The Neural Substrate of Human Empathy: Effects of Perspective-taking and Cognitive Appraisal

Claus Lamm[1,3], C. Daniel Batson[2], and Jean Decety[1,3]

Abstract

■ Whether observation of distress in others leads to empathic concern and altruistic motivation, or to personal distress and egoistic motivation, seems to depend upon the capacity for self–other differentiation and cognitive appraisal. In this experiment, behavioral measures and event-related functional magnetic resonance imaging were used to investigate the effects of perspective-taking and cognitive appraisal while participants observed the facial expression of pain resulting from medical treatment. Video clips showing the faces of patients were presented either with the instruction to imagine the feelings of the patient (''imagine other'') or to imagine oneself to be in the patient's situation (''imagine self''). Cognitive appraisal was manipulated by providing information that the medical treatment had or had not been successful. Behavioral measures demonstrated that perspective-taking and treatment effectiveness instructions affected participants' affective responses to the observed pain. Hemodynamic changes were detected in the insular cortices, anterior medial cingulate cortex (aMCC), amygdala, and in visual areas including the fusiform gyrus. Graded responses related to the perspective-taking instructions were observed in middle insula, aMCC, medial and lateral premotor areas, and selectively in left and right parietal cortices. Treatment effectiveness resulted in signal changes in the perigenual anterior cingulate cortex, in the ventromedial orbitofrontal cortex, in the right lateral middle frontal gyrus, and in the cerebellum. These findings support the view that humans' responses to the pain of others can be modulated by cognitive and motivational processes, which influence whether observing a conspecific in need of help will result in empathic concern, an important instigator for helping behavior. ■

INTRODUCTION

Empathy refers to the capacity to understand and respond to the unique affective experiences of another person (Decety & Jackson, 2004; Batson, Fultz, & Schoenrade, 1987). This psychological construct denotes, at a phenomenological level of description, a sense of similarity between the feelings one experiences and those expressed by others. Despite the various definitions of empathy among psychologists, there is broad agreement on three primary components: (1) an affective response to another person, which some believe entails sharing that person's emotional state; (2) a cognitive capacity to take the perspective of the other person; and (3) some monitoring mechanisms that keep track of the origins (self vs. other) of the experienced feelings. Depending on how empathy is triggered, the automatic tendency to mimic the expressions of others (bottom-up processing) and the capacity for the imaginative transposing of oneself into the feeling and thinking of another (top-down processing) may be differentially involved. It also seems likely that both processes rely upon, to some extent, neural mechanisms that are involved when the self experiences emotion. It is not plausible, however, that this sharedness is absolute. A complete overlap between self and other representations would produce distress and hamper the ability to toggle between self and other perspectives.

In recent years, there has been a growing interest in research on the neural mechanisms that mediate empathy, particularly following the target article by Preston and de Waal (2002), in which they reviewed an impressive array of evidence in support of the perception–action model and its fundamental role in social interaction. This model posits that perception of emotion activates the neural mechanisms that are responsible for the generation of emotions. Such a system prompts the observer to resonate with the emotional state of another individual, with the observer activating the motor representations and associated autonomic and somatic responses that stem from the observed target (i.e., a sort of inverse mapping). For instance, a handful of functional magnetic resonance imaging (fMRI) studies have shown that the observation of pain in others is mediated by several brain areas that are implicated in processing the affective and motivational aspects of pain (see Jackson, Rainville, & Decety, 2006, for a review). In one study, participants received painful stimuli in some trials and, in other trials, observed a signal that their partner, who was present in

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[1]INSERM Unit 280, France, [2]University of Kansas, [3]University of Chicago

the same room, would receive the same stimuli (Singer et al., 2004). The anterior medial cingulate cortex (aMCC; Vogt, 2005), the anterior insula, and the cerebellum were activated during both conditions. Similar results were reported by Morrison, Lloyd, di Pellegrino, and Roberts (2004), who applied a moderately painful pinprick stimulus to the fingertips of their participants, and—in a second condition—showed them a video clip showing another person undergoing similar stimulation. Both conditions resulted in common hemodynamic activity in pain-related areas of the right cingulate cortex. In contrast, the primary somatosensory cortex showed significant activations in response to tactile stimuli only, but not to visual stimuli. The different response patterns in the two areas are consistent with the role of the aMCC in coding the motivational-affective dimension of pain, which is associated with the preparation of behavioral responses to aversive events (Vogt, 2005; Paus, 2001). In another study, participants were shown photographs depicting right hands and feet in painful or neutral everyday-life situations, and were asked to imagine the level of pain that these situations would produce (Jackson, Meltzoff, & Decety, 2005). Significant activation in regions involved in the network processing the affective aspect of pain, notably the aMCC and the anterior insula, was detected. Moreover, the level of activity within the aMCC was strongly correlated with participants' mean ratings of pain attributed to the different situations. These results lend support to the idea that common neural circuits are involved in representing one's own and others' affective pain-related states. Recently, Singer and colleagues (2006) demonstrated that the hemodynamic response in this circuit is modulated by learned social preferences, especially in male participants.

Imagining how another person feels and how one would feel in a particular situation requires distinct forms of perspective-taking that likely carry different emotional consequences (Batson, Early, & Salvarini, 1997). Research in social psychology (e.g., Batson et al., 2003; Underwood & Moore, 1982) has documented this distinction by showing that the former may evoke empathic concern (defined as an other-oriented response congruent with the perceived distress of the person in need), whereas the latter induces both empathic concern and personal distress (i.e., a self-oriented aversive emotional response). In a recent fMRI study, participants were shown pictures of people with their hands or feet in painful or nonpainful situations with the instruction to imagine themselves or to imagine another individual experiencing these situations (Jackson, Brunet, Meltzoff, & Decety, 2006). Both the self-perspective and the other-perspective were associated with activation in the neural network involved in pain processing, including the parietal operculum, the aMCC, and the anterior insula. These results reveal the similarities in neural networks representing first-person and third-person information, which is consistent with the shared representations account of social interaction (Decety & Grèzes, 2006; Decety & Sommerville, 2003). In addition, the self-perspective yielded higher pain ratings and involved the pain matrix (Derbyshire, 2000) more extensively in the secondary somatosensory cortex, the posterior part of the anterior cingulate cortex (ACC), and the middle insula. These results highlight important differences between the self- and other-perspectives. For instance, although the anterior insula is activated both when participants imagine their own and when they imagine another's pain, nonoverlapping clusters can be identified within the middle insula. Likewise, both self- and other-perspectives are associated with a common subarea in the aMCC, but the self-perspective selectively activated another part of this region.

Finally, being aware of one's own emotions and feelings enables us to reflect on them. Among various emotion regulation strategies when observing a target in pain, reappraisal by denial of relevance (i.e., taking a detached observer position), by implicitly or explicitly generating an image of the observing self which is unaffected by the target, is known to reduce the subjective experience of anxiety, sympathetic arousal, and pain reactivity (Kalisch et al., 2005). Such a strategy is likely to play an important role in preventing empathic overarousal (think about a psychotherapist and his/her client). fMRI studies have identified a limited number of regions in the anterolateral prefrontal and medial prefrontal/orbito-frontal cortices that mediate such function (Kalisch et al., 2005; Ochsner, Bunge, Gross & Gabrieli, 2002).

The goal of the present experiment was to assess the respective contribution of the processes that mediate empathy: affective sharing, perspective-taking, and cognitive appraisal. We exposed participants to video clips showing the faces of persons who were described as patients suffering a neurological disease affecting their audition. As a cover story, participants were told that patients underwent a sound therapy supposed to improve their medical status; however, as this therapy involved being stimulated with sounds of a certain frequency, patients had to suffer great pain during treatment. Participants were requested to watch the videos adopting two different perspectives, that is, either imagining how they themselves would feel if they were in the place of the other (imagine self), or imagining how the other feels (imagine other). In addition, participants were told that the video clips had been shot from two groups of individuals. In one group, patients got better after treatment, whereas patients from the other group did not benefit from that treatment. This manipulation was performed to elicit different cognitive appraisals by observers watching identical stimuli, but with knowledge of different implications. It was anticipated that witnessing another person suffering and knowing that the treatment had not been effective would increase emotional distress in the observer (and vice versa). During scanning, participants had to rate intensity and unpleasantness of pain imagined when watching the video clips. After the scanning session, additional behavioral data, including an emotional response scale and two memory tests, were collected. It was anticipated that the neural network involved in the processing of the affective and motivational aspects of pain (MCC/ACC and insula) would not only be activated by the perception of pain in others, but also be modulated by the perspective-taking instructions as well as by the cognitive appraisal resulting from knowledge about the current state of the patients. Notably, different aspects of the aMCC/ACC and insula were expected to be differentially associated with these two factors. Further, if imagining self in pain leads to more personal distress than imagining other, one may anticipate stronger signal increase in the amygdala for the former than for the latter. In addition, the process of self–other differentiation during perspective-taking was expected to selectively activate left and right temporoparietal areas (Decety & Grèzes, 2006).

METHODS

Participants

Seventeen right-handed healthy volunteers (8 women), aged between 18 and 31 years (mean = 23.5 years, *SD* = 4.4), participated in the main experiment of this study. They gave informed written consent and were paid for their participation. No subject had any history of neurological, major medical, or psychiatric disorder. The study was approved by the local Ethics Committee and was conducted in accordance with the Declaration of Helsinki. From a pretest sample of 64 candidates, we selected those having at least moderately high scores on the Empathic Concern Scale of the Interpersonal Reactivity Index (IRI; Davis, 1996), and an IRI Perspective Taking score of at least 11. This was done to exclude participants with low empathy and perspective-taking abilities (see Results). In order to reduce social desirability, study-compliant responding, and priming effects, questionnaires were completed without information about the purpose of the study several weeks before the study. In addition, 111 volunteers participated in behavioral experiments designed for stimulus selection and validation.

Stimulus Preparation and Validation

Two types of stimuli were generated for this study: aversive sounds and video clips showing persons listening to these sounds. Sounds and video clips were validated in two independent behavioral experiments. Thirty aversive sounds were composed by mixing three highly dissonant tone pairs in a frequency range from 1300 to 11,000 Hz (to minimize interference with MR gradient noise). Sounds were composed using S_TOOLS-STx (v3.6.1; Acoustics Research Institute of the Austrian Academy of Sciences, Vienna, Austria) and were digitally amplified to yield sound pressure levels of approximately 95 dB(A). Affective reactions to these sounds were evaluated using the SAM manikin approach (Bradley & Lang, 2000), and sounds with an average unpleasantness rating of ≥ 8 were selected for further use (with ratings ranging from 1 = very pleasant to 9 = very unpleasant). Video clips (without sound) showing the face of individuals listening to these sounds were recorded from 50 healthy individuals (targets), who were either professional actors or experienced pantomime players (26 women, age range: 18–37). Video clips were shot from a frontal view using a digital color camcorder, were centered on the target's nose, and showed the whole head and parts of the shoulders. Targets were instructed to direct their gaze at a point approximately 50 cm below the camcorder lens to avoid direct eye contact. In order to imply that videos had been taken in a hospital environment, videos were taken against a light blue background curtain (as used in hospitals), and targets were wearing a white medical blouse and audiometric headphones. Targets were instructed to emphasize their painful response to the sounds in order to yield facial expressions of strong pain. Video clips were edited to show the transition from a neutral facial expression to the painful reaction resulting from sound presentation (Figure 1).

Video clips in which targets displayed brow lowering, orbit tightening, and either cursing or pressing of the

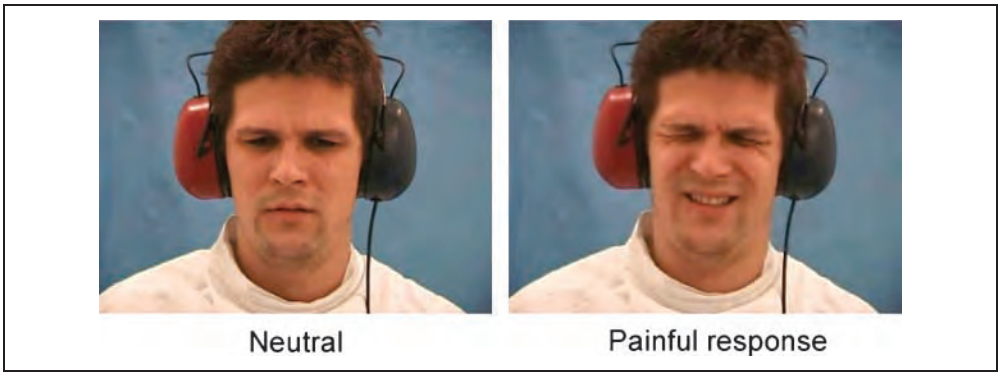

Figure 1. Sample frames extracted from a video clip used in this study showing the transition from neutral to painful facial expression triggered by the presentation of an aversive, painful sound.

lips, or mouth opening or stretching, were selected for further analysis, as these movements have consistently been attributed to the facial expression of pain (e.g., Craig, Prkachin, & Grunau, 2001). Only video clips displaying a natural pain response were selected (although recent evidence documents that the deliberate exaggeration of pain does not yield unrealistic facial expressions; Prkachin, 2005). This selection procedure yielded 105 video clips that were shown to a sample of 94 healthy participants (67 women, age range: 18–54), who rated the pain experienced by targets on a 7-point Likert-type scale ranging from ''not painful at all'' to ''extremely painful.'' The resulting mean ratings ranged between $M = 2.568$ and $M = 6.274$ for the 105 video clips (mean and standard deviation of all clips: $M = 4.593$, $SD = 0.966$). Fifty-five different clips of 24 targets (12 women) with the highest pain ratings were selected for the fMRI study. The mean rating of these clips was $M = 5.419$ ($SD = 0.493$, range: $M = 4.579 – 6.274$).

Experimental Procedure

Using a standardized written and verbal instruction procedure, participants were informed that they would watch video clips of patients experiencing painful auditory stimulation due to medical treatment. According to instructions, the patients were suffering from a neurological disease (*Tinnitus aurium*) that had been treated using a new therapy. The new therapy required repeated stimulation of patients by sounds of specific frequencies and amplitudes, resulting in great pain. As this new therapy was being used for the first time, some of the patients benefited from it, whereas others did not. Participants were instructed to watch the video clips adopting either of two perspectives (imagine self vs. imagine other), and were told to which treatment group (effective vs. not-effective treatment) each patient belonged. A sample of the sounds was played to participants, pointing out that the pain evoked in patients was considerably stronger due to their neurological illness. Before scanning, participants performed several practice trials to familiarize them with the experimental design as well as with the button box used for responding.

A 2 × 2 factorial design with factors perspective-taking (levels: imagine self vs. imagine other) and treatment effectiveness (levels: treatment effective vs. not-effective) was implemented. A mixed blocked/event-related presentation mode was used for stimulus presentation. Before each block, an instruction screen was shown that indicated the perspective to adopt, and whether the patients to be shown belonged to the effective or to the not-effective treatment group. Each block consisted of four video clips (i.e., trials) of four different patients, showing the transition from a neutral facial expression (0.5 sec) to the expression of strong pain triggered by auditory stimulation (3 sec). The last video clip of each block had to be evaluated in terms of intensity and unpleasantness of pain (see Behavioral Measurements section). In order to control for the intensity of visual stimulation, scrambled static images with a centered fixation dot were shown during intertrial intervals (ITIs). Mean ITI duration was 6 sec, and ITIs were randomly jittered to reduce stimulus predictability and to allow efficient event-related signal estimation (Donaldson & Buckner, 2001).

Four consecutive fMRI runs comprising five blocks each were performed, with the sequence of blocks being pseudorandomized and counterbalanced across participants, and with no condition being repeated more than once per run. In each condition, different video clips of three male and female patients were shown. A patient shown in one condition was never shown in any of the other conditions. Some of the clips were repeated (not more than once) to yield a final number of 20 trials per condition. Video clips of conditions had equal mean ratings and standard deviations, and identical ITI distributions. Assignment of patients to conditions was counterbalanced across participants. After each run, a short break was provided to participants, and before starting the next run, perspective-taking and emotion regulation instructions were briefly recapitulated verbally.

In addition to the empathy-related fMRI runs, a localizer task was performed to identify the sensory and affective neural network activated by the first-hand experience of painful auditory stimulation. Aversive sounds were presented in an ON/OFF block design with 9 ON and 10 OFF epochs (duration 6 and 16 sec, respectively). After each ON epoch, participants had to evaluate the intensity and unpleasantness of the pain evoked by the sound.

Behavioral Measures

A variety of behavioral measures was employed to investigate the effects of experimental manipulations and to assess the relationships between personal traits and neural activity. In the scanner, intensity and unpleasantness of the imagined pain were rated on a 4-point scale ranging from ''no pain'' to ''worst imaginable pain.'' Mean ratings of conditions were analyzed using a 2 × 2 repeated-measures analysis of variance (ANOVA), with factors perspective taking and treatment effectiveness. After scanning, participants were submitted to a recognition memory test, a forced-choice memory test, and a behavioral experiment assessing self-reported emotional responses. They were also extensively debriefed using a structured semistandardized interview. In the recognition memory test, 52 static photos of faces were presented. Half of them depicted patients that had been shown during MRI scanning, and half of them were false targets. Participants were asked to decide whether the person on the photo was one of the patients shown during MRI scanning. Photos were edited to contain only the faces and not the entire heads of targets in order to avoid recognition by nonfacial characteristics such as hair color, hair cut, characteristic ears, foreheads, or the like. In the forced-choice memory test, participants had to determine for each of the 24 patients to which treatment group he/she belonged. Data of the two memory tests were analyzed using correct recognition or correct classification rates as dependent variables. It was predicted that the perspective-taking instructions would lead to a self-referential memory effect (Rogers, Kuipers & Kirker, 1977), that is, better recognition and classification rates should be associated with patients viewed using the self-perspective.

Emotional responses in the four experimental conditions were assessed using a procedure developed by Batson, Early, et al. (1997). Participants were shown four video clips per condition, and rated the degree to which they experienced 14 emotional states (e.g., alarmed, concerned, compassionate, distressed) while watching a clip (1 = not at all, 8 = extremely). In addition, intensity and unpleasantness of pain were evaluated in the same way as in the MR scanner, but using an 8-point rating scale. Ratings of emotional states were aggregated by calculating empathic concern and personal distress indices (see Batson, Early, et al., 1997, for details). Indices were analyzed using repeated-measures ANOVAs with the factors index, perspective, and treatment effectiveness. We predicted that imagining how oneself would feel in the place of the patient would lead to higher personal distress, whereas imagining how the other felt would trigger more empathic concern. Behavioral data (including pretest data) were analyzed using SPSS 12.0.1 (SPSS, Chicago, IL, USA), and significance was defined as $p \leq .05$.

Finally, participants completed four dispositional measures: the IRI (Davis, 1996), Empathy Quotient [EQ] (Baron-Cohen & Wheelwright, 2004), Emotional Contagion Scale [ECS] (Doherty, 1997), and Emotion Regulation Scale [ERS] (Gross & John, 2003). The IRI is probably the most widely used self-report measure of dispositional empathy. Its four subscales (empathic concern, perspective taking, fantasy scale, and personal distress) assess different aspects of empathic responses. The EQ is a recently developed and well-validated questionnaire tapping cognitive empathy, emotional reactivity to others, and social skills. It was used as an alternative assessment of dispositional empathy. The ECS assesses the susceptibility to other's emotions from afferent feedback generated by mimicry. We expected such mimicry during watching the facial expression of pain. Finally, two different strategies of emotion regulation—emotion suppression and emotion reappraisal—were assessed using the ERS.

fMRI Data Acquisition and Analysis

MRI was performed using a whole-body 1.5-T Siemens Sonata scanner (Siemens, Erlangen, Germany). Functional images were acquired using an echo-planar imaging (EPI) sequence (echo time TE = 60 msec, repetition time TR = 1990 msec, flip angle = 90°, 21 axial slices with 4.5 mm slice thickness and 0.45 mm gap, in-plane resolution = 3.6×3.6 mm^2, 64×64 matrix, FOV = 230×230 mm^2). Images were acquired using an ascending interleaved sequence with no temporal gap between consecutive image acquisitions. The influence of in-plane susceptibility gradients in orbito-frontal regions was reduced by orienting image slices according to recommendations by Deichmann et al. (2003). Four fMRI runs with 162 image acquisitions were performed to investigate hemodynamic responses related to empathy, and one run with 158 images was performed for the localizer task. The first nine scans of each run served to achieve steady-state magnetization conditions and were discarded from analyses.

Stimulus presentation and response collection were performed using the Presentation software (Neurobehavioural Systems, Albany, CA, USA), with block onsets being temporally synchronized with functional magnetic resonance image acquisition. Visual stimuli were presented using a back-projection system, with video clips subtending a visual angle of 9.47° × 7.56°. MR-compatible headphones (CONFON HP-SI01; MR Confon GmbH, Magdeburg, Germany) were used to present auditory stimuli at sound pressure levels of approximately 95 dB(A). A button box consisting of four buttons pressed using the dominant right hand recorded the responses of subjects.

Image processing was carried out using SPM2 (Wellcome Department of Imaging Neuroscience, London, UK), implemented in MATLAB 6.5 (Mathworks, Sherborn, MA, USA). Preprocessing included slice-timing correction, correction for head motion (realignment to first image volume), normalization to the EPI template provided in SPM2, and smoothing using a 6-mm full-width half-maximum isotropic Gaussian kernel. Event-related responses were assessed by setting up fixed-effects general linear models for each subject. Regressors of interest modeling the four experimental conditions, the instruction display, and the evaluation epochs were set up, and regressors were convolved with a canonical hemodynamic response function (hrf) and their temporal and dispersion derivatives. The latter were incorporated into the model to account for potential timing differences in the (neural and hemodynamic) response to the video stimuli (Friston et al., 1998). Hemodynamic responses in the localizer task were modeled using the canonical hrf only. Fixed-effects models incorporated a high-pass filter with a frequency cutoff at 128 sec. Following model estimation, contrasts were calculated for each subject to assess differences between factor levels (Self > Other, Other > Self, Effective > Not-effective, Not-effective > Effective, positive and negative interaction). In addition, signal changes in relationship to the inherently modeled baseline were assessed. The resulting contrast images, containing parameter estimates for each of the three basis functions, were entered into second-level random effects repeated measures ANOVAs. Nonsphericities of ANOVAs were accounted for by using Greenhouse–Geisser correction, as implemented in SPM2. *F*-contrasts incorporating all three basis parameters as well as *T*-contrasts assessing the parameter estimates for the canonical hrf only were computed. As analyses assessing derivatives did not yield relevant effects, only the results of the *T*-contrasts will be reported here. Activity common to the observation of pain in others and the first-hand experience of pain were analyzed using a masking analysis. This analysis consisted of a random-effects *t* test for the contrast Watching Pain > Baseline that was masked (inclusively) by the contrast Sound > Baseline. For analyses of activity differences between factor levels, a voxel-level threshold of $p = .001$ (uncorrected) and a spatial extent threshold of $k = 5$ was chosen. The contrast Watching Pain > Baseline was thresholded at $p = .00001$ (uncorrected), $k = 20$, and a threshold of $p = .0001$ (uncorrected), $k = 20$ was used for the sound localizer task, as the latter had lower power due to fewer stimulus repetitions and fewer image acquisitions. Choice of thresholds was based upon former studies of our group using similar task manipulations (Jackson et al., 2005, 2006), as well as upon exploratory data analyses. Note also that similar thresholds were used in the region-of-interest (ROI) analyses of Botvinick et al. (2005) and Singer et al. (2004). In addition, for analyses focusing on the more subtle differences between factor levels, the threshold was lowered to $p = .005$ to assess whether there was below threshold activation in a priori defined regions involved in the perception of pain and in emotion regulation. Anatomic and Brodmann's area labeling of activity clusters was performed using the Anatomy Toolbox (v1.0; Eickhoff et al., 2005), Anatomic Automatic Labeling [AAL] (Tzourio-Mazoyer, Landeau, Papathanassiou, Crivello, Etard et al., 2002), and the Talairach Demon database (http://ric.uthscsa.edu/projects/tdc). Nomenclature for activations in the cingulate cortex is based on a recent review by Vogt (2005). In addition to the whole-brain analyses, an ROI analysis of amygdala activity was performed using the MarsBaR toolbox, v0.38 (www.sourceforge.net/projects/marsbar). This analysis extracted parameter estimates of activity in the left and right amygdala (structurally defined with ROIs provided in the MarsBaR toolbox) to analyze them using repeated-measures ANOVA.

In order to assess the relationship between behavioral data and brain activity, random-effects correlation analyses were performed. Scores on the Empathic Concern subscale of the IRI, the EQ questionnaire, and the normalized values of the empathic concern index were correlated with parameter estimates of the contrast Other > Baseline. In addition, Self > Baseline was correlated with the IRI Personal Distress subscale and normalized personal distress index values, and ECS scores were correlated with Watching Pain > Baseline. A rather liberal significance threshold of $p = .001$ (uncorrected) and $k = 5$ was selected for these analyses. In order to avoid an abundance of false positives associated with the multitude of analyses, significant correlations were only interpreted if they were located in a priori defined regions of the pain matrix (Derbyshire, 2000).

RESULTS

Dispositional Measures

Table 1 compares responses to the dispositional measures with published normative data. This comparison shows that IRI and EQ scores were slightly lower, but clearly within the range of the norm values—despite the fact that we had preselected subjects to exclude those with low empathic concern and perspective-taking abilities. Thus, albeit empathic concern in our final sample was not above average, the truncated range should be kept in mind when comparing our results to other studies. Emotional contagion was noticeably lower than in the norm population. Emotion regulation by means of reappraisal was higher than in the norm population, whereas emotion suppression was slightly lower. Note though that we are comparing Anglo-American norm populations with a French sample filling out French translations of the questionnaires.

Behavioral Data

Due to equipment failure, the behavioral data of one participant were not available. Ratings acquired during MR scanning revealed significant effects of the perspective-taking and the treatment-effectiveness factors. Pain intensity was significantly affected by treatment effectiveness [main effect of the effectiveness factor, $F(1,15) = 6.059$, $p = .026$, $\eta^2 = 0.288$], with pain intensity ratings being higher when the treatment was not effective [*M*(Effective) = 3.116, *M*(Not-effective) = 3.398]. Perspective-taking did not significantly affect the ratings (no main effect of factor perspective taking, $p = .350$), and the interaction term also was not significant ($p = .869$). A similar result was obtained with the unpleasantness ratings [main effect of treatment effectiveness, $F(1,15) = 37.31$, $p < .001$, $\eta^2 = 0.713$; *M*(Effective) = 2.814, *M*(Not-effective) = 3.567; other effects, $p > .381$]. Evaluations collected during the postscanning behavioral experiment indicated that watching patients undergoing ineffective treatment resulted in higher unpleasantness [main effect of treatment effectiveness, $F(1,15) = 6.534$, $p = .022$, $\eta^2 = 0.303$; other effects, $p > .611$]. No significant results were obtained for pain intensity ratings ($p > .455$ for all effects). Ratings of the aversive sounds during the localizer task yielded a mean intensity rating of 2.931 (*SD* = 0.563) and a mean unpleasantness rating of 2.872 (*SD* = 0.666).

The recognition memory test revealed that patients viewed with the self-perspective were remembered better

Table 1. Mean Scores and Standard Deviations for the Dispositional Measures

	Interpersonal Reactivity Index (IRI)				*Empathy Quotient*	*Emotional Contagion Scale*	*Emotion Regulation Questionnaire*	
	PT	*EC*	*PD*	*FS*			*Reappraisal*	*Suppression*
Sample (n = 17) Mean (*SD*)	16.35 (2.91)	19.76 (1.95)	9.94 (6.15)	17.12 (5.07)	38.13 (9.98)	43.56 (3.37)	31.35 (4.23)	13.59 (6.26)
Normative Data[a] Mean (*SD*)	17.37 (4.79)	20.36 (4.02)	10.87 (4.78)	Not available	41.8[b]/47.2[c] (11.2[b]/10.2[c])	54.3 (8.1)	27.6[b]/27.66[c] (5.64[b]/6.12[c])	14.56[b]/12.56[c] (4.44[b]/4.72[c])

The table provides results for the sample investigated in our study, and published normative values.

PT = perspective taking; EC = empathic concern; PD = personal distress; FS = fantasy. Maximum Scores: IRI Subscales = 28; Empathy Quotient = 80; Emotional Contagion = 60; Reappraisal = 42; Suppression = 28.

[a] Normative data derived and transformed to sum scores from: IRI (Bellini, Baime, & Shea, 2002); EQ (Baron-Cohen & Wheelwright, 2004); ECS (Doherty, 1997); ERS (Gross & John, 2003).

[b] Male sample.

[c] Female sample.

[main effect of perspective taking, $F(1,15) = 4.623$, $p = .048$, partial $\eta^2 = 0.236$; M(Self) = 34.375, *SD* = 15.478; M(Other) = 27.083, *SD* = 13.088]. Treatment effectiveness did not have a significant effect on recognition rates ($p = .485$), nor was the interaction term significant ($p = .736$). In addition, patients displaying stronger pain were more likely to be recognized (as indicated by a significant correlation between the perceived intensity of pain determined in the pretests and the percentage of correct hits, $r = .429$, $p = .004$). The forced-choice memory test showed that the self-perspective led to a higher percentage of correct classifications [main effect of perspective taking, $F(1,14) = 4.421$, $p = .054$, $\eta^2 = 0.24$; M(Self) = 34.444, *SD* = 15.387; M(Other)= 24.444, *SD* = 17.385]. Neither the treatment-effectiveness main effect ($p = .815$) nor the interaction term was significant ($p = .526$). The main effect of perspective-taking missed the chosen threshold because one participant showing stereotyped response behavior had to be excluded from the analysis, resulting in a reduction of degrees of freedom; note though that estimated effect size (partial η^2) is slightly higher than in the recognition memory test. Correlation with perceived pain intensity was not significant ($r = .191$, $p = .220$).

Analysis of the behavioral experiment performed after scanning confirmed our predictions concerning the effects of perspective-taking on empathic concern and personal distress. Empathic concern was considerably stronger when participants focused on the feelings of the other, whereas adopting the self-perspective led to stronger personal distress [interaction between indices and perspective factor, $F(1,15) = 16.715$, $p = .001$, partial $\eta^2 = 0.527$; Figure 2A]. In addition, personal distress was generally more pronounced if the treatment was not effective [main effect of treatment effectiveness, $F(1,15) = 10.103$, $p = .006$, partial $\eta^2 = 0.402$]. These effects were additionally modulated by the treatment effectiveness manipulation: Whereas the treatment outcome had almost no modulating effect on empathic concern for the self-perspective, adopting the other-perspective strongly increased personal distress when the treatment was not effective [three-way interaction, $F(1,15) = 5.884$, $p = .028$, partial $\eta^2 = 0.282$; Figure 2B].

The semistandardized interviews performed during experimental debriefing revealed that participants were able to differentiate the four different conditions, and that there were no suspicions concerning the authenticity of the cover story. The majority of participants reported reacting to both patient groups in similar ways, but that they used reappraisal strategies when watching patients undergoing effective treatment. For example, self-reassuring statements such as ‘‘the patient is in pain, but he/she will be OK soon’’ were used. During the other-condition, participants adopted a more other-oriented perspective and focused more on the facial expressions of the patients than during the self-perspective. Notably, 14 subjects reported overt facial mimicry while watching

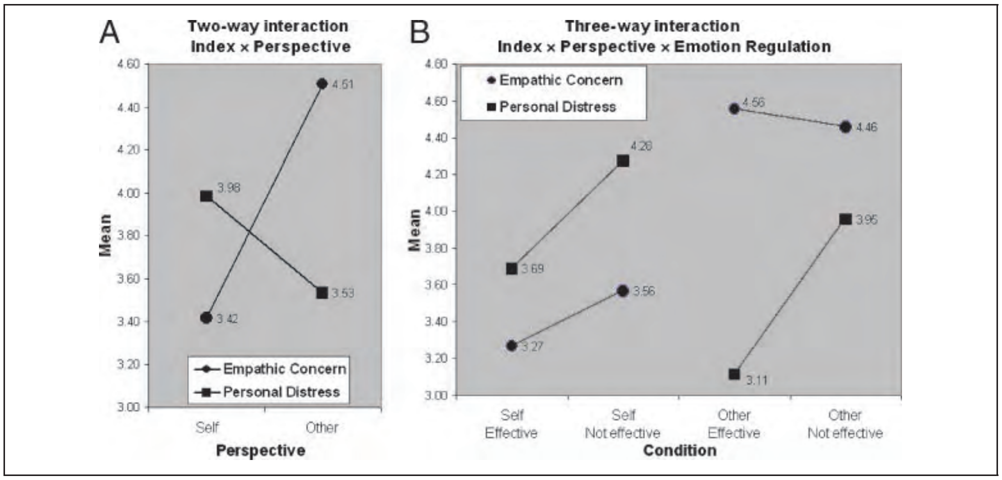

Figure 2. Mean values for the empathic concern and personal distress indices. (A) Note that adopting the self-perspective elicits higher personal distress, whereas the other-perspective triggers higher empathic concern. (B) This effect is modulated by the treatment effectiveness factor (effective vs. not-effective treatment). See text for further details.

the videos, with reports of mimicry being stronger in the self-perspective in eight of these subjects.

Network of Areas Involved in the Observation of Pain

Observation of pain expressed by the patients activated a widely distributed network of brain regions, reflecting the sensory, cognitive–motor, and affective processing of the stimuli (Figure 3). Clusters comprising (bilaterally) medial and lateral occipital cortex, including the fusiform gyrus, indicate the visual processing of the stimuli. Activity in bilateral anterior and in the left middle insula, aMCC, thalamus, basal ganglia (pallidum and caudate nucleus), and bilateral periamygdalar region reveals the affective response to the observation of pain. Additional significant clusters were detected in motor control-related regions, such as the cingulate and supplementary motor area (CMA/SMA) and the lateral precentral gyrus, as well as in temporo-parietal and lateral prefrontal areas (Brodmann's areas 8 and 9).

Analysis of the localizer task resulted in bilateral hemodynamic changes in the posterior superior temporal gyrus, comprising the Heschl gyrus and overlapping with the probabilistic cytoarchitectonic maps of the primary auditory cortices provided in the Anatomy Toolbox (Morosan et al., 2001). Also, activity was detected bilaterally in the anterior insula, in the left middle

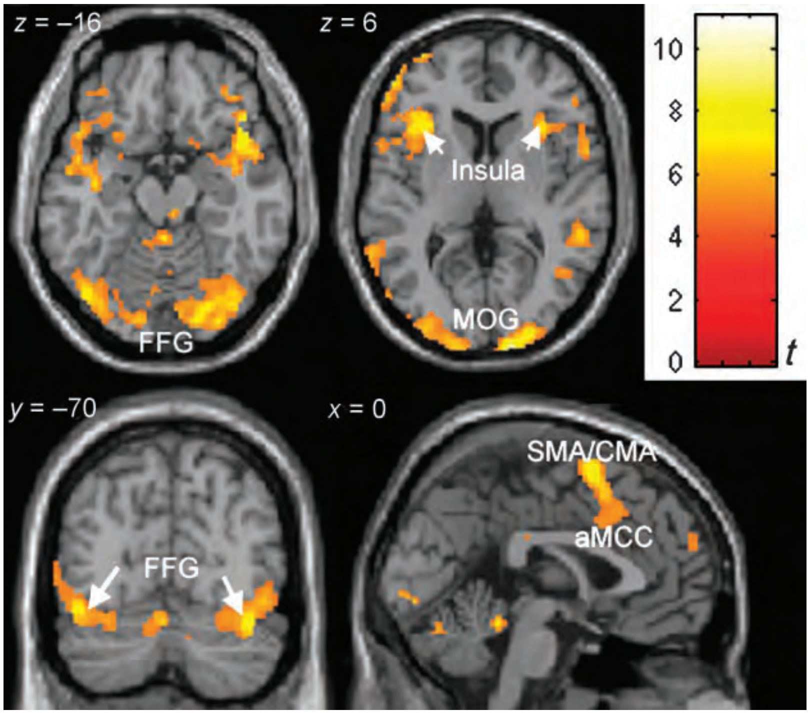

Figure 3. Significant hemodynamic response to the observation of patients expressing pain (Watching Pain > Baseline). Activation was detected in the neural network involved in the sensory (FFG = fusiform gyrus, MOG = middle occipital gyrus) and the affective processing of pain (insula, aMCC). Results are superimposed on axial ($z = -16$, $z = 6$), coronal ($y = -70$), and sagittal sections ($x = 0$) of the single-subject structural MNI MRI template (used in all figures and displayed in neurological convention). Threshold $p = .00001$ (uncorrected), $k = 20$.

Table 2. Common Hemodynamic Responses during the Observation of Patients Expressing Pain and the First-hand Experience of Pain (Masking Analysis, Voxel Threshold: $p = .00001$, Uncorrected; Cluster Size Threshold: $k = 20$; Masking Threshold: $p = .001$, Uncorrected)

			MNI Coordinates		
Brain Region	*L/R/M*	*t Value*	*x*	*y*	*z*
Middle Temporal Gyrus	L	9.45	−52	−2	−16
x Temporal Pole of STG	L	8.49	−38	2	−20
x STG	L	6.47	−48	−8	−12
SMA	M	8.84	0	6	62
x SMA/CMA	M	7.09	0	14	50
Insula	R	7.17	42	−2	−18
Anterior Insula	R	9.66	34	18	6
Anterior Insula	L	8.66	−38	18	4
x Anterior Insula	L	7.87	−36	26	4
x IFG	L	7.86	−32	26	−10
STG	R	8.18	50	−44	18
x STG	R	6.90	40	−42	4
aMCC	L	7.98	−10	12	40
Orbital part of IFG	R	7.35	44	20	−16
x Temporal Pole of STG	R	6.38	50	6	−14
Olfactory Bulb/Gyrus Rectus	R	7.09	22	10	−16
x Amygdala	R	6.98	26	0	−22

Stereotactic coordinates and t values are provided for the local voxel maxima in the respective cluster. x = subpeaks of a cluster; L = left hemisphere; R = right hemisphere; M = medial activation; IFG = inferior frontal gyrus; STG = superior temporal gyrus; aMCC = anterior medial cingulate cortex; SMA = supplementary motor area; CMA = cingulate motor area.

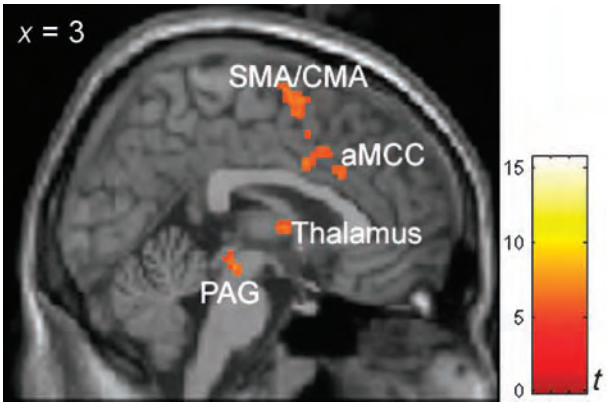

Figure 4. Significant hemodynamic response to painful auditory stimulation (Sound > Baseline). Results are superimposed on a sagittal section ($x = 3$). PAG = periaqueductal gray. Threshold $p = .0001$ (uncorrected), $k = 20$.

insula, in several subclusters in the aMCC, in the rostral thalamus, in a mesencephalic cluster containing the corpus geniculatum mediale and the periaqueductal gray, and in areas involved in motor control (pallidum and caudate nucleus, SMA, CMA, and right precentral gyrus; Table 2 and Figure 4).

The masking analysis revealed a vastly overlapping neural network, including several subclusters in bilateral anterior and left middle insula, a cluster in the aMCC and the right amygdala, as well as in the SMA, CMA, and right precentral gyrus (see Table 2 and Figure 5).

Responses Related to Perspective-taking and Treatment Effectiveness

Contrasting the self with the other conditions revealed different responses in a number of brain regions involved in pain processing, perspective-taking, and agency (see Table 3, Figures 6 and 7). The contrast Self > Other revealed stronger responses with the self-perspective in bilateral insula, left supramarginal gyrus (BA 40), left middle frontal gyrus (Brodmann's area 9), and in several areas involved in motor control such as the SMA, the right dorsal premotor cortex (lateral BA 6), the putamen, and the caudate nucleus. Note that clusters in the insula are located in an area classified as the middle (dysgranular) insula (Mesulam & Mufson, 1982) and

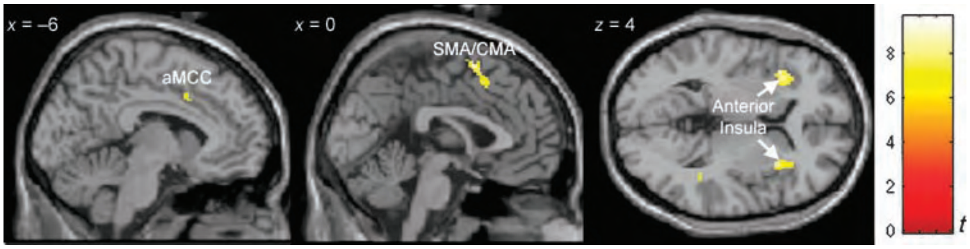

Figure 5. Brain areas commonly activated by the observation and the first-hand experience of pain (masking analysis). Results are superimposed on sagittal ($x = -6$, $x = 0$) and axial sections ($z = 4$), showing shared neural activation in areas coding the motivational–affective aspects of pain. Threshold $p = .00001$ (uncorrected), $k = 20$. Threshold for the mask: $p = .001$ (uncorrected).

Table 3. Differences in Hemodynamic Responses When Adopting Different Perspectives during the Observation of Patients Expressing Pain (Imagine Self vs. Imagine Other); Voxel Threshold: $p = .001$ (Uncorrected); Cluster Size Threshold: $k = 5$

			MNI Coordinates		
Brain Region	*L/R/M*	*t Value*	*x*	*y*	*z*
Self > Other					
Supramarginal Gyrus	L	4.31	−52	−26	26
x Supramarginal Gyrus	L	3.63	−60	−34	24
Insula	R	3.79	42	8	−2
Caudate Nucleus	L	4.03	−16	−4	14
Putamen/Insula	L	4.08	−30	2	8
x Insula	L	4.07	−36	8	4
SMA	M/R	4.01	8	0	54
Precentral Gyrus	R	3.97	46	−14	56
Precentral Gyrus	R	3.57	22	−32	66
STG	L	3.64	−38	−10	−12
Middle Frontal Gyrus	L	4.10	−36	36	34
Rolandic Operculum	L	3.47	−60	8	2
Other > Self					
Superior Parietal Lobe	R	4.10	26	−76	56
x Inferior Parietal Lobe	R	3.98	38	−68	56
x Superior Parietal Lobe	R	3.91	24	−66	64
Angular Gyrus	R	3.49	48	−64	44

Refer to Table 2 for abbreviations.

are clearly distinct from the more rostral clusters of the contrast Watching Pain > Baseline. When lowering the threshold to $p = .005$, two additional clusters were identified in the aMCC (MNI coordinates of cluster maxima: $x = 0$, $y = 16$, $z = 24$; $t = 3.28$; and $x = -6$, $y = 4$, $z = 40$; $t = 3.25$). Also, although the size of the clusters in the middle insula increased considerably, no additional clusters were identified in the anterior or posterior parts of the insular cortex. The reverse contrast (Other > Self) revealed significant clusters in the right superior and right inferior parietal lobe (Table 3).

Observing patients undergoing ineffective treatment (Not-effective > Effective) evoked a stronger response in the perigenual ACC (pgACC; $x = -4$, $y = 38$, $z = 20$; $t = 3.76$). This cluster was clearly rostral to the clusters detected with the contrast Self > Other and with the localizer task. Lowering the threshold yielded two additional clusters in the ventromedial part of the orbitofrontal cortex (OFC; $x = 16$, $y = 22$, $z = -14$; $t = 3.39$; $x = 20$, $y = 46$, $z = -14$; $t = 3.06$; Figure 7). The reverse contrast (Effective > Not-effective) revealed a significant cluster in the cerebellum ($x = 16$, $y = 22$, $z = -14$; $t = 4.64$). Note also that watching patients undergoing effective treatment (Effective > Baseline) clearly activated the aMCC, the insula, and the amygdala (see Discussion).

Contrasts assessing the interaction between the perspective-taking and the treatment-effectiveness manipulations resulted in a significant positive interaction in the pgACC ($x = 0$, $y = 48$, $z = 0$; $t = 3.37$) and the right middle frontal gyrus ($x = 36$, $y = 28$, $z = 50$; $t = 4.02$), showing that the treatment-effectiveness manipulation had a stronger effect in these regions when participants adopted the other-perspective (i.e., (Other Effective − Other Not-effective) > (Self Effective − Self Not-effective). Note that the difference in the pgACC

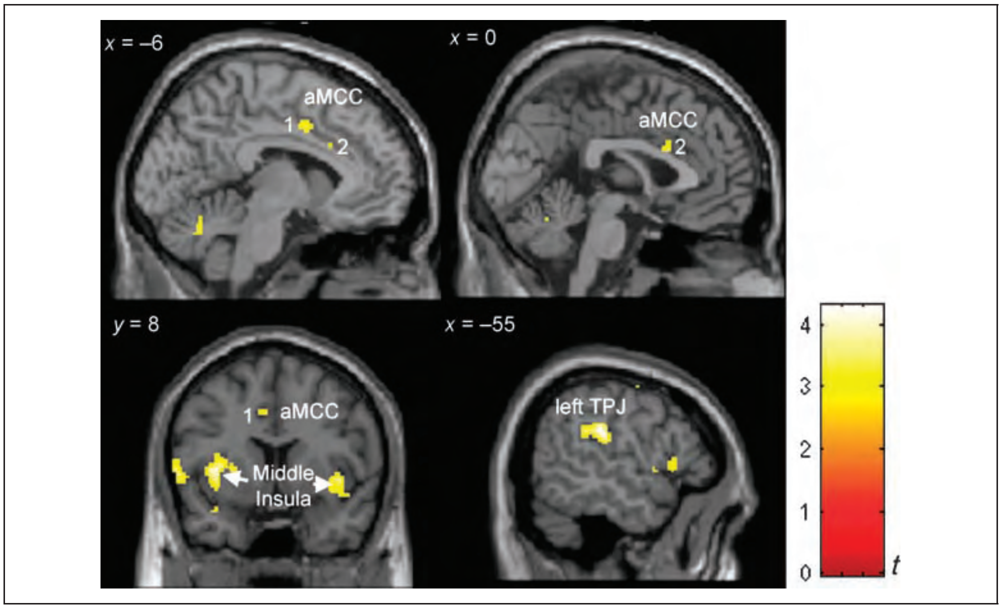

Figure 6. Brain areas showing stronger hemodynamic responses when adopting the self-perspective (contrast Self > Other). Activity is stronger in areas coding the motivational–affective aspects of pain (middle insula, clusters 1 and 3 in the aMCC), and in the left temporo-parietal junction (left TPJ), reflecting self–other distinction. Results are superimposed on sagittal ($x = -6$, $x = 0$, $x = -55$) and coronal ($y = 8$) sections. Threshold $p = .005$ (uncorrected), $k = 5$.

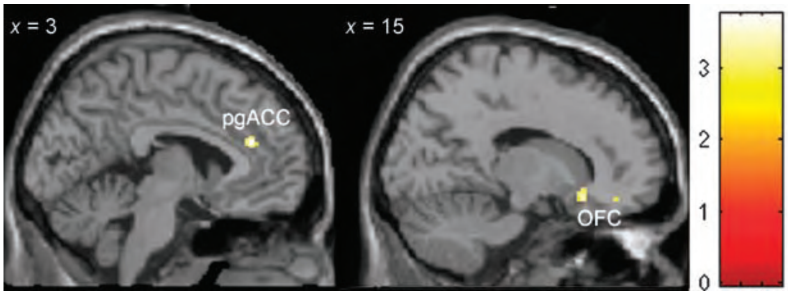

Figure 7. Brain areas showing stronger hemodynamic responses when observing patients who did not benefit from the painful sound treatment (Not-effective > Effective). Results are superimposed on sagittal sections. Threshold p = .005 (uncorrected), k = 5.

reflects a difference in relative deactivation that was more pronounced with the other-perspective [mean parameter estimates: M(Other Effective) = −4.15, M(Other Not-effective) = 0.4, M(Self Effective) = −0.48, M(Self Not-effective) = −3.4].

The ROI analysis of amygdala activity revealed a stronger response in the amygdala with the self-perspective [trend-like main effect for the perspective factor, $F(1,16) = 4.38$, $p = .053$, partial $\eta^2 = 0.215$], with this difference being slightly more pronounced in the left hemisphere [trend-like interaction Perspective × Hemisphere, $F(1,16) = 3.077$, $p = .099$, partial $\eta^2 = 0.161$; Figure 8].

Correlation of Brain Activity with Behavioral Data and Dispositional Measures

Analysis of the EQ scores revealed significant correlations in the right putamen, the left posterior/middle insula, the aMCC, and the left cerebellum. Scores of the empathic concern index correlated with a similar cluster in the aMCC. No significant correlation was observed for the Empathic Concern scale of the IRI, the personal distress index, and the Personal Distress scale of the IRI. Scores of the Emotional Contagion scale correlated with activity in brain regions involved in affective pain processing (insula and aMCC) and movement control (SMA, lateral premotor area; Table 4, Figure 9). In addition, two clusters in the left and right parietal cortex close to the ones revealed by the Self–Other contrasts indicated stronger hemodynamic responses with higher Emotional Contagion scores in these regions.

DISCUSSION

There are good reasons to posit that witnessed pain in others may result in anxiety, promoting at least cautious approach behavior or general threat-defense mechanisms (MacDonald & Leary, 2005). The affective experience of pain signals an aversive state and motivates behavior to terminate, reduce, or escape exposure to the source of the noxious stimulation (Price, 1999). Indeed, negative feelings triggered by pain usually motivate organisms to avoid dangerous stimuli and move away from danger. However, the observation of pain in others may also instigate an altruistic motivation to help the other, which is quite different from the egoistic motivation to reduce personal distress.

The aim of our study was to investigate the effects of perspective-taking and cognitive appraisal on the behavioral and neural correlates of pain observation. To this end, participants watched video clips of patients displaying an aversive emotional response due to painful auditory stimulation under different conditions. Using a number of both state and trait behavioral measures and event-related fMRI, we were able to demonstrate distinct behavioral and neural responses that are in good agreement with both empirical findings and theoretical concepts concerning the promotion of empathic emotion and, ultimately, altruistic motivation (Batson

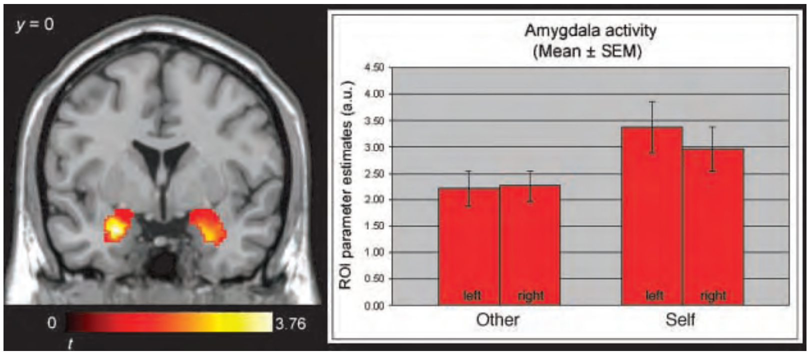

Figure 8. Stronger hemodynamic responses in left and right amygdala when subjects adopted the self-perspective (contrast Self > Other). Left: t values from the contrast Self > Other, overlaid on a coronal section of the single-subject structural MNI MRI template. Right: mean (±SE) parameter estimates for signal changes in the whole amygdala.

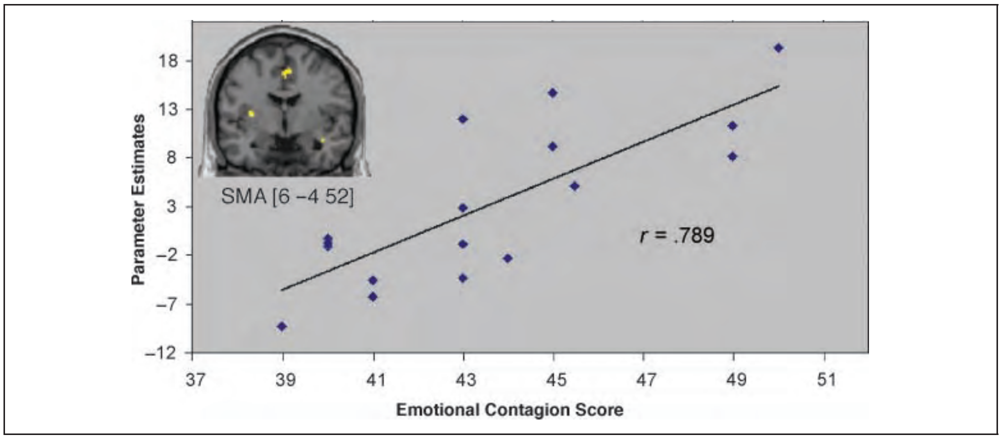

Figure 9. Correlation between hemodynamic activity in the SMA and Emotional Contagion scores.

et al., 2003; Batson, Early, et al., 1997; Batson, Sager, et al., 1997).

Behavioral Data

Data of the emotional response indices clearly confirm that perspective-taking and treatment-effectiveness manipulations were effective. As predicted by previous social psychology experiments (Batson et al., 2003; Batson, Early, et al., 1997), adopting the perspective of the other evoked stronger empathic concern, whereas personal distress was higher when imagining oneself to be in the painful situation. In addition, ineffective treatment triggered higher personal distress when patients were watched with the other-perspective. This might indicate that participants did not focus on the sensory aspects of the observed pain, but rather its ultimate unpleasantness or ''badness'' by taking into account the long-term consequences for the patient. Pain ratings support this interpretation, as they were also modulated by treatment effectiveness—although no difference in patients' actual expression of pain existed because patients were naïve to the treatment effectiveness. Further, memory tests demonstrated significant effects of perspective-taking, as participants showed better recognition and classification rates for patients watched using the self-perspective. This finding is in line with studies indicating that events that are more relevant for the self are more likely to be remembered (''self-referential bias''; Rogers et al., 1977).

Table 4. Areas Showing Significant ($p < .001$) Correlations between Hemodynamic Response, Behavioral Data, and Dispositional Measures

Analysis and Brain Region	*L/R/M*	*r*	*MNI Coordinates*		
			x	*y*	*z*
Empathy Quotient—Other					
Putamen	R	.837	26	0	10
Insula	L	.795	−36	−2	12
aMCC	M	.826	0	−4	42
Cerebellum	L	.833	−22	−46	−24
Empathic Concern Index—Other					
aMCC	R	.802	14	16	28
Emotional Contagion—Watching Pain					
Insula	R	.867	30	16	12
x IFG/Operculum	R	.847	44	18	8
Insula	L	.848	−32	−10	10
aMCC/CCMA	R	.737	16	−26	42
SMA	M	.789	6	−4	52
Precentral Gyrus	R	.740	50	−14	44
Supramarginal Gyrus	R	.752	64	−38	34
Inferior Parietal Lobe	L	.749	−50	−42	36
Inferior Parietal Lobe	L	.742	−56	−44	56

r = Pearson's correlation coefficient, other abbreviations as in Table 2.

Shared Neural Circuits during Observation and First-hand Experience of Pain

Watching the video clips was associated with hemodynamic changes in the medial and lateral occipital cortex (BA 18) and in the fusiform gyrus. These changes reflect the sensory processing of stimuli, as already reported in previous neuroimaging studies using static and dynamic face stimuli (e.g., Botvinick et al., 2005; Grosbras & Paus, 2006; Haxby, Hoffman & Gobbini, 2000). In addition, as predicted, the video clips elicited increased activity in a number of areas associated with the first-hand experience of pain, such as the insular cortex, dorsal and ventral areas of the cingulate cortex, the thalamus, and areas involved in motor control (basal ganglia, medial and lateral premotor areas). The existence of shared neural circuits between the experience and the observation of pain is specifically corroborated by the masking analysis. This analysis relies upon a localizer task that induces affective responses similar to the ones experienced by the patients shown. Masking revealed that the observation of pain in others, and its first-hand experience, activated a largely overlapping neural network. It is worth noting that this overlap did not include areas coding the sensory aspects of pain, as neither the auditory cortex nor the primary or secondary somatosensory cortices were activated. Common activation was confined to areas involved in the motivational–affective dimension of pain processing, such as the anterior insula, the aMCC, and the amygdala, as well as to areas involved in motor control. This confirms several recent fMRI studies (Jackson et al., 2005, 2006; Singer et al., 2004, 2006; Botvinick et al., 2005; Morrison et al., 2004), which indicate that ACC and anterior insula activity during the observation of pain is related to the affective aspects of pain processing rather than to its sensory-discriminative aspects. This interpretation gets additional support by neurophysiological evidence suggesting that the anterior dysgranular part of the insula plays a central role in mediating subjective feeling states, possibly conveyed via mechanisms of interoceptive awareness (Critchley, Wiens, Rotshtein, Öhman, & Dolan, 2005; Craig, 2002). It is also worth noting that electrical stimulation of the posterior part of the insula, but not of the anterior part, evokes painful sensations (Ostrowsky et al., 2002). Altogether, these findings are in agreement with the proposal that indirect pain representations (as elicited by the observation or imagination of pain in others) partially overlap with, but are nevertheless qualitatively different from, first-hand experiences of pain (Craig, 1968).

Correlation of Brain Activity with Behavioral Data and Dispositional Measures

Correlation of hemodynamic activity with behavioral data and dispositional measures further supports the hypothesis that the affective network of pain processing is specifically involved in the perception of pain in others. Subjects scoring higher on EQ showed stronger activity in the left middle insula, the cingulate cortex, and the striatum, and higher empathic concern indices were associated with a stronger hemodynamic response in the aMCC. A similar result was reported by Singer et al. (2004) for the bilateral anterior insula and the aMCC using the Empathic Concern scale of the IRI. However, no significant correlations with empathic concern were found in our study. Note though that empathic concern correlated with EQ scores only weakly ($r = .351$) in our sample, and that our range of IRI scores was considerably smaller due to the preselection of participants with high EC scores (17–24 as opposed to 12–24 in Singer et al., 2004).

Further, emotional contagion scores indicated brain–behavior correlations in similar areas, as well as in areas involved in motor control (i.e., SMA/CMA, dorsal and ventral precentral gyrus, and posterior parietal cortex). These areas belong to a circuit involved in the preparation and planning of self-generated motor action. Correlation of emotion contagion scores with activity in these motor areas might thus reflect the ‘‘inverse mapping’’ mechanism posited by the perception–action account of empathy, which assigns a primary role to motor mimicry and emotional contagion (Preston & de Waal, 2002). Such a mechanism may be triggered by overtly or covertly mirroring in the self the facial pain expressions displayed by the target. Indeed, comments in debriefing indicated that some subjects used overt mimicry, especially in the self condition. Another possibility is that witnessing pain in others automatically prompts motor responses to withdraw oneself from pain. These two responses tap similar neural mechanisms and are difficult to separate experimentally.

Effect of Perspective-taking

Imagining the self and imagining the other in pain activate similar neural mechanisms. However, a complete blurring of self and other would be detrimental and is not the purpose of empathy. Therefore, activation of additional neural mechanisms is needed to distinguish the self from other. This distinction has been associated with the sense of agency (i.e., the feeling of being causally involved in an action), which relies on the comparison between self-generated and externally produced signals. Neuroscience research has provided clues to the existence of a cerebral network specifically devoted to this distinction. Attribution of an action to another agent has been associated with increased activity in the right parietal cortex (e.g., Farrer et al., 2003). The inferior parietal cortex is a multisensory integration area that is ideally suited to detect distinctions between self-generated and external signals. Interestingly, perspective-taking instructions in our study resulted in the activation of distinct subregions of the left and right parietal cortex. The self-perspective elicited higher activity in the left parietal cortex, whereas the right parietal cortex was selectively involved when the other-perspective was adopted. This pattern of activity is consistent with the major role of inferior posterior parietal areas in self-agency and perspective-taking (Decety & Grèzes, in press; Blanke & Arzy, 2005; Decety & Sommerville, 2003; Ruby & Decety, 2003). Accumulating evidence from neuroimaging studies and lesion studies in neurological patients indicates that the right inferior parietal cortex has a critical function in the distinction between self-produced actions and actions generated by others (Jackson & Decety, 2004; Blakemore & Frith, 2003). Importantly, this is also true when behavior is merely mentally simulated. For example, imagining somebody else performing an action (Ruby & Decety, 2001) or experiencing an emotion (Ruby & Decety, 2004), as opposed to imagining performing the action or experiencing the emotion oneself, revealed a very similar modulation of left- versus right-hemispheric parietal hemodynamic activities. A recent fMRI study of social perception and empathy demonstrated that activity in the inferior parietal cortex was negatively associated with the degree of overlap between self and other, and that less self–other overlap led to increased accuracy during social perception (Lawrence et al., 2006).

Further, the self-perspective led to higher activity in brain areas involved in the affective response to threat or pain, such as the amygdala, the insula, and the aMCC. This is consistent with the idea that personal distress can be elicited by imagine-self instructions, as first demonstrated in social psychology studies (e.g., Batson, Early, et al., 1997). Moreover, such a finding is in good agreement with another fMRI study that used a similar perspective-taking manipulation and demonstrated that the first-person perspective taps into affective processes to a greater extent than the more detached third-person perspective (Jackson et al., 2006). The amygdala plays a critical role in fear-related behaviors, such as the evaluation of actual or potential threats (LeDoux, 2000). Interestingly, the amygdala receives nociceptive information from the spino-parabrachial pain system and the insula, and its activity appears closely tied to the context and level of aversiveness of the stimuli (Zald, 2003). Imagining oneself to be in a painful and potentially dangerous situation thus might trigger a stronger fearful and/or aversive response than imagining someone else to be in the same situation. Higher activity in the middle insula may reflect the sensory aspects evoked by the imagination of pain. A meta-analysis of imaging studies reporting insular activations (Wager & Feldman Barrett, 2004) suggests that the middle part of the insula plays a role in coding the sensory–motor aspects of painful stimulation. Importantly, this region has strong connections with the basal ganglia (Chikama, McFarland, Amaral & Haber, 1997), in which activity was also higher when adopting the self-perspective (Table 3). Taken together, activity in this part of the insula possibly reflects the simulation of the sensory aspects of the painful experience. This simulation might both lead to the mobilization of motor areas (including the SMA) in order to prepare defensive or withdrawal behavior, and to interoceptive monitoring associated with autonomic changes evoked by this simulation process (Critchley et al., 2005).

When lowering the threshold, two additional clusters were detected in the aMCC, a region involved in processing the affective, evaluative, and attentional aspects of pain perception (Peyron, Laurent, & Garcia-Larrea, 2000). In addition, activity in this region has been related to the monitoring of autonomic function (Critchley et al., 2003). We thus suggest that the self-perspective results in the evaluation of the affective, autonomic, and motivational consequences obtained from the imagination of a painful experience, in line with the evocation of personal distress. This interpretation is also in line with a review of Bush, Posner, and Luu (2000), labeling this area as the ''cognitive division'' of the ACC.

Effect of Cognitive Appraisal

Humans have the striking capacity to regulate their emotions (Beer & Heerey, 2003; Tice, Bratslavsky & Baumeister, 2001). This capacity involves the initiation of new or the alteration of ongoing emotional responses through the action of regulatory processes (Ochsner & Gross, 2005). We suggest that such regulatory processes play an important role when observing distress in others, as they enable us to show supportive behavior even in potentially dangerous or harmful situations. The majority of neuroimaging studies on emotion regulation have provided explicit instructions as to how participants should reappraise or suppress elicited emotions (see Ochsner & Gross, 2005, for review). In contrast, we presented information designed to affect cognitive appraisal, as our aim was to create a situation as close as possible to an everyday context. It was anticipated that witnessing another person suffering and knowing that his/her treatment had not been effective would increase the emotional response in the observer. Conversely, knowing that a treatment had been beneficial for the patient was expected to elicit down-regulation of the perceptually triggered affective response. Both the behavioral and hemodynamic data supported this hypothesis. Behavioral data showed higher pain intensity and unpleasantness ratings when the treatment had not been effective. This finding was paralleled by activity differences in a number of brain regions involved in affective coding and emotion regulation, such as rostral and perigenual ACC and the ventromedial OFC. Note also that observing ineffectively treated patients triggered strong activation in the aMCC, the insula, and the amygdala, indicating an affective response. Based on self-report and behavioral data, we suggest that this response was regulated (reappraised) via top-down mechanisms such as focusing on the long-term consequences of the treatment.

A recent review of cingulate cortex functions in pain and emotion indicates that a subregion in the rostral ACC is involved in coding fearful responses (Vogt, 2005). Similarly, Bush et al. (2000) labeled this part of the ACC as its ''affective division,'' in contrast to the more posterior-dorsal ''cognitive division'' (see above). Activity in this area may hence be related to a stronger defensive response in cases where the treatment had no benefit, and thus, the patient's overall situation was perceived as being more unpleasant or distressing (as indicated by the behavioral data). Alternatively and more speculatively, ACC activity may have resulted from an anger-related reaction triggered by the fact that the patient had to suffer pain without benefiting from it. That participants experienced more anger when watching patients undergoing ineffective treatment is—at least indirectly—indicated by significantly higher scores for the adjective ''upset'' on the emotional response scale when the therapy was not effective [$t(15) = 2.695$, $p = .027$, $\eta^2 = .326$]. Note also that self-generation of anger activates a similar part of the ACC (Damasio et al., 2000).

While watching the videos, the participants in our study had to consider whether the overall effect of the painful treatment was positive or negative. This manipulation of the context in which pain occurred differentially elicited OFC activity, which plays an important role in the evaluation of positive and negative reinforcements, and in the motivational and emotional aspects of social behavior (Rolls, 2004). The OFC is also involved in emotion reappraisal, as attending to a negatively valenced picture evokes stronger activity in the ventromedial OFC than reappraising that picture in a way that it no longer elicited a negative response (Ochsner et al., 2002). Similarly, watching patients undergoing ineffective treatment was associated with higher activity in this region, whereas effective treatment was associated with a decreased OFC response. Note that the OFC was active in both conditions (data not shown). Activity in the OFC thus might reflect differing requirement to evaluate the overall positive and negative aspects of the presented stimuli. This top-down process might operate upon the visually conveyed information about the affective state of the patients. Interestingly, watching effective versus ineffective treatment patients did not modulate activity in either the visual–sensory areas or in the insula (even when the threshold was lowered to $p = .05$). This suggests that the two patient groups were differentiated *after* perceiving their emotional reactions (but not necessarily after participants reacted emotionally themselves), and that top-down mechanisms did not operate on perceptual processing at an early stage. Keep in mind, however, that this finding might be influenced by the requirement for participants to evaluate the pain of the patients.

The interaction between perspective-taking and treatment effectiveness yielded increased activity in the pgACC and the middle frontal gyrus. Involvement of the pgACC most likely indicates a difference in perspective-taking requirements, which are more complex when imagining the feelings of patients who—in contrast to the observer—do not know the ultimate outcome of the treatment. In fact, increased activity in the rostral cingulate and the paracingulate cortex when performing mentalizing tasks has reliably been found (see Gallagher & Frith, 2003, for review). Thus, we speculate that the stronger deactivation with the other-perspective indicates a stronger requirement to inhibit mentalizing, which might be counterproductive in a case where participants have to focus on the long-term consequences of the treatment and not the immediate affective reaction of the patient. The middle frontal gyrus, on the other hand, may be associated with emotion down-regulation, as indicated by a recent fMRI study on emotion regulation (Ochsner et al., 2004). However, studies using explicit emotion regulation instructions show stronger involvement of lateral prefrontal cortical regions than our study. This highlights the role of these regions in deliberately exerting top-down control, whereas appraisal-based regulation might be supported by brain structures involved in relatively automatic assessment of reward properties (such as the OFC).

Conclusion

Our findings are consistent with the view that humans' responses to the pain of others can be modulated both by cognitive and motivational processes. These processes are likely to influence whether observing a conspecific in need of help will result in empathic concern, an important instigator of helping behavior, or personal distress. These two types of affective responses are qualitatively distinct and have different motivational consequences. Empathic concern may instigate an altruistic motivation to help the other; personal distress may produce an egoistic motivation to reduce personal distress (Batson et al., 1987). It was thus important to demonstrate both the similarities in the neural networks underlying the sharing of pain with others and the specific mechanisms that permit distinguishing the self from others, which is critical for the experience of empathy (Decety & Hodges, 2006; Decety & Lamm, 2006; Decety, 2005). Such an experience cannot be identical to the actual perception of pain because personal and vicarious experiences differ neurophysiologically as demonstrated by our behavioral and fMRI data (as also demonstrated by Craig, 1968, for autonomic nervous system measurements). Indeed, in order for the subjective experience to be labeled empathy, the observer must recognize that the emotion she/he is experiencing is a response to the other's emotional state. Finally, our results demonstrate that both bottom-up (automatic) and top-down (controlled) processes interact to produce the experience of empathy. Knowledge about the context in which the pain experience occurs provides important clues to the role of top-down cognitive appraisal in the regulation of the vicarious affective pain reaction.

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Reprint requests should be sent to Jean Decety, Social Cognitive Neuroscience, Department of Psychology, The University of Chicago, 5848 S University Avenue, Chicago, IL 60637, USA, or via e-mail: decety@uchicago.edu.

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