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Different circuits for different pain: Patterns of functional connectivity reveal distinct networks for processing pain in self and others

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The ability to empathize with the suffering of others is critical for maintaining relationships and engaging in prosocial behavior. Recently, a series of studies have demonstrated that while watching other people experience pain (other pain), participants engage the anterior insula (AI) and anterior cingulate cortex (ACC), brain regions involved in the direct experience of pain (self pain). Here we test the hypothesis that common activity in ACC and AI may reflect the operation of distinct but overlapping networks of regions that support perception of self or other pain. To address this possibility, we scanned participants using fMRI while they received noxious thermal stimulation (self pain) or watched short videos of other people sustaining painful injuries (other pain). We isolated overlapping regions for self and other pain in the ACC and AI and then used them as seed regions for two kinds of functional connectivity analyses. These analyses identified areas whose activity co-varied with ACC and AI activity during self or other pain either across time (intra-individual connectivity) or across participants (inter-individual connectivity). Both connectivity analyses identified clusters in the midbrain and periaqueductal gray with greater connectivity to the AI during self pain as opposed to other pain. The opposite pattern was found in the dorsal medial prefrontal cortex, that showed greater connectivity to the ACC and AI during other pain than during self pain using both types of analysis. Intra-individual connectivity analyses also revealed regions in the superior temporal sulcus, posterior cingulate, and precuneus that became more connected to ACC during other pain as compared to self pain. Together, these data demonstrated that regions showing similar activity during self and other pain may nonetheless be part of distinct functional networks. These networks could not have been detected in prior work that examined overlap between self and other pain in terms of average activity, but not connectivity.

INTRODUCTION

The ability to empathize with the suffering of other people is a central part of human social behavior. Empathy promotes prosocial behavior towards close others and strangers (Batson et al., 2003; Eisenberg & Miller, 1987), and a lack of emotional empathy is an important symptom of psychopathy and sociopathy (Blair, 2005).

One important conceptual issue in the study of empathy is the extent to which it relies on ''shared representations'' of pain in the self and in others, enabling perceivers to understand the sensory and affective state of a social target. While some theories hold shared representations as the single most central component of empathy (Gallese, 2003; Gallese, Keysers, & Rizzolatti, 2004), others claim that ''empathy is not a simple resonance of

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affect between the self and other,'' and instead requires more complex perspective taking and distinct representations of pain-related responses for self and other (Decety & Jackson, 2004).

In the past few years, these issues have been examined in several fMRI studies of pain empathy. These studies generally compared the experience of painful physical stimulation (self pain) with the experience of seeing other people experience pain (other pain). All studies employing this kind of design have reported that two key regions, the anterior cingulate cortex (ACC) and the anterior insula (AI) become engaged both during self and other pain (Botvinick et al., 2005; Morrison, Lloyd, di Pellegrino, & Roberts, 2004; Singer et al., 2004, 2006). Further studies have also shown that activity in ACC tracks with the amount of pain perceivers believe someone else is experiencing (Jackson, Meltzoff, & Decety, 2005; Saarela et al., 2007).

The role of ACC and AI in empathic pain has been interpreted as reflecting recruitment of systems for computing the emotional or affective value of pain experienced directly by a perceiver or by another person.

Findings of self/other overlap in pain processing have been influential, and have often been used as evidence for the centrality of shared representations in empathy. However, both conceptually and empirically, there are reasons to believe that there may be differences between pain processing for self and other. On one hand, primary sensory cortex involved in coding the location and intensity, rather than the affective value of pain (Peyron et al., 1999; Rainville, 2002) has only been engaged during perception of pain in the self, and not when pain is given to others (Singer et al., 2004). Furthermore, the direct experience of self pain may uniquely engage forms of coping or regulation not engaged during other pain. For example, descending projections from the ACC, AI, and thalamus innervate pain-related brainstem nuclei such as the periaqueductal gray (PAG) and the midbrain nucleus cuneiformis, which can modulate the output of pain-related afferents, changing the experience of pain according to changes in expectancy (Fields, 2004; Keltner et al., 2006; Wager, 2005a; Zambreanu, Wise, Brooks, Iannetti, & Tracey, 2005).

On the other hand, registering the suffering of another may require taking that person's perspective in order to draw inferences about what he or she might be feeling. These mental state attributions may affect a perceiver's empathic reaction to a target's pain, including the perceiver's subsequent behavior towards that target (Batson et al., 2003). Candidate brain regions for making mental state attributions during the perception of others' pain include the medial prefrontal cortex (MPFC), which is involved in both cognitive and affective perspective taking (Mitchell, Heatherton, & Macrae, 2002; Ochsner et al., 2004a; Vollm et al., 2006), and superior temporal sulcus (STS), which is involved in assessing the social significance of nonverbal cues (Pelphrey, Morris, & McCarthy, 2004; Saxe, Xiao, Kovacs, Perrett, & Kanwisher, 2004).

Previous functional imaging studies have provided initial support for dissociations in activity between self and other pain. For example, some studies have found areas in PFC and STS to be preferentially active during other pain, and cerebellum and brainstem to be active preferentially during self pain (Botvinick et al., 2005; Morrison et al., 2004; Ochsner et al., under review; Singer et al., 2004). However, no study has found the MPFC to be active during empathic pain, a striking absence in light of the MPFC's centrality to social cognition. Furthermore, it is unclear whether cerebellar, frontal, and other activations found uniquely during self or other pain represent processing steps unrelated to the perception of pain, or whether they are part of unique, overlapping circuits used to process self and other pain, respectively.

One way to test this is through analyses of *functional connectivity* during self and other pain. Whereas standard contrast analyses create a ''snapshot'' of regional brain activity in response to a task or condition, functional connectivity analyses can identify patterns of communication between regions that contrast analyses may not detect. Connectivity analyses can identify regions whose activity co-varies with activity in ACC and AI during self and other pain, helping to create a dynamic model of circuits underlying each type of pain perception. In the context of empathy, this type of analysis provides a means for testing the extent to which overlapping representations underlie empathy for pain.

In order to explore patterns of connectivity during self and other pain, we scanned participants using fMRI while they either received painful heat stimulation, or watched short videos of other people in pain. We identified regions of overlap between self and other pain in AI and ACC that were similar to those reported by previous studies (the main effects of this study

are reported in Ochsner et al., under review). We then used two methods to assess differences in functional connectivity with the commonly recruited regions of AI and ACC.

One analysis examined *inter-individual* connectivity. This analysis searched for regions showing stronger task-related activation in participants who also showed stronger activation in ACC or AI. Significant correlations indicate that individuals who show high ACC (or AI) activity also show high activity in ''connected'' regions; thus, there is a coherent network involving the ACC (or AI) that is more engaged by some individuals than others. The interpretation of task-state effects is that coherent individual differences in correlated activity across regions are greater in some tasks (i.e., self pain) than others (i.e., other pain). Variants of inter-individual connectivity analyses have previously been used to asses several types of network activity, including prefrontal regulation of pain-related activity in the thalamus and midbrain (Lorenz, Minoshima, & Casey, 2003), and prefrontal modulation of emotion-related activity in the amygdala (Ochsner et al., 2004b).

A second analysis examined *intra-individual* connectivity using psychophysiological interaction analyses (PPI; Friston et al., 1997). This analysis searched for brain regions whose activation across time co-varied with that of ACC and AI more in one state than in another in each subject, and then assessed the reliability of these connectivity patterns across subjects. Within subject connectivity analyses have been used previously to assess functional circuits engaged by emotion regulation and executive control of attention (Egner & Hirsch, 2005; Etkin, Egner, Peraza, Kandel, & Hirsch, 2006).

We chose these two analyses because they complement each other methodologically, and consistent findings across the two would strengthen our ability to draw inferences about the brain regions interacting with our seed regions. Task-evoked changes in functional connectivity might be expected to be detected by both methods, but they measure somewhat different quantities and so have complementary advantages. The main advantage of the PPI analysis is that it assesses co-variance between regions across time, and so provides a test of task effects on connectivity within subjects. Advantages of the inter-individual connectivity analysis are: (a) it is less susceptible to timeseries artifacts than PPI; (b) it is more robust to variations in the shape of the hemodynamic response across regions; and (c) it directly compares inter-regional correlations across task conditions, whereas PPI tests a difference in the slope of the relationship among regions, which may be influenced by changes in activation magnitudes in one region.[1] It is important to note, however, that neither of these analyses can establish causal links between regions (i.e., activity in region A causes activity in region B). Instead, these analyses allow inferences that regions are coactive across participants (inter-individual) and across time (PPI), that they are doing so in a way that is functionally relevant, and that the strength of co-activation is modulated by task state.

We expected several differences in connectivity patterns to emerge via these analyses. On one hand, we hypothesized that regions involved in perspective taking, such as medial PFC and the STS, would be preferentially connected to ACC and AI during other pain. On the other hand, we hypothesized that regions involved in processing the sensory and autonomic aspects of pain, such as somatosensory cortex, and the periaqueductal gray (PAG) would be more connected to ACC and AI seed regions during self pain. The goal was to directly test the hypothesis that pain affect is associated with overlapping, but qualitatively different, processing networks depending on whether pain is experienced by participants themselves or by another person.

METHODS

Participants

Thirteen participants (M age = 29.5 years; 6 male) were recruited in compliance with the human subjects regulations of Stanford University Medical School.

Behavioral paradigm

In a single experimental session described in detail elsewhere (Ochsner et al., under review), participants completed both self pain and other pain tasks in counterbalanced order. In the self

[1] That is, if Regions A and B are functionally coupled, and task state S increases activity in A but not B, then apparent connectivity in a PPI analysis may increase, even if no true change in functional coupling has occurred.

pain task, noxious (painful) thermal and non-noxious (neutral) thermal stimulation was delivered to the right distal lateral forearm by a computer-controlled thermal stimulator with an MRI compatible 30 mm^2 Peltier probe (TSA-2001, Medoc, Chapel Hill, NC). Twenty-second blocks of noxious thermal stimuli (45–50°C) alternated with 30 s blocks of neutral stimuli (38°C) five times. Temperatures used for the noxious thermal blocks were determined on a participant-by-participant basis in a pre-scanning session. Noxious temperatures elicited the maximum level of pain without causing movement, which roughly corresponded to a participant-defined 7 out of 10 on a verbal rating scale (0 = *no pain*, 10 = *worst pain imaginable*). 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-minute video clip depicting 17 events in which individuals suffered injuries in sporting events (e.g., a leg break in a soccer match), stunts (e.g., injuring an arm or leg while skateboarding), or vehicular accidents (e.g., a young girl being struck by train). Participants were instructed to attend to and watch all events presented during the course of the video.

As described in detail in Ochsner et al. (under review), a separate behavioral study was conducted to characterize and verify pain perception during the novel other pain task. Thirteen participants (age and gender matched to those in the imaging study) completed the same self and other pain paradigms as in the scanner study while also using a 10-point scale to provide continuous ratings of either self or other pain affect. Paired sample *t*-tests comparing self report painful and non-painful video segments verified that injuries included in the video were effective in creating the perception of pain, $t(12) = 3.20$, $p = .008$. Similar ratings during the self pain condition verified the efficacy of the thermal stimulus in generating the experience of pain during the application of noxious heat, $t(12) > 20$, $p < .001$.

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 SPM2 (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 the Montreal Neurological Institute (MNI) standard template brain, interpolated to $2 \times 2 \times 2$ mm voxels, and smoothed with a Gaussian filter (6 mm full width–half maximum). First-level analyses for the self pain task modeled noxious and neutral blocks with boxcar regressors convolved with the canonical hemodynamic response. First-level analyses for the other pain task modeled observed physical injuries as events (whose onset was the moment a physical injury occurred) convolved with the canonical hemodynamic response. All other portions of the video depicting the same actors engaged in non-painful activities served as the no-pain baseline against which activation related to other pain events was determined. These regressors were fitted to fMRI data from each task using the general linear model. Contrast images for each participant summarized differences between (1) noxious and non-noxious blocks for the self pain task, and (2) 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 SPM maps of regions more active either for the experience of noxious heat as compared to non-noxious warmth, or during the observation of painful as compared to non-painful events experienced by others.

To identify differential patterns of functional connectivity during self and other pain, we followed a two-step analysis procedure. First, we identified commonly activated regions for self and other pain by using the *t*-map for the self pain contrast as an inclusive mask for the other pain

contrast. Each contrast was voxel-level thresholded at $p < .005$, which yields maps of active overlap regions at a height threshold of $p < .000025$ across both tasks using the Fisher method for combining probabilities (Kampe, Frith, & Frith, 2003; Ochsner et al., 2004b). As described in detail elsewhere (Ochsner et al., under review), this analysis identified regions of ACC and AI active during both self and other pain similar to those identified in other studies of pain empathy (Botvinick et al., 2005; Jackson et al., 2005; Morrison et al., 2004).

To assess intra-individual connectivity, we employed a psychophysiologic interaction (PPI) analysis implemented in SPM to identify regions whose timecourse co-varied with the timecourse of activity in either the ACC or AI. A PPI analysis convolves the timecourse of activity in a seed region with a psychological variable of interest and uses this vector as a regressor in a subsequent whole-brain analysis. In this way, PPI analyses identify regions that are functionally connected to the seed region *more strongly* in one condition than in another (Friston et al., 1997). We performed PPI analyses separately for self and other pain. For each condition, we identified the activation peak in each individual that was closest—in Euclidian distance—to the group overlap peaks in ACC and AI, extracted timecourses from each peak, and computed PPI models for each subject based on their own ACC and AI peaks. These individual PPI analyses were then used in group-level paired-sample *t*-tests, comparing connectivity during self pain with connectivity during other pain. Contrasts on those *t*-tests were then estimated to identify: (1) regions that were more connected to AI or ACC during self pain than during other pain; (2) regions that were more connected to AI or ACC during other pain than during self pain; and (3) regions that were connected to AI or ACC during both self and other pain. These contrasts were thresholded at $p < .005$, uncorrected, with an extent threshold of 10 voxels.

To verify that each region from PPI analyses was consistently active in conditions of interest, the Brain Imaging Toolbox (http://web.mit.edu/swg/www/software.htm) was used to extract parameter estimates for each participant 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.

The second, *inter-individual* method for computing functional connectivity examined how individual differences in task-evoked activation of ACC and AI co-varied with task-evoked activation in other brain regions, and whether this connectivity was modulated by the self versus other task condition. These analyses were performed using custom Matlab scripts written by one of the authors (TDW). Data consisted of contrast magnitude maps for self and other pain for each participant. Mean contrast values in the AI and ACC were used as "seeds," and we calculated maps of correlations between each voxel and the seed for both self and other pain contrasts. We searched for voxels with higher correlations during self versus other pain by comparing the two correlation values using methods developed by Steiger (1980). This search was conducted in regions of interest defined by PPI analyses, namely: MPFC; superior temporal sulcus (STS); ACC; PCC; insula; supplementary motor area; and midbrain, and thresholded at $p < .005$, uncorrected, with an extent threshold of 10 contiguous voxels. As noted in the introduction, task-evoked changes in functional connectivity might be expected to be detected by both methods, but they measure somewhat different quantities and so have complementary advantages.

RESULTS

Imaging results

Regions common to self and other pain perception. As reported elsewhere (Ochsner et al., under review), "standard" contrast analyses revealed common recruitment of anterior mid cingulate cortex (MNI coordinates: 4, 10, 40) and right ventral anterior insula (MNI coordinates: 42, 22, −12), as well as middle frontal gyrus, premotor cortex, and dorsal thalamus during both self and other pain as compared to self and other non-pain conditions. Additional interaction contrasts revealed a set of premotor, parietal, and lateral prefrontal regions that responded preferentially to other pain, and clusters in the anterior and posterior insula responding more strongly to self pain. As these data have been commented upon in detail elsewhere, we will not elaborate them here. For our present purposes, the results of connectivity analyses with the ACC and AI regions commonly recruited for both self and other pain are of primary interest.

Connectivity with ACC. Regions showing increased intra-individual connectivity in PPI analyses with the ACC seed region during other pain as compared to self pain included the right STS, MPFC and rostrolateral prefrontal cortex, posterior cingulate cortex, parahippocampal gyrus, premotor cortex, and fusiform gyrus (Table 1). Interestingly, some of these regions (i.e., premotor cortex and RLPFC) had already been shown by contrast analyses to be more *active* during other pain than during self pain. However, the PPI analysis identified two additional regions—STS and MPFC—that, while not more active during the perception of other pain, did show increased connectivity with ACC during this condition.

Regions showing increased connectivity to the ACC seed during self pain than during other pain included an additional region in ACC anterior and superior to the seed region, as well as an insula region posterior and superior to the overlap AI region and clusters in the parietal lobe and cerebellum. Analysis of parameter estimates for the ACC region demonstrated that differential connectivity for self and other pain was driven by a strong *decoupling* of this region's activity from that of the seed region during other pain, as opposed to a significant positive correlation between these regions during self pain (see Figure 1 and Table 2). This was the only region whose differential connectivity was driven by such an effect.

The inter-individual connectivity analyses revealed patterns consistent with PPI connectivity analyses in MPFC and STS but did not reproduce the differential connectivity pattern observed in the ACC.

Connectivity with AI. Regions showing increased intra-individual connectivity with the AI during other as compared to self pain again included a priori regions of interest in the MPFC (which was found in inter-individual analyses also), as well as clusters in the posterior cingulate and precuneus, lingual gyrus, and precentral gyrus (see Figure 2 and Table 2). Of these, only the precentral and lingual gyri were found by simple contrasts to become more active during other pain.

Regions showing increased connectivity with the AI during self as compared to other pain included the periaqueductal gray (PAG), right mid insula and right middle temporal gyrus, as well as a cluster in the midbrain adjacent to the nucleus cuneiformis (Keltner et al., 2006). Inter-individual connectivity analyses showed results consistent with much of this pattern, mirroring timecourse connectivity results in the PAG and mid insula.

Common patterns of connectivity with ACC or AI. To determine whether any regions showed functional connectivity with ACC or AI during both self and other pain, we calculated overlap images of the results of each of the four primary analyses (i.e., intra- and inter-individual connectivity analyses for the ACC and AI). The only analysis yielding a pattern of functional connectivity common to both self and other pain was the intra-individual connectivity analysis for the AI,

TABLE 1
Regions showing common activation for self pain and other pain, as assessed by masked contrast analyses

		Coordinates				
Region of activation	*Lat*	*x*	*y*	*z*	*T-score*	*Volume (vox)*
Middle frontal gyrus	R	46	28	20	4.4	59
Anterior cingulate	M	4	10	40	4.13	11
Premotor gyrus	R	48	8	40	3.99	23
Anterior insula (AI)	R	42	22	−12	7.76	56
	R	28	28	2	5.2	57
	R	28	16	6	5.18	(L)
	R	30	20	−2	4.75	(L)
Dorsal thalamus	R	12	−2	10	5.2	56
	R	20	−6	14	4.03	(L)
	R	16	−10	20	3.78	(L)

Notes: Local maxima for clusters are designated with (L). Hemisphere is designated as midline (M) for maxima within 6 mm of the midline. Coordinates are in MNI space. Vox = voxels.

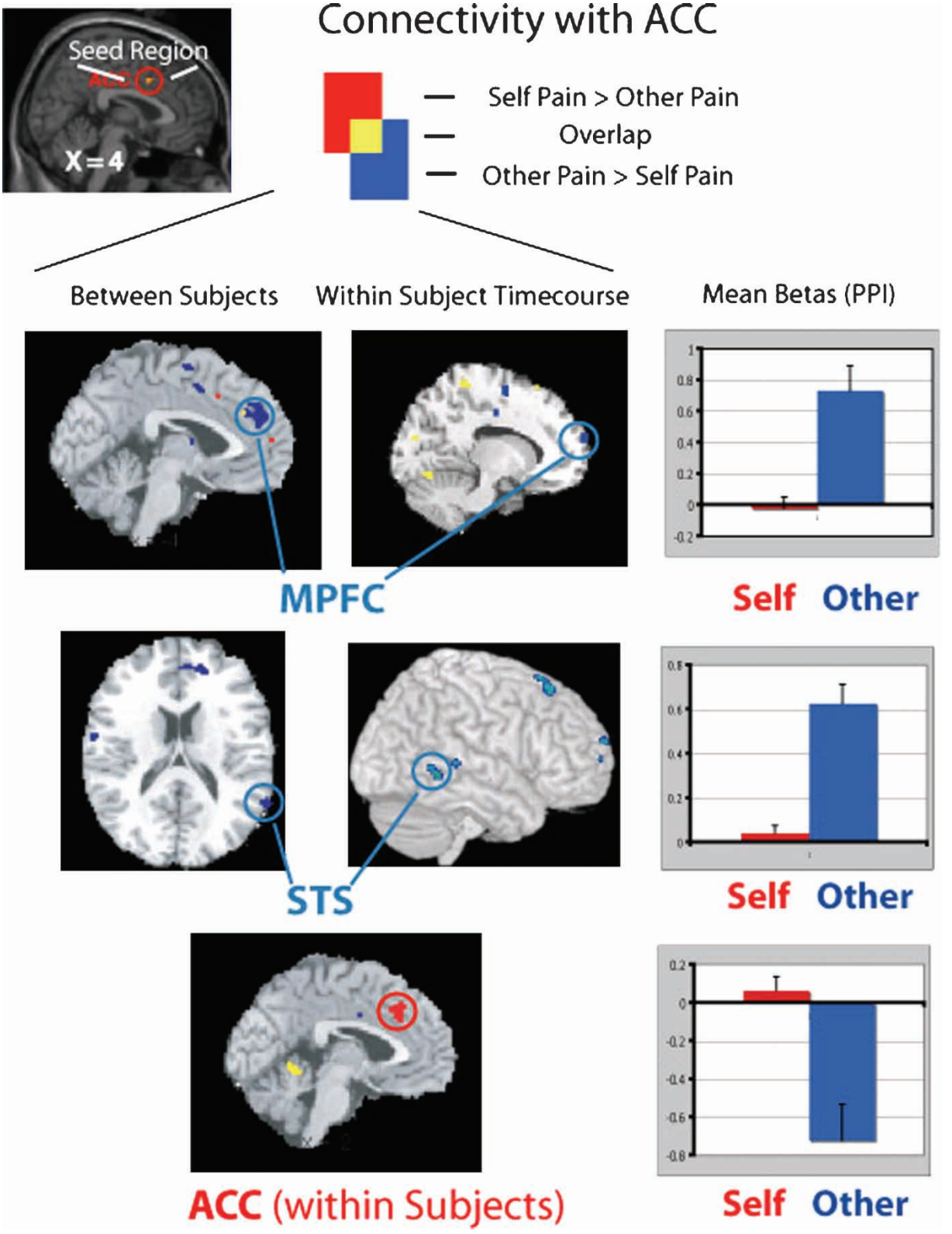

Figure 1. Regions showing increased connectivity with the ACC during other and self pain, respectively. Parameter estimates are drawn from within subject timecourse connectivity analyses. MPFC = medial prefrontal cortex; STS = superior temporal sulcus; STG = superior temporal gyrus; ACC = anterior cingulate cortex.

TABLE 2
Comparison of regions found in intra-individual (within subjects) and inter-individual (between subjects) connectivity analyses

		Intra-Individual Analysis					*Inter-Individual Analysis*				
		Coordinates					*Coordinates*				
Region of activation	*Lat*	*x*	*y*	*z*	*T-score*	*Nvox*	*x*	*y*	*z*	*T-score*	*Nvox*
ACC Self > Other											
Anterior cingulate cortex	M	2	26	32	4.19	22					
Inferior parietal lobe	L	−60	−44	30	4.53	32					
	−60	−42	22	4.47	(L)						
ACC Other > Self											
Dorsomedial frontal gyrus	R	12	64	18	5.36	16	12	48	12	3.98	32
							−4	60	18	4.56	26
Rostrolateral PFC	R	24	60	4	4.99	32					
Rostrolateral PFC	R	24	52	10	3.93	(L)					
Precentral gyrus	L	−30	−18	66	4.33	40					
Precentral gyrus	L	−30	−20	58	4.05	(L)					
Superior temporal sulcus	R	60	−46	−4	7.29	26	50	−42	−12	5.92	24
Superior temporal gyrus	R	52	−18	−12	5.29	24					
Superior temporal gyrus	R	56	−12	−4	3.51	(L)					
Superior temporal gyrus	R	42	−20	16	5.2	47					
Superior parietal lobe	L	−22	−50	68	4.2	25					
Superior parietal lobe	L	−18	−50	52	3.91	(L)					
Inferior parietal lobe	L	−50	−54	34	5.47	30					
Posterior cingulate cortex	M	8	−10	38	4.63	20	6	6	44	4.32	16
AI Self > Other											
Mid insula	R	46	−2	−4	4.37	21	44	−2	8	5.12	40
Middle temporal	R	56	−68	12	4.74	37					
PAG	M	−6	−32	−10	4.6	20	−6	−34	−6	4.27	14
Midbrain	M	6	−24	−26	4.92	29	−4	−20	−24	4.19	32
AI Other > Self											
Medial frontal gyrus	R	10	56	34	5.07	26	6	40	24	4.75	18
Posterior cingulate cortex	R	12	−14	48	4.86	15	8	−6	50	5.34	38
Precentral gyrus	R	18	−30	74	3.88	17					
Lingual gyrus	R	20	−48	−2	5.27	35					
Precuneus	L	−20	−78	42	5.53	39					
Overlap											
Inferior temporal gyrus	R	50	−60	−8	5.88	36					

Notes: Local maxima for clusters are designated with (L). Hemisphere is designated as midline (M) for maxima within 6 mm of the midline. Coordinates are in MNI space. Nvox = cluster size (in number of voxels).

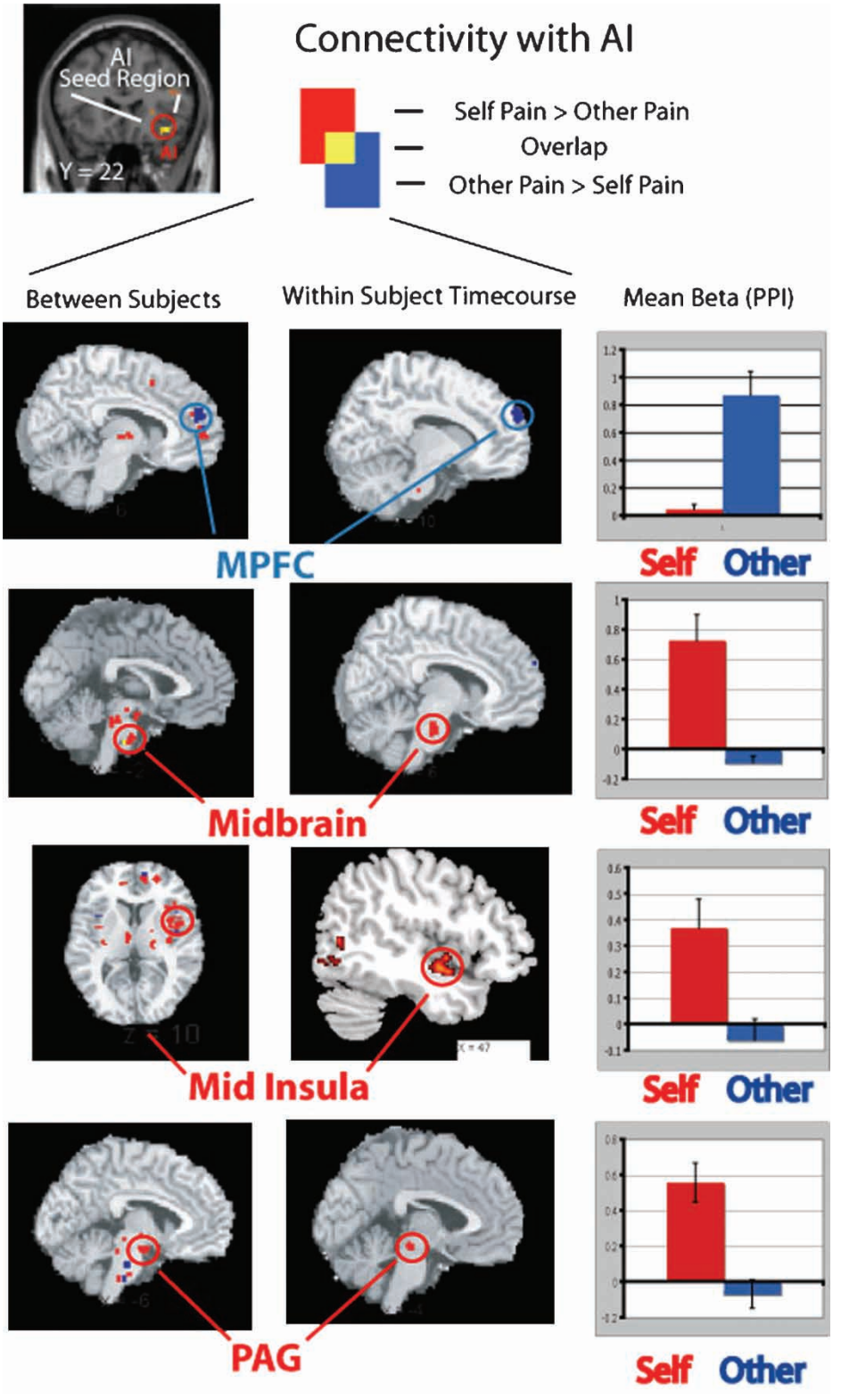

Figure 2. Regions showing increased connectivity with the AI during other and self pain, respectively. Parameter estimates are drawn from within subject timecourse connectivity analyses. The inset shows orthogonal views of the cluster in the PAG, overlaid on a mean anatomical image drawn from all of our subjects. MPFC = medial prefrontal cortex; PAG = periaqueductal gray; MI = mid insula.

which identified a region of the right inferior temporal gyrus connected to the seed region during both self and other pain.

DISCUSSION

Both experiencing pain directly and observing others in pain have been shown to recruit regions of mid ACC and AI implicated previously in the emotional distress accompanying physical pain (Botvinick et al., 2005; Hutchison, Davis, Lozano, Tasker, & Dostrovsky, 1999; Jackson, Brunet, Meltzoff, & Decety, 2006; Morrison et al., 2004; Singer et al., 2004, 2006). This is the first neuroimaging study in which functional connectivity analyses have been used to address questions about how networks involved in pain perception may vary depending on whether the person in pain is the subject themselves or another person. Consistent with our expectations, analyses indicated that overlapping, but qualitatively different, functional networks are involved in perceiving either one's own pain or the pain of another person.

To appreciate the functional significance of these different patterns of connectivity one must first consider the functional roles played by the commonly recruited regions of ACC and AI. Consider, for example, that the mid portion of the ACC activated in our self/other overlap contrast receives ascending nociceptive inputs (Craig, 2003; Devinsky, Morrell, & Vogt, 1995; Vogt, 2005) and in imaging studies is activated by perception of pain applied either externally or internally to the viscera (Farrell, Laird, & Egan, 2005; Hebben, Corkin, Eichenbaum, & Shedlack, 1985; Jackson et al., 2006; Morrison et al., 2004; Peyron et al., 2000). ACC activity in response to pain is modulated by attention and anxiety (Seminowicz & Davis, 2006; Valet et al., 2004) and expectation (Wager, 2005b; Wager et al., 2004). Additionally, this region projects to motor and premotor cortex and has been associated with the initiation of actions, as well as monitoring of the affective consequences of these actions (Paus, 2001; Rushworth, Walton, Kennerley, & Bannerman, 2004). Finally, the dorsal ACC has been associated with monitoring and responding to conflict, as for example when subjects make an error on a cognitive control task (Carter et al., 1998).

In this context, engagement of the ACC during both self and other pain conditions could reflect several different types of processing. ACC activity could play a role in motivational aspects of pain, including urges or desires to stop painful events. It could also represent participants' inhibition of urges to pull away from painful stimulation, or to look away from gruesome depictions of others in pain. Importantly, the fact that ACC activity may not only represent a single process of ''pain affect,'' but instead may be related to several types of motivation, leaves open the possibility that ACC activation indexes different processes across self and other pain conditions. If anything, our connectivity results suggest that this may be the case, as ACC activity co-varies with quite different brain regions in each condition.

The overlap region of insula found in our study and others has also been implicated in affective processing. This region corresponds most closely to the anterior and ventral agranular portion of the insula (Wager & Feldman Barrett, 2004), which is heavily interconnected with the orbitofrontal cortex and temporal operculum (Mesulam & Mufson, 1982), and is considered part of a set of ''paralimbic'' regions responsible for assessing the hedonic value of internal and external cues. This region may also be involved in interoceptive processing, or gathering information about and actively regulating internal bodily states (Craig, 2002; Critchley, 2004; Critchley, Melmed, Featherstone, Mathias, & Dolan, 2002). Taken together, these data suggest that, during empathic pain, the ACC may be involved in directing attention and mobilizing responses to painful stimuli, whereas the AI may be involved in associating pain cues with negative bodily and affective states.

Against this backdrop, we can now consider how affective representations in ACC and AI can be generated through the concerted actions of processing networks whose constituent regions may differ during the perception of self or other pain. This experiment tested two hypotheses about such networks. The first hypothesis was that empathic pain would involve affective perspective taking. Our second hypothesis was that the perception of self pain would differentially depend upon regions involved in coding somatic and autonomic responses to stimuli delivered directly to one's body, and that the network of brain regions involved in perceiving pain in the self, but not in others, would include midbrain and somatosensory cortex. Consistent with our predictions, we found that during other pain, the ACC and AI were functionally connected with prefrontal and posterior cortical regions related

to ToM and interpretation of socially relevant nonverbal cues. By contrast, during self pain, the ACC and AI were more functionally connected with regions involved in the ascending transmission of pain.

Functional networks supporting the perception of pain in self and other

Based on these data, as well as knowledge about anatomical connections between regions involved in nociceptive processing, we can begin to construct a model of the common and distinct networks involved in the empathic perception of pain in others as well as in the direct perception of one's own pain. Figure 3 represents an initial step towards such a model, though it is by no means a complete picture of the anatomical or functional connections between regions supporting direct or empathic pain processing. Here, red and blue lines indicate functional connectivity found in our data to be greater during self and other pain, respectively. Yellow lines highlight relevant inter-regional anatomical connections we can infer are involved in perspective taking or nociception, based on prior anatomical studies.

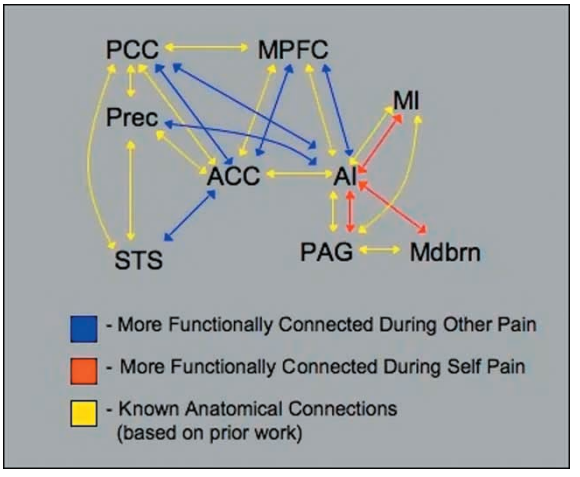

Figure 3. A circuit model diagramming the interaction of brain areas during self and other pain only, as well as interactions occurring during both types of pain. Connections in the model are based both on data from this study, and on existing information about intrinsic physical connections between these regions. Note that data from the current study imply *functional* connectivity, but do not prove that these connections occur through monosynaptic or direct connections. MPFC = medial prefrontal cortex; STS = superior temporal sulcus; MI = mid insula; ACC = anterior cingulate cortex; AI = anterior insula; PAG = periaqueductal gray; Prec = precuneus; PCC = posterior cingulate cortex; MdBrn = midbrain.

As highlighted by the blue connections in Figure 3, the empathic perception of pain in others depends upon regions of ACC and AI that register the affective value of painful events as well as a network of regions implicated in various aspects of social cognition. Perhaps foremost among the social-cognition-related regions are portions of the rostral and dorsal medial prefrontal cortex, which here were identified in both the intra- and inter-individual connectivity analyses as functionally connected with both ACC and AI during other pain. These MPFC subregions have been implicated in tasks involving mental state attribution, including inferring false beliefs and judgments of preferences, emotions, and traits in others (Amodio & Frith, 2006; Mitchell, Macrae, & Banaji, 2004, 2005; Ochsner et al., 2004a). Examination of parameter estimates demonstrated that connectivity between the MPFC and seed regions in the ACC and AI during other pain is not only robust, but is virtually absent during self pain.

Another social-cognition-related region, the superior temporal sulcus (STS), showed increased connectivity during other pain with only the ACC. The STS is involved in interpreting the intentional and emotional meaning of socially significant movements (Grosbras & Paus, 2006; Pelphrey et al., 2004) and speech (Sander et al., 2004). Previously, empathic pain studies using static pain-related images did not report STS activity during other pain (Jackson et al., 2006; Saarela et al., 2007), whereas those using videos—including ours—have found STS activity (Botvinick et al., 2005). The fact that the STS became selectively connected with the ACC but not the AI during other pain is consistent with the interpretation that the social salience of someone else's pain influences allocation of attentional resources via connectivity between the STS and the ACC. At least in rhesus monkeys, the posterior STS and supergenual ACC do not share many direct connections (Vogt & Pandya, 1987), and, as such, functional connectivity between these regions should be explained via a third region. Candidate regions for transmitting socially significant information between the STS and ACC are the precuneus and adjacent posterior cingulate cortex (PCC). These two regions share connections with both STS and ACC, and are thought to be involved in helping guide attention towards salient environmental cues (Cavanna & Trimble, 2006; Vogt, Vogt, & Laureys, 2006). Our analyses showed that the PCC became more

functionally connected with AI and ACC during other pain than during self pain, consistent with this interpretation.

In comparison to the results for the empathic perception of pain in others, heat pain administered directly to participants caused quite disparate regions to become functionally connected with the AI and ACC. As highlighted by the red connections in Figure 3, the direct perception of one's own pain depends upon regions of ACC and AI that register the affective value of painful events as well as a network of regions implicated in somatic and autonomic responses to pain. Most notably, we found that during self, but not other, pain the AI became functionally connected with the periaqueductal gray (PAG), a midbrain region dorsal to the pons, adjacent to the nucleus cuneiformis (NCOs), and the mid insula, posterior to the AI seed cluster. The PAG is a key region in the top-down control of pain transmission in the spinal cord through influences on the medulla (Fields, 2004; Wager, 2005a). While the PAG is often associated with inhibiting pain transmission via top-down mechanisms such as the placebo effect, it can also become activated during anticipatory anxiety preceding pain. Furthermore, this region shows dense interconnectivity with the midbrain NCOs, which is also involved in pain anticipation. Similarly, the mid insula is thought to be involved in processing information about the location and intensity of pain, as opposed to the affective and motivational information encoded in more ventral and anterior portions of the insula (Wager & Feldman Barrett, 2004).

Increased connectivity of mid insula, PAG, and midbrain with the AI during self as opposed to other pain suggests that the direct experience of pain is necessary to engage these ascending nociceptive pathways. While the PAG showed self pain related connectivity with the AI through both analyses, it showed significant self-pain-related connectivity with the ACC only when examined through inter-individual analyses. This discrepancy could be caused by our inter-individual connectivity analysis being more sensitive to the coactivity of regions that show sustained activation throughout the entire duration of a task.

Overall, our data suggest that partially dissociable networks drive empathic pain-related activity in the ACC and AI. During self pain, brainstem afferents, as well as the mid insula, interact with affective pain processing in the AI. Conversely, during other pain medial prefrontal and posterior cingulate activity interact with both the ACC and AI, whereas posterior cortical areas, such as the superior temporal sulcus and extra striate visual areas, become connected selectively with the ACC via the precuneus.

Caveats

It is important to acknowledge two limitations to the current research. First, the self and other pain conditions in this study differed along multiple dimensions. While self pain was administered through heat in periods of 20 seconds, other pain was presented in events that occurred throughout a short video. This opens our data to the possibility that differences in pain-related activity and connectivity across conditions may have been related to differences between the predictability, timecourse, or complexity of their respective stimuli. That being said, it is important to consider these potential limitations in light of principled reasons for choosing these particular stimuli.

All studies of empathic pain necessarily involve dissociations between the experiences participants have across conditions. Self pain always involves direct stimulation with the threat of tissue damage, whereas other pain involves (usually visual) cues about injury or discomfort in someone else. As such, some difference in computations between conditions is inevitable. Previous studies of empathic pain have dealt with this fact in differing ways. Some (Morrison et al., 2004; Singer & Frith, 2005) have attempted to equate their stimuli as much as possible by using similar pain-delivery techniques to subjects and their social targets. Others (Botvinick et al., 2005) have used stimuli that differ (heat vs. facial expressions of pain) in ways similar to ours. Studies employing both strategies have been consistent both in finding overlapping activation for self and other pain in the ACC and AI, and in finding dissociations in activation in the prefrontal cortex, which responds more to other pain, and sensory cortex, which responds preferentially to self pain. Our findings dovetail with these prior results, and encourages our belief that these findings occur not based on stimulus non-comparability, but rather as a function of self and other pain processing *per se*.

We do, however, acknowledge the fact that the differences in processing self and other pain (and

in the resulting connectivity of neural circuitry involved in each process) found in this study may partially result from the differences in stimulus type across conditions. We believe this to be a limitation to the study of empathic pain and empathy more generally

A second limitation in this study is inherent in the connectivity analyses used. Because we were interested in exploring many possible regions for interconnections with ACC and AI during pain processing, we used exploratory functional connectivity analyses rather than model-based approaches such as structural equation modeling or dynamic causal modeling. Consequently, the results of our connectivity analyses, unlike model-based approaches, do not allow us to make inferences about the *direction* of influence between connected regions. In other words, we cannot be sure whether regions such as the medial prefrontal cortex drive ACC activity in the context of other pain, ACC activity drives MPFC activity, or if this correlation represents processes in the ACC and MPFC *both* being driven by a third locus of activation not identified in our analyses. Future research should address the directionality of influence in these circuits.

Implications and future directions

The present findings have a number of implications for current and future work on pain empathy and social cognition. First, they suggest new interpretations for findings of overlapping activation in ACC and AI during self and other pain. Until now, these activations have been taken as supporting shared representations in empathy. Shared representations, in turn, have been cited as the fundamental feature underlying empathic and social cognitive ability in humans. One problem with positing shared representations as the sole basis for social cognition, however, is that regions involved in shared representations (such as the ACC, AI, and premotor mirror neuron regions) are not typically activated in studies that require participants to report on the mental states of another person. Instead, tasks requiring judgments about mental states show activity in a network of distinct regions including the STS, PCC, and MPFC. Here, we report connectivity between brain regions underlying social cognition and shared representations only in the context of perceiving others in pain.

These findings build a bridge between pain empathy studies that until now have emphasized the functional roles played by ''shared representations'' of pain affect in ACC and AI, and studies of mental state attribution that until now have emphasized the role of MPFC and other midline structures in social cognition. More broadly, they show the way that brain structures can support the relationship between different types of empathic subprocesses. An outstanding problem in empathy research has been the use of the broad term ''empathy'' to refer to several subprocesses that may in fact differ extensively from each other. This problem was noted by Davis (1994) who wrote that a ''central, recurrent, and intractable problem'' in pain empathy research is that ''the term empathy is routinely used to refer to two distinctly separate phenomena, cognitive role taking and affective reactivity to others'' (p. 9). The current findings suggest mechanisms through which these subprocesses of empathy may work together when a perceiver sees someone else in pain. Negative pain affect may be supported by the ACC and AI for both self and other pain, whereas only when observing others in painful situations do these systems interact with MPFC systems supporting perspective taking. The present findings can not tell us whether one of these two types of processing precedes or drives the other, of course. It is possible either that taking the perspective of another facilitates affective responses, or that automatically evoked affective reactions motivate perspective taking and higher-level cognition about another's plight.

A second implication of the present work concerns the use of functional connectivity analyses. Previous work on pain empathy has not shown activity in MPFC regions. The fact that we observed MPFC using connectivity analyses, but not in simple contrasts (see Ochsner et al., under review), suggests that empathy-related computations performed by MPFC may have gone unnoticed in prior work. More generally, our findings highlight the kinds of functional inferences that can be drawn on the basis of connectivity as compared to contrast analyses. Whereas contrasts can identify regions that are functionally co-active but whose activity may be uncorrelated, connectivity analyses can identify regions whose activity co-varies but may not appear as active in group-averaged contrasts. Future work employing both kinds of analyses will refine our understanding of the regions

showing tonic as opposed to phasic network activity during empathic interactions.

Third, the present findings may suggest a route by which our understanding of another's intentions may impact our feelings of empathy for them. Prior work has shown that social context can importantly alter our reactions to the suffering of others (de Quervain et al., 2004; Lanzetta & Englis, 1989; Singer et al., 2006). For example, competition with someone can weaken a perceiver's autonomic and neural reaction to that opponent's pain, whereas instructing participants to take the perspective of another can increase these responses (Jackson et al., 2006; Lamm, Batson, & Decety, 2007). These manipulations can have important behavioral consequences, changing perceivers' willingness to engage in helping behavior (Batson et al., 1997, 2003). Given the role of MPFC in regulating emotion via strategies that involve changing one's interpretation of another's affective states (Ochsner et al., 2004a), our results suggest that MPFC may in some cases support the role of perspective taking in modulating responses to another's pain and distress.

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