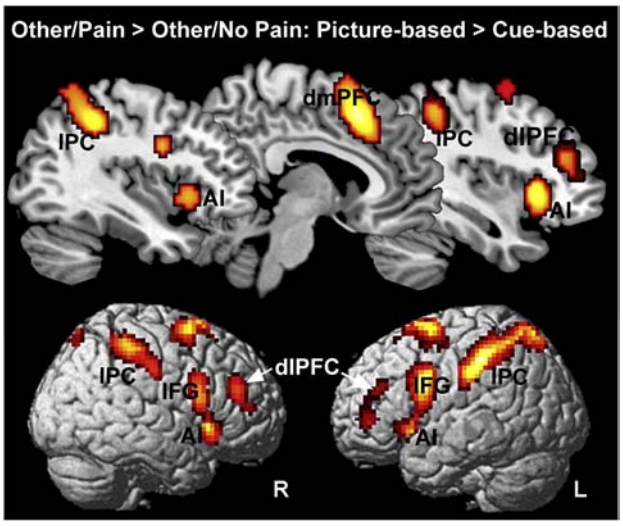

Fig. 3. Higher activation during picture-based than during cue-based studies, in IPC, dmPFC, dorso-lateral Prefrontal Cortex (dlPFC), IFG, and AI. Surface renderings (lower part) are maximum-intensity projections generated using SPM8 (threshold: $P = 0.05$, FWE corrected on cluster-level, $P = 0.00001$ voxel selection threshold for display purposes; R/L = right/left hemisphere, other specifications as in Fig. 1).

cortex. Additionally, this cluster included occipital cortex (bilateral cuneus, left lingual gyrus). In the medial frontal cortex, activation encompassed ventral medial prefrontal cortex, including medial orbitofrontal cortex and an area that has been referred to as paracingulate cortex (Gallagher and Frith, 2003). The bilateral clusters in middle/superior temporal cortex extended from the posterior aspects of superior temporal gyrus/sulcus to anterior temporal cortex and the temporal poles (Fig. 4, Table 4). The posterior parts of this cluster bilaterally included the temporo-parietal junction. Notably, the significant clusters of this contrast resulted from a pattern of activation and deactivation where Other/Pain: Cue-based was the only contrast showing activation compared to the fixation baseline, while all other contrasts showed deactivations (Supplementary Fig. 1).

Direct experience of pain compared to seeing others in pain: shared and distinct activations

A central aim of our study was to assess the overlap of activation between being in pain oneself and seeing another person in pain. The conjunction between the contrasts Self/Pain>Self/No Pain and Other/Pain>Other/No Pain (both from the cue-based studies only) revealed significant clusters in aMCC/pACC, in left fronto-insular cortex, and in the precuneus (Table 2, Fig. 5). In addition, activation slightly above ($P_{FWE} = 0.055$) the chosen threshold was detected in left ventral AI and right dorsal fronto-insular cortex.

Based on this finding, exploring activation at a slightly lower cluster-selection threshold ($P = 0.0005$, $k = 50$) revealed activation of larger extent in clusters already detected at the higher threshold, and additional clusters in left AI (ventral), right AI (dorsal and ventral), and thalamus. Assessing differences between the direct experience of pain and empathy for pain (Pain>No Pain: Self>Other) did not reveal significant clusters at the chosen cluster-defining threshold. Lowering this value to $P = 0.0005$, $k = 50$, resulted in a number of large significant clusters in anterior and posterior medial cingulate cortex (dorsally extending into supplementary motor area and dmPFC), in primary and secondary somatosensory cortices, anterior thalamus, putamen, and the head of the caudate nucleus. The reverse contrast testing for stronger activation in the Other/Pain compared to the Self/Pain condition showed a significant cluster in left inferior frontal gyrus (central pars opercularis of inferior frontal gyrus, Area 44).

ROI analyses of somatosensory activation

Activation in somatosensory ROIs during self- and other-related conditions was statistically assessed using repeated measures ANOVAs with factors Target (Self, Other), Stimulus (Pain, No Pain), and Hemisphere (Left, Right). This analysis was restricted to those participants whose pain electrode had been placed on the same side as in the target person (i.e., all 16 participants from Singer et al., 2004, and 15 participants from Singer et al., 2006 who had received right-hand stimulation and observed targets with electrodes placed on the right hand as well). The results show a distinct response in contralateral left S1 during the direct experience of pain, and activation levels close to zero during the two other-related conditions and during non-painful stimulation of the self (Fig. 6; interaction Stimulus × Target × Hemisphere, $F(1,30) = 6.668$, $P = 0.015$, partial $\eta^2 = 0.182$; in addition, significant lower-order effects were observed for Hemisphere, $F(1,30) = 10.640$, $P = 0.003$, partial $\eta^2 = 0.262$; Hemisphere x Target, $F(1,30) = 11.863$, $P = 0.002$, partial $\eta^2 = 0.283$; Hemisphere x Pain, $F(1,30) = 5.349$, $P = 0.028$, partial $\eta^2 = 0.151$; note also that none of the conditions except Self/Pain in contralateral S1 significantly differed from zero, $P = 0.005$, all other Ps>0.055). A similar pattern was obtained for S2. As in S1, none of the other-related conditions evoked significant activation, and the only difference to S1 was that activation during Self/Pain was significantly higher than during Self/No Pain also in the ipsilateral hemisphere (Target x Pain: $F(1,30) = 3.017$, $P = 0.093$, partial $\eta^2 = 0.091$; Hemisphere × Pain: $F(1,30) = 7.005$, $P = 0.013$, partial $\eta^2 = 0.189$; Pain: $F(1,30) = 12.607$, $P = 0.001$, partial $\eta^2 = 0.296$; Target: $F(1,30) = 21.191$, $P < 0.001$, partial $\eta^2 = 0.414$; Hemisphere: $F(1,30) = 6.848$, $P = 0.014$, partial $\eta^2 = 0.186$). In addition, comparing activation during Other/Pain and Other/No Pain, in S1 or S2 and for each hemisphere separately, revealed no significant results (Ps>0.466), except for right S2 ($P = 0.034$).

For the picture-based studies, the 41 contrast images from Lamm et al. (2007, 2010; i.e., the two studies in which participants had seen pictures of left hands) were analyzed using repeated measures ANOVAs with factors Hemisphere and Pain (Fig. 6). For S1, this revealed significantly higher bilateral activation during Other/Pain than during Other/No Pain ($F(1,40) = 4.776$, $P = 0.035$, partial $\eta^2 = 0.107$). Interestingly, activation was generally stronger in the left hemisphere, i.e., ipsilateral to the hand

Table 4
Activation differences between the two paradigm types (contrasts: Other/Pain>Other/No Pain: Picture-based>Cue-based, and Cue-based>Picture-based). Coordinates and z-values pertain to peak coordinates of identified clusters, thresholded at $P=0.05$ (cluster-size correction for multiple comparison, cluster-defining threshold $P=0.0001$, cluster size $k=50$).

Cluster size	z-value	x	y	z	Anatomical areas
Picture-based>Cue-based					
1571	>8	6	18	48	Medial: pre-supplementary motor area, dorso-medial prefrontal cortex, anterior medial cingulate cortex Lateral: lateral premotor areas/frontal eye fields
659	>8	−57	9	30	Inferior frontal gyrus (pars opercularis)
1059	>8	−63	−24	39	Inferior parietal cortex, postcentral gyrus
476	>8	33	21	0	Anterior insula, extending to inferior frontal gyrus (pars opercularis)
486	6.79	48	−36	51	Inferior parietal cortex, postcentral gyrus
185	6.37	42	39	24	Dorsolateral prefrontal cortex
222	5.56	−51	39	24	Dorsolateral prefrontal cortex
114	5.2	−18	3	3	Pallidum/caudate/thalamus
90	5.15	15	6	0	Pallidum/caudate/putamen/thalamus
113	5.08	15	−75	60	Superior parietal lobule
69	4.78	−57	−72	−6	Inferior occipital cortex
Cue-based>Picture-based					
3759	>8	−3	−51	42	Precuneus, extending to posterior cingulate cortex, superior parietal lobe, cuneus
2191	7.59	63	−60	21	Middle/superior temporal cortex (posterior and anterior)
1939	6.92	−51	−63	24	Middle/superior temporal cortex (posterior and anterior)
831	6.64	6	42	−9	Medial ventral prefrontal cortex, medial orbitofrontal cortex
97	4.98	−27	−12	−24	Hippocampus
86	4.39	−24	−27	75	Post/precentral gyrus

shown on the pictures (Hemisphere: $F(1,40)=41.470$, $P<0.001$, partial $\eta^2=0.509$). However, the difference in activation levels was not modulated by hemisphere (interaction Pain x Hemisphere: $P=0.194$). For S2, we observed a significant interaction Pain×Hemisphere ($F(1,40)=10.230$, $P=0.003$, partial $\eta^2=0.204$), and a main effect of Hemisphere ($F(1,40)=19.234$, $P<0.001$, partial $\eta^2=0.325$), reflecting a difference between pain conditions in the right hemisphere only, while activation levels in the left hemisphere did not differ.

Gender differences

We did not find any evidence for gender-specific activation differences, in any of our analyses, not even when lowering the threshold to very liberal levels.

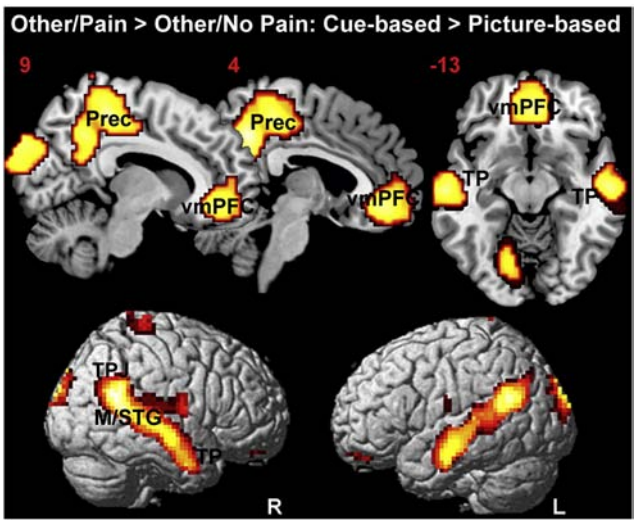

Fig. 4. Higher activation during cue-based than during picture-based studies (Precuneus (Prec), ventral medial Prefrontal Cortex (vmPFC), Medial and Superior Temporal Gyrus (M/STG), Temporo-Parietal Junction (TPJ), and Temporal Pole (TP), other specifications as in Fig. 3).

Discussion

The main objective of this study was to establish the existence of a core network underpinning neural responses to the pain of others. To this end, we performed an image-based meta-analysis using the original activation maps from 168 participants that had participated in nine different fMRI studies of empathy for pain. To corroborate the generalizability of the image-based results, we also performed a coordinate-based meta-analysis of 32 fMRI studies of empathy for pain. In addition to assessing shared activations for the direct and vicarious experience of pain, we compared two different types of paradigms typically employed in former studies of pain empathy: Picture-based paradigms using photographs of people's limbs in painful situations, and cue-based paradigms which did not involve any pain-related pictorial stimuli but involved target persons receiving painful stimulation while participants were scanned. Moreover, we addressed the debate whether empathizing with others in pain involves sharing only their affect, or also the somatosensory components of the painful experience.

A core neural network for pain empathy: AI and aMCC/pACC

Our results establish a crucial role of insular and medial/anterior cingulate cortex in empathy for pain: bilateral AI and aMCC/pACC were consistently activated across all nine studies during empathy for pain—irrespective of the way in which empathy had been induced. Activation in AI and aMCC has been repeatedly associated with the affective-motivational component of nociception (e.g., Peyron et al., 2000; Rainville, 2002). Their robust neural response when empathizing with the pain of others is in line with the shared representations account of understanding others, which proposes that neural circuits involved in the personal experience of an emotion underpin the understanding and sharing of the same emotion perceived in others (de Vignemont and Singer, 2006; Decety and Sommerville, 2003; Keysers and Gazzola, 2006). The overlap of empathy-related activation in AI and aMCC/pACC with activation triggered by painful stimulation of the self, in the same participants, provides the most explicit support for this account.

The coordinate-based meta-analysis provided further evidence that clusters in bilateral AI and aMCC are most consistently activated during empathy for pain. For example, 28 out of the 32 studies contributed to the cluster in aMCC, which in general showed a similar localization and

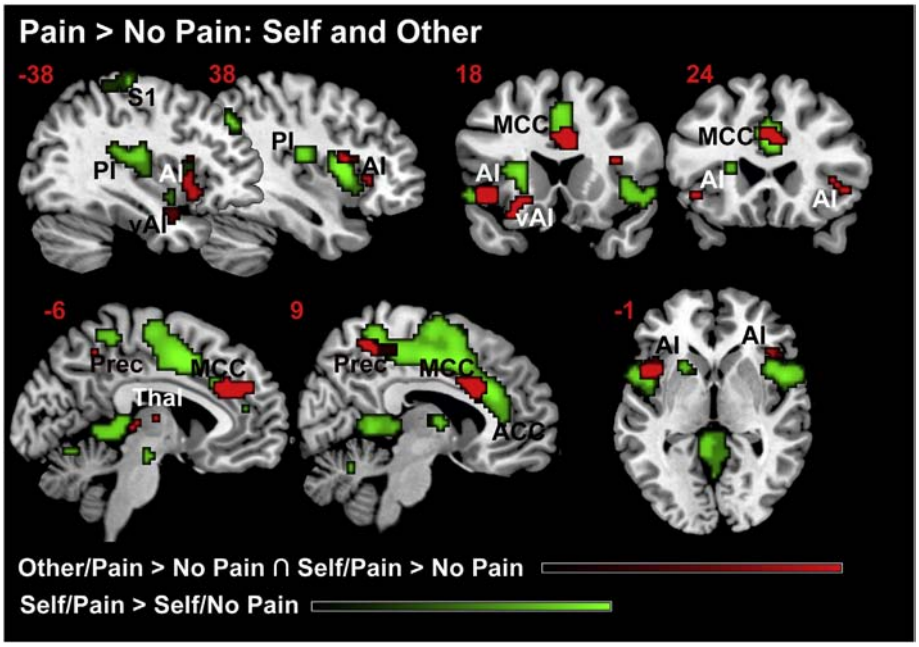

Fig. 5. Common and distinct activation when observing others in pain, and experiencing pain oneself. Areas of common activation include AI, MCC/ACC, Prec and Thalamus (conjunction of other- and self-related activations, color-coded in red, displayed at the voxel-wise conjunction threshold $P = 0.0001$, uncorrected); distinct activations for self-related responses only are observed in posterior insula (PI), primary somatosensory cortex (S1), and in large parts of medial and anterior cingulate cortex (MCC/ACC; color-coded in green, displayed at a threshold of $P(\mathrm{FWE}) = 0.01$, $k = 20$).

extent as the cluster identified by the image-based meta-analysis, with the exception that it dorsally extended more into dmPFC. These findings corroborate that the core network identified by the image-based meta-analysis can be generalized to studies not included in this analysis. Note also that the additional clusters of the coordinate-based meta-analysis resulted from smaller subsets of studies, and were mainly driven by studies that had used picture-based paradigms. The latter was particularly true for the clusters in left and right IPC, which supports the finding of the image-based meta-analysis that the picture-based studies are associated with higher activation in these areas.

The possible functions of AI and aMCC/pACC have recently received considerable attention. One influential view holds that AI and aMCC/pACC are part of a tightly connected neural network engaged in interoceptive awareness and meta-representations of global emotional moments (Craig, 2002, 2009). This idea has been extended by a conceptual framework suggesting that AI might be employed for current and prospective representations of both self- and other-related affective states, and that these representations play an important role in adaptive behavior, guiding decision making and homeostatic regulation (Singer et al., 2009, for review). The present results are in line with this proposal of insular function. Moreover, our results indicate both ventral and dorsal subdivisions of bilateral AI to be activated during empathy for pain. As previously suggested, these subdivisions might subserve different functions (Lamm and Singer, 2010, for review). While ventral

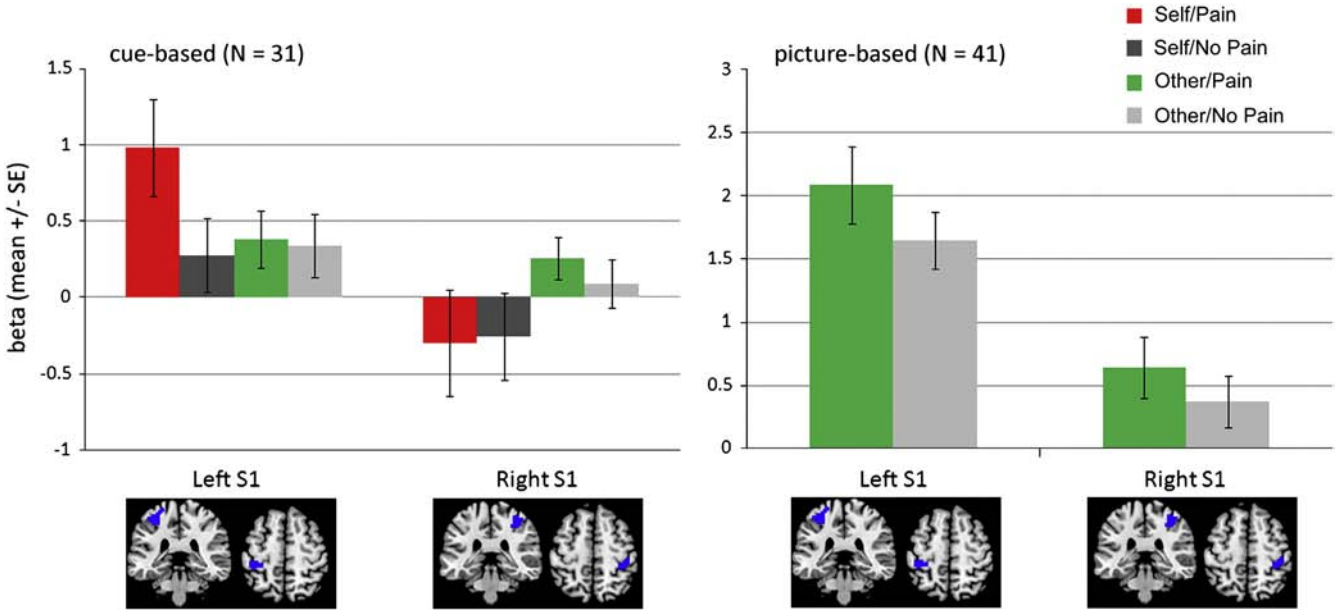

Fig. 6. Activation (average beta values) in left and right S1 and S2 during experiencing pain one self, or observing it in others. Only the Self/Pain condition in S1 (left-most red bar) as well as the other-related conditions of the picture-based studies (right panel) show significant somatosensory responses. Anatomical slices below panels display overlaid regions of interest (in blue) from which beta values were extracted (see text for details).

AI seems to be connected to areas such as the amygdala and medial orbitofrontal cortex, and therefore might play a more dominant role in processing valence and affective information, neurons in the dorsal subdivision of AI show stronger connections with areas related to motor processing and might therefore be more tightly related to motor control, as well as homeostatic regulation. Interestingly, the subdivision of aMCC revealed by our results has been explicitly related to viscero-motor functions in homeostatic regulation (Craig, 2003a). and it has been proposed that this part of the cingulate cortex may play a crucial role in preparing appropriate motor responses to painful and aversive events in general (Morrison and Downing, 2007). Notably, intracerebal recordings in medial cingulate cortex of humans indicate that there might be a special class of neurons that show increased firing both when receiving painful stimulation, and when observing it in someone else (Hutchison et al., 1999). The evidence for this is so far rather weak, though, as only one such neuron was detected in four patients.

Distinct neural networks engaged by the two paradigms

A number of recent models of empathy propose that our capacity to understand the affective and cognitive states of others is enabled by different mechanisms or "routes" (Decety and Hodges, 2006; Decety and Jackson, 2004; Singer, 2006). Our results support such models as they indicate the preferential recruitment of two separate neural networks by the two paradigms, in addition to the common core network of empathy. On the one hand, pictures of body parts in painful situations activated neural structures such as anterior inferior parietal cortex (supramarginal gyrus, intraparietal sulcus), and ventral premotor areas (inferior frontal gyrus, pars opercularis, Area 44). The joint activation of inferior parietal and inferior frontal cortex is a hallmark feature of studies on action observation (Van Overwalle and Baetens, 2009), and it has been suggested that action understanding is the core function of this cortical network (Rizzolatti et al., 2006). Note that recruitment of this network does not necessarily require visual stimuli or dynamic displays of action, as it has been demonstrated that hearing or reading action sentences (Aglioti and Pazzaglia, 2010, for review), and even the presentation of sequences of abstract nonbiological stimuli also activate inferior parietal and ventral premotor areas (Schubotz and von Cramon, 2004). Based upon the latter finding the prediction of external events has been proposed as the major computational mechanism supported by this network (Schubotz, 2007). In the present context, its recruitment might therefore relate to predicting and understanding the outcome of the shown situations, which in turn triggers inferences about their affective consequences. Such a mechanism might be particularly relevant when considering that participants were explicitly instructed to imagine the affective responses of the targets, based on pictures of body parts only. Our findings are also in line with recent evidence suggesting that motor simulation triggers empathic simulation in insular cortex when exposed to videos depicting emotional facial expressions (Jabbi and Keysers, 2008). However, motor simulation does not seem to take place on the level of primary motor representations, as no activation differences in primary motor cortex were observed in our study.

The cue-based studies, on the other hand, recruited areas associated with "Theory of Mind" or "mentalizing" to a stronger extent—such as the precuneus, ventral parts of medial prefrontal cortex, posterior superior temporal cortex, temporo-parietal junction, and the temporal poles (Gallagher and Frith, 2003; Van Overwalle and Baetens, 2009, for recent meta-analysis). Accumulating evidence links the same network not only to the attribution of intentions and beliefs to others, but also to self-referential thought ("default mode function"; Raichle et al., 2001; Laird et al., 2009; Schilbach et al., 2008, for recent meta-analyses). A similar network is also activated during episodic memory recall and reflecting about both one's own and others' future events (Buckner and Carroll, 2007, for review). Hence, it has been suggested that the core function of this network is to draw inferences on self- as well as other-related social information in the past, present, and future. This simulation enables sharing the other's state based upon one's own previous experiences and knowledge (Mitchell, 2009, for review), and it might be particularly important in situations in which externally provided sensory information about the other's mental state is lacking. Finally, it is important to note that the cue-based and picture-based paradigms also differ in the ecological validity of their experimental manipulations. The cue-based paradigms used "real people" that were present in the scanner room with participants who observed their painful stimulation while being scanned. The picture-based paradigms, on the other hand, employed photographs of past events and hence displayed pain whose negative consequences had already passed, and only showed body parts but not actual persons. This might explain why the cue-based paradigms recruited areas involved in mentalizing and reflecting about the actual state of another person to a stronger extent, including the right TPJ. Notably, computations in this area seem to be crucial for self/other distinction (Decety and Lamm, 2007), which has been identified as a prerequisite for empathic responses in many theoretical models of empathy.

Unique effects of the experience of pain

Our study has important implications for the debate whether only the affective or also the somatosensory components of pain are shared during empathy for pain (Avenanti et al., 2005; Bufalari et al., 2007; Singer and Frith, 2005). ROI analyses of primary and secondary somatosensory cortex activation suggest that seeing pictures of body parts in painful situations was accompanied by significant hemodynamic responses in both S1 and S2. Furthermore, while significant activation was also triggered by the non-painful situations, activation strength was higher during the painful situations. This suggests generalized somatosensory processing when exposed to pictures of body parts, which is additionally amplified by painful situations. This observation is in line with the fact that previous studies reporting specific sensorimotor resonance had exclusively used (static or dynamic) pictorial presentations of persons in pain (Avenanti et al., 2005, 2006; Bufalari et al., 2007; Cheng et al., 2008; Lamm et al., 2007, 2008, 2010).

Consistent with initial reports suggesting activation of the sensory-discriminative component of the pain-matrix only in the direct experience of pain in self (e.g., Singer et al., 2004), inferring the feelings of others based on abstract visual cues did not significantly recruit contralateral S1 and S2—even though strong activations were observed in contralateral S1 and bilateral S2 during the *direct* experience of pain. Taken together, this pattern of findings suggests that differences in the experimental instigation of empathy account for discrepant findings of former studies. Our results indicate that sensory components might only be involved when empathy is instigated by strong visual cues depicting situations involving explicit somatosensory manipulation of body parts. Note, though, that during the picture-based paradigm activation was observed bilaterally, that activation was higher in ipsilateral S1 and S2, and that both painful and non-painful stimuli were accompanied with significant activation. This speaks against a specific somato-sensory matching of the somatosensory and nociceptive components of both the painful and the non-painful experiences. Furthermore, a recent fMRI study showed that patients with congenital insensitivity to pain also displayed significant activation in bilateral primary somatosensory cortex when seeing pictures of others in pain (Danziger et al., 2009). Hence, we propose that somatosensory activation during empathy for pain paradigms reflects rather unspecific co-activation elicited by the display of body parts being touched rather than a specific matching of the other's somatosensory and nociceptive state (see also Keysers et al., 2010).

The image-based meta-analysis revealed that in addition to somatosensory areas, other areas were uniquely involved in the

experience of pain and not shared with activation during empathic experiences. Thus, despite the fact that a subset of voxels in AI and aMCC/pACC is jointly activated by the direct and empathic experience of pain, our results reveal more differences than similarities between these conditions (see also Jabbi et al., 2008; Zaki et al., 2007). There is clear evidence for a posterior-to-anterior gradient within insular cortex suggesting that only the direct experience of pain activates posterior subdivisions associated with sensory components of nociception, while anterior subdivisions related to affective representations and interoception are activated by both empathy and self-pain (Fig. 5). In a similar vein, while activation in cingulate cortex during empathy is restricted to subdivisions associated with affective-motivational functions, pain in the self activates a much larger portion of cingulate cortex, including areas explicitly related to action control. These differences are of particular importance for "simulationist" accounts of intersubjectivity. These accounts should not only consider similarities in neural activity between self and other, but also their differences (Gallese, 2003; Goldman, 2006), as they may be a crucial mechanism allowing us to distinguish between self-relevant and vicarious experiences.

Absence of gender differences

The lack of gender differences in our analyses was unexpected, in particular given recent neuroimaging findings documenting gender effects, with much lower sample sizes (Derntl et al., 2010; see also Singer et al., 2006, who found gender differences with specific task manipulations). The absence of effects in our study despite the large sample size cautions against underpowering future investigations of gender differences. Note though that our result is a "null finding" which only reveals that there were no consistent gender differences across all studies. Given the recent result of a lack of generalizability of gender differences even within the same sample (Ihnen et al., 2009), future studies will have to determine whether what we observed is a true null finding or whether previous evidence was based on false positives.

Scope of the present work

Given the selection criteria of the meta-analyses, our conclusions are restricted to empathy for physical pain. Another important question is whether the identified neural responses are predominantly related to empathy-related processes, or whether they result from unspecific and/or sensory-driven responses triggered by the presentation of the visual stimuli. While automatic bottom-up mechanisms are certainly relevant for vicarious emotional responses both in the current paradigms and in everyday life situations (Singer and Lamm, 2009, for review; see also Preston and de Waal, 2002), several arguments speak against interpreting them as the dominant cause of activation in aMCC and bilateral AI. First, the cue-based paradigms revealed activation in AI and aMCC. These responses could only have been triggered by the abstract visual cues indicating that another person would receive a painful shock, as no pictorial representations of pain or painful situations was used. Furthermore, for the picture-based paradigms, it has been repeatedly reported that responses in AI and aMCC emerge only when participants are actively attending to or imagining the affect of the targets, while responses in this network are absent when attention is focused on features of the stimuli not related to target affect (Gu and Han, 2007; Lamm et al., 2010). This speaks against the interpretation that responses observed when participants are instructed to empathize with the persons on the photographs are purely perceptually or bottom-up driven. Importantly, more than 50% of studies including subjective measures (questionnaires or affect ratings) report correlations with the core network of empathy. For instance, in about 60% of the cases state measures of empathy (either trial-by-trial affective ratings, or post-scan ratings related to the empathy conditions used during scanning) correlated significantly with activation in MCC and/or AI. Interestingly, state measures which might capture the responses to the experimental manipulations more directly seem to be more sensitive than trait measures of empathic concern (see Supplementary Table 1). In addition, the modulation of neural signals in aMCC and bilateral AI during empathy conditions as a function of factors such as the affective link between participants and target, perceived fairness, group membership, or contextual appraisal suggests that brain activation in the core network is sensitive to top-down influences. This reflects that valuation of the other and the situation he/she is in, rather than an unspecific arousal response to the presented stimuli, determines neural responses in aMCC and AI (reviewed in Hein and Singer, 2008; see also Valentini, 2010 for recent discussion). Furthermore, it has been shown that the ability to understand one's own emotions is linearly associated with activation intensity in AI observed during both introspection on one's own emotions, and during empathy for pain—speaking for a crucial role of this area in self- and other-related affective processing (Bird et al., 2010; Silani et al., 2008). Finally, and in line with the empathy-altruism hypothesis (Batson, 1991), recent evidence shows that individual differences in insular activation in a cue-based empathy paradigm predicts prosocial behavior (Hein et al., 2010). Taken together, these observations strongly suggest that activity in the core network of empathy, and in particular in bilateral AI, seems to be related to the processing of vicarious feelings.

Conclusions

The present work provides robust meta-analytic evidence that bilateral anterior insula and a region at the border of anterior medial cingulate cortex and posterior anterior cingulate cortex constitute a core network for pain empathy, and that this pattern holds true across studies performed in different countries, by different investigators on different MRI scanners, and using different types of paradigms. The consistency of activations across studies reveals that complex social phenomena such as empathy can be investigated with high reliability by social neuroscience paradigms. Moreover, the overlap of this empathic network with the neural network involved in the direct experience of pain further supports theoretical accounts which place shared neural representations at the root of our ability for intersubjectivity and understanding others. The present findings demonstrate that this core network can be recruited by two different pathways, one underlying the understanding of actions and the other the understanding of mental states. Which pathway will be predominantly recruited to elicit empathy depends on the type of information available for the elicitation of empathy (concrete vs. abstract), and how 'social' the situation is in which the subjects are placed. Similarly, our study also demonstrates that the type of information conveyed determines whether somatosensory representations will or will not be engaged. Finally, our findings confirm that meta-analyses are a valuable tool to integrate the results of individual studies, potentially allowing resolving debates created by focusing on results of individual studies only, and aiding the generation of new hypotheses for future research.

Acknowledgments

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Appendix A

Study	Contrast	Stimulus material
Akitsuki, Y., Decety, J., 2009. Social context and perceived agency affects empathy for pain: an event-related fMRI investigation. NeuroImage 47, 722-734.	Other/Pain > Other/No Pain	picture sequence
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.	Other/Pain > Other/No Pain	video clips
*Bird, G., Silani, G., Brindley, R., White, S., Frith, U., Singer, T., 2010. Empathic brain responses in insula are modulated by levels of alexithymia but not autism. Brain 133, 1515-1525.	Other/Pain > Other/No Pain 4 groups	cue-based
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.	Other/Pain> Other/No Pain	video clips
Cheng, Y., Chen, C., Lin, C.P., Chou, K.H., Decety, J., 2010. Love hurts: an fMRI study. NeuroImage 51, 923-929.	Other/Pain> Other/No Pain control group	picture sequence
Cheng, Y., Lin, C.P., Liu, H.L., Hsu, Y.Y., Lim, K.E., Hung, D., Decety, J., 2007. Expertise modulates the perception of pain in others. Curr Biol 17, 1708-1713.	Other/Pain> Other/No Pain	still pictures
Costantini, M., Galati, G., Romani, G.L., Aglioti, S.M., 2008. Empathic neural reactivity to noxious stimuli delivered to body parts and non-corporeal objects. Eur J Neurosci 28, 1222-1230.	Other/Pain> Other/No Pain	video clips
Danziger, N., Faillenot, I., Peyron, R., 2009. Can we share a pain we never felt? Neural correlates of empathy in patients with congenital insensitivity to pain. Neuron 61, 203-212.	Other/Pain> Other/No Pain, control group, both experiments	still pictures, video clips
Decety, J., Echols, S., Correll, J., 2010. The Blame Game: The effect of responsibility and social stigma on empathy for pain. J Cogn Neurosci 22, 985-997	Other/Pain> Fixation groups collapsed	video clips
Gu, X., Han, S., 2007. Attention and reality constraints on the neural processes of empathy for pain. NeuroImage 36, 256-267.	Rating Other/ Pain>Counting Other/Pain	still pictures
Gu, X., Liu, X., Guise, K.G., Naidich, T.P., Hof, P.R., Fan, J., 2010. Functional dissociation of the frontoinsular and anterior cingulate cortices in empathy for pain. J Neurosci 30, 3739-3744.	Other/Pain> Other/No Pain	still pictures
Han, S., Fan, Y., Xu, X., Qin, J., Wu, B., Wang, X., Aglioti, S.M., Mao, L., 2009. Empathic neural responses to others' pain are modulated by emotional contexts. Hum Brain Mapp 30, 3227-3237.	Other/Pain> Other/No Pain	video clips
*Hein, G., Silani, G., Preuschoff, K., Batson, C.D., Singer, T., 2010. Neural responses to ingroup and outgroup members' suffering predict individual differences in costly helping. Neuron 68, 149–160.	Other/Pain> Other/No Pain ingroup	cue-based
Immordino-Yang, M.H., McColl, A., Damasio, H., Damasio, A., 2009. Neural correlates of admiration and compassion. Proc Natl Acad Sci U S A 106, 8021-8026.	Other/Pain> Other/No Pain physical pain narratives	narratives
*Jackson, P., Brunet, E., Meltzoff, A., Decety, J., 2006. Empathy examined through the neural mechanisms involved in imagining how I feel versus how you feel pain. Neuropsychologia 44, 752-761.	Other/Pain> Other/No Pain perspectives collapsed	still pictures
*Jackson, P., Meltzoff, A., Decety, J., 2005. How do we perceive the pain of others? A window into the neural processes involved in empathy. NeuroImage 24, 771-779.	Other/Pain> Other/No Pain	still pictures
Lamm, C., Batson, C.D., Decety, J., 2007. The neural substrate of human empathy: effects of perspective-taking and cognitive appraisal. J Cogn Neurosci 19, 42-58.	Other/Pain> Fixation perspectives collapsed	video clips
Lamm, C., Decety, J., 2008. Is the Extrastriate Body Area (EBA) sensitive to the perception of pain in others? Cereb Cortex 18, 2369-2373.	Other/Pain> Other/No Pain	still pictures
*Lamm, C., Meltzoff, A.N., Decety, J., 2010. How do we empathize with someone who is not like us? A functional magnetic resonance imaging study. J Cogn Neurosci 22, 362-376.	Other/Pain> Other/No Pain "like me" patient	still pictures
*Lamm, C., Nusbaum, H.C., Meltzoff, A.N., Decety, J., 2007. 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.	Other/Pain> Other/No Pain intensity judgments	still pictures
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.	Other/Pain> Other/No Pain control group	still pictures
Morrison, I., Downing, P.E., 2007. Organization of felt and seen pain responses in anterior cingulate cortex. NeuroImage 37, 642-651.	Other/Pain> Other/No Pain	video clips
Morrison, I., Lloyd, D., di Pellegrino, G., Roberts, N., 2004. Vicarious responses to pain in anterior cingulate cortex: is empathy a multisensory issue? Cogn Affect Behav Neurosci 4, 270-278.	Other/Pain> Rest	video clips
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.	Other/Pain> Other/No Pain	picture sequence
Osborn, J., Derbyshire, S.W., 2010. Pain sensation evoked by observing injury in others. Pain 148, 268-274.	Other/Pain> Fixation responders, non-responders	still pictures
Saarela, M.V., Hlushchuk, Y., Williams, A.C., Schurmann, M., Kalso, E., Hari, R., 2007. The compassionate brain: humans detect intensity of pain from another's face. Cereb Cortex 17, 230-237.	Other/Pain> Other/No Pain provoked-chronic	still pictures
Simon, D., Craig, K.D., Miltner, W.H., Rainville, P., 2006. Brain responses to dynamic facial expressions of pain. Pain 126, 309-318.	Other/Pain> Other/No Pain male and female	video clips
*Singer, T., Seymour, B., O'Doherty, J., Kaube, H., Dolan, R.J., Frith, C.D., 2004. Empathy for pain involves the affective but not the sensory components of pain. Science 303, 1157-1161.	Other/Pain> Other/No Pain	cue-based
*Singer, T., Seymour, B., O'Doherty, J.P., Stephan, K.E., Dolan, R.D., Frith, C.D., 2006. Empathic neural responses are modulated by the perceived fairness of others. Nature 439, 466-469.	Other/Pain> Other/No Pain fair, male and female	cue-based
*Singer, T., Snozzi, R., Bird, G., Petrovic, P., Silani, G., Heinrichs, M., Dolan, R.J., 2008. Effects of oxytocin and prosocial behavior on brain responses to direct and vicariously experienced pain. Emotion 8, 781-791.	Other/Pain> Other/No Pain placebo group	cue-based
Xu, X., Zuo, X., Wang, X., Han, S., 2009. Do you feel my pain? Racial group membership modulates empathic neural responses. J Neurosci 29, 8525-8529.	Other/Pain> Other/No Pain in group	video clips
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. Social Neuroscience 2, 276-291.	Other/Pain & Self/Pain conjunction	video clips

Appendix B. Supplementary data

Supplementary data to this article can be found online at doi:10.1016/j.neuroimage.2010.10.014.

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