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How Do We Empathize with Someone Who Is Not Like Us? A Functional Magnetic Resonance Imaging Study

Claus Lamm[1], Andrew N. Meltzoff[2], and Jean Decety[1]

Abstract

■ Previous research on the neural underpinnings of empathy has been limited to affective situations experienced in a similar way by an observer and a target individual. In daily life we also interact with people whose responses to affective stimuli can be very different from our own. How do we understand the affective states of these individuals? We used functional magnetic resonance imaging to assess how participants empathize with the feelings of patients who reacted with no pain to surgical procedures but with pain to a soft touch. Empathy for pain of these patients activated the same areas (insula, medial/anterior cingulate cortex) as empathy for persons who responded to painful stimuli in the same way as the observer. Empathy in a situation that was aversive only for the observer but neutral for the patient recruited areas involved in self–other distinction (dorsomedial prefrontal cortex) and cognitive control (right inferior frontal cortex). In addition, effective connectivity between the latter and areas implicated in affective processing was enhanced. This suggests that inferring the affective state of someone who is not like us can rely upon the same neural structures as empathy for someone who is similar to us. When strong emotional response tendencies exist though, these tendencies have to be overcome by executive functions. Our results demonstrate that the fronto-cortical attention network is crucially involved in this process, corroborating that empathy is a flexible phenomenon which involves both automatic and controlled cognitive mechanisms. Our findings have important implications for the understanding and promotion of empathy, demonstrating that regulation of one's egocentric perspective is crucial for understanding others. ■

INTRODUCTION

A growing number of neuroimaging studies document a striking overlap in the neural underpinnings of the first-hand experience of pain and its perception in others (see Jackson, Rainville, & Decety, 2006, for a review). This overlap is most consistent in areas coding affective–motivational aspects of pain, such as the anterior and mid-cingulate cortex and anterior insula (AI) (e.g., Lamm, Batson, & Decety, 2007; Singer et al., 2004). In addition, areas processing the sensory-discriminative aspect of pain also seem to be activated by the perception of pain in others (e.g., Cheng et al., 2007, 2008; Bufalari, Aprile, Avenanti, Di Russo, & Aglioti, 2007; Lamm, Nusbaum, Meltzoff, & Decety, 2007; Moriguchi et al., 2007). These findings lend credence to the idea that empathy draws upon automatic somatic and somatosensory resonance between other and self, offering a possible (yet only partial) route to understanding the mental states of others (Decety & Meyer, 2008; Decety & Grèzes, 2006; Decety & Jackson, 2004). This resonance seems to rely upon the perception–action coupling mechanism which underpins processes such as emotional contagion (Preston & de Waal, 2002).

An important gap in the neuroscientific investigation of empathy is that previous work exclusively created affective situations that could have been experienced in a similar or identical way by both the observer and the afflicted person (the target). Therefore, our knowledge about how we empathize with people who are not like us is limited. This question is of high ecological validity, as many everyday situations require understanding others whose experiences, attitudes, and response tendencies are different from our own. The question of how we empathize with dissimilar others is also interesting on a theoretical level because it stresses the cognitive component of empathy. This component is perhaps unique to humans and possibly apes (De Waal, 2006; Decety & Lamm, 2006), and crucially relies upon the awareness of self–other distinction and executive functions—including controlled attention for activating relevant representations and keeping them in an active state while inhibiting irrelevant ones. For instance, a recent fMRI study demonstrated that physicians who practice acupuncture activate dorsolateral and medial prefrontal cortex, and not the pain matrix (as control participants did), when they are visually presented with body parts being pricked by needles, and

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that this activation correlates with decreased activation of the AI (Cheng et al., 2007). Similarly, perceiving stimuli which are painful and aversive for the self but known to be nonpainful for the target (such as surgery performed on an anesthetized body part) recruited areas involved in self–other distinction and prefrontal cortex underpinning affective appraisal (Lamm, Nusbaum, et al., 2007).

The aim of the current study, therefore, was to examine the neural response to situations in which the observer is requested to empathize with a person who is not like her or him, as opposed to a person sharing one's own bodily experience. To this end, we created situations that the observer and the target shared, and contrasted them with situations in which the symmetry between observer and target was broken. This was implemented by presenting pictures of two groups of targets experiencing needle injections or being touched by a soft object (a Q-tip). One group of targets responded to these situation in the same way the participants would respond to them (*similar patients*, responding with pain to injections, and with no pain to touch), whereas the second group reacted in an opposite, nonshared way due to a neurological dysfunction (*dissimilar patients*, who responded with pain to soft touch, and with no pain to injections). Participants were instructed to imagine the feelings of the targets in order to share and evaluate their affective states. The valence of the shared feelings could therefore be either neutral (in the case of nonpainful stimulations) or negative (in the case of painful stimulations).

An increasing number of social neuroscience studies suggest that the experience of empathy is a flexible phenomenon, which is malleable by a number of motivational, situational, and dispositional factors (Hein & Singer, 2008; Decety & Lamm, 2006; Hodges & Wegner, 1997). Empathic responses can be generated even in the absence of direct perception of the other's emotional response, by means of imagery, perspective-taking, and other types of top–down control. Therefore, we predicted that empathy for dissimilar targets would rely upon areas overlapping with those involved in empathy for similar targets. Hence, empathy for pain triggered by a neutral stimulus was expected to activate areas crucial during empathy for pain (AI, cingulate cortex; see Jackson, Rainville, et al., 2006, for a review). In addition, neural circuits involved in self–other distinction and executive function are predicted to subserve perspective-taking and the regulation of the observer's egocentric response tendencies (Decety, 2005). For the former, stronger responses in dorsal medial prefrontal cortex (dmPFC) were predicted, as this region is related to adopting the perspective of dissimilar others (e.g., Mitchell, Macrae, & Banaji, 2006); increased activation was also expected for the right temporo-parietal junction (TPJ) (Corbetta, Patel, & Shulman, 2008; Decety & Lamm, 2007). Inhibition of egocentric affective responses was predicted to recruit right inferior frontal cortex (rIFC), as this area plays an important role in response inhibition and cognitive control (e.g., Brass, Derrfuss, Forstmann, & Von Cramon, 2005; Aron, Robbins, & Poldrack, 2004). Using effective connectivity analyses, we explored whether this inhibition was achieved by stronger functional interactions with neural networks associated with affective coding. Notably, we expected neural and behavioral effects to be strongest in situations where stronger pre-established emotional response tendencies existed in the observer, that is, in participants watching dissimilar targets undergoing needle injections.

In order to test these predictions, we performed an event-related fMRI study. Functional segregation fMRI analyses were used to localize the brain areas involved in sharing the target's affect. In addition, select effective connectivity analyses assessed the neural interaction between these areas and trait measures of perspective-taking were correlated with hemodynamic responses to assess brain–behavior relationships more specifically.

METHODS

Participants

Twenty-four right-handed healthy volunteers aged between 19 and 34 years participated in the fMRI study. An independent group of 23 participants was recruited for an eye-tracking control study (age range = 20–35 years, 23 right-handed, 12 men). All participants gave informed written consent; were paid for participation; and reported no history of neurological, psychiatric, or major medical disorder and no current use of psychoactive medications. The study was approved by the local Ethics Committees (The University of Chicago and University of Oregon, where scanning was performed), and conducted in accordance with the Declaration of Helsinki. Sample size for the MRI study was chosen based upon general statistical power considerations for fMRI studies (Murphy & Garavan, 2004; Desmond & Glover, 2002) and upon power estimates from previous studies using similar designs (Lamm, Batson, et al., 2007; Lamm, Nusbaum, et al., 2007; Jackson, Brunet, Meltzoff, & Decety, 2006; Jackson, Meltzoff, & Decety, 2005; Singer et al., 2004). One participant was excluded due to a general lack of activation in task-related areas and behavioral data suggesting lack of compliance with task instructions, resulting in a final sample size of 23 participants (age M = 24.522, SE = 0.893; 12 women).

Experimental Design

Participants watched color photographs of human left hands or right upper arms either being touched by a Q-tip or receiving an injection using a hypodermic needle (Figure 1). Stimuli had been validated in a behavioral study with n = 115 participants confirming that needle injections are perceived as considerably painful.

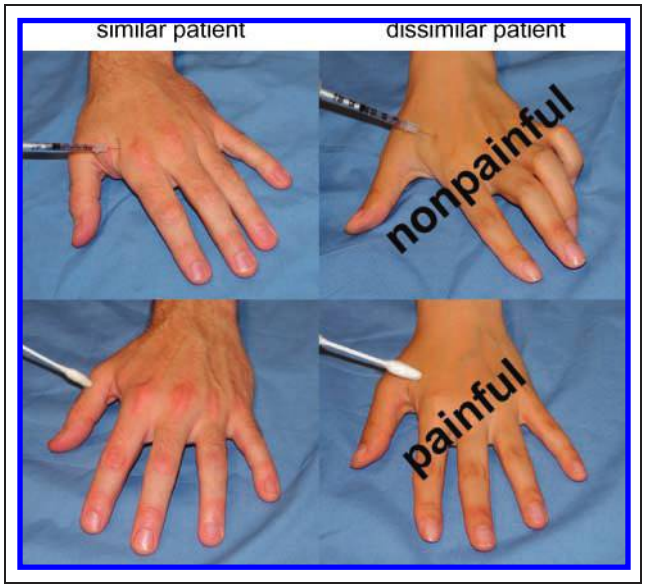

Figure 1. Sample stimuli used in the study. Inserts ''painful'' and ''nonpainful'' were not presented to participants and are provided for illustrative purposes.

Participants were instructed to share the affect of the targets by vividly imagining the pain (or nonpain) caused by the displayed situations. According to the cover story, the photographs had been taken from two different groups of targets. Neurological patients (*dissimilar others*) ostensibly suffered from a rare neurological disease causing pain when touched by a soft object (such as a Q-tip), but experienced a touch-like sensation and no pain when being pricked by a needle. Normal patients (*similar others*) also suffered from a disease (*Tinnitus aurium*), but this disease was unrelated to their somatosensation and nociception. Therefore, they reacted to needle injections with pain and to being touched by a Q-tip with touch and no pain. Hence, the design implemented in this study was a 2 × 2 factorial design, with the factors target (dissimilar and similar patient) and stimulus (needle and Q-tip). Crucially, depending upon the target, identical stimuli could have either painful or nonpainful consequences. Also, because the goal of this study was the observation of pain *in others*, at no point did the participants themselves receive any painful stimulation.

Stimuli were presented in blocks of 12 trials, with block order being counterbalanced across participants. An instruction screen at the beginning of each block showed a picture of the patient, which informed participants about the group of patients the following 12 photographs had been taken off. A trial consisted of a photograph of a hand or an arm displayed for a duration varying between 2 and 5 TRs (2420 and 6050 msec; mean duration 3 TRs) followed either by a response screen or a white fixation cross on black background (interstimulus interval [ISI]). ISIs were randomly varied between 2 and 5 TRs (mean duration = 2.5 TRs). Stimulus and ISI durations were varied to optimize extraction of task-related event-related responses versus responses related to unspecific effects such as stimulus perception or orienting (e.g., Ecker, Brammer, David, & Williams, 2006). Responses either required rating the amount of pain felt by the target using a visual analog scale (VAS) or a forced-choice matching task (see below). Thirty trials were run for each of the four conditions (15 trials for each body part). Design efficiency was optimized by generating various trial sequences (with randomly varied stimulus duration, condition order, ISI duration, and response requests) and their associated design matrices. Regressors in these matrices were convolved with the canonical hemodynamic response function (hrf) and tested for collinearity between regressors (i.e., the four task conditions, as well as between stimuli and responses) and the efficiency of the target contrasts (Henson, 2007).

In addition, it was assessed whether the conscious perception of needle injections into others is sufficient to trigger a response in areas of the so-called pain matrix (Derbyshire, 2000), or whether attention to the affective consequences of the stimulation is required. This was investigated in a separate scanning run (henceforth called automaticity localizer) in which needle injections and Q-tip stimuli were presented (for 800 msec) with the instruction to pay close attention to the physical characteristics of the photographs in order to indicate whether a certain photograph deviated from the other ones by some unspecified unusual attribute (such as a missing tip of a needle, which was the case in 3 out of the 90 stimuli). Finally, primary and secondary somatosensory areas involved in the perception of normal touch were individually localized in a separate scanning run (labeled touch localizer). This run consisted of 12 blocks in which either the left hand or the right upper arm where repetitively touched (frequency 2 Hz) for a duration of 20 sec. A rest baseline of equal length but with no stimulation was interspersed between blocks, with block order randomly alternating and counterbalanced.

Dispositional and Behavioral Measures

Three self-report dispositional questionnaires were filled in several weeks before the fMRI experiment and with participants being blind to the experiment's purpose: the Interpersonal Reactivity Index (Davis, 1994), the Emotional Contagion Scale (Doherty, 1997), and the Empathy Quotient (Baron-Cohen & Wheelwright, 2004). The Interpersonal Reactivity Index (IRI) is the most widely used self-report measure of dispositional empathy. Importantly, it contains a perspective-taking subscale which was of particular interest in this study (see below). The Emotional Contagion Scale (ECS) assesses the susceptibility to other's emotions from afferent feedback generated by mimicry, using questions such as ''I clench my jaws

and my shoulders get tight when I see the angry faces on the news.'' The Empathy Quotient (EQ) was used as an alternative assessment of dispositional empathy.

Behavioral measures during scanning included pain ratings using a VAS (with scores ranging from 0 = no pain to 100 = very severe pain) and a forced-choice matching task (see Figure 2, response collection). Responses were requested randomly for 50% of the trials. The VAS measured the amount of pain imagined by participants, and response time was determined as the time from scale onset until first movement of the cursor. In the forced-choice matching task, the patient's face was shown either expressing pain or a neutral expression. Participants had to decide whether the displayed expression matched the target's affective state as imagined during the preceding stimulus presentation. The rationale for using two different response types as well as response omissions was to decrease response preparation during performance of the pain imagery task—such as preparing the VAS response already before stimulus offset.

After scanning, emotional responses in the four experimental conditions were assessed using a procedure proposed by Batson, Early, and Salvarini (1997). Participants were shown two trials of each condition (counterbalanced across participants) and rated the degree to which they experienced 14 emotional states while imagining the target's pain (e.g., alarmed, concerned, compassionate, distressed; 0 = not at all, 6 = extremely). Ratings of emotional states were aggregated by calculating empathic concern and personal distress indices (Batson et al., 1997 for details). Indices were analyzed using repeated measures ANOVAs with factors target, stimulus, and index. Behavioral data and dispositional measures were analyzed using SPSS 15.0 for Windows (SPSS, Chicago, IL), and STATISTICA 5.1 for linear contrasts (Stat Soft, Tulsa, OK), with a $p = .05$ significance threshold for all analyses.

MRI Scanning

MRI data were acquired on a 3-Tesla Siemens Magnetom Allegra equipped with a standard quadrature head coil. Changes in BOLD signal were measured using a T2*-weighted single-shot echo-planar imaging (EPI) sequence (repetition time [TR] = 1210 msec, echo time [TE] = 30 msec, flip angle = 80°, 20 axial slices/volume with 5 mm slice thickness and 0.5 mm interslice gap,

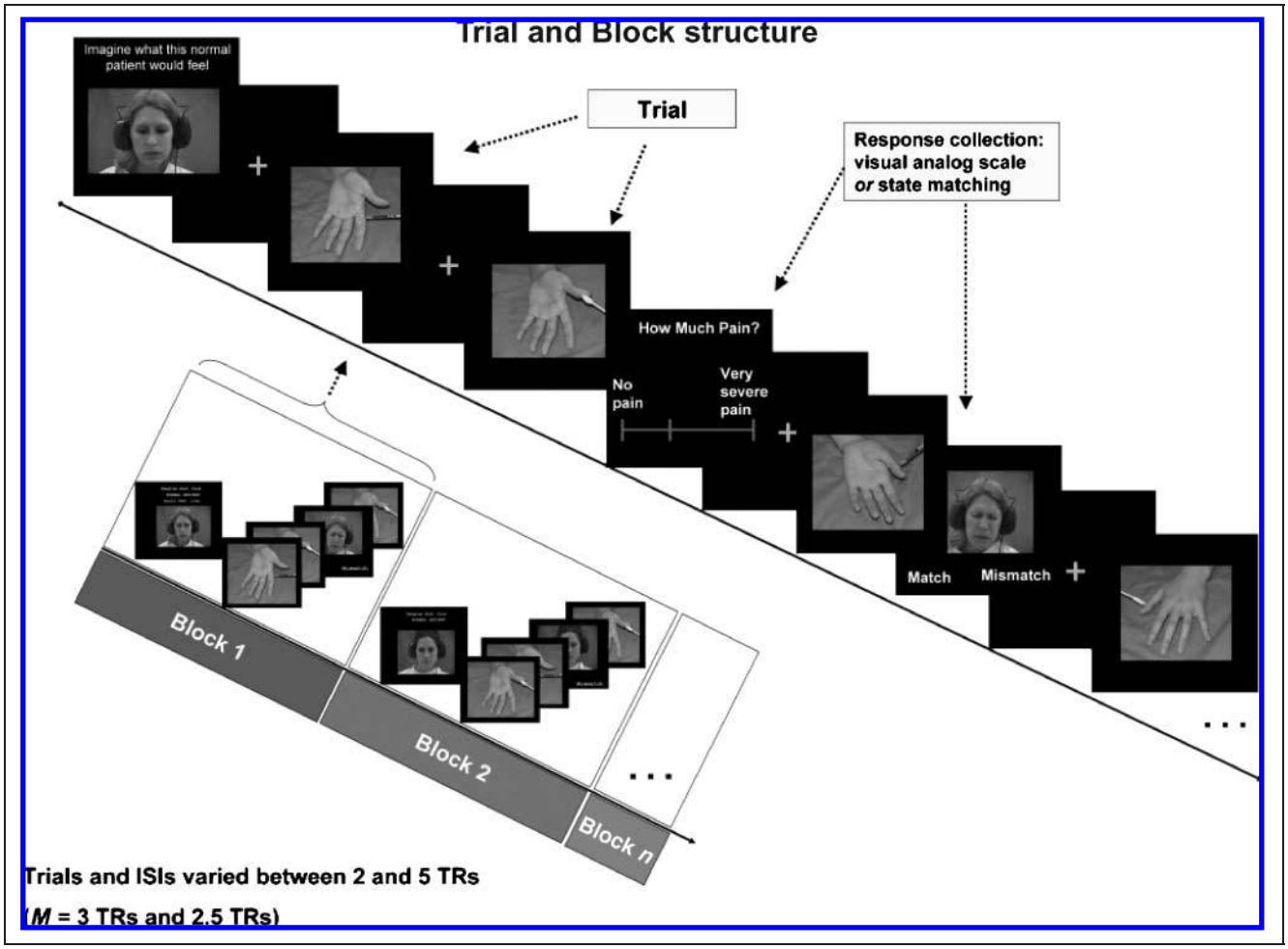

Figure 2. Block and trial structure used in the fMRI experiment.

in-plane resolution = 3.125 × 3.125 mm^2, 64 × 64 matrix, FOV 200 × 200 mm^2, ascending interleaved slice acquisition, whole-brain coverage excluding lower parts of the cerebellum in some participants). The effective temporal resolution was increased to 605 msec (1/2 TR) by synchronizing half of the acquisition onsets with stimulus onset and the other half with $^1/_2$ TR after stimulus onset (Miezin, Maccotta, Ollinger, Petersen, & Buckner, 2000). Each run was preceded by several dummy scans ensuring steady-state magnetization conditions. Stimulus presentation and response collection were performed using the Presentation software (Neurobehavioural Systems, Albany, CA). Visual stimuli were presented using a back-projection system and a button box recorded the responses of subjects, which were entered using their dominant right hand. For the experimental conditions, three runs separated by short breaks and with 535 TRs per run were performed, with 333 volumes acquired for the automaticity localizer and 332 volumes acquired for the touch localizer run.

MRI Analyses

Image processing was performed using SPM5 (Wellcome Department of Imaging Neuroscience, London, UK), implemented in MATLAB 7 (Mathworks, Sherborn, MA). Preprocessing included, in the following order, slice-timing correction (reference slice including superior–inferior center of the AI), correction for head motion (realignment to mean image volume, using the default unwarp and realign function to account for susceptibility–movement interactions in orbito-frontal regions), normalization from the mean realigned and unwarped EPI image to the EPI template provided in SPM5 (normalization performed using default SPM parameters), and smoothing using a 6-mm FWHM isotropic Gaussian kernel. Event-related responses were assessed by setting up fixed effects general linear models for each subject. Regressors of interest modeling the experimental conditions (separately for hand and arm stimuli), the instruction display and the response epochs were set up and convolved with the canonical hrf. All models included a high-pass filter with a cutoff at 128 sec in order to remove scanner drifts. The three runs were concatenated for all analyses, with run-specific effects considered in the model as regressors of no interest.

Analyses of Functional Segregation (Localization)

Following model estimation, contrasts were calculated for each subject to assess differences between conditions. In addition, signal changes in relation to the implicitly modeled fixation baseline were assessed. The resulting first-level contrast images were entered into second-level random effects (rfx) analyses to assess differences between conditions with population inference. Activation differences against baseline were interpreted using a voxel-level threshold of $p = .05$ and a spatial extent threshold of $k = 20$, corrected for multiple comparisons using random field theory. The more subtle activation differences between conditions were assessed using a voxel-level threshold of $p = .001$ and $k = 20$ (uncorrected for multiple comparisons). Selection of an appropriate statistical threshold in functional neuroimaging is a controversially discussed problem (e.g., Poldrack et al., 2008). The chosen thresholding approach is in line with a multitude of other studies assessing empathy for pain (Lamm, Batson, et al., 2007; Lamm, Nusbaum, et al., 2007; Jackson, Brunet, et al., 2006; Jackson, Rainville, et al., 2006; Singer et al., 2004, 2006; Jackson et al., 2005), which show highly replicable and well-segregated activations in the pain matrix. Our threshold therefore enables direct comparability of results, and it also reflects our experience with the effect sizes typically encountered in social neuroscience paradigms. Note, though, that in all analyses without correction for multiple comparisons, we do not have quantified control over the amount of false positives.

Whether trait perspective-taking skills correlated with hemodynamic responses in dmPFC and rIFC was assessed by correlating parameter estimates of clusters in these regions from the contrasts *No Pain: Dissimilar > Similar* and *Pain: Dissimilar > Similar* with (mean-normalized) scores of the perspective-taking subscale of the IRI. We predicted higher response inhibition and self–other distinction, indexed by dmPFC and rIFC, to be correlated with higher perspective-taking skills.

Significant clusters were anatomically labeled using structural neuroanatomy information and probabilistic cytoarchitectonic maps provided in the Anatomy Toolbox (version 1.4; Eickhoff et al., 2005) and the Anatomic Automatic Labeling toolbox (Tzourio-Mazoyer et al., 2002). For brain regions not covered by these toolboxes, a brain atlas (Duvernoy, 1991) was used. Nomenclature for activations in cingulate cortex was based on a recent review of cingulate anatomy and function (Vogt, 2005). Caret5 (Washington University; http://brainmap.wustl.edu; Van Essen et al., 2001) was used to visualize SPMs on the surface of cerebral cortex for SI Figure 1.

Exploratory data analyses showed stronger behavioral and neural responses to stimuli showing hands (irrespective of the target group). Because the efficiency of the current event-related design was particularly high due to the high temporal resolution, the variation of stimulus durations, and the optimization of design efficiency (Ecker et al., 2006; Miezin et al., 2000), we restricted analyses to trials showing hand stimuli ($n = 15$ per condition). This also applied to the behavioral analyses.

Analyses of Effective Connectivity (PPI)

Although functional segregation analyses inform about whether a brain area is active during an experimental

paradigm, the goal of effective connectivity analyses is to assess whether the influence two neural networks exert over each other is modulated by certain psychological factors (Friston et al., 1997). To this end, psychophysiological interaction (PPI) analyses determine whether the effective connectivity between a seed region and all other voxels in the brain is changed by an experimental condition of interest. Based upon the hypothesis that dmPFC and rIFC would be involved in empathizing with dissimilar others, we explored PPIs for volumes of interest (VOIs) in these areas. rIFC was assessed for its crucial role in response inhibition and action decoding (Aron et al., 2004), whereas dmPFC has been specifically associated with perspective-taking and reasoning about dissimilar others (D'Argembeau et al., 2007; Mitchell et al., 2006). Given the central role of the right AI in empathy for pain, we explored whether connectivity of this region with other areas associated with affective coding and interoceptive awareness would increase (Decety & Lamm, 2006; Jackson, Brunet, et al., 2006; Jackson, Rainville, et al., 2006). All VOIs were defined as a 6-mm-radius sphere, with the center of this sphere being the individually determined local maximum closest to the respective cluster maximum determined by the rfx main effect of the segregation analysis (i.e., *mean of all four conditions > baseline*). The reason for using the mean activation instead of the more specific contrast *No Pain: Dissimilar other > Similar other* was because the latter would have biased the PPI analyses to areas found to be active during that contrast. The significance threshold for VOI extraction was set to $p = .001$, $k = 5$ (uncorrected). In case no significant voxels were detected, no VOI data were extracted for that participant. Given the scarcity of effective connectivity analyses in the domain of empathy for pain, PPI analyses were of a rather exploratory nature, which is one reason for using a more liberal threshold than for the segregation analyses. As a safeguard against false positives, results were only interpreted for areas showing significant responses in the functional segregation analyses (which also substantially reduced the number of statistical comparisons). Also, given the results of the functional segregation analyses, which did not reveal higher activation in any of the a priori expected areas, PPI analyses were restricted to the contrast *No Pain: Dissimilar > Similar*.

PPI analyses were performed in the following way: (a) extraction of the time-series data of the first eigenvariate of the seed VOI (high-pass filtered and mean corrected, BOLD-deconvolved to get an estimate of the actual neural response; Gitelman, Penny, Ashburner, & Friston, 2003); (b) generating a vector contrasting the time series of the estimated neural response for the targeted conditions (representing the interaction between the psychological and physiological factors, i.e., the PPI regressor), a second vector representing the main effect of the selected contrast (the psychological variable, i.e., the P regressor), and a third vector representing the VOI time course (the physiological variable, Y regressor); and (c) forward-convolving these regressors with the canonical hrf in order to estimate the effects of the PPI regressor. The resulting statistical parametric maps (SPMs) showed clusters for which connectivity differed in the chosen conditions.

Tracking of Eye Movements

Averting the gaze from aversive situations is a potential emotion regulation strategy. This strategy has been associated with activation in brain areas that are also related to perspective-taking and self–other distinction (van Reekum et al., 2007). In our paradigm, overcoming one's egocentric aversive response when watching needle injections into dissimilar others might have been achieved by averting the gaze. In order to exclude this interpretation and to make sure that activations in our study were not confounded by different eye gaze patterns, we performed a control study using eye tracking outside of the MRI scanner. This study was performed with an independent group of participants to avoid habituation and practice effects. Eye movements were recorded with a Tobii T120 eye tracker (Tobii Technology AB, Danderyd, Sweden) using a 120-Hz data sampling rate and an automatic calibration procedure using 9 calibration points. Stimulus presentation (visual angle, luminance, and screen resolution) and the experimental paradigm were kept as similar as possible to the fMRI paradigm. Eight randomly permuted blocks (four for each patient group) with eight randomly permuted stimuli were presented, with stimulus duration being 2 sec, resulting in a total of 16 trials per conditions. Data were analyzed using Tobii Studio (v 1.1.12), using the in-built automatic fixation detection algorithm (Tobii Fixation Filter, detection radius 35 pixels on a screen with a resolution of 1280 × 1024 pixels). Circular areas of interest (AOIs) with a radius of 64 pixels were drawn centered on the points where the needle penetrated or where the Q-tip touched the skin. Fixation duration for these AOIs was determined for the last 1500 msec of image display. The first 500 msec were discarded because eye movements during this interval were related to moving the gaze from the centrally located fixation cross preceding each task stimulus to the stimulus of interest itself (i.e., the contact point between needle/Q-tip and hand). A repeated measures ANOVA was performed to assess differences in fixation durations between conditions. In addition, we used heat map, gaze plot, and bee swarm visualizations to explore the dynamics of eye movements and to assess patterns that might have been missed by the AOI analysis. These analyses visualized fixation times for all aspects of the picture [heat maps and the temporal sequence of registered fixations (gaze plots)], and dynamically visualized all gaze changes from stimulus onset until offset as a movie (bee swarm).

RESULTS

Behavioral Results and Dispositional Measures

Pain ratings using the VAS were in line with the actual affective states of the targets [Figure 3; significant interaction Target × Stimulus: $F(1, 22) = 1891.558$, $p < .001$, partial $\eta^2 = 0.989$]. Injections into dissimilar others were rated as significantly more painful than the equally painless stimulations (Q-tip) of similar others [linear contrast *No pain: Dissimilar vs. Similar*: $F(1, 22) = 10.687$, $p = .004$, partial $\eta^2 = 0.486$]. Analysis of response times revealed that response time was longest for needle injections into dissimilar others, whereas response times for painful stimuli did not differ [significant interaction Target × Stimulus: $F(1, 22) = 5.520$, $p = .028$, partial $\eta^2 = 0.201$; linear contrast *No pain: Dissimilar vs. Similar*: $F(1, 22) = 4.09$, $p = .055$, partial $\eta^2 = 0.186$; injection into dissimilar other ($M \pm SE$) = 1366 ± 56 msec, touch of similar other = 1224 ± 79 msec]. No significant differences (either for ratings or for response times) were obtained when contrasting painful stimulation of dissimilar with painful stimulation of similar others.

When matching the facial expression associated with the emotional state of a patient to its actual affective state (forced choice matching task), the percentage of incorrect answers was significantly higher for dissimilar others—in particular, for the needle injections (Likelihood ratio test, $p = .044$; similar other injection = 3%, touch = 0.6% vs. dissimilar other injection = 8.7%, touch = 2.69%). Also, response times in the matching task were longer for needle injections into dissimilar others [interaction Target × Stimulus: $F(1, 22) = 11.402$, $p = .003$, partial $\eta^2 = 0.341$; mean ± *SE* of response times, similar other injection = 1595 ± 103 msec, touch = 1679 ± 355 msec; dissimilar injection = 2090 ± 767 msec, touch = 1679 ± 287 msec].

Empathic concern (EC) and personal distress (PD) triggered by witnessing the patients' affective states were higher for painful stimulations (i.e., touch of dissimilar others, injections into similar others; Figure 3, right-hand side). Although EC for matched stimulation consequences did not differ between targets, PD was higher during injections into dissimilar others [significant three-way interaction Target × Stimulus × Scale: $F(1, 23) = 11.442$, $p = .003$, partial $\eta^2 = 0.342$; post hoc linear contrast PD injection dissimilar other vs. touch similar other: $F(1, 22) = 10.459$, $p = .001$, partial $\eta^2 = 0.63$].

Dispositional measures (SI Table 1) were well within published norms and comparable to previous neuroimaging studies (e.g., Lamm, Batson, et al., 2007; Lamm, Nusbaum, et al., 2007).

fMRI Results

Functional Segregation (Localization)

The first step was to determine whether activation patterns associated with empathy for pain experienced by similar others was consistent with previous studies. This was clearly the case, as the contrast *Pain > No Pain: Similar* others revealed signal changes in large parts of the pain matrix involved in the first-hand experience of pain, such as bilateral anterior insular cortex, medial cingulate cortex (MCC) and anterior cingulate cortex (ACC), as well as various sensorimotor areas. This consistency check enabled us to assess differences between the target groups.

Dissimilar > similar targets. Brain activity triggered by empathizing with the pain of a target that is dissimilar to the observer was assessed using the contrast *Pain > No Pain: Dissimilar* (i.e., Q-tip touch vs. needle injection into a dissimilar target). This revealed clusters which vastly overlapped with those found for *Pain > No pain: Similar*, including key structures of the pain matrix such as bilateral AI, MCC and ACC, medial dorsal and

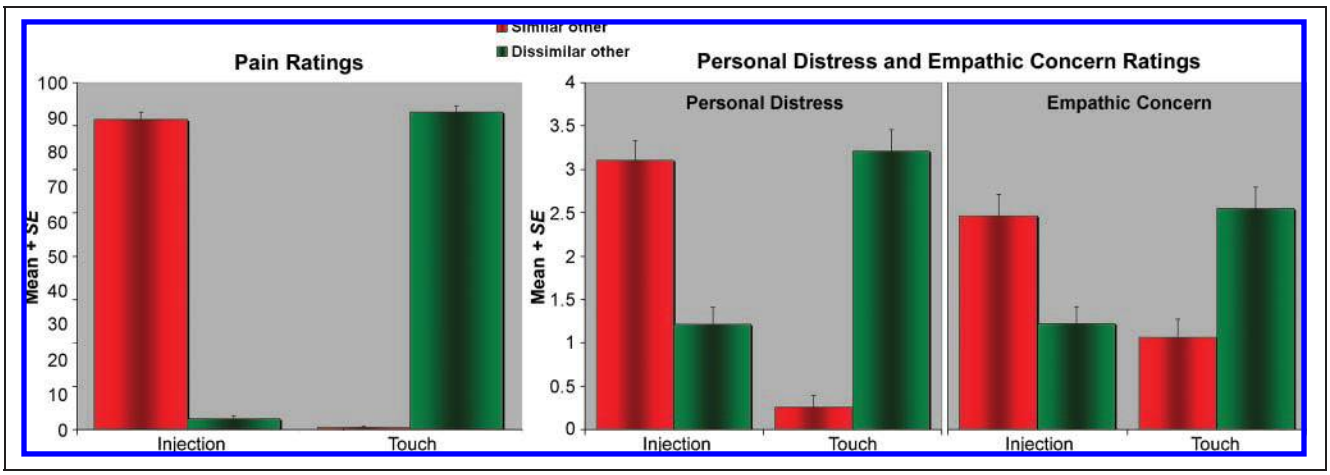

Figure 3. Pain, personal distress, and empathic concern ratings (mean plus standard error of the mean, *SE*) for the four different conditions.

ventrolateral premotor areas, inferior and superior parietal cortex, as well as thalamus and striatum (Figure 4). In order to determine whether these areas showed stronger activation than during pain empathy for similar others, we calculated the contrast *Pain: Dissimilar > Similar* (i.e., Q-tip touch of dissimilar vs. needle injection into similar target). This contrast revealed no significant differences, even when lowering the threshold to $p = .005$, $k = 5$ (uncorrected).

Subsequently, we assessed the neural network involved in overcoming one's emotional response to an aversive stimulus that is neutral for the other using the contrast *No pain: Dissimilar > Similar* (i.e., needle injection into a dissimilar patient vs. a Q-tip touching a similar patient; note that both conditions are equally nonpainful). This contrast revealed higher activation in several cortical and subcortical areas, including dmPFC, rIFC, bilateral AI, dorsal anterior cingulate cortex (dACC), dorsal and ventrolateral striatum (head of the caudate and pallidum), inferior parietal lobule (supramarginal gyrus), and a number of occipital areas involved in visual processing (Table 1 and Figure 5).

Similar > dissimilar targets. The contrast *Pain: Similar > Dissimilar other* (i.e., needle injection into similar patient vs. Q-tip touch of dissimilar patient) assessed which areas showed stronger responses during empathy for pain in similar patients. It revealed significant clusters in the contralateral (right) postcentral gyrus (primary somatosensory cortex), supplementary motor area and right dorsolateral premotor cortex, MCC and cingulate motor area, left fronto-insular cortex, and in various other cortical and subcortical areas (SI Table 2). Notably, activation in the contralateral postcentral gyrus substantially overlapped with independently determined clusters related to hand somatosensation (touch localizer; SI Figure 1).

Automaticity localizer. The automaticity localizer showed no activation in any area of the pain matrix, not even at a very liberal threshold of $p = .05$ (uncorrected for multiple comparisons, no extent threshold; contrast *Injection > baseline*). The only significant clusters (both for the needle and Q-tip stimuli) were located in visual cortical areas such as bilateral medial and lateral occipital cortex and superior parietal cortex.

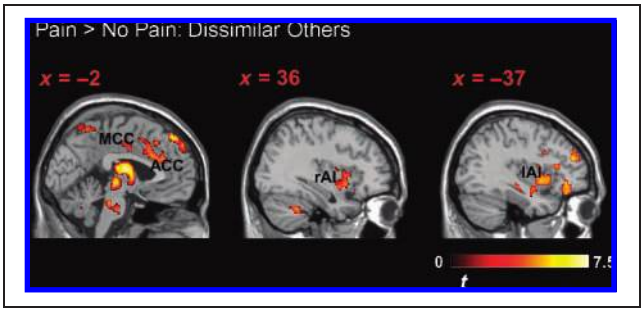

Figure 4. Significant clusters in selected brain regions from the contrast *Pain > No Pain: Dissimilar others*. Thresholded activation ($p = .001$, $k = 20$, uncorrected) is overlaid on sagittal views of a high-resolution structural brain scan in standard stereotactic space (MNI). Red numbers indicate slice number in *x*/*y*/*z* direction.

Brain–behavior correlations. The correlation of perspective-taking scores with parameter estimates from the contrast *No Pain: Dissimilar > Similar* revealed a significant cluster in rIFC, with peak coordinates *x*/*y*/*z* = 50/4/22, and a (peak) correlation of $r = .62$. No significant correlations were observed in other areas identified in this study, including the cluster in dmPFC. The same applies to correlation analyses using parameter estimates from the contrast *Pain: Dissimilar > Similar*.

Functional Integration—PPI Analyses

PPI analyses were performed for the individually identified VOIs listed in SI Table 3. PPIs for the contrast *No Pain: Dissimilar > Similar* for dmPFC showed connectivity increases almost exclusively with occipital (medial and lateral) and superior parietal areas, and no modulation of connectivity with areas specifically associated with affect processing and pain empathy. In contrast, rIFC's connectivity increased with dACC, right AI, the periaqueductal gray, and the putamen (Figure 6). Connectivity of the right AI increased with other affect-encoding areas, such as dACC, left AI, the periaqueductal gray, and the striatum (caudate and putamen; Figure 7).

Eye Movements

In all four conditions, participants spent the majority of time (on average, about 1200 msec of the analyzed 1500 msec) looking at those parts of the stimulus depicting the object penetrating or touching the target's hand (SI Table 4, SI Figure 2). The main effects of the repeated measures ANOVA were nonsignificant (ps > .227), but the interaction was [$F(1, 21) = 7.831$, $p = .011$, partial $\eta^2 = 0.272$; data of one participant had to be excluded due to equipment failure]. This interaction was driven by fixation time for injections into similar others being disproportionately longer than those for Q-tip touch, as compared to dissimilar targets (SI Table 4). Note though that differences between conditions were generally very small (around 50 msec from the mean across all conditions), indicating that in no condition did participants spend considerably different amounts of time averting their gaze from the object. Note, in particular, that needle injections into dissimilar others did not result in reduced fixation times when compared to nonpainful touch of similar others [linear contrast $F(1, 21) = 0.263$, $p = .613$]. In addition, qualitative analyses of

Table 1. Significant Differences from the Functional Segregation Contrast *No Pain: Dissimilar > Similar Other*

Cluster Size k	*t*	*x*	*y*	*z*	*Anatomical Location and Area*
Frontal and Insular Cortex					
264	8.32	16	16	60	dorsomedial PFC
X	4.97	4	14	62	SMA (area 6)
X	4.75	6	22	48	dorsomedial PFC
1007	7.84	60	12	18	vPMC, pars opercularis (area 44)
X	7.00	58	20	22	vPMC, pars triangularis (area 45)
X	6.70	54	12	30	vPMC, pars opercularis (area 44)
309	5.29	−48	6	16	vPMC, Rolandic operculum (area 44)
X	5.26	−50	22	−2	vPMC, pars triangularis (area 45)
X	4.86	−52	8	6	vPMC, pars opercularis (area 44)
65	4.49	42	44	−2	IFG
29	4.35	−44	30	20	vPMC, pars triangularis (area 45)
21	4.36	−60	6	22	vPMC (area 44)
142	5.11	44	28	−6	IFG, pars orbitalis
X	4.71	36	18	−4	anterior insular cortex
26	4.85	−6	32	42	superior frontal gyrus
25	4.64	48	36	32	middle frontal gyrus
Occipital and Temporal Cortex					
73	5.88	−36	−94	−4	middle occipital gyrus
311	5.72	52	−58	−18	inferior temporal gyrus
X	5.25	50	−60	−10	inferior temporal gyrus
X	5.12	54	−70	−8	inferior temporal gyrus
304	5.54	−56	−70	2	middle temporal/inferior occipital gyrus
X	5.31	−48	−74	−10	inferior occipital gyrus
X	5.13	−46	−76	−2	inferior occipital gyrus
75	5.09	38	−92	6	middle occipital gyrus
X	5.04	38	−92	−6	inferior occipital gyrus
X	3.79	36	−82	2	middle occipital gyrus
40	4.48	32	−76	40	middle occipital gyrus
53	4.36	−36	−90	20	middle occipital gyrus
X	4.05	−40	−88	12	middle occipital gyrus
66	4.32	16	−86	8	calcarine sulcus/cuneus
Parietal Cortex					
275	5.25	58	−30	52	inferior parietal lobule/SMG
X	4.85	62	−24	42	inferior parietal lobule/SMG
X	4.32	36	−38	48	SMG/postcentral gyrus
204	5.05	−58	−42	46	inferior parietal lobule

Table 1. (*continued*)

Cluster Size k	*t*	*x*	*y*	*z*	*Anatomical Location and Area*
X	4.90	−62	−38	34	SMG
X	4.08	−56	−26	40	SMG/postcentral gyrus
52	5.01	32	−52	60	superior parietal lobule
11	4.36	52	−34	44	SMG/postcentral gyrus
19	4.32	−12	−76	44	superior parietal lobule
84	4.27	−42	−46	50	inferior parietal cortex
Subcortical Areas					
17	5.36	14	2	−2	striatum (putamen, caudate)
21	4.69	−16	16	8	caudate
25	4.33	−20	2	0	pallidum/putamen
53	4.10	20	10	6	putamen
X	3.67	18	4	12	caudate
25	4.33	−20	2	0	pallidum/putamen

Threshold $p = .001$ (uncorrected), cluster size threshold $k = 20$.

Stereotactic coordinates and *t* values are provided for the local voxel maxima in the respective cluster. X = subpeak of a cluster; cytoarchitectonic areas (in brackets) determined based upon probabilistic cytoarchitectonic maps provided in the Anatomy Toolbox; PFC = prefrontal cortex; SMA = supplementary motor area; vPMC = ventral premotor cortex; IFG = inferior frontal gyrus; SMG = supamarginal gyrus.

the dynamics of eye movements did not indicate any other differences between conditions.

DISCUSSION

Previous neurophysiological explorations of empathy were limited to situations in which affective stimuli triggered the same response in both the observer and the target. This paradigm cannot address the question of how we understand someone who is not like us, and whose affective responses are not matched to our own. We investigated this question by reversing the stimulus–response mapping of target and observer, preventing the latter to infer the targets' mental and affective states by using a direct perception–action coupling mechanism. On the contrary, participants had to rely upon perspective-taking and other cognitive mechanisms of top–down executive control in order to understand the sensations and feelings. Although we expected such effects irrespective of the affective state of the target, we predicted that cognitive control would be more pronounced for more firmly established response tendencies—such as when observing someone else receiving an injection which would be aversive and painful for the observer, but not for the target.

The behavioral and hemodynamic results are largely in line with these predictions. Painful stimulation of dissimilar others with an object that was neutral for the observer resulted in extensive activation of the pain matrix, in particular in areas coding affect such as the bilateral AI, MCC, and ACC. This indicates that sharing the painful affective state of dissimilar targets relies upon neural mechanisms that are also at play when empathizing with the pain of similar others. Contrary to our expectations, though, areas involved in self–other distinction or cognitive control did not show higher activation during

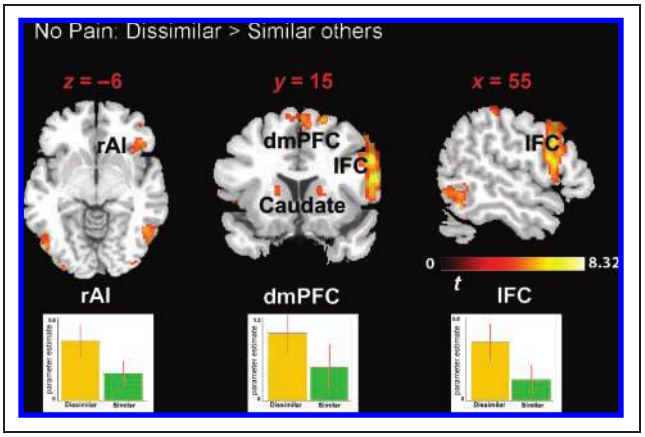

Figure 5. Significant clusters in selected brain regions from the contrast *No Pain: Dissimilar > Similar others*. Bars show mean and 90% confidence interval of parameter estimates for the respective condition (against baseline). See text for abbreviations and Figure 4 for other specifications.

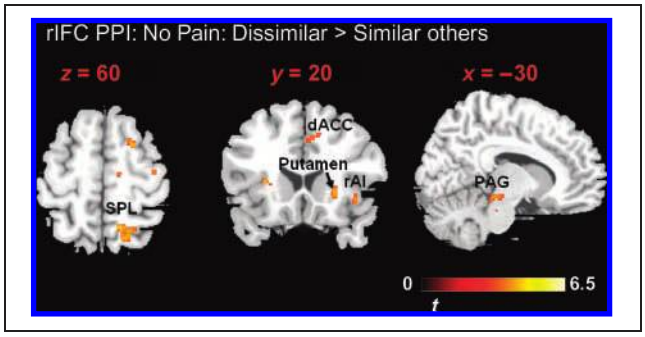

Figure 6. Significant changes in effective connectivity (contrast *No Pain: Dissimilar > Similar others*) between the seed region in the right inferior frontal cortex and the shown clusters (threshold $p = .001$, $k = 5$, uncorrected). See text for abbreviations and Figure 4 for other specifications.

empathy for pain. We speculate that this and the considerable overlap in activations results from a mechanism enabling direct affective sharing with dissimilar others in situations where no strong emotional response mappings have been established. In the current paradigm, this was the case for touch by a Q-tip, which is of neutral valence for the observer. Notably, the behavioral indices also did not reveal any differences when the two target groups underwent painful stimulation. However, although generally similar processes might be at play during empathy for pain, a distinction between the two different target groups is still taking place as indicated by higher hemodynamic activation in a number of areas when empathizing with the pain of similar others (see also below). Differences in the timing of the neural responses to the pain of the two target groups might not be adequately captured by the relatively low temporal resolution of hemodynamic measures, an issue we are currently addressing by a high-density event-related potential study. In addition, future investigations should vary the degree and quality of congruent and incongruent emotional response associations in order to substantiate our claim that empathy for dissimilar targets can be based on a direct mapping of other-related responses in the absence of pre-established emotional response tendencies. From a daily life perspective, such a direct mapping mechanism has high ecological validity because, in many cases, it is easier to understand the feelings of someone else in situations we have never experienced before (such as, for example, breaking a bone while never having broken one oneself).

On the contrary, sharing the (absence of) feelings in situations that are distressing or harmful for the self is much more challenging. This is captured by the behavioral results. Participants not only showed more evaluation errors, longer response times, and more erroneous pain ratings but also higher personal distress when watching dissimilar others undergoing injections. The fMRI results reveal activation increases only when empathy for nonpainful stimulation in dissimilar patients was required. Compared to the similarly nonpainful stimulation of normal patients, activation increased in a number of brain areas associated with cognitive control and perspective-taking (rIFC and dmPFC). Activation was also increased in areas processing the affective component of pain (AI and dACC). In addition, trait perspective-taking skills correlated with hemodynamic responses in rIFC only when participants were witnessing nonpainful stimulation.

In many respects, the situation our participants were exposed to resembles the ones created in task-switching paradigms. In these paradigms, a previously established stimulus–response association has to be replaced by a new association (Monsell, 2003). In the current study, participants switched from their own stimulus–response association to representing how someone dissimilar to them would respond. In addition to cognitive control mechanisms, this required assessing the sensory and affective consequences of the witnessed stimulations, that is, adopting the perspective of the target in order to share their feelings. Task-switching paradigms demonstrate the necessity to both inhibit pre-established response tendencies and to monitor whether this inhibition has to take place (e.g., Botvinick, Braver, Barch, Carter, & Cohen, 2001). As elucidated by neuroimaging and lesion studies, rIFC plays a decisive role in response inhibition, attention, and cognitive control (Brass et al., 2005; Aron et al., 2004; Corbetta & Shulman, 2002). These cognitive functions are predominantly associated with a large area encompassing the (right) ventral premotor area (pars opercularis and pars triangularis, cytoarchitectonic areas 44 and 45) and a more posterior cortical region labeled as the inferior frontal junction area (Brass et al., 2005). This area was strongly involved in the current study, as indicated by a large cluster encompassing rIFC. We propose that activation in this cluster is associated with inhibition of one's aversive response when observing painless injections. In addition to the correlation analysis which suggests that higher inhibitory control goes along with better self-reported perspective-taking skill, the PPI results support this view as well, showing increased connectivity with areas coding affective representations such as ventral posterior MCC and the dACC, the periaqueductal gray, and the right AI. Although PPI analyses do not allow

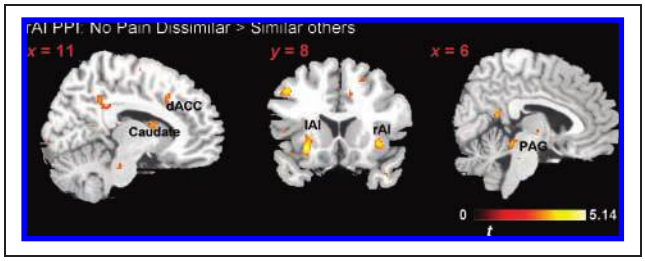

Figure 7. Significant changes in effective connectivity (contrast *No Pain: Dissimilar > Similar others*) between a seed region in the right anterior insula and the shown clusters. See text for abbreviations and Figure 4 for other specifications.

inferences about the causality of interactions, it is tempting to interpret them as an increase in inhibitory control of areas coding one's own aversive response to the perceived situation. Future studies, including disruptive techniques such as transcranial magnetic stimulation, should therefore assess how specific and causal activation in rIFC is in regulating empathic responses to dissimilar others.

Recent reviews (van Overwalle, in press; Amodio & Frith, 2006) suggest that ventral aspects of mPFC are primarily associated with thinking about others based upon one's own mental representations, whereas dorsal regions are involved in taking the perspective of others—in particular when they are dissimilar from the self (Jenkins, Macrae, & Mitchell, 2008; D'Argembeau et al., 2007; Mitchell et al., 2006). Adopting the subjective perspective of another individual crucially relies upon representing two (or more) distinct perspectives, and upon distinguishing whether they belong to the self or the other (Decety & Jackson, 2004; Ruby & Decety, 2004). Self–other distinction enables us to generate appropriate self or other-related responses (Meltzoff & Decety, 2003). A recent meta-analysis assigns an important role to dorsal mPFC in pre-response conflict resolution and in responding under uncertainty (Ridderinkhof, Ullsperger, Crone, & Nieuwenhuis, 2004). Pre-response conflict resolution and uncertainty are also given when adopting the perspective of others who respond differently as we do. Hence, activation in dorsal mPFC might represent a low-level mechanism for self–other distinction in the current paradigm. The TPJ has been assigned a similarly important role for self–other distinction in previous studies on social cognition (e.g., Decety & Lamm, 2007; Lamm, Nusbaum, et al., 2007; Farrer et al., 2004; Ruby & Decety, 2001), and we expected it to play a crucial role in the present paradigm. The role of the TPJ in self–other distinction is usually explained by its multisensory neural connections that allow the matching of (egocentric) somatosensory signals with allocentric information, which is usually conveyed in the visual or auditory domain. The requirement of perceptual matching might have been precluded by dmPFC in the current study, as indicated by its increased connectivity with visual cortical areas.

A recent combined fMRI and eye-tracking study might suggest an alternative interpretation of dmPFC activation (van Reekum et al., 2007). This study demonstrated that negative responses to emotionally evocative scenes can be decreased and reappraised by averting one's gaze from the visual stimulus, and that dmPFC is substantially related to such a strategy. Watching injections with nonpainful consequences (i.e., needle injections into dissimilar targets) are particularly prone for such a reappraisal strategy. We therefore performed a control study in order to make sure that dmPFC activation in our fMRI study did not result from different eye movement patterns. Results showed that fixation times for needle injections into dissimilar others were not significantly shorter than fixation times for the nonpainful touch of similar patients—speaking against the interpretation that dmPFC activation in this study was related to averted eye gaze. The eye tracking study also showed that fixation times slightly varied across conditions, and that painful stimulation of similar others resulted in the longest looking times. Hence, parts of the effects we might see in the current as well as in other empathy paradigms might be attributed to different attentional and perceptual phenomena. Future studies should attempt to take these processes into account more explicitly, for example, by recording eye movements during scanning in order to treat them as a potential covariate.

Apart from a neural network associated with cognitive control and associative learning, areas coding the affective–motivational aspects of pain, such as ventral posterior MCC, dACC, AI, and periaqueductal gray, were also engaged when observing painless needle injections. As demonstrated by the automaticity localizer, these activations do not result from an automatic response triggered by the sight of an injection or aversive stimulation (see also Gu & Han, 2007). Both MCC and the AI play an important role in empathy for pain, a role that has been connected to interoceptive awareness (Critchley, Wiens, Rotshtein, Oehman, & Dolan, 2004; Craig, 2002). The increased connectivity between right AI and MCC/ACC during empathy for a nonpainful situation might result from the *process* of evaluating the affective consequences of the shown situations, as opposed to the actual *outcome* of the evaluation. This is in line with activation in these areas when participants evaluated the ''painful'' consequences of a Q-tip touching similar others (data not shown), as well as with previous results showing that evaluating ''pain'' caused by nonpainful stimuli also triggers activation in the insula and MCC (Lamm, Nusbaum, et al., 2007; Lamm & Decety, unpublished data).

In addition to the insights gained for how we respond to dissimilar others, this study also makes an important contribution toward how we understand similar others. Current accounts of empathy suggest that attending to another's affective state activates representations of that state in the observer, along with their corresponding somatic and autonomic responses (e.g., Preston & de Waal, 2002). Our results extend this hypothesis by showing that somatosensory areas present stronger activation when we empathize with the pain of someone whose sensory experiences and response-tendencies we share (contrast *Pain: Similar* > *Dissimilar*). The independent localization of the hand area combined with activation contralateral to the stimulated hand suggests, for the first time in such a specific manner for an fMRI study, that primary somatosensory representations are shared on the level of the affected body part.

A limitation of the current study is the use of stimuli which did not allow to infer the affective state of the target from overt affective displays (such as facial or vocal

expressions), but instead had to be based solely upon previously provided context information. This design was chosen on purpose because we explicitly wanted to know how we infer affective states without relying upon emotional contagion or direct perception–action coupling. Future studies should therefore investigate the role of cognitive control in situations which convey the target's affective state to the observer directly.

Conclusion

Empathizing with someone whose bodily and affective representations are distinct from our own is a task requiring the integration of cognitive control with processes of self–other distinction and perspective-taking (see Karniol, 2003). These processes crucially rely on executive functions for activating relevant representations and keeping them active while inhibiting irrelevant ones. The fact that all of our participants were able to correctly infer the affective state of the dissimilar patients demonstrates the mental flexibility of the human mind. Notably, it seems that sharing the pain triggered by a situation with neutral emotional valence for the observer relies upon the same mechanisms as sharing the pain of someone who is like us. Behavioral and neural indicators, however, suggest that it is more challenging (yet without doubt possible) to share the affect of dissimilar others in a situation that is aversive for the observer. This flexibility is a cornerstone of our ability to empathize with diverse others—from animals to anthropomorphized objects such as pets to people from different cultural backgrounds. The current study casts new light on the neural mechanisms involved in this mental flexibility. It also contributes to our understanding of the fundamental mechanisms involved in empathy by showing that emotion contagion and perception–action coupling do not represent the only route to empathy for pain. Rather, our results support a model of empathy that involves a complex interaction between bottom–up (i.e., direct matching between perception and action) and top–down (i.e., regulation and control) information processes (Lamm, Porges, Cacioppo, & Decety, 2008; Decety & Lamm, 2006; Goubert et al., 2005; Decety & Jackson, 2004). The low level, which is automatically activated (unless inhibited) by perceptual input, accounts for emotion sharing. Executive functions, implemented in prefrontal cortex, serve to regulate both cognition and emotion, notably through selective attention and self-regulation.

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