

# Your pain or mine? Common and distinct neural systems supporting the perception of pain in self and other

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**Humans possess a remarkable capacity to understand the suffering of others. Cognitive neuroscience theories of empathy suggest that this capacity is supported by ‘shared representations’ of self and other. Consistent with this notion, a number of studies have found that perceiving others in pain and experiencing pain oneself recruit overlapping neural systems. Perception of pain in each of these conditions, however, may also cause unique patterns of activation, that may reveal more about the processing steps involved in each type of pain. To address this issue, we examined neural activity while participants experienced heat pain and watched videos of other individuals experiencing injuries. Results demonstrated (i) that both tasks activated anterior cingulate cortex and anterior insula, consistent with prior work; (ii) whereas self-pain activated anterior and mid insula regions implicated in interoception and nociception, other pain activated frontal, premotor, parietal and amygdala regions implicated in emotional learning and processing social cues; and (iii) that levels of trait anxiety correlated with activity in rostral lateral prefrontal cortex during perception of other pain but not during self-pain. Taken together, these data support the hypothesis that perception of pain in self and other, while sharing some neural commonalities, differ in their recruitment of systems specifically associated with decoding and learning about internal or external cues.**

**Keyword:** Empathy; pain; self; emotion; anterior cingulate; anterior insula

The remarkable human capacity to understand the feelings of others was put to an unusual test during the live broadcast of (American) Monday Night Football on 18 November 1985. On a second quarter play that later would be voted by ESPN.com readers as the Number 1 Most Shocking Sports Moment in Football History,<sup>1</sup> Washington Redskins Quarterback Joe Theismann was tackled from behind by New York Giants linebacker Lawrence Taylor. As Theismann went down, his leg twisted and snapped in a gruesome compound fracture that ended his distinguished 12-year playing career. What was the response of millions of viewers as they watched—with countless replays—‘The Hit That No One Who Saw It Can Ever Forget’?<sup>2</sup>

The answer to this question may hinge upon our capacity for empathy. This ability to understand how others feel

provides us with essential information about our fellows. Empathy enables us to infer the causes of another’s behavior, to act appropriately towards them, to predict what they might do next and to learn about more broadly about what we should approach or avoid (‘If X hurt her, X might hurt me too’) (Ickes, 1997). Our empathic experiences are perhaps no more salient than when we suffer along with those who are in pain. Everyday examples of empathic pain are unfortunately quite common, and range from football fans vicariously experiencing the agony of a quarterback’s broken leg to parents feeling the pain of their child’s cut hand or scraped knee. Understanding these kinds of painful suffering seems intuitive, but how do we do it?

One answer is that we understand others in much the same way that we understand ourselves (Blakemore and Decety, 2001; Mitchell *et al.*, 2005). This answer has been favored by contemporary cognitive neuroscience analyses of empathy and social cognition that posit sets of ‘shared representations’ underlying both self and other perception (Meltzoff and Decety, 2003; Gallese *et al.*, 2004; Jackson *et al.*, 2006b). In support of this account, functional imaging studies have found that regions of premotor and parietal cortices associated with motor planning are activated both when individuals execute a simple finger, hand or facial movement and when they see the same movement executed by someone else (Decety *et al.*, 2002; Chaminade *et al.*, 2005;

Received 28 November 2007; Accepted 31 January 2008

Advance Access publication 15 March 2008

The authors wish to thank Elaine Robertson for assistance in preparation of the manuscript and to acknowledge support by a grant from the John and Dodie Rosekrantz Endowment (S.C.M.), grant BCS-93679 from the NSF (K.N.O.), grant DA022541 from the NIDA (K.N.O.), a NARSAD Young Investigator grant (K.N.O.) and grant RR 09784 from the NIH (G.H.G.).

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<sup>1</sup> See <http://espn.go.com/page2/s/list/readers/shockingNFL.html>.

<sup>2</sup> This was the name given to the tackle by a Washington Post columnist whose vivid recounting of the event, and its aftermath, can be found at: [http://www.washingtonpost.com/wp-dyn/content/article/2005/11/17/AR2005111701635\\_pf.html](http://www.washingtonpost.com/wp-dyn/content/article/2005/11/17/AR2005111701635_pf.html). The first author, who viewed this game as a teenager, is one of the many who could not forget that play.

Iacoboni, 2005). Similarly, regions of the anterior insula (AI) associated with viserosensation and orofacial movement are active both when an individual feels disgusted and when they see someone else expressing disgust (Wicker *et al.*, 2003). Data like these have been taken to support the idea that one way of understanding others is by using our own experiences as a basis and guide.

There is increasing evidence for the recruitment of shared representations during pain perception as well (Jackson *et al.*, 2006b). Several functional imaging studies have examined overlapping patterns of activation associated with experiencing pain directly and perceiving that someone else is experiencing pain. All have shown recruitment of dorsal anterior cingulate (dACC) and AI when participants receive a shock themselves and when they see a cue indicating that someone else is receiving a mildly painful electrical shock (Singer *et al.*, 2004, 2006), when participants receive or watch videos of a stranger receiving a pinprick to a finger (Morrison *et al.*, 2004, 2007; Morrison and Downing, 2007), and when they receive painful thermal stimulation or watch photographs of facial expressions of pain (Botvinick *et al.*, 2005; Lamm *et al.*, 2007). The latter finding suggests that the common substrate of pain empathy may be recruited simply by observing pain-related behaviors. This conclusion is supported by the results of two other studies that examined only the perception of pain in others. dACC and AI activity was observed when participants viewed images of limbs in potentially painful situations (Jackson *et al.*, 2005) and was found to correlate with the amount of pain subjects judged a grimacing individual to be experiencing (Saarela *et al.*, 2007).

Common recruitment of dACC and AI for pain perception in self and other is thought to reflect the roles these regions play in the emotional and physical distress that accompanies painful stimulation (Singer *et al.*, 2004). The mid ACC and mid/posterior dorsal insula receive ascending nociceptive spino-thalamo-cortical projections, return afferents to the spinal cord via the peri-aqueductal gray (Craig, 2002, 2003), and both are commonly activated by the direct experience of a variety of painful stimuli (Wager and Feldman Barrett, 2004; Vogt, 2005). In general, the dACC is thought to function as an all-purpose 'alarm' that signals when ongoing behavior has hit a snag (Botvinick *et al.*, 2001, 2004; Ochsner *et al.*, 2001; Eisenberger and Lieberman, 2004). Physical pain provides perhaps the most primitive signal of this sort (Eisenberger and Lieberman, 2004), and the ACC is critical to assessing the salience and affective quality of pain (Downar *et al.*, 2002, 2003). For example, shifting subjective perceptions of pain, such as through hypnosis (Rainville *et al.*, 1997) typically alleviate the emotional suffering accompanying pain not the ability to perceive it, and also inhibit ACC activity in response to pain. In addition to its pain-related inputs, the AI receives many other modalities of viscerosensory input as well (Craig, 2004). It is thought to play an important role in perception

of and attention to a variety of aversive cues, ranging from disgusting odors and disgust facial expressions to the experience of pain (Phillips *et al.*, 1997; Phan *et al.*, 2002; Krolak-Salmon *et al.*, 2003; Wicker *et al.*, 2003; Wager and Feldman Barrett, 2004).

Although there is intriguing evidence for shared representations underlying perception of pain in self and the other, there are bound to be processes specific to perceiving pain in one target person or the other. We can directly experience and attend to sensory components of our own pain that are not available when perceiving others, including its location, type and intensity. Because we lack this primary sensory information when observing others, we may rely upon other perceptual or social cues when making judgments about their pain. These cues may include facial expressions, bodily movements and situational factors that enable us to infer just how painful something might be. When perceiving one's own pain, we might therefore expect greater activation in regions associated with attention to viscerosensory cues, such as the insula and somatosensory cortex (Peyron *et al.*, 2000; Anderson *et al.*, 2003; Craig, 2004; Critchley, 2005; Ochsner *et al.*, 2006). In contrast, when perceiving pain in others, we might expect greater activation in neural systems associated with processing visual cues relevant to pain, such as superior temporal and inferior parietal regions associated with perception of non-verbal cues and the representation of actions (Allison *et al.*, 2000; Farrer *et al.*, 2003; Keysers and Perrett, 2004; Chaminade *et al.*, 2005). We might also expect activation in neural systems associated with inferences about mental and emotional states, such as the medial and orbitofrontal cortices (Gallagher and Frith, 2003; Goel and Dolan, 2003; Ochsner *et al.*, 2004; Hynes *et al.*, 2006; Vollm *et al.*, 2006) that, along with the amygdala, might be important for learning vicariously about how other's actions can lead to unpleasant outcomes (Olsson and Phelps, 2004; Delgado *et al.*, 2006).

Evidence that self and other pain are processed distinctly by the ACC has been provided by Morrison and Downing (2007), who looked at individual subjects' activations during self and other pain, and found that ACC activations in response to each were not entirely overlapping, calling into question the assumptions of identical mechanisms for processing each type of pain. Another way of addressing hypotheses about the similarities and differences between different types of pain would be to examine interaction effects identifying brain regions whose response to pain perception is moderated by the target of that pain (i.e. region A is more responsive to pain if it is delivered to the self, whereas region B is more responsive to pain if it is delivered to another target). The studies employing a self/other overlap design provide initial support for the hypotheses enumerated above, although none was specifically designed to address them. For example, the only study to compute interaction effects (Singer *et al.*, 2004) found that self-pain differentially activated pain-related sensory regions,

including primary and secondary somatosensory cortex, whereas other pain differentially activated the left lateral occipital cortex. This study may not provide the best test of whether perception of pain in others depends upon regions associated with perception of and inferences about non-verbal cues, however: Singer *et al.*'s subjects viewed colored lights indicating who would be the recipient of painful shock (the participant or their romantic partner), but did not observe either the delivery of painful stimuli or their partner's reaction to it, and thereby limited the cues available to subjects about the other person's pain. The designs of both Botvinick *et al.* (2005) and Morrison *et al.* (2004) did not include baseline no-pain conditions for both self and other pain, and so did not permit computation of interaction effects. In the absence of such effects is difficult to know, for example, whether activation of the superior temporal sulcus and orbitofrontal cortex (OFC) for perception of facial expressions of pain (as compared with direct thermal stimulation) reflects the perception of faces *per se*, or inferences about their pain expressions (Botvinick *et al.*, 2005). A study of perspective taking for painful situations found that the TPJ and precuneus were uniquely involved for allocentric perspective taking, but this study did not include self-pain conditions (Jackson *et al.*, 2006a).

The primary aim of the present study was to use functional magnetic resonance imaging (fMRI) to determine whether the systems supporting perception of painful stimulation delivered to one's own body are similar to or different than the systems supporting perception of painful events experienced by others. Our design included both pain and no-pain conditions for both self and other trials, which enabled identification of systems these two types of pain perception have in common (overlap of pain *vs* no-pain for each trial type), or are distinctly associated with one or the other (interaction of pain *vs* no-pain and self *vs* other). The direct application of noxious thermal stimuli was used for the self-pain condition because this type of painful stimulation has proved to reliably activate pain-related systems such as the dACC and AI. For the other pain condition we selected video clips of individuals experiencing accidental injuries (e.g. ankle twists, leg breaks and arm breaks) of the sort experienced by Washington Redskins quarterback Joe Theismann. The selection of these videos was intended to provide a stimulus set that included a broad sampling of the kinds of non-verbal and situational cues indicative of pain experience in everyday life, including the kinds of sports injuries suffered by athletes that television viewers may witness. We hypothesized that perception of pain in self and others would recruit common regions of dACC and AI, but would depend distinctly upon regions associated either with internal viscerosensory or external visual sensory cues to the perception of pain, respectively.

Because it is known that individual differences in affective style may influence reactivity to emotional stimuli (Davidson, 2002), including physical pain (Ochsner *et al.*, 2006),

we examined relationships between activity in regions involved in perception of self-pain or other pain and scores on measures of general anxiety (the state-trait anxiety inventory, or STAI) (Spielberger *et al.*, 1983) and pain-related anxiety (the Anxiety Sensitivity Index, or ASI) (Blais *et al.*, 2001) or fear (the fear of pain questionnaire, or FPQ) (McNeil and Rainwater, 1998). Our previous work has shown that scores on the FPQ, but not scores on the STAI or ASI, predict dACC activity related to the perception of self-pain (Ochsner *et al.*, 2006). Here, we asked how pain-related fear and anxiety, as well as generalized anxiety, predicts neural responses to regions commonly or distinctly involved in the perception of pain in self or others.

## METHODS

### Participants

Thirteen participants ( $M$  age = 29.5 years,  $s.d.$  = 7 years, Range 19–42, 6 male) were recruited in compliance with the human subjects regulations of Stanford University Medical School.

### Behavioral paradigm

In a single experimental session, participants completed both self-pain and other pain tasks in counterbalanced order. Individual difference analyses correlating pain-related fear and anxiety to neural activity during the self-pain task have been reported previously (Ochsner *et al.*, 2006). Here we focus on the relationship between the self-pain task and the other pain task. Prior to completing these tasks, participants completed an image viewing task that has been reported separately (Ochsner *et al.*, 2004) followed by an 8 min filler word judgment task in which participants were asked to generate the names of US cities from single letter cues (e.g. N\_\_\_\_\_). They were given 15 different blanks and were instructed that all were to be filled. When all were filled they could add a second city to each blank, and they should not add a third city to any blank until a second city had been generated for each, and so on. This task provided a neutral buffer between the image and pain tasks.

In the self-pain task, noxious (painful) thermal and non-noxious (i.e. warm but non-painful) thermal stimulation was delivered to the right distal lateral forearm by a computer controlled thermal stimulator with an MRI compatible 30 mm<sup>2</sup> Peltier probe (TSA-2001, Medoc, Chapel Hill, NC). The task began with the first 20 s block of noxious thermal stimuli, which alternated with 30 s blocks of non-noxious stimuli five times with temperatures ramping up and down at a rate of 1.5°C/s. Temperatures used for the noxious thermal blocks were determined on a participant by participant basis in a pre-scanning session ( $M$  = 47.0,  $s.d.$  = 1.35, range = 43.5–49.0°C). Noxious temperatures elicited the maximum level of pain without causing movement, which roughly corresponded to a subject-defined 7 out of 10 on a verbal rating scale (0 = no pain, 10 = worst pain imaginable). The temperature used for the non-noxious

thermal stimulus (38°C) was chosen to represent a warm sensation. Once temperatures reached the pre-determined setting within a block they remained constant throughout the block until the ramp-down at the block's end. Participants were instructed to attend to the stimulus throughout the task and not distract themselves. Immediately upon exiting the scanner, participants used a verbal rating scale (0 = not unpleasant, 10 = most unpleasant experience imaginable) to rate the unpleasantness of the noxious stimulation they had received (i.e. pain affect).

In the other pain task participants viewed a 2 min video clip depicting 17 events in which individuals suffered injuries in sporting events (e.g. a leg break in a soccer or wrestling match, or an ankle twist in a tennis match), or recreational activities (e.g. scraping or breaking an arm or leg while skateboarding or falling off a bike). The moments of injury embedded in the context of each depicted action lasted ~1 s each, and presentation of the injury associated with each action in the video clip was jittered such that some injury events occurred in close proximity to one another and others were interspersed with longer intervals. Participants were instructed to attend to and watch all events presented during the course of the video.

After exiting the scanner, participants completed three individual difference measures assessing generalized and pain-related fear and anxiety. Measures included the ASI (Blais *et al.*, 2001), FPQ III (McNeil and Rainwater, 1998) and the trait form of the STAI (Spielberger *et al.*, 1983).

**Validation of other pain task.** Because retrospective reports of pain intensity can be inaccurate (Ochsner and Schacter, 2000; Rainville *et al.*, 2004), we chose not to rely on scanned subjects' retrospective reports to validate the presence of pain in our other pain task. Instead, a separate behavioral study was conducted with a separate group of 13 participants (age and gender matched to those in the imaging study) using the same self and other pain paradigms as in the scanner study with one exception: participants provided continuous ratings of experience during each task on a 10 point scale. The scale consisted of a horizontal bar at the bottom of the computer screen (below the video) with endpoints labeled in the same way as during threshold testing (i.e. 0 = not unpleasant, 10 = most unpleasant experience imaginable). Participants could use a computer mouse to move a cursor above the scale to indicate their current level of pain. The computer continuously recorded the mouse position, which was later transformed into scalar values for pain affect. For the other pain task, participants provided a continuous rating of the pain affect experienced by the actors in the video clip using the same scale. For the self-pain task, participants provided a continuous rating of their own pain affect. Participants in the scanner study were not asked to provide these ratings before, during or after scanning because (i) asking participants to provide pre-scan ratings would introduce confounds due to multiple sessions with each experimental stimulus, (ii) concurrent evaluation

of the emotional qualities of a stimulus, and/or one's emotional state, may recruit additional neural systems and/or modify activation in pain processing systems (Taylor *et al.*, 2003) and (iii) research indicates that retrospective reports of painful and/or emotional experiences can be biased and at times unreliable, suggesting that post-scan ratings could be unreliable (see, e.g. Fredrickson and Kahneman, 1993; Ochsner, 2000; Levine and Safer, 2002).

To determine whether viewing injuries to others resulted in the perception of pain, we computed the mean pain affect ratings given during the 2 s interval just before a given injury was presented ( $M = 4.62$ ,  $s.d. = 2.08$ ) and the 2 s interval just after that injury was presented ( $M = 5.34$ ,  $s.d. = 2.00$ ). These ratings were thought to reflect perception of pain in a target other during periods when that other is or is not experiencing pain (i.e. the moment just before an injury would occur and the person is not yet in acute pain, and the moment just after one has witnessed the occurrence of the acutely painful injury). Paired sample *t*-tests verified the efficacy of the injuries depicted in the pain video for generating the perception of pain in another person [ $t(12) = 3.20$ ,  $P = 0.008$ ].

For the self-pain task we computed the mean pain affect rating given during the time periods when heat pain was applied ( $M = 5.94$ ,  $s.d. = 1.89$ ) and when it was not applied ( $M = 0.862$ ,  $s.d. = 0.417$ ). These ratings verified the efficacy of the thermal stimulus in generating the experience of pain [ $t(12) > 20$ ,  $P < 0.001$ ]. Importantly, ratings of pain affect for the painful portions of the self and other pain tasks did not differ significantly ( $P = n.s.$ ), which means that differences in activation observed between the two tasks should not be attributable to differences in perceived pain affect.

### MRI data acquisition

During completion of both tasks a T2\*-sensitive gradient echo spiral-out pulse sequence (30 ms TE, 2000 ms TR, 2 interleaves, 60° flip angle, 24 cm field of view, 64 × 64 data acquisition matrix) was used to collect whole brain fMRI data (32 axial slices, 3.5 mm thick) at 3T (GE Signa LX Horizon Echospeed scanner). High order shimming was performed before functional scans (Glover, 1999). For anatomical reference T2-weighted flow-compensated spin-echo scans were acquired using the same slice prescription (2000 ms TR; 85 ms TE).

### Data analysis

Preprocessing and statistical analyses were carried out using SPM99 (Wellcome Department of Cognitive Neurology). Functional images were slice time and motion corrected, normalized using parameters derived from the normalization of coregistered anatomical images to a standard template brain, interpolated to 2 × 2 × 2 mm voxels, and smoothed with a Gaussian filter (6 mm full width-half maximum). First level fixed effects analyses for the self-pain task modeled noxious and non-noxious blocks with boxcar

regressors convolved with the canonical hemodynamic response. Boxcars include the timepoints when the pain stimulus had already ramped up to the participants pre-set threshold level of intensity and did not include the non-painful moments during the ramp-up and ramp-down of pain. First level fixed effects analyses for the other pain task modeled observed physical injuries as events (whose onset was the moment a particular physical injury occurred) represented by the canonical hemodynamic response. All other portions of the video, which depicted the same actors engaged in non-painful activities for the other pain task, were not explicitly modeled and therefore served as the no-pain baseline against which activation related to other pain events was determined. These regressors were correlated voxelwise with activation in each task using the general linear model implemented in SPM99. Contrast images for each participant summarized differences between (i) noxious and non-noxious blocks for the self-pain task and (ii) differences between observed painful events and all other portions of the video depicting non-painful activities for the other pain task. These contrast images were used to create second level group average random effects SPM maps of regions more active either for the experience of noxious heat as compared with non-noxious warmth, or during the observation of painful as compared with non-painful events experienced by others. These images were thresholded at  $P < 0.001$  uncorrected for multiple comparisons, with an extent threshold of 10 voxels.

To identify regions active for both the self and other pain contrasts, the  $t$ -map for the first contrast was used as an inclusive mask for the second contrast. Each contrast was voxel-level thresholded at  $P < 0.005$ , which yields regions active with probability  $P < 0.000025$  across both tasks using the Fisher method for combining probabilities (Kampe *et al.*, 2003; Ochsner *et al.*, 2004). This masking approach is conservative in that it requires activation to be significant for *both* conditions of interest. To visualize activity in each overlap region, and to verify that each region was similarly and significantly activated, the Brain Imaging Toolbox (or BIT, see <http://web.mit.edu/swg/www/software.htm>) then was used to extract parameter estimates for each subject from the peak voxel of each overlap cluster identified at the group level. Mean parameter estimates for each condition were then computed for each condition and were compared using paired sample  $t$ -tests.

In order to isolate brain regions that were uniquely responsive to pain in self or other while correcting for each subject's main effect of pain, the main effect contrasts were compared in a paired sample  $t$ -test {calculated as [(other pain – other non-pain) – (self-pain – self non-pain)] and vice-versa}. Resulting activation maps were thresholded at  $P < 0.001$  with an extent threshold of 10 voxels. Because the results of this contrast represent the difference between two main effects, it was important to determine whether a significant interaction reflected relative increases in

pain-related activity for one main effect, relative decreases in pain-related activity for the comparison main effect, or both. To address this issue, the Brain Imaging Toolbox again was used to extract parameter estimates for each cluster significantly active at the group level and paired sample  $t$ -tests were used to compare condition means for each functionally activated region of interest. In addition, SPM's small volume correction tool was used to identify activations in the amygdala for all contrasts. This was done because activation of the amygdala was expected on a priori grounds, and because amygdala activation may be difficult to observe in whole brain analyses due to signal loss in the medial temporal lobe (Preston *et al.*, 2004).

To examine the relationship between individual differences in fear, anxiety and neural activity during self and other pain perception, we (i) extracted betas from regions identified as being commonly or distinctly involved in the perception of either self-pain or other pain and (ii) computed correlations between activation in each region and scores on either the ASI, FPQ, or STAI-T.

## RESULTS

### Behavioral results

For the self-pain task, post-scan ratings of pain affect ( $M = 6.73$ ,  $s.d. = 1.86$ ) confirmed the experience of pain and initial threshold settings.

### Imaging results

*Main effects of self or other pain perception.* Regions activated during the self-pain task were identified in the noxious > non-noxious contrast and, as reported previously, (Ochsner *et al.*, 2006), included regions of anterior cingulate and insular cortex, as well as thalamic, lateral prefrontal and parietal cortical regions commonly identified in pain studies (Peyron *et al.*, 2000). Regions activated during the other pain task were identified in the contrast of other pain events > events observed in the non-painful portions of the video and included regions of anterior cingulate and insular cortex, as well as amygdala, thalamus, lateral prefrontal cortex and temporal and parietal cortex. The distribution of these regions to either self or other pain perception, or both, is described below.

*Regions common to self and other pain perception.* Regions commonly activated by the experience and observation of pain were identified by masking the painful *vs* non-painful self-pain contrast with the painful *vs* non-painful other pain event contrast (Table 1 and Figure 1) (Kampe *et al.*, 2003; Ochsner *et al.*, 2004). This analysis revealed common recruitment of anterior cingulate and AI cortices, middle frontal gyrus (MFG), premotor cortex and dorsal thalamus.

*Regions distinctly activated by self or other pain perception.* Regions selectively activated by either the experience or the observation of pain were identified in interaction contrasts comparing activation in the self-pain *vs* self no-pain

contrast to activation in the other pain vs other no-pain contrast (Table 2 and Figure 2). Regions more active for self-pain included several activation peaks spanning the right insula, continuing more dorsally and posterior to the superior

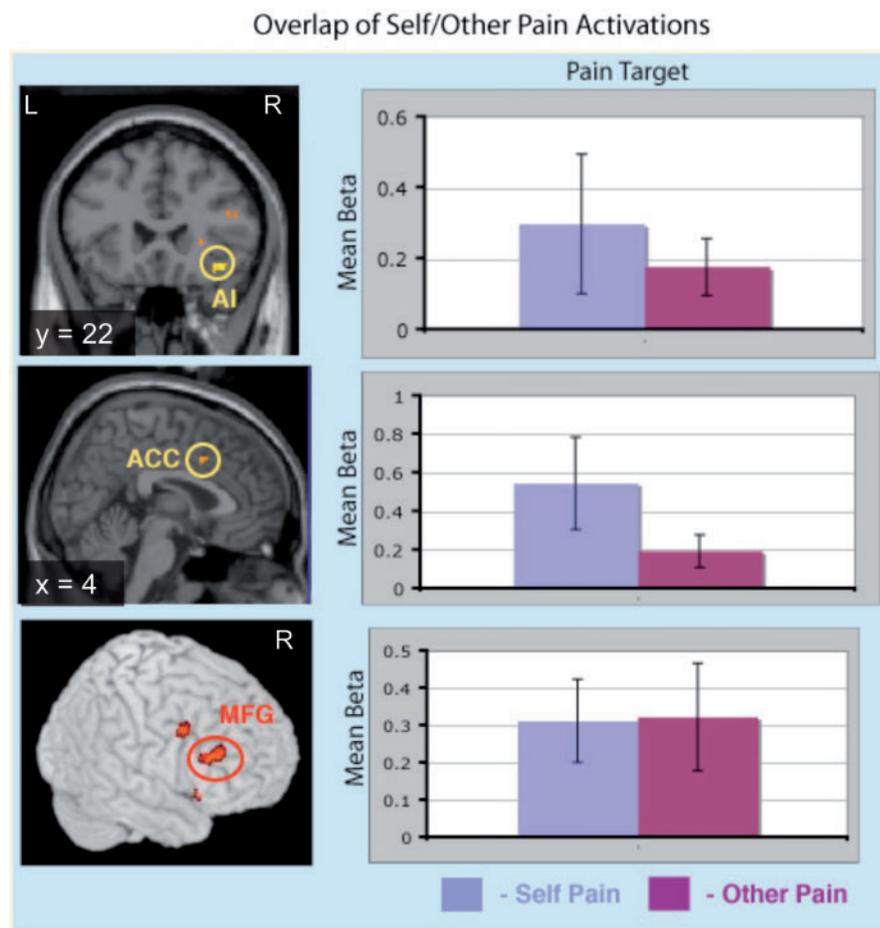
**Table 1** Regions showing common activation for self-pain and other pain

Region of Activation	Coordinates				Volume		
	Lat	x	y	z	Z-score	Voxels	mm <sup>3</sup>
Middle frontal gyrus	R	46	28	20	3.33	59	478
Anterior cingulate		4	10	40	3.19	11	88
Premotor gyrus	R	48	8	40	3.12	23	184
Anterior insula (AI)	R	42	22	-12	4.56	56	448
AI	R	28	28	2	3.69	57	456
AI	R	28	16	6	3.68	(L)	
AI	R	30	20	-2	3.5	(L)	
Dorsal thalamus	R	12	-2	10	3.69	56	448
Thalamus	R	20	-6	14	3.14	(L)	
Thalamus	R	16	-10	20	3.01	(L)	

Note: Local maxima for clusters are designated with (L). Hemisphere is not designated maxima within 6 mm of the midline. Coordinates are in MNI space. One voxel = 8 mm<sup>3</sup>.

temporal gyrus, but not reaching the superior temporal sulcus. These findings were confirmed by extracting parameter estimates extracted from activated regions, computing pain > no-pain difference scores for each group, and comparing the magnitude of difference scores using planned paired sample *t*-tests (all *P*s < 0.05). In addition, paired sample *t*-tests for the AI peak confirmed that it was active for both self and other pain relative to their respective control conditions but that activity in self-pain was significantly greater than activity for other pain (*P*s < 0.05). This result is sensible, given that the peak voxel in the interaction effect cluster is also a peak for the overlap between self and other pain described above. A cluster in right premotor cortex showed the same pattern, and a cluster in the left insula displayed this trend but did not reach significance at 0.005.

Many regions were more active for other than for self-pain (Table 2 and Figure 2). These included bilateral rostrolateral prefrontal cortex (RLPFC), medial OFC, premotor cortex, precentral gyrus, superior parietal cortex and the medial parietal lobe spanning the part of the precuneus. Analysis of mean parameter estimates for these clusters revealed that while RLPFC and OFC were both significantly more active



**Fig. 1** Overlap regions commonly activated in the Other pain vs Other non-pain and Self-pain vs Self non-pain contrasts. Graphs at right show mean beta values for self and other pain for each region. Bars on graphs indicate s.d. from the mean. Coordinates for overlap regions can be found in Table 1. ACC, anterior cingulate cortex; AI, anterior insula; MFG, middle frontal gyrus.

for other pain than for other no-pain, the interaction effect was also driven by decreases in activity in these regions for self-pain relative to self no-pain trials. Unlike these frontal peaks, however, the medial parietal and premotor cortices showed an interaction that was driven exclusively by increased engagement during other pain. Also, as shown in Figure 3, small volume corrected analyses of amygdala activity identified bilateral clusters of activity more active for other than for self-pain (*L*: -18, -2, -26; 23 voxels,  $P=0.001$ ; *R*: 30, -2, -18; 13 voxels,  $P=0.002$ ).

*Correlations with individual differences in fear and anxiety.* To determine the relationship between individual

**Table 2** Regions showing greater activation for either self or other pain

Region of Activation	Coordinates				Volume		
	Lat	<i>x</i>	<i>y</i>	<i>z</i>	Z-score	Voxels	mm <sup>3</sup>
<b>SELF &gt; OTHER</b>							
Middle frontal gyrus	R	46	2	54	4.32	17	136
Middle frontal gyrus	R	54	6	50	3.14	(L)	
Anterior insula (AI)	R	38	12	-2	2.97	190	1520
AI	R	40	4	-12	2.84	(L)	
AI	R	46	14	-4	2.78	(L)	
AI	R	26	2	2	2.81	10	80
AI	R	44	0	10	3.18	11	88
AI	L	-60	2	4	2.64	10	80
PI	R	36	-20	20	3.10	14	112
<b>OTHER &gt; SELF</b>							
Rostral lateral PFC (RLPFC)	R	28	64	4	4.67	69	552
Rostral lateral PFC (RLPFC)	R	24	60	-2	3.55	(L)	
Rostral lateral PFC	L	-30	56	8	3.78	11	88
Orbitofrontal cortex	R	8	58	-20	3.77	13	104
Precentral gyrus (PrcG)	L	-24	-6	46	3.98	21	168
PrcG	L	-34	0	46	3.89	(L)	
PrcG	L	-26	-48	56	3.3	(L)	
Precentral gyrus (PrcG)	L	-16	-6	58	3.66	51	408
PrcG	L	-24	-8	62	3.61	(L)	
PrcG	L	-20	0	62	3.57	(L)	
Precuneus/Medial parietal	R	6	-34	64	4.66	29	232
Medial parietal	R	10	-26	66	3.72	(L)	
Medial parietal	R	8	-30	74	3.71	(L)	
Precuneus/Medial parietal	L	-14	-26	76	3.83	22	172
Precuneus/Medial parietal	L	-16	-42	68	3.89	22	172
Superior parietal	R	14	-28	48	4.11	93	744
Superior parietal	R	22	-32	46	4.05	(L)	
Superior parietal	R	10	-30	56	3.83	(L)	
Superior parietal	L	-32	-42	42	4.18	20	160
Superior parietal	L	-36	-50	64	3.9	34	252
Superior parietal	L	-38	-46	54	3.66	21	168
Superior occipital	R	20	-88	44	4.07	20	160
Posterior parietal	R	16	-66	52	4.06	28	224
Posterior parietal	L	-26	-62	60	3.69	15	120
Amygdala*	L	-18	-2	-26	3.27	17	136
Amygdala*	L	-26	0	-24	2.38	(L)	
Amygdala*	L	-16	-6	-14	2.62	23	184
Amygdala*	L	-20	-8	-10	2.51	(L)	
Amygdala*	R	30	-2	-18	2.32	13	104

Note: Local maxima for clusters are designated with (L). Hemisphere is not designated maxima within 6 mm of the midline. Coordinates are in MNI space. \**sv* denotes voxels identified in small volume corrected analyses for the amygdala (for details, see 'Methods' and 'Results' section). One voxel = 8 mm<sup>3</sup>

differences in fear and anxiety and activity related to self-pain or other pain, correlations were computed between scores on the ASI, FPQ and STAI-T and beta values extracted from regions commonly or distinctly activated by each task. To reduce the likelihood of false positive findings, correlations were Bonferroni corrected for multiple comparisons. These analyses revealed that activation in none of the common or distinct regions was significantly correlated with ASI scores. Although FPQ scores did not correlate with any of the regions found in the interaction analyses, they did correlate significantly with activation of the ACC region identified in the overlap analyses, but only in response to self-pain ( $r=0.610$ ,  $P=0.027$ , as we found in a previous report focusing solely on the self-pain task (Ochsner et al., 2006) and not in response to other pain ( $r=-0.08$ ,  $P=0.780$ ). STAI-T scores failed to correlate significantly with activity in common regions, but did predict activity in bilateral regions of RLPFC distinctly associated with the perception of other pain. The specificity of this correlation to the other pain condition is illustrated in Figure 4, which shows that both left (coords = -32, 54, 12) and right (coords = 26, 56, 12) RLPFC showed activity that was highly correlated with STAI scores during other pain (right:  $r=0.793$ ,  $P<0.001$ ; left:  $r=0.850$ ,  $P<0.001$ ), whereas neither cluster's activity correlated with trait anxiety during self-pain (right:  $r=-0.162$ ,  $P=0.596$ ; left:  $r=-0.138$ ,  $P=0.653$ ).

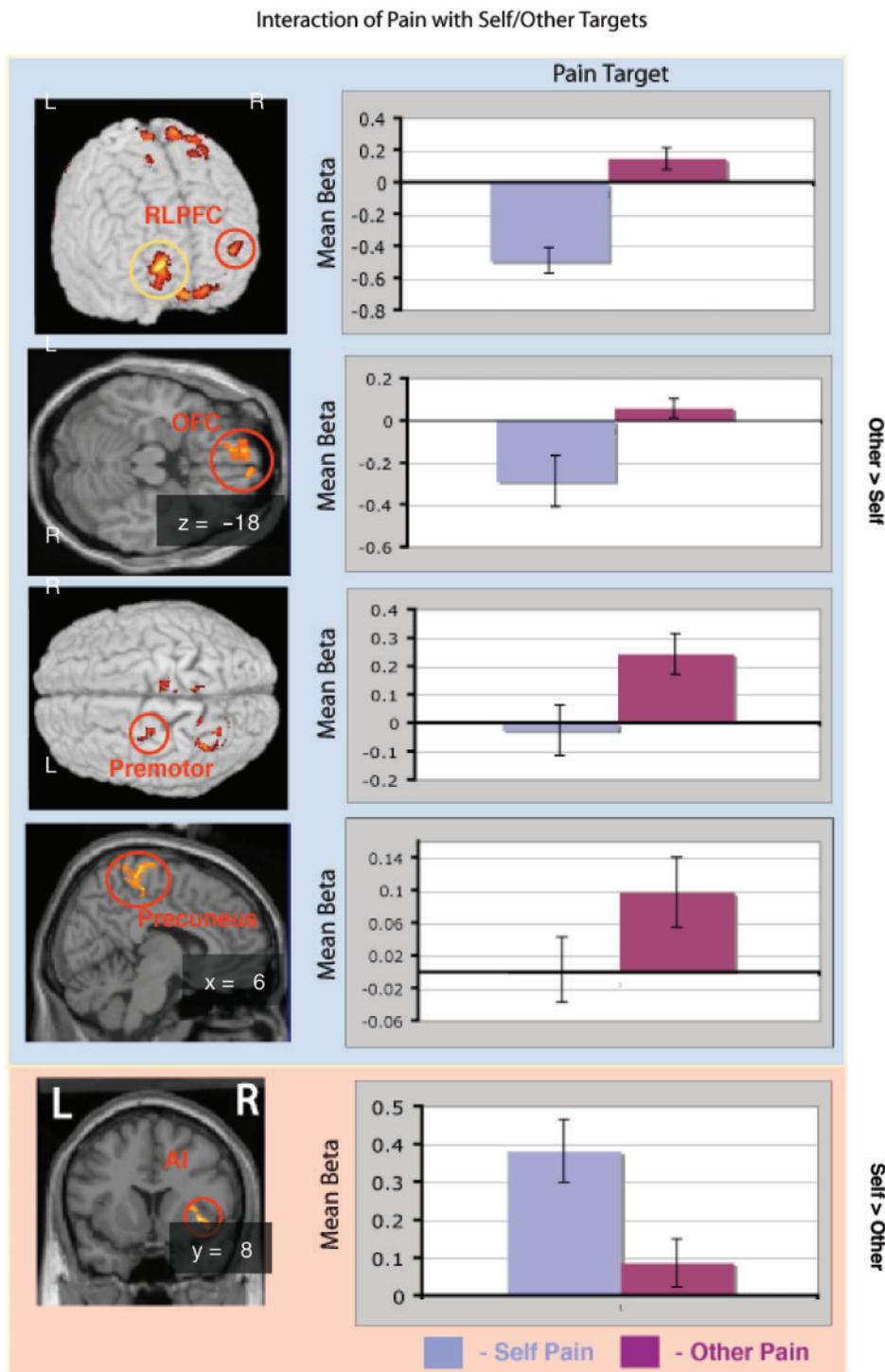
## DISCUSSION

This is the first functional imaging study to directly address the question of which common or distinct neural systems mediate the perception of pain in self and other using video stimuli depicting physical injuries of the sorts individuals may experience in everyday life, and that we might witness being experienced by athletes on television.

### Common regions supporting the perception of pain in self and other

In keeping with prior findings (Hutchison et al., 1999; Morrison et al., 2004; Singer et al., 2004, 2006; Botvinick et al., 2005; Jackson et al., 2005), experiencing self-pain and observing others in pain commonly recruited the mid ACC and AI, which have been implicated previously in the emotional and physical distress accompanying physical pain.

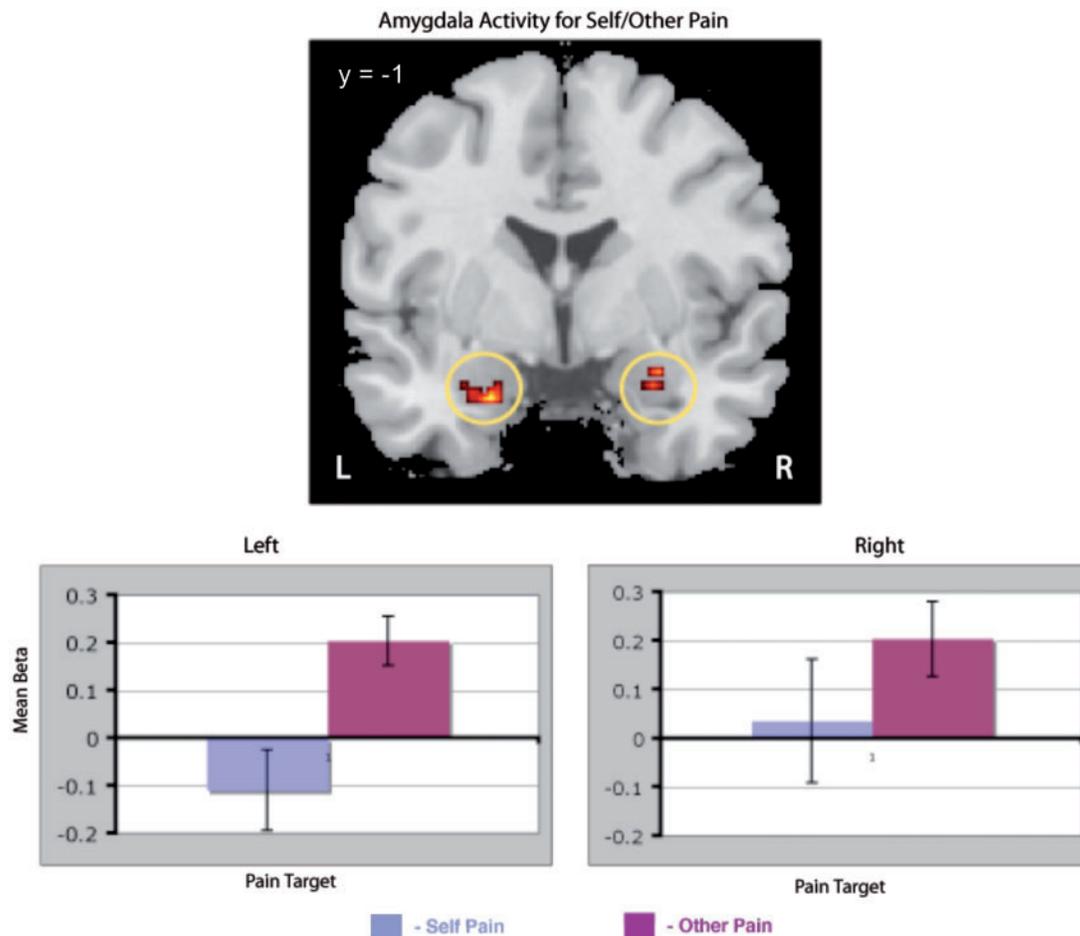
The mid portion of the ACC activated here receives ascending nociceptive inputs (Devinsky et al., 1995; Craig, 2003; Vogt, 2005) and has been shown in functional imaging and lesion studies to be involved in the perception and experience of physical pain deriving from externally applied heat, cold, or mechanical stimulation, as well as pain in the internal viscera (Hebben, 1985; Peyron et al., 2000; Morrison et al., 2004; Farrell et al., 2005; Jackson et al., 2006b). Mid ACC, which projects to motor and premotor cortex, has been thought to play a role in the motivational aspects of pain, including urges or desires to stop painful events



**Fig. 2** Regions more active for perception of either self-pain or other pain relative to their respective non-pain baselines. Graphs show mean beta values for self and other pain for each region. Bars on graphs indicate s.d. from the mean. Coordinates of each interaction region are in Table 2. Bilateral RLPFC, OFC and Premotor cortex were more engaged by the perception of pain directed to an external target. In RLPFC and OFC these interactions represented both activation during other pain and deactivation during self-pain conditions, whereas a cluster in right anterior insula was more engaged for self than other pain, though it was significantly engaged in both conditions. RLPFC, rostralateral prefrontal cortex; OFC, orbitofrontal cortex; AI, anterior insula.

(Devinsky *et al.*, 1995; Craig, 2003), and assessing their salience and affective quality (Downar *et al.*, 2002, 2003). In this context it is noteworthy that we observed activity common to self and other pain in premotor cortex as well

as mid ACC. Intriguingly, like the present experiment, two of the four extant pain empathy studies had participants watch actions that led to painful outcomes for others and they too found activation of premotor (Morrison *et al.*, 2004)



**Fig. 3** Small volume corrected clusters of amygdala activity identified in the interaction contrast of other > self-pain, and mean beta values for these clusters during self and other pain. Bars on graphs indicate s.d. from the mean. Bilateral clusters of activity were found to be significantly active for other pain vs other non-pain, but not in self-pain vs self non-pain.

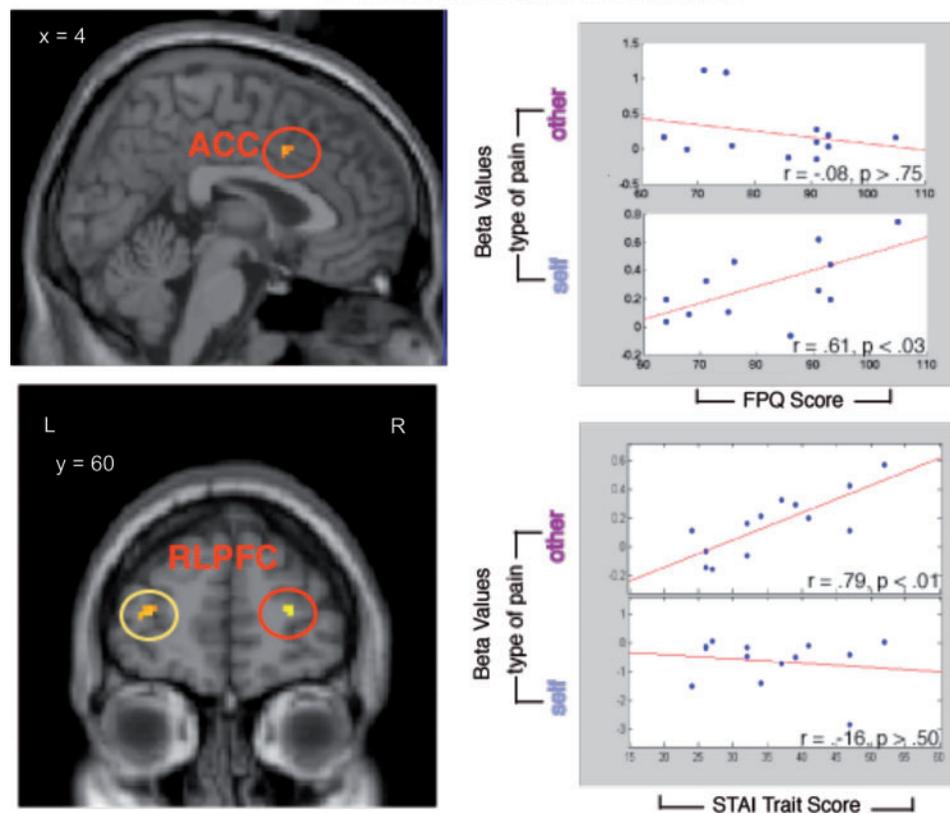
or supplementary motor (Jackson *et al.*, 2005) cortices as well as ACC. In contrast, the two pain empathy studies that did not report activity in motor cortices asked participants to view either symbolic cues or facial expression indicating that another was in pain (Singer *et al.*, 2004; Botvinick *et al.*, 2005). Taken together, these data suggest that self and other pain may commonly recruit a mid ACC region involved in translating aversive inputs into avoidance behaviors, as suggested by Morrison *et al.* (2004), but that the strength of the avoidant motivation may depend upon the stimulus cue. That is, the desire for avoidance behavior (as indexed by motor activity) is relatively reflexive when directly perceiving that one's own or someone else's actions cause pain, but is less automatic when one simply possesses the abstract knowledge that another person is experiencing pain.

The ventral AI region commonly activated by self and other pain is interconnected with nearby OFC, and has been shown in functional imaging studies to be involved in the perception of multiple types of pain (Peyron *et al.*, 2000; Farrell *et al.*, 2005), in negative emotional experience in

general (Wager and Feldman Barrett, 2004), and the experience of disgust or revulsion in response to odors or images in particular (Calder *et al.*, 2001; Wicker *et al.*, 2003). This suggests that the ventral AI's role in pain empathy may relate to its more general role in the registration and representation of aversive stimulus properties, contributing to the unpleasantness of watching another in pain.

The thalamus and MFG also were commonly recruited during self-pain and other pain. Activation of dorsal lateral PFC and/or thalamus has been observed in prior pain empathy studies (Botvinick *et al.*, 2005; Jackson *et al.*, 2006b). The dorsal thalamus shares reciprocal connections with the MFG, and both have been implicated in the maintenance of information in working memory and the encoding of information into declarative memory (Bunge *et al.*, 2001; Thompson-Schill *et al.*, 2002; Ranganath *et al.*, 2003). Thalamic and MFG activation has been found in studies of pain perception and pain anticipation, which suggests that in the present study, common recruitment of DLPFC and dorsomedial thalamus may indicate the use

Correlations with FPQ and STAI Trait Scores



**Fig. 4** Correlations between pain-related activity and scores on individual difference measures of fear and anxiety. Top panels show region of ACC identified in the overlap analysis that correlated with scores on the fear of pain questionnaire (FPQ) only for the self-pain task. Bottom panels show regions of RLPFC identified as more active for other than for self-pain whose activity correlated with trait anxiety as measured by the trait subscale of the STAI. STAI = state-trait anxiety inventory. Correlations for red-circled regions are shown on the right. ACC, anterior cingulate cortex; RLPFC, rostralateral prefrontal cortex.

of cognitive processes that elaborate the meaning of, and encode into memory, various types of painful stimuli (Peyron *et al.*, 2000; Wager *et al.*, 2004; Farrell *et al.*, 2005).

#### Distinct neural systems supporting the perception of pain in self and other

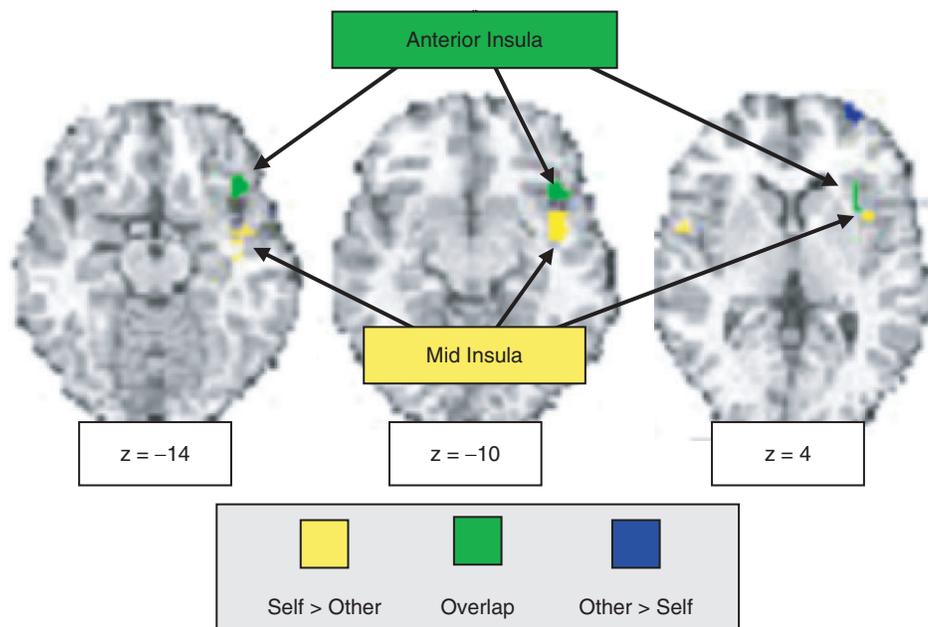
Directly contrasting activation between self and other pain identified regions differentially involved in each type of task.

Two regions were more active for self-pain than for other pain. The first was a large region of the mid insula located posterior and slightly more dorsal to the region activated commonly by both self and other pain. Relative to the ventral AI, which plays a role in affective responding, mid portions of the insula have stronger connections with parietal and frontal regions involved in attention and cognitive control (Mesulam and Mufson, 1982; Mufson and Mesulam, 1982; Wager and Feldman Barrett, 2004). The relationship between these two regions of the insula is illustrated in Figure 5. The second was a region of the right MFG posterior and dorsal to the region commonly activated by both tasks. Right lateral PFC is generally involved in working memory and selective attention during conditions of response competition (Bunge *et al.*, 2001; Milham *et al.*, 2001). This suggests

that during self-pain, affective representations in the ventral AI and motivational representations in the ACC may gain access to attentional control networks via the mid insula and lateral PFC, perhaps to control the desire to move one's arm away from the painful thermal stimulus.

Two sets of regions with distinct functional correlates were more active in the other than in the self-pain task. The first set included regions implicated in shifting attention and/or perspective taking. These activations encompassed portions of premotor and superior parietal cortex involved in controlling visuospatial attention and spatial working memory (Postle *et al.*, 2004; Curtis *et al.*, 2005) as well as portions of the precuneus and medial parietal lobe thought to play a role in perspective taking and making attributions about one's own or other peoples enduring traits and current states (Vogel and Fink, 2003; Lou *et al.*, 2004; Ochsner *et al.*, 2004, 2005; Cavanna and Trimble, 2006).

The second set was comprised of three regions implicated in memory and affective learning. The first was a region of rostralateral prefrontal cortex commonly activated in studies of autobiographical memory and in complex higher-order cognitive tasks that require the self-generation of rules necessary to solve problems (Christoff and Gabrieli, 2000;



**Fig. 5** Plots of activation peaks found in overlap and interaction analyses. Of note is an anterior-posterior pattern, such that anterior insula is engaged by both self and other pain, and more posterior and dorsal peaks in the insula are preferentially engaged by self-pain.

Christoff *et al.*, 2003). The second was a region of medial OFC thought to play a role in integrating affective states with cognitive processes (Bechara, 2002; Beer *et al.*, 2004) and in learning about the affective consequences of actions (O'Doherty *et al.*, 2003; O'Doherty, 2004), and inferring emotional states in others (Hynes *et al.*, 2006; Vollm *et al.*, 2006). In the context of person perception, OFC may play a role in decoding the affective or intentional meaning of social cues, as suggested by impairments in perceiving facial and vocal expressions (Hornak *et al.*, 2003), detecting faux pas (Stone *et al.*, 1998) and experiencing embarrassment (Beer *et al.*, 2003) sometimes shown by OFC lesion patients. The third region was the amygdala, which is thought to play a role in detecting arousing and goal-relevant stimuli including faces, facial expressions, and non-verbal cues and modulating their consolidation into long-term memory (Phelps and Anderson, 1997; Anderson and Phelps, 2001; Calder *et al.*, 2001). Through their rich interconnections, the OFC and amygdala are thought to work together to code the affective significance of various kinds of stimuli (Bechara *et al.*, 2003; Schoenbaum *et al.*, 2003). Although the present study cannot address the specific computations performed by these three regions during the other pain task, their common recruitment may reflect encoding of the social and affective value of stimuli (Adolphs, 2003). This interpretation is consistent with prior findings of RLPFC activity during reflective processing (Christoff *et al.*, 2003), OFC and amygdala activation when viewing facial expressions of pain but not during the application of heat pain (Botvinick *et al.*, 2005), and activation of the amygdala when acquiring learned fear responses by watching others undergo a conditioning procedure (Olsson *et al.*, 2007) or when engaging

in perspective taking when viewing facial expressions of pain (Lamm *et al.*, 2007). In addition, it should be noted that failure to observe amygdala activation during the self-pain condition could be attributable to habituation due to repeated stimulation with the same pain stimulus (Becerra *et al.*, 1999).

As a whole, the results of our interaction analyses suggest that in addition to recruiting pain-related processing systems and systems that encode goal related information into memory, the perception of pain in self and other also recruit regions specific to the processing demands intrinsic to each task. In the case of experiencing one's own physical pain, task-specific processes may include those involved in attending to and controlling one's reaction to painful somatic states. In the case of observing pain in another person, task-specific processes may include those important for making attributions and learning about the internal states of pain recipients as well as regions important for deploying spatial attention across an unfolding scene.

These differences could qualify and inform extant theories of what overlapping activations in ACC and AI signify. Rather than indicating identical, co-localized processing steps being used to feel pain and 'mirror' pain observed in others, overlapping activity in these regions may indicate common coding of the salience or affective quality of pain stimuli, regardless of whether it is observed or directly experienced. This coding, however, may be caused by, and may interact with, disparate cognitive operations, such as perspective taking for other pain and sensory discrimination for self-pain. Neurally, this would be represented by overlapping but distinct networks of brain activity for each type of pain as were found in this study. The results of functional

connectivity analyses using these data dovetail with this conclusion. These analyses showed that ACC and AI, while engaged by both self and other pain, are functionally connected with disparate brain regions during each pain type (Zaki *et al.*, 2007). During other pain, both ACC and AI showed functional connectivity with rostral/dorsal medial prefrontal cortex (mPFC), a region implicated in perspective taking and mental state attribution more generally (Mitchell *et al.*, 2002; Gallagher and Frith, 2003; Ochsner *et al.*, 2004), whereas during self-pain, the AI demonstrated connectivity with the periaqueductal gray and midbrain, structures involved in the processing nociceptive information (Craig, 2002, 2003).

Taken together, these results help clarify when and how common or distinct neural systems support the experience of an event experienced directly by oneself or vicariously through observation of that event as experienced by another. On the one hand, it appears that in many circumstances observers may use similar systems for the direct and vicarious experiential understanding of pain, as observed here and in the work cited above, of simple motor actions (Decety and Jackson, 2004; Gallese *et al.*, 2004; Dapretto *et al.*, 2006), and of certain emotional states (Carr *et al.*, 2003; Wicker *et al.*, 2003). Although these 'shared representations' have been suggested as the general basis for understanding the meaning and intentionality of another individual's behavior, it has not been clear whether shared motor and affective representations by themselves provide sufficient basis for understanding more complex social and emotional behaviors. Others have suggested that beyond the use of shared representations, additional higher-level inferential processes may be necessary for complete empathic understanding and social cognition more generally (Decety and Jackson, 2004; Beer and Ochsner, 2006; Mitchell, 2006; Singer *et al.*, 2006). The structure most commonly implicated in drawing high-level inferences about mental states—whether affective or non-affective—is the mPFC (Gallagher and Frith, 2003; Ochsner *et al.*, 2005; Mitchell, 2006), which is commonly activated in studies of emotional perspective taking or empathy that explicitly direct participants to empathize with or think about the emotional states of others (Farrow *et al.*, 2001; Ochsner *et al.*, 2004; Ruby and Decety, 2004; Shamay-Tsoory *et al.*, 2005). MPFC has been shown to play a role in maintaining high-level beliefs about the nociceptive value of stimuli, as suggested by the findings that MPFC activity may track the subjective sense that a stimulus is painful during hypnotic suggestion or when participants expect a non-painful stimulus to be painful (Sawamoto *et al.*, 2000; Raij *et al.*, 2005). But mPFC activity has been observed in only one (Botvinick *et al.*, 2005) of the pain empathy studies published to date that employ a self/other overlap design and uninstructed perception of stimuli. The present work may suggest a way of resolving this discrepancy by revealing two ways in which perceiving self and other pain are unique. First, above and beyond the use

of shared representations, the bottom-up perception of self-pain and other pain differentially activate brain systems involved in processing one's internal states or external perceptual stimuli. Second, the connectivity analyses of these data, as mentioned above (Zaki *et al.*, 2007), suggest that even the regions that self and other pain appear to have in common may participate in their own distinct functional networks. During the perception of other pain these networks include MPFC, suggesting that at least in some cases regions implicated in explicit higher level attributions may interact with regions supporting 'shared representations' to support empathic understanding. Future work will be needed to clarify when and how different types of affective, motor, somatosensory and inferential processes come into play during empathy.

### The role of fear and anxiety in pain perception

Another way of understanding the function of brain systems involved in pain empathy is by determining the extent to which individuals who differ in their tendencies to respond emotionally to painful events also differ in the extent to which they recruit specific brain systems during pain perception. In this way, correlational analyses relating brain activity to levels of anxiety or fear can inform both our understanding of the functions of basic brain mechanisms and individual differences as well.

With this in mind, we computed correlations between brain activity during self and other pain and individual difference measures related to fear and anxiety, hypothesizing that these trait level differences may importantly influence the way people construe and react to cues about salient and threatening stimuli. Previous work has shown that activity in the ACC during painful stimulation can be directly related to subjects' tendency to fear painful events as measured by the fear of pain questionnaire, or FPQ (Ochsner *et al.*, 2006). The current work extended these findings in two ways.

First, we observed a positive correlation between FPQ scores and ACC activity only for the self-pain but not for the other pain task, demonstrating that fear of pain predicts ACC response only in the face of painful threats to one's own body. This makes sense given that the FPQ assesses fear of bodily insults, and as discussed above, activity in the mid ACC may be related to pain affect and the motivation to avoid or withdraw from an injurious stimulus (Devinsky *et al.*, 1995; Craig, 2003). The correlation of ACC activity with FPQ scores for self but not other pain therefore could represent the operation of process not involved in empathic sensitivity *per se*, but rather a process reflecting distress in response to personal injury. In this context it is interesting that scores on individual difference measures of emotional empathy have been found to correlate with ACC activity when participants knew that their significant other was in pain (Singer *et al.*, 2004). Given that subsequent studies (including this one) have involved watching strangers and

have not observed such correlations, it is possible that Singer *et al.*'s ACC activity indexed personal distress at seeing a close other in pain, as opposed to domain general empathic ability. Finally, it is worth noting that previous work has found that ACC may correlate with individual differences the severity of pain that subjects perceive in themselves (Coghill *et al.*, 2003) or in others (Jackson *et al.*, 2005; Saarela *et al.*, 2007). Because we did not collect on-line ratings of perceived pain during the self or other pain tasks, we are unable to determine whether similar correlations could be observed here.

In contrast to the findings for fear of pain—with one exception—neither body-focused anxiety (as indexed by the ASI) nor general trait anxiety (as measured by the STAI) correlated with activity in any overlap or interaction regions. The exception was that STAI-T scores showed strong correlations with activity in bilateral regions of RLPFC active only during the other pain task. Behavioral research suggests that trait anxious individuals are vigilant for potential threats in the environment (Wilson and MacLeod, 2003; Etkin *et al.*, 2004; Putman *et al.*, 2006) and a recent imaging study (Seminowicz and Davis, 2006) found that individual differences in 'catastrophizing' correlated with activity in lateral PFC during mild pain stimulation. In light of those findings, and the fact that RLPFC is involved in the evaluation of self-generated information (Christoff *et al.*, 2003), it is possible that anxious individuals are more sensitive to detecting facial and body cues to pain, and/or elaborating negative interpretations of pain events, which in turn might lead them to feel differently about them than less anxious individuals. The possibility that differential experience of discrete emotions, such as fear, may have played a role in this study is considered in more detail below in the section on future directions.

The striking selectivity of the fear and anxiety-related correlations to conditions of self-pain or other pain constrains and strengthens our understanding of their underlying neural mechanisms. Whereas the correlation involving fear of pain supports a role for the ACC in motivated responses to self-directed damage or injury, the correlation involving trait anxiety may reflect a role for RLPFC in reflection upon the potential for threats from the environment.

### Limitations when comparing self and other pain

Although the results of the present study dovetail with, and extend, the results of prior studies of pain empathy, it is important to highlight aspects of the present experiment's design—some of which are unique to this study, and some of which are shared by all studies of pain empathy—that may qualify the inferences that can be drawn. Consideration of these limitations may both clarify the nature of the present findings and highlight the kinds of experimental design choices inherent in studying pain empathy. Perhaps most salient is the fact that the stimuli and timing parameters used

in self-pain and other pain tasks differed, which raises a concern that the patterns of common and distinct activation might in some way reflect idiosyncratic aspects of stimulus presentation and timing. Four points should be noted here.

First, in any pain empathy study, one might worry that self-pain responses may be on a qualitatively different scale than are other pain responses, and so comparison of them may be difficult. Most prior studies were concerned with what is common to self and other pain (e.g. Singer *et al.*, 2004), or only examined the perception of others in pain (e.g. Jackson *et al.*, 2005), and so avoided facing this problem. Because the present study sought to determine not only what is similar and what is different about self and other pain, we addressed this problem by not directly comparing responses to self-pain and other pain. Instead, we first calculated activation for self-pain and other pain relative to their respective baselines, and then compared and contrasted regions of activation across these comparisons. Thus, we compared and contrasted the statistical reliability of two effects, controlling for differences in scale by comparing each to its respective baseline condition. As such, the comparisons of self and other pain made here are (at least partially) controlled for differences in stimuli.

Second, some differences between the stimuli in the self-pain and other pain conditions are unavoidable given the question at hand. What is of interest is the extent to which these two disparate types of stimuli elicit common as opposed to distinct patterns of underlying neural activity. In this regard, the logic of the present experiment is the same as that employed in some prior studies of pain empathy (Botvinick *et al.*, 2005), and more generally in any cognitive neuroscience study examining the extent to which to different tasks—with differing stimuli, timing, etc.—rely upon common underlying neural activity. For example, this logic has guided examinations of common and distinct patterns of activity associated with different cognitive control tasks (see e.g. Fan *et al.*, 2003; Sylvester *et al.*, 2003; Wager *et al.*, 2005) or with pain and selective attention (Davis *et al.*, 1997; Derbyshire *et al.*, 1998). In all cases, the extent to which two differing types of tasks elicit common patterns of activation is informative about the nature of the processes involved in each one. Although we can never be sure whether some of the observed activity reflects differences in aspects of stimulus processing that are not of central concern rather than distinct types of self or other-related processing, the finding of common ACC and AI activity during self-pain mitigates this concern. This finding dovetails with the findings from other studies of pain empathy that, like the present one, have used self and other pain stimuli that differ to varying degrees (as described below). If differences in stimulus type were responsible for self or other-related activations, then overlapping ACC and AI activity might not have been observed.

Third, it is worth noting participants might anticipate the occurrence of pain stimuli in both the self and other pain

tasks, and if the spontaneous anticipatory processes that occur during the two tasks are different, this might in turn influence observed patterns of activation. This concern applies for the present study and for other studies using film or photo stimuli in the other pain condition and heat stimuli in the self-pain condition (e.g. Botvinick *et al.*, 2005; Jackson *et al.*, 2005). Given the kind of cross-stimulus comparison of interest here (see above discussion) this is somewhat unavoidable, and to date no studies have been designed to disentangle stimulus-related and anticipatory processes during pain empathy. That being said, we did attempt to address this possibility in the present study by asking participants during verbal debriefing to indicate whether they consciously anticipated when painful events would occur in each task. No participants indicated that they did.

In this context, it is interesting that in our pre-scan stimulus norming study (involving a group of participants separate from those who were scanned), the mean rating of pain affect for the non-painful portions of the video was relatively high, suggesting perhaps that participants were feeling some anticipatory negative affect before the painful events transpired. Here it is useful to keep in mind that participants in this norming study were explicitly instructed to be aware of their emotional experience, which may have led them to anticipate the occurrence of emotional events when none were transpiring. Strikingly, it has been found that attending to emotion during the presentation of aversive events has been shown to suppress emotional responses (Taylor *et al.*, 2003). This suggests that the normative ratings of affect in the pre-scanner study may both overestimate the anticipatory effects of the non-pain-related portions of the video clip, and at the same time underestimate the affective punch of the pain-related events. The experiential difference between the non-painful and painful portions of the video clip could therefore be greater for scanned participants who were not paying attention to and continuously rating how they felt. In addition, to the extent that the non-painful portions of the video involved elicitation of some negative affect, activity in the cingulate, insula and amygdala during other pain *vs* other non-pain conditions becomes difficult to explain. Comparison of non-pain and pain-related events for the other pain video might, therefore, provide a fairly conservative test of whether or not activation in pain and affect related regions would be observed. Consistent with this interpretation, pain affect ratings in the normative sample were lower (5.94) than were ratings provided by the scanned sample (6.73). For the normative sample, continuous attention to their affective responses may have diminished their pain experience.

Fourth and last, we note that although the decision to use distinct stimuli in the self and other conditions may qualify the inferences one may draw from this or other pain empathy studies, our stimulus choice was made with the intention to avoid another kind of inferential conundrum that may arise when the cues used in self and other

conditions are quite similar. This problem can be illustrated in the design of one of the first pain empathy studies (Singer *et al.*, 2004). In this study, female participants saw a visual cue indicating that either they or their male partner would receive a mild electric shock on that trial. Although the stimuli that triggered perception of pain in self and other were equated in this study, because the participant and their partner received precisely the same type of shock with the same duration, it is possible that on other pain trials, the participant was experiencing not an empathic experience of what their partner might be feeling, but rather a recollection of their own pain on a prior trial. The present experiment avoided this particular inferential problem by using other pain stimuli that the participant had not personally experienced. As such, the consistency in findings of ACC and AI activity in self and other pain across the two studies suggests that as opposed to either affective recall or unique stimulus-bound effects, these activations truly represent the common processing of pain affect across conditions.

## CONCLUSIONS AND FUTURE DIRECTIONS

The ability to empathically understand the internal states of other people is both adaptive and essential. Indeed, this ability is so essential that empathic impairments produce profound dysfunction of social and emotional behavior (Frith, 2001; Blair, 2003; Baron-Cohen *et al.*, 2005). From a social-evolutionary perspective, recruitment of pain processing systems when perceiving another experiencing pain would be adaptive both because it would help us understand their internal state and might spark us to aid and assist them, and because it could serve as a platform for vicarious learning about painful experiences that we should avoid. In the present study, both the first person experience and the third person observation of pain recruited pain-related cingulate and insular systems, as well thalamic and prefrontal systems involved in memory. These findings dovetail with previous work demonstrating similar effects (Jackson *et al.*, 2006a), suggesting that recruitment of these systems may provide the neural core for empathic understanding of pain. When experiencing pain directly, additional recruitment of the anterior and mid insula and PFC may support attention to and control of pain responses. When perceiving other's actions lead to painful outcomes, additional recruitment of the amygdala, OFC and attentional systems may help support vicarious learning about its consequences (Olsson *et al.*, 2007).

There is also an intriguing question as to whether the pain tasks may have elicited other types of affective responses, such as fear or surprise, in addition to the direct or vicarious experience of pain. Although we did not collect ratings of discrete emotions in response to the stimuli used here, the question as to whether personally experienced or observed painful events elicit complex mixtures of emotion is important. It is, however, beyond the scope of the present research. In this regard, it is noteworthy that no prior study on pain

empathy has attempted to distinguish potential differences in discrete emotions elicited by self and other pain. Future work may shed light on this important issue.

When viewed against the backdrop of the growing social cognitive neuroscience literature on empathy, the present findings support a neural answer to the question posed in the 'Introduction' section: how do we effortlessly and empathically experience another individual's pain and suffering? We suffer because perceiving another individual suffering a physical injury activates regions used to process our own experience of physical pain. This conclusion suggests a reason why Joe Thiesmann's leg break was rated as the most shocking moment in sports history, and still evinces articles about the event 20 years later. Television viewers may have felt the break to be not just a shocking event for Mr Theismann, but may have felt it as a shock to their own system as well.

## REFERENCES

- Adolphs, R. (2003). Cognitive neuroscience of human social behaviour. *Nature Reviews Neuroscience*, 4, 165–78.
- Allison, T., Puce, A., McCarthy, G. (2000). Social perception from visual cues: role of the STS region. *Trends in Cognitive Sciences*, 4, 267–78.
- Anderson, A.K., Christoff, K., Panitz, D., De Rosa, E., Gabrieli, J.D. (2003). Neural correlates of the automatic processing of threat facial signals. *Journal of Neuroscience*, 23, 5627–33.
- Anderson, A.K., Phelps, E.A. (2001). Lesions of the human amygdala impair enhanced perception of emotionally salient events. *Nature*, 411, 305–9.
- Baron-Cohen, S., Knickmeyer, R.C., Belmonte, M.K. (2005). Sex differences in the brain: implications for explaining autism. *Science*, 310, 819–23.
- Becerra, L.R., Breiter, H.C., Stojanovic, M., et al. (1999). Human brain activation under controlled thermal stimulation and habituation to noxious heat: an fMRI study. *Magnetic Resonance in Medicine*, 41, 1044–57.
- Bechara, A. (2002). The neurology of social cognition. *Brain*, 125, 1673–5.
- Bechara, A., Damasio, H., Damasio, A.R. (2003). Role of the amygdala in decision-making. *Annals of the New York Academy of Sciences*, 985, 356–69.
- Beer, J.S., Heerey, E.A., Keltner, D., Scabini, D., Knight, R.T. (2003). The regulatory function of self-conscious emotion: insights from patients with orbitofrontal damage. *Journal of Personality and Social Psychology*, 85, 594–604.
- Beer, J.S., Ochsner, K.N. (2006). Social cognition: a multi level analysis. *Brain Research*, 1079, 98–105.
- Beer, J.S., Shimamura, A.P., Knight, R.T. (2004). Frontal lobe contributions to executive control of cognitive and social behavior. In: Gazzaniga, M.S., editor. *The Cognitive Neurosciences: III*, Cambridge, MA: MIT Press, pp. 1091–104.
- Blair, R.J. (2003). Neurobiological basis of psychopathy. *British Journal of Psychiatry*, 182, 5–7.
- Blais, M.A., Otto, M.W., Zucker, B.G., et al. (2001). The anxiety sensitivity index: item analysis and suggestions for refinement. *Journal of Personality Assessment*, 77, 272–94.
- Blakemore, S.J., Decety, J. (2001). From the perception of action to the understanding of intention. *Nature Review Neuroscience*, 2, 561–7.
- Botvinick, M., Jha, A.P., Bylsma, L.M., et al. (2005). Viewing facial expressions of pain engages cortical areas involved in the direct experience of pain. *Neuroimage*, 25, 312–9.
- Botvinick, M.M., Braver, T.S., Barch, D.M., Carter, C.S., Cohen, J.D. (2001). Conflict monitoring and cognitive control. *Psychological Review*, 108, 624–52.
- Botvinick, M.M., Cohen, J.D., Carter, C.S. (2004). Conflict monitoring and anterior cingulate cortex: an update. *Trends in Cognitive Sciences*, 8, 539–46.
- Bunge, S.A., Ochsner, K.N., Desmond, J.E., Glover, G.H., Gabrieli, J.D. (2001). Prefrontal regions involved in keeping information in and out of mind. *Brain*, 124, 2074–86.
- Calder, A.J., Lawrence, A.D., Young, A.W. (2001). Neuropsychology of fear and loathing. *Nature Review Neuroscience*, 2, 352–63.
- Carr, L., Iacoboni, M., Dubeau, M.C., Mazziotta, J.C., Lenzi, G.L. (2003). Neural mechanisms of empathy in humans: a relay from neural systems for imitation to limbic areas. *Proceedings of the National Academy of Sciences of the United States of America*, 100, 5497–502.
- Cavanna, A.E., Trimble, M.R. (2006). The precuneus: a review of its functional anatomy and behavioural correlates. *Brain*, 129, 564–83.
- Chaminade, T., Meltzoff, A.N., Decety, J. (2005). An fMRI study of imitation: action representation and body schema. *Neuropsychologia*, 43, 115–27.
- Christoff, K., Gabrieli, J.D.E. (2000). The frontopolar cortex and human cognition: evidence for a rostrocaudal hierarchical organization in human prefrontal cortex. *Psychobiology*, 28, 168–86.
- Christoff, K., Ream, J.M., Geddes, L.P., Gabrieli, J.D. (2003). Evaluating self-generated information: anterior prefrontal contributions to human cognition. *Behavioral Neurosciences*, 117, 1161–8.
- Coghill, R.C., McHaffie, J.G., Yen, Y.F. (2003). Neural correlates of interindividual differences in the subjective experience of pain. *Proceedings of the National Academy of Sciences of the United States of America*, 100, 8538–42.
- Craig, A.D. (2002). How do you feel? Interoception: the sense of the physiological condition of the body. *Nature Reviews Neuroscience*, 3, 655–66.
- Craig, A.D. (2003). Interoception: the sense of the physiological condition of the body. *Current Opinion in Neurobiology*, 13, 500–05.
- Craig, A.D. (2004). Human feelings: why are some more aware than others? *Trends in Cognitive Sciences*, 8, 239–41.
- Critchley, H.D. (2005). Neural mechanisms of autonomic, affective, and cognitive integration. *The Journal of Comparative Neurology*, 493, 154–66.
- Curtis, C.E., Sun, F.T., Miller, L.M., D'Esposito, M. (2005). Coherence between fMRI time-series distinguishes two spatial working memory networks. *Neuroimage*, 26, 177–83.
- Dapretto, M., Davies, M.S., Pfeifer, J.H., et al. (2006). Understanding emotions in others: mirror neuron dysfunction in children with autism spectrum disorders. *Nature Neuroscience*, 9, 28–30.
- Davidson, R.J. (2002). Anxiety and affective style: role of prefrontal cortex and amygdala. *Biological Psychiatry*, 51, 68–80.
- Davis, K.D., Taylor, S.J., Crawley, A.P., Wood, M.L., Mikulis, D.J. (1997). Functional MRI of pain- and attention-related activations in the human cingulate cortex. *Journal of Neurophysiology*, 77, 3370–80.
- Decety, J., Chaminade, T., Grezes, J., Meltzoff, A.N. (2002). A PET exploration of the neural mechanisms involved in reciprocal imitation. *Neuroimage*, 15, 265–72.
- Decety, J., Jackson, P.L. (2004). The functional architecture of human empathy. *Behavioral and Cognitive Neuroscience Reviews*, 3, 71–100.
- Delgado, M.R., Olsson, A., Phelps, E.A. (2006). Extending animal models of fear conditioning to humans. *Biological Psychology*, 73, 39–48.
- Derbyshire, S.W., Vogt, B.A., Jones, A.K. (1998). Pain and Stroop interference tasks activate separate processing modules in anterior cingulate cortex. *Experimental Brain Research*, 118, 52–60.
- Devinsky, O., Morrell, M.J., Vogt, B.A. (1995). Contributions of anterior cingulate cortex to behaviour. *Brain*, 118, 279–306.
- Downar, J., Crawley, A.P., Mikulis, D.J., Davis, K.D. (2002). A cortical network sensitive to stimulus salience in a neutral behavioral context across multiple sensory modalities. *Journal of Neurophysiology*, 87, 615–20.
- Downar, J., Mikulis, D.J., Davis, K.D. (2003). Neural correlates of the prolonged salience of painful stimulation. *Neuroimage*, 20, 1540–51.

- Eisenberger, N.I., Lieberman, M.D. (2004). Why rejection hurts: a common neural alarm system for physical and social pain. *Trends in Cognitive Sciences*, 8, 294–300.
- Etkin, A., Klemenhagen, K.C., Dudman, J.T., et al. (2004). Individual differences in trait anxiety predict the response of the basolateral amygdala to unconsciously processed fearful faces. *Neuron*, 44, 1043–55.
- Fan, J., Flombaum, J.I., McCandliss, B.D., Thomas, K.M., Posner, M.I. (2003). Cognitive and brain consequences of conflict. *Neuroimage*, 18, 42–57.
- Farrell, M.J., Laird, A.R., Egan, G.F. (2005). Brain activity associated with painfully hot stimuli applied to the upper limb: a meta-analysis. *Human Brain Mapping*, 25, 129–39.
- Farrer, C., Franck, N., Georgieff, N., Frith, C.D., Decety, J., Jeannerod, M. (2003). Modulating the experience of agency: a positron emission tomography study. *Neuroimage*, 18, 324–33.
- Farrow, T.F., Zheng, Y., Wilkinson, I.D., et al. (2001). Investigating the functional anatomy of empathy and forgiveness. *Neuroreport*, 12, 2433–8.
- Fredrickson, B.L., Kahneman, D. (1993). Duration neglect in retrospective evaluations of affective episodes. *Journal of Personality and Social Psychology*, 65, 45–55.
- Frith, U. (2001). Mind blindness and the brain in autism. *Neuron*, 32, 969–79.
- Gallagher, H.L., Frith, C.D. (2003). Functional imaging of 'theory of mind'. *Trends in Cognitive Sciences*, 7, 77–83.
- Gallese, V., Keysers, C., Rizzolatti, G. (2004). A unifying view of the basis of social cognition. *Trends in Cognitive Sciences*, 8, 396–403.
- Glover, G. (1999). 3D Z-shim method for reduction of susceptibility effects in BOLD fMRI. *Magnetic Resonance in Medicine*, 42, 290–9.
- Goel, V., Dolan, R.J. (2003). Reciprocal neural response within lateral and ventral medial prefrontal cortex during hot and cold reasoning. *Neuroimage*, 20, 2314–21.
- Hebben, N. (1985). Toward the assessment of clinical pain. In: Aronoff, G.M., editor. *Evaluation and Treatment of Chronic Pain*. Baltimore: Urban & Schwarzenburg, pp. 451–62.
- Hornak, J., Bramham, J., Rolls, E.T., et al. (2003). Changes in emotion after circumscribed surgical lesions of the orbitofrontal and cingulate cortices. *Brain*, 126, 1691–712.
- Hutchison, W.D., Davis, K.D., Lozano, A.M., Tasker, R.R., Dostrovsky, J.O. (1999). Pain-related neurons in the human cingulate cortex. *Nature Neuroscience*, 2, 403–5.
- Hynes, C.A., Baird, A.A., Grafton, S.T. (2006). Differential role of the orbital frontal lobe in emotional versus cognitive perspective-taking. *Neuropsychologia*, 44, 374–83.
- Iacoboni, M. (2005). Neural mechanisms of imitation. *Current Opinion in Neurobiology*, 15, 632–7.
- Ickes, W.J. (1997). *Empathic accuracy*. Guilford Press, NY, 1997.
- 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. *Neuropsychologia*, 44, 752–61.
- 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, 771–9.
- 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.
- Kampe, K.K., Frith, C.D., Frith, U. (2003). "Hey John": signals conveying communicative intention toward the self activate brain regions associated with "mentalizing," regardless of modality. *Journal of Neuroscience*, 23, 5258–63.
- Keysers, C., Perrett, D.I. (2004). Demystifying social cognition: a Hebbian perspective. *Trends in Cognitive Sciences*, 8, 501–7.
- Krolak-Salmon, P., Henaff, M.A., Isnard, J., et al. (2003). An attention modulated response to disgust in human ventral anterior insula. *Annals of Neurology*, 53, 446–53.
- Lamm, C., Batson, C.D., Decety, J. (2007). The neural substrate of human empathy: effects of perspective-taking and cognitive appraisal. *Journal of Cognitive Neuroscience*, 19, 42–58.
- Levine, L.J., Safer, M.A. (2002). Sources of bias in memory for emotions. *Current Directions in Psychological Science*, 11, 169–73.
- Lou, H.C., Luber, B., Crupain, M., et al. (2004). Parietal cortex and representation of the mental Self. *Proceedings of the National Academy of Sciences of the United States of America*, 101, 6827–32.
- McNeil, D.W., Rainwater, A.J. 3rd. (1998). Development of the fear of pain questionnaire-III. *Journal of Behavioral Medicine*, 21, 389–410.
- Meltzoff, A.N., Decety, J. (2003). What imitation tells us about social cognition: a rapprochement between developmental psychology and cognitive neuroscience. *Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences*, 358, 491–500.
- Mesulam, M.M., Mufson, E.J. (1982). Insula of the old world monkey. III: efferent cortical output and comments on function. *Journal of Comparative Neurology*, 212, 38–52.
- Milham, M.P., Banich, M.T., Webb, A., et al. (2001). The relative involvement of anterior cingulate and prefrontal cortex in attentional control depends on nature of conflict. *Brain Research Cognitive Brain Research*, 12, 467–73.
- Mitchell, J.P. (2006). Mentalizing and Marr: an information processing approach to the study of social cognition. *Brain Research*, 1079, 66–75.
- Mitchell, J.P., Banaji, M.R., Macrae, C.N. (2005). The link between social cognition and self-referential thought in the medial prefrontal cortex. *Journal of Cognitive Neuroscience*, 17, 1306–15.
- Mitchell, J.P., Heatherton, T.F., Macrae, C.N. (2002). Distinct neural systems subservise person and object knowledge. *Proceedings of the National Academy of Sciences of the United States of America*, 99, 15238–43.
- Morrison, I., Downing, P.E. (2007). Organization of felt and seen pain responses in anterior cingulate cortex. *Neuroimage*, 37, 642–51.
- Morrison, I., Lloyd, D., di Pellegrino, G., Roberts, N. (2004). Vicarious responses to pain in anterior cingulate cortex: is empathy a multisensory issue? *Cognitive, Affective and Behavioral Neuroscience*, 4, 270–8.
- Morrison, I., Peelen, M.V., Downing, P.E. (2007). The sight of others' pain modulates motor processing in human cingulate cortex. *Cerebral Cortex*, 17, 2214–22.
- Mufson, E.J., Mesulam, M.M. (1982). Insula of the old world monkey. II: afferent cortical input and comments on the claustrum. *Journal of Comparative Neurology*, 212, 23–37.
- O'Doherty, J., Critchley, H., Deichmann, R., Dolan, R.J. (2003). Dissociating valence of outcome from behavioral control in human orbital and ventral prefrontal cortices. *Journal of Neuroscience*, 23, 7931–9.
- O'Doherty, J.P. (2004). Reward representations and reward-related learning in the human brain: insights from neuroimaging. *Current Opinion in Neurobiology*, 14, 769–76.
- Ochsner, K.N. (2000). Are affective events richly recollected or simply familiar? The experience and process of recognizing feelings past. *Journal of Experimental Psychological: General*, 129, 242–61.
- Ochsner, K.N., Beer, J.S., Robertson, E., et al. (2005). The neural correlates of direct and reflected self-knowledge. *Neuroimage*, 28, 797–814.
- Ochsner, K.N., Knierim, K., Ludlow, D., Hanelin, J., Ramachandran, T., Mackey, S. (2004). Reflecting upon feelings: An fMRI study of neural systems supporting the attribution of emotion to self and other. *Journal of Cognitive Neuroscience*, 16, 1746–72.
- Ochsner, K.N., Kosslyn, S.M., Cosgrove, G.R., et al. (2001). Deficits in visual cognition and attention following bilateral anterior cingulotomy. *Neuropsychologia*, 39, 219–30.
- Ochsner, K.N., Ludlow, D.H., Knierim, K., et al. (2006). Neural correlates of individual differences in pain-related fear and anxiety. *Pain*, 120, 69–77.
- Ochsner, K.N., Schacter, D.L. (2000). A social cognitive neuroscience approach to emotion and memory. In: Borod, J.C., editor. *The Neuropsychology of Emotion*. London: Oxford University Press, pp. 163–93.
- Olsson, A., Nearing, K.I., Phelps, E.A. (2007). Learning Fears by Observing Others: The Neural Systems of Social Fear Transmission. *Social Cognitive and Affective Neuroscience*, 2, 3–11.

- Olsson, A., Phelps, E.A. (2004). Learned fear of "unseen" faces after Pavlovian, observational, and instructed fear. *Psychological Science*, *15*, 822–8.
- Peyron, R., Laurent, B., Garcia-Larrea, L. (2000). Functional imaging of brain responses to pain. A review and meta-analysis. *Neurophysiologie Clinique*, *30*, 263–88.
- Phan, K.L., Wager, T., Taylor, S.F., Liberzon, I. (2002). Functional neuroanatomy of emotion: a meta-analysis of emotion activation studies in PET and fMRI. *Neuroimage*, *16*, 331–48.
- Phelps, E.A., Anderson, A.K. (1997). Emotional memory: what does the amygdala do? *Current Biology*, *7*, R311–4.
- Phillips, M.L., Young, A.W., Senior, C., et al. (1997). A specific neural substrate for perceiving facial expressions of disgust. *Nature*, *389*, 495–8.
- Postle, B.R., Awh, E., Jonides, J., Smith, E.E., D'Esposito, M. (2004). The where and how of attention-based rehearsal in spatial working memory. *Brain Research Cognitive Brain Research*, *20*, 194–205.
- 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*, 291–301.
- Putman, P., Hermans, E., van Honk, J. (2006). Anxiety meets fear in perception of dynamic expressive gaze. *Emotion*, *6*, 94–102.
- Raij, T.T., Numminen, J., Narvanen, S., Hiltunen, J., Hari, R. (2005). Brain correlates of subjective reality of physically and psychologically induced pain. *Proceedings of the National Academy of Sciences of the United States of America*, *102*, 2147–51.
- Rainville, P., Doucet, J.C., Fortin, M.C., Duncan, G.H. (2004). Rapid deterioration of pain sensory-discriminative information in short-term memory. *Pain*, *110*, 605–15.
- Rainville, P., Duncan, G.H., Price, D.D., Carrier, B., Bushnell, M.C. (1997). Pain affect encoded in human anterior cingulate but not somatosensory cortex. *Science*, *277*, 968–71.
- Ranganath, C., Johnson, M.K., D'Esposito, M. (2003). Prefrontal activity associated with working memory and episodic long-term memory. *Neuropsychologia*, *41*, 378–89.
- Ruby, P., Decety, J. (2004). How would you feel versus how do you think she would feel? A neuroimaging study of perspective-taking with social emotions. *Journal of Cognitive Neuroscience*, *16*, 988–99.
- 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. *Cerebral Cortex*, *17*, 230–7.
- Sawamoto, N., Honda, M., Okada, T., et al. (2000). Expectation of pain enhances responses to nonpainful somatosensory stimulation in the anterior cingulate cortex and parietal operculum/posterior insula: an event-related functional magnetic resonance imaging study. *Journal of Neuroscience*, *20*, 7438–45.
- Schoenbaum, G., Setlow, B., Saddoris, M.P., Gallagher, M. (2003). Encoding predicted outcome and acquired value in orbitofrontal cortex during cue sampling depends upon input from basolateral amygdala. *Neuron*, *39*, 855–67.
- Seminowicz, D.A., Davis, K.D. (2006). Cortical responses to pain in healthy individuals depends on pain catastrophizing. *Pain*, *120*, 297–306.
- Shamay-Tsoory, S.G., Lester, H., Chisin, R., et al. (2005). The neural correlates of understanding the other's distress: a positron emission tomography investigation of accurate empathy. *Neuroimage*, *27*, 468–72.
- 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*, 1157–62.
- 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*, 466–9.
- Spielberger, C.D., Gorsuch, R.L., Lushemne, R., Vagg, P.R., Jacobs, G.A. (1983). *Manual for the State-Trait Anxiety Inventory (Form Y)*. Palo Alto, CA: Consulting Psychologists Press.
- Stone, V.E., Baron-Cohen, S., Knight, R.T. (1998). Frontal lobe contributions to theory of mind. *Journal of Cognitive Neuroscience*, *10*, 640–56.
- Sylvester, C.Y., Wager, T.D., Lacey, S.C., et al. (2003). Switching attention and resolving interference: fMRI measures of executive functions. *Neuropsychologia*, *41*, 357–70.
- Taylor, S.F., Phan, K.L., Decker, L.R., Liberzon, I. (2003). Subjective rating of emotionally salient stimuli modulates neural activity. *Neuroimage*, *18*, 650–9.
- Thompson-Schill, S.L., Jonides, J., Marshuetz, C., et al. (2002). Effects of frontal lobe damage on interference effects in working memory. *Cognitive, Affective and Behavioral Neuroscience*, *2*, 109–20.
- Vogele, K., Fink, G.R. (2003). Neural correlates of the first-person-perspective. *Trends in Cognitive Sciences*, *7*, 38–42.
- Vogt, B.A. (2005). Pain and emotion interactions in subregions of the cingulate gyrus. *Nature Reviews, Neuroscience*, *6*, 533–44.
- Vollm, B.A., Taylor, A.N., Richardson, P., et al. (2006). Neuronal correlates of theory of mind and empathy: a functional magnetic resonance imaging study in a nonverbal task. *Neuroimage*, *29*, 90–8.
- Wager, T.D., Feldman Barrett, L. (2004). From affect to control: functional specialization of the insula in motivation and regulation. *PsychExtra*.
- Wager, T.D., Jonides, J., Smith, E.E. (2005). Individual differences in multiple subtypes of switching attention. *Cognitive, Affective and Behavioral Neuroscience*, *5*, 127–43.
- Wager, T.D., Rilling, J.K., Smith, E.E., et al. (2004). Placebo-induced changes in fMRI in the anticipation and experience of pain. *Science*, *303*, 1162–7.
- Wicker, B., Keysers, C., Plailly, J., Royet, J.P., Gallese, V., Rizzolatti, G. (2003). Both of us disgusted in My insula: the common neural basis of seeing and feeling disgust. *Neuron*, *40*, 655–64.
- Wilson, E., MacLeod, C. (2003). Contrasting two accounts of anxiety-linked attentional bias: selective attention to varying levels of stimulus threat intensity. *Journal of Abnormal Psychology*, *112*, 212–8.
- Zaki, J., Ochsner, K.N., Hanelin, J., Wager, T.D., Mackey, S. (2007). Different circuits for different pain: Patterns of functional connectivity reveal distinct networks for processing pain in self and others. *Social Neuroscience*, *2*, 276–91.