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Left hemisphere dominance in reading the sensory qualities of others' pain?

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Seeing or imagining others in pain may activate both the sensory and affective components of the neural network (pain matrix) that is activated during the personal experience of pain. Transcranial magnetic stimulation (TMS), proved adept at highlighting the sensorimotor side of empathy for pain in studies where mere observation of needles penetrating body parts of a human model brought about a clear corticospinal motor inhibition. By using TMS, we investigated whether inferring the sensory properties of the pain of a model influenced the somatomotor system of an onlooker. Moreover, we tested the possible lateralization of the motor substrates underlying this reading process. We recorded motor-evoked potentials (MEPs) to left and right motor cortex stimulation during the observation of ''flesh and bone'' painful stimulations of right and left hands respectively. We found a significant reduction of onlookers' MEPs amplitudes specific to the muscle penetrated in the model. Subjective inferences about localization and intensity of the observed pain were associated with specific patterns of motor modulation with larger inhibitory effects following stimulation of the left motor cortex. Thus, results indicate that the mental simulation of the sensory qualities of others' pain may be lateralized to the left hemisphere.

INTRODUCTION

The specific ability to understand that others as well as ourselves have beliefs, desires and intentions is referred to as ''theory of mind'' (ToM; Baron-Cohen, Tager-Flusberg, & Cohen, 2000; Frith & Frith, 2005; Saxe, Carey, & Kanwisher, 2004). Interest in this very human ability of mental states attribution has engendered an increasing number of studies on the neural underpinnings of social cognition (Gallagher & Frith, 2003). Mental states attribution, however, does not simply imply attribution of thoughts and knowledge, but also of emotional, motor, perceptual or attentional states. Related to mental states attribution is the multidimensional complex of mechanisms and phenomena that allow the interindividual sharing of feelings and experiences of others, commonly referred to as ''empathy'' (Davis, 1996; Decety & Jackson, 2004; Gallese, 2003; Preston & de Wall, 2002). Although empathy has long attracted the interest of psychologists and philosophers, only recently has this subject attracted neuroscientists (Decety & Jackson, 2004; Gallese, 2003; Preston & de Waal, 2002).

Current neuroscientific models of empathy posit that observing motor, sensory or emotional states of other individuals automatically activates a representation of the very same state in the observer (Decety & Jackson, 2004; Gallese, 2003; Preston & de Waal, 2002). In keeping with this view, a number of studies have provided evidence for common brain activations between the personal experience of disgust (Wicker, Keysers, Plailly, Royet, Gallese, & Rizzolatti, 2003), touch

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(Blakemore, Bristow, Bird, Frith, & Ward, 2005; Keysers, Wicker, Gazzola, Anton, Fogassi, & Gallese, 2004) or pain (Avenanti, Bueti, Galati, & Aglioti, 2005; Avenanti, Minio-Paluello, Bufalari, & Aglioti, 2006; Botvinick, Jha, Bylsma, Fabian, Solomon, & Prkachin, 2005; Jackson, Brunet, Meltzoff, & Decety, 2006; Jackson, Meltzoff, & Decety, 2005; Morrison, Lloyd, di Pellegrino, & Roberts, 2004; Saarela, Hlushchuk, Williams, Schurmann, Kalso, & Hari, 2006; Singer, Seymour, O'Doherty, Kaube, Dolan, & Frith, 2004; Singer, Seymour, O'Doherty, Stephan, Dolan, & Frith, 2006) and the observation or imagination of the same feelings in others. These empathic ''mirror'' resonant responses may be related to the simulation of different somatomotor and emotional aspects of others' experience (Avenanti & Aglioti, 2006; Gallese, Keyser, & Rizzolatti, 2004).

The notion of shared representation also applies to empathy for pain. Pain is a complex unpleasant sensory and emotional mental state associated with actual or potential body damage (IASP Task Force on Taxonomy, 1994). Sensory (e.g., evaluation of locus, duration and intensity of a noxious stimulus) and affective components (e.g., unpleasantness of the noxious stimulus) of pain are mapped in different nodes of a complex neural network dedicated to pain, the so-called ''pain matrix'' (Ingvar, 1999; Peyron, Laurent, & Garcia-Lerrea, 2000; Rainville, 2002). Animal studies indicate that sensorimotor cortices contain nociceptive neurons that code key features of the sensory-discriminative dimension of stimulus processing such as spatial, temporal, and intensive aspects of noxious somatosensory stimuli (Craig, 2003); accordingly, neuroimaging studies in humans indicate that sensorimotor cortices process sensory features of pain (Porro, Cettolo, Francescato, & Baraldi, 1998; Rainville, 2002) and display a somatotopical organization (Bingel et al., 2004). Affective and motivational components of pain are coded in the affective node of the pain matrix, which includes anterior cingulate cortex (ACC) and anterior insula (AI). It is worth noting that the subjective feeling of unpleasantness is strictly associated with neural activity in these structures (Craig, 2003; Ingvar, 1999; Peyron et al., 2000; Rainville, 2002). Moreover, lesions to sensorimotor or affective areas may induce a specific loss of pain sensation or unpleasantness in brain-damaged patients (Berthier, Starkstein, & Leiguarda, 1988; Craig, 2003; Greenspan, Lee, & Lenz, 1999; Ploner, Freund, & Schnitzler, 1999). Recent studies demonstrated that somatomotor and affective nodes in the pain matrix are also implicated in the empathic sharing of others' emotional and sensory components of pain (Avenanti & Aglioti, 2006; Decety & Grèzes, 2006; Singer & Frith, 2005). Most of the pain empathy fMRI studies carried out so far indicate that experimental conditions involving others' pain elicit neural activity mainly in the affective division of the pain matrix (ACC and AI), thus suggesting that only emotional components of pain are shared between self and other (Botvinick et al., 2005; Jackson et al., 2005, 2006; Morrison et al., 2004; Singer et al., 2004, 2006). In two recent fMRI studies by Singer et al. (2004, 2006) the observation of arbitrary visual cues signaling impending painful stimuli to another person brought about an increase of BOLD signal mainly in ACC and AI. Activation in these structures was also found in paradigms in which subjects watched pain-related facial expressions (Botvinick et al., 2005; Saarela et al., 2006) or observed potentially painful situations (Jackson et al., 2005, 2006; Morrison et al., 2004; Ogino, Remoto, Inui, Saitol, Kakigi, & Goto, 2006).

However, using Transcranial Magnetic Stimulation (TMS) we have found that the direct observation of ''flesh and bone'' painful stimulations on a human model elicits inhibitory responses in the observer's corticospinal motor system (Avenanti et al., 2005, 2006) similar to those found in subjects who actually experience painful stimulations (Farina et al., 2001; Farina, Tinazzi, Le Pera, & Valeriani, 2003; Svensson, Miles, McKay, & Ridding, 2003; Urban, Solinski, Best, Rolke, Hopf, & Dieterich, 2004). These ''mirror'' responses were specific to the body part that the subjects observed being stimulated and correlated with the intensity (but not the unpleasantness) of the pain ascribed to the model thus hinting at the sensorimotor side of empathy for pain (Avenanti et al., 2005, 2006; Avenanti & Aglioti, 2006). Specific activity in the sensorimotor node of the pain matrix during empathy for pain has also been recently reported in TMS (Feactau, Pascual-Leone, & Theoret, 2006) and fMRI (Jackson et al., 2006; Ogino et al., 2006; Saarela et al., 2006) studies.

No studies concerning the role of mental state attribution on somatomotor responses to the direct observation of ''flesh and bone'' painful stimulation in others has been carried out. Here we add a new dimension to current knowledge by exploring whether the onlookers' empathic inference about localization and spread of the pain

in a model may influence somatomotor responses in an onlooker.

Studies in healthy subjects (Landis, Assal, & Perret, 1979; McKeever & Dixon, 1981) and brain-damaged patients (Adolphs, Damasio, Tranel, Cooper, & Damasio, 2000; Benowitz, Bear, Rosenthal, Mesulam, Zaidel, & Sperry, 1983; Borod et al., 1998; Cicone, Wapner, & Gardner, 1980) provide evidence in favor of cortical right hemisphere specialization for emotional processing (see Demaree, Everhart, Youngstrom, & Harrison, 2005, for a review). This seems to be especially true for the emotions with a negative valence and associated with withdrawal behaviors (Adolphs, Damasio, Tranel, & Damasio, 1996; Borod et al., 1998; Coan, Allen, & Harmon-Jones 2001; Ekman, Davidson, & Friesen, 1990; Harmon-Jones, 2003; Silberman & Weingartner, 1986). Interestingly, specific right hemisphere regions may play a critical role in mentalizing and empathizing (Happé, Brownell, & Winner, 1999; Saxe & Wexler, 2005; Shamay-Tsoory, Tomer, Berger, & Aharon-Peretz, 2003).

The issue of asymmetric activation of the cortical network underlying empathy for pain has not been directly addressed. Yet, the two hemispheres may differently contribute to empathic processes. Most fMRI studies report that empathy for pain induces activation in medial structures or in both hemispheres (Botvinick et al., 2005; Jackson et al., 2005; Singer et al., 2004, 2006). Bilateral activation of ACC and AI was reported when participants imagined others' pain (Singer et al., 2004, 2006), watched facial expression of pain (Botvinick et al., 2005) or observed static pictures of potentially painful situations (Jackson et al., 2005). However, specific activation in right-sided affective and higher-order areas have also been reported. For example, a selective activation of right ACC was found during the observation of pinpricking stimuli delivered to an unknown model's hand (Morrison et al., 2004). In another fMRI study in which subjects observed static pictures of potentially painful conditions, right AI and right temporo-parietal junction (along with medial structures) were preferentially activated when subjects were asked to adopt the psychological perspective of the model depicted in the images (Jackson et al., 2006). Importantly, the sensory qualities of others' pain may be more represented in the left hemisphere, as suggested by a recent fMRI study in which left infero-parietal cortex, left precentral gyrus, left ACC (but also bilateral AI) were activated by the observation of images depicting facial expression of pain (Saarela et al., 2006). These activations correlated with the intensity of the pain attributed to the observed models, suggesting that these structures specifically encoded sensory qualities of others' pain (Saarela et al., 2006).

Although sparse, current evidence would suggest that while the right hemisphere may be mainly involved in the emotional aspects of empathy for pain, the left hemisphere may be dominant in simulating sensory features of others' pain. This is also in agreement with pain studies showing stronger right sided changes of BOLD fMRI signal in cortical areas involved in attentional and emotional processing of pain stimuli (Coghill, Gilron, & Iadarola, 2001; Symonds, Gordon, Bixby, & Mande, 2006), and left hemisphere predominance of laser-evoked potentials sources related to sensory-discriminative dimensions of pain processing (Schlereth, Baumgartner, Magerl, Stoeter, &, Treede, 2003).

Our previous TMS studies indicate that the left somatomotor cortex selectively encodes sensory qualities of others' pain (Avenanti et al., 2005, 2006). Nothing is known, however, about the possible role of the right somatomotor cortex in this type of effect. The present single-pulse TMS study aims to explore whether: (1) different readings of the pain sensory qualities of a model induces different modulations in the motor system of an onlooker; and (2) the two cerebral hemispheres play any differential role in this process.

MATERIAL AND METHODS

Participants

Twenty-eight subjects (12 men, mean age 25 years, range 20–32), right handed according to a standard handedness inventory (Oldfield, 1971), participated in the study. None of the subjects had neurological, psychiatric, or other medical problems or any contraindication to TMS (Wassermann, 1998). All participants gave their written informed consent to take part in the study. The study was approved by the ethics committee of the Fondazione Santa Lucia and was carried out in accordance with the ethical standards of the 1964 Declaration of Helsinki. No discomfort or adverse effects during TMS were reported or noticed.

EMG and TMS recordings

Motor evoked potentials (MEPs) were recorded simultaneously from the FDI muscle (in the dorsal region of the hand between the index finger and the thumb) and TE (on the palm region just beneath the thumb) by means of a Viking IV (Nicolet biomedical, USA) electromyograph. EMG signals were band-pass filtered (20 Hz–2.5 kHz, sampling rate fixed at 10 kHz), digitized and stored on a computer for off-line analysis. Fourteen subjects (6 men, mean age 25 years, range 20–31) were stimulated over the left M1 and fourteen (6 men, mean age 25 years, range 20–32) were stimulated over the right M1 while MEPs were recorded from contralateral FDI and TE. Pairs of silver/silver chloride surface electrodes were placed over the muscle belly (active electrode) and over the associated joint or tendon of the muscle (reference electrode). A circular ground electrode with a diameter of 30 mm was placed on the dorsal surface of the wrist. A figure-of-eight coil connected to a Magstim Super Rapid Transcranial Magnetic Stimulator (Magstim, Whitland, Dyfed, UK) was placed over M1 contralateral to the recorded muscles. The intersection of the coil was placed tangentially to the scalp with the handle pointing backward and laterally at a 45 degree angle away from the midline. In this way the current induced in the neural tissue was directed approximately perpendicular to the line of the central sulcus, optimal for trans-synaptic activation of the corticospinal pathways (Brasil-Neto, Cohen, Panizza, Nilsson, Roth, & Hallett, 1992; Mills, Boniface, & Schubert, 1992). By using a slightly suprathreshold stimulus intensity, the coil was moved to determine the optimal position from which maximal amplitude MEPs were elicited in the FDI muscle. The optimal position of the coil was then marked on the scalp with a pen to ensure correct coil placement throughout the experiment. The intensity of magnetic pulses was set at 120% of the resting motor threshold, defined as the minimal intensity of the stimulator output able to produce MEPs in both FDI and TE muscles with amplitude of at least 50 μV with 50% probability (Rossini et al., 1994). The absence of voluntary contraction was continuously verified visually and, prior to the recording session, by auditory monitoring of the EMG signal.

Visual stimuli

Different types of video-clips were presented on a 19-inch screen located 80 cm away from the participants. Video-clips showed the following: (1) fixation cross; (2) static view of the dorsal surface of a hand; (3) needle deeply penetrating the FDI muscle of a hand. Video-clips depicting a right hand had been used in our previous studies (Avenanti et al., 2005, Experiments 1, 4, and 5; Avenanti et al., 2006, Experiment 2). Left-hand video-clips were obtained by manipulating the right-hand video-clips with Adobe Premiere® software (www.adobe.com). Subjects in whom TMS was delivered to the left M1 and MEPs were recorded from their right hand and were presented with the right-hand video-clips. The opposite was true in the subjects in whom TMS was delivered to the right M1 and MEPs were recorded from their left hand.

Previous TMS studies report that observing moving body parts brings about an increase in corticospinal excitability (Fadiga, Craighero, & Olivier, 2005; Fadiga, Fogassi, Pavesi, & Rizzolatti, 1995; Rizzolatti & Craighero, 2004) and that observing a hand using tools elicits activation of the primary motor cortex (Järveläinen, Schürmann, & Hari, 2004). To avoid such effects in the present empathy for pain study, we checked that no hand movements were evoked by the puncture. We also checked that the syringe holder was not visible in any of the videos.

Procedure

The experiment was programmed using Psychophysics Toolbox (www.psychotoolbox.org) and Matlab (www.mathworks.com) software to control the sequence and duration of video clips, and to trigger TMS and EMG recording. Each type of video-clip was presented in separate blocks. The first and the last block served as baseline and consisted of video-clips showing the fixation cross. The order of the other two blocks (static hand, pain) was counterbalanced. The fixations blocks consisted of 18 trials each, the static hand and pain blocks consisted of 21 trials each; thus, during the recording session, subjects were presented with a total of 78 trials.

In each block, a central cross (1000 ms duration) indicated the beginning of a trial and initiated EMG recording. The duration of each

video was 1800 ms. In each trial, a magnetic pulse was randomly delivered between 200 and 600 ms before the end of the movie to avoid any priming effects that could affect MEP size. A black screen was shown for 7.2 seconds in the intertrial intervals. The choice of a long intertrial interval was based on a study demonstrating that TMS delivered for 1 hour at 0.1 Hz frequency did not induce any change in excitability (Chen et al., 1997).

In all observation conditions, participants were asked to watch carefully and pay attention to the events shown in the video clips. Moreover, in the conditions involving observation of body parts, participants were instructed to focus on what the stimulated individual may have felt, as used in our previous studies (Avenanti et al., 2005; Avenanti et al., 2006, Experiment 2).

After each TMS session, subjects were presented with all videos and asked to judge sensory (intensity, localization) and affective (unpleasantness) qualities of the pain supposedly felt by the model in each condition. Pain qualities were measured by means of the Italian version (Maiani & Sanavio, 1985) of the McGill Pain Questionnaire (MPQ; Melzack, 1975) that includes four subscales: Sensory (items 1–10), Affective (items 11–15), Sensory-mix (items 17–19) and Affective-mix (item 20). Moreover, we specifically evaluated pain localization by asking the subjects to judge whether the painful sensation purportedly felt by the model may have been likely localized to the region in which the needle entered (FDI region) or may have spread to the thenar eminence. Based on pain localization judgment, subjects were divided into two groups: ''Localized on FDI'' (8 left M1, and 9 right M1) and ''Spread to TE'' (6 left M1 and 5 right M1).

Data analysis

Neurophysiological data were processed off-line. Trials with EMG activity prior to TMS were discarded from the analysis (less than 10% for each condition and muscle). This procedure implied the exclusion of FDI data from one subject (''Spread to TE''–''Right M1'') and of TE data from another subject (''Localized on FDI''–''Left M1'') due to the presence of a high number (35–40%) of artifacts visible in the EMG recordings. Mean MEP amplitude values in each condition were measured peak-to-peak (in mV). Logarithmic transformation was applied to amplitude values, log (mean MEP amplitude value + 1), to normalize data distribution. MEP amplitude values recorded during ''Static Hand'' and ''Needle in FDI'' conditions were divided by MEP amplitude values recorded during ''Fixation'' (MEP ratios). Data analysis was performed by means of Statistica® software v 6.0 (StatSoft, Inc, USA). MEP ratios were entered into mixed four-way ANOVAs, with Hemisphere (''Left M1,'' ''Right M1'') and Type of pain (''Localized on FDI,'' ''Spread to TE'') as between-subjects and Condition (''Static Hand,'' ''Needle in FDI'') and ''Muscle'' (FDI, TE) as within-subjects factors. The two subjects with missing data from one muscle were excluded from the mixed-model ANOVA but were entered in the other analyses. Mixed three-way ANOVAs were used to analyze each subscale of the MPQ with Hemisphere, Type of Pain and Condition as factors. Planned comparisons were performed to analyze significant main effects and interactions. In addition, for each theoretically relevant comparison we computed an effect size index that unlike significance tests is independent from sample size. The Cohen d statistic, representing the number of standard deviations between two means, is typically used to compute between-group effect sizes, $(m_1 - m_2)/\sigma$. Being the index biased by the correlation between two items in repeated measures designs (Morris & De Shon, 2002), we calculated within-subject effect sizes using a modified d: $t[2(1-r)/n]^{1/2}$, where t is the statistic for correlated samples, and r is the correlation across pairs of means (Dunlap, Cortina, Vaslow, & Burke, 1996). Cohen's (1992) interpretational guidelines indicate that $d = 0.5$ (medium) is apparent to the discernable observer, $d = 0.2$ (small) is clearly smaller than medium but not trivial, and $d = 0.8$ (large) is clearly larger than medium.

We carried out a correlation analysis between neurophysiological and subjective measures (pain qualities). We computed MEP amplitude differences for each muscle by subtracting the normalized MEPs value recorded during ''Static Hand'' from the normalized MEP value recorded during ''Needle in FDI'' condition, (''Needle in FDI'' – ''Static Hand'')/''Fixation''. Then, Pearson correlation coefficients between MEP amplitude difference and subjective reports (sensory, sensory-mix, affective, affective-mix MPQ subscales) were computed.

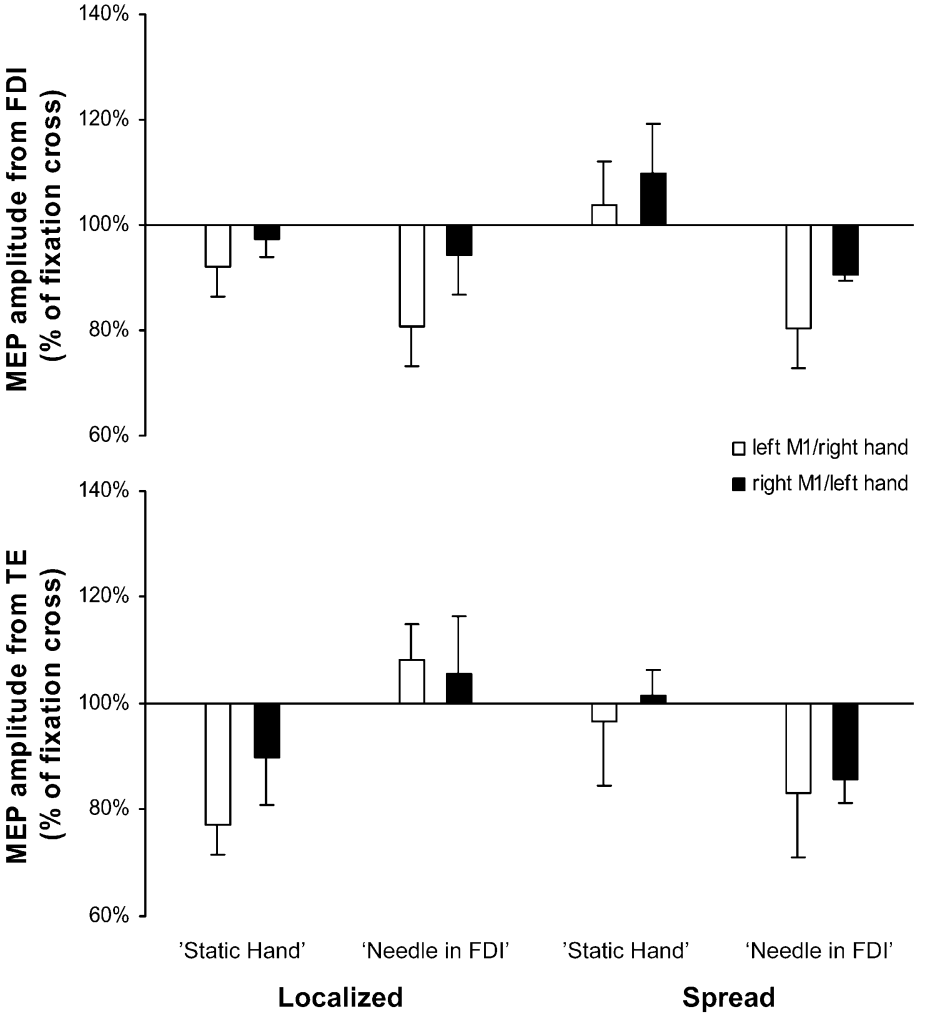

Figure 1. Amplitude of MEPs (% of baseline) during the observation of "Static hand" and "Needle penetrating FDI." MEPs from the FDI and TE are shown in the top and bottom part of the figure respectively. White columns indicate MEPs to stimulation of the left M1 recorded from the hand; black columns indicate MEPs to stimulation of the right M1 recorded from left hand. MEPs in the "Localized on FDI" group and in the "Spread to TE" group are shown in the left and right part of the figure respectively. Error bars denote *SEM*.

RESULTS

Participants were divided in four subgroups according to the stimulated hemisphere ("Left M1," "Right M1") and according to how they judged painful sensations to be ("Localized on FDI," "Spread to TE"). Figure 1 shows normalized ratios of MEP amplitudes. It is worth noting that in the subjects who received TMS over the left M1, MEPs were recorded from the right hand during presentation of right-hand stimuli. By the same token, in the subjects who received TMS over the right M1 MEPs were recorded from the left hand during presentation of left-hand stimuli. Thus, compatibility between the observers' and the models' hand occurred in all subjects.

ANOVA on normalized MEPs ratios (% of fixation) revealed a significant interaction Muscle $\times$ Condition, $F(1, 22) = 25.77$, $p = .00004$. In the FDI muscle, MEP amplitude during "Needle in FDI" was lower than "Static Hand" ($p = .001$, $d = 0.67$); by contrast, pain was comparable to static hand in the TE ($p = .25$, $d = 0.37$). Thus, in keeping with previous TMS studies (Avenanti et al., 2005, 2006; Fecteau et al., 2006) observing pain brought about a selective reduction of excitability from the muscle the subjects observed being penetrated. Interestingly, the interaction Muscle $\times$ Condition $\times$ Hemisphere approached statistical significance, $F(1, 22) = 3.78$, $p = .06$. The selective reduction of MEPs in the FDI muscle was strong in the left hemisphere

TABLE 1
Mean (standard deviation) of pain qualities ascribed to the model in pain

	Left M1		*Right M1*	
	Localized on FDI (N = 8)	*Spread to TE (N = 6)*	*Localized on FDI (N = 9)*	*Spread to TE (N = 5)*
MPQ Sensory	13.5 (6.4)	16.5 (7.6)	15.9 (5.8)	18.4 (7.3)
MPQ Affective	3.0 (3.2)	3.2 (3.1)	2.1 (3.0)	4.2 (1.9)
MPQ Sensory-mix	7.5 (3.3)	5.7 (4.1)	7.1 (4.0)	10.4 (0.9)
MPQ Affective-mix	2.1 (2.2)	3.0 (2.3)	2.0 (1.8)	3.2 (1.6)

($p = .002$, $d = 0.87$) but not in the right hemisphere ($p = .07$, $d = 0.47$). No modulation was found in TE for both left ($p = .17$, $d = 0.57$) and right hemisphere ($p = .80$, $d = 0.18$).

ANOVA also showed a triple interaction Muscle × Condition × Diffusion, $F(1, 22) = 6.21$, $p = .02$. In the "Spread to TE" group, amplitude of MEPs from the FDI muscle was lower in "Needle in FDI" than in "Static Hand" ($p = .002$, $d = 1.22$), while the same comparison was not significant in the "Localized on FDI" ($p = .14$, $d = 0.34$). These findings indicate that the major contribution to the observational pain-related inhibitory effect is due to those participants who judged the model's pain to be diffused to the thenar eminence. In the "Localized on FDI" group, amplitude of MEPs from the TE were higher in "Needle in FDI" than in "Static Hand" ($p = .0002$, $d = 0.94$); by contrast, in the "Spread to TE" group, MEPs from the TE tended to be lower in "Needle in FDI" than "Static Hand" ($p = .09$, $d = 0.65$). Thus, MEP modulation recorded from the TE during pain observation was highly dependent on the judgment about the localization of pain attributed to the model. Subjects who imagined the pain as being localized on the FDI muscle were facilitated in the TE, whereas subjects who imagined the pain as being spread to TE were slightly inhibited in that muscle. Figure 2 shows raw MEP data from two representative subjects of "Localized on FDI" and "Spread to TE" subgroups (left M1).

The different modulation of MEPs found in the two groups of subjects who reported different types of pain ("Localized to FDI," "Spread to TE") cannot be accounted for by the different

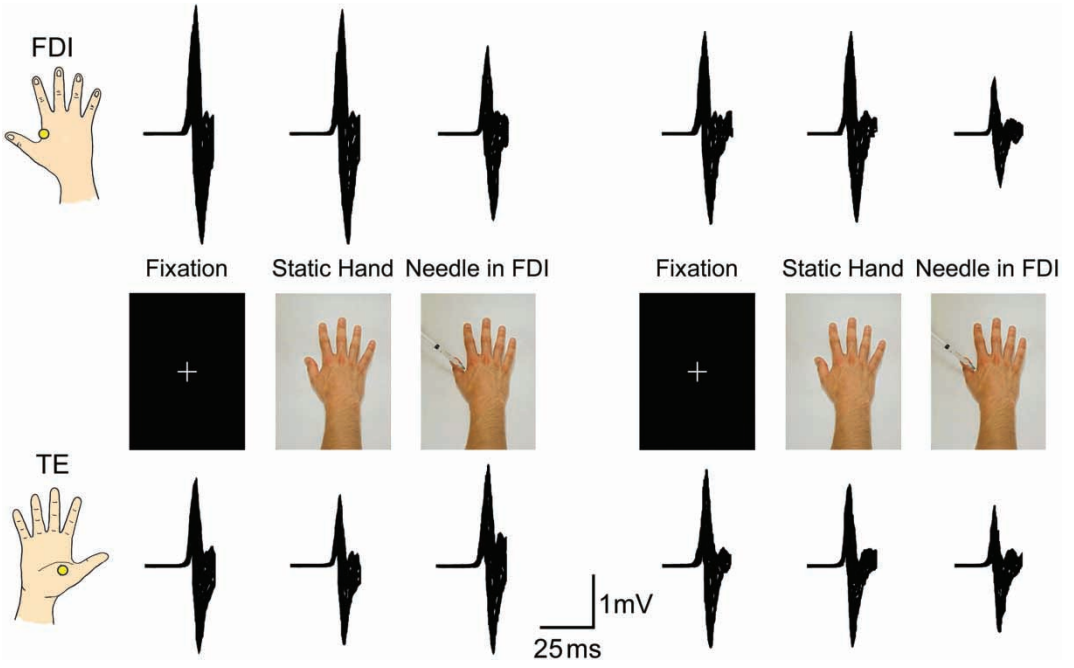

Figure 2. Raw amplitude of MEPs in two representative subjects of "Localized on FDI" (left) and "Spread to TE" (right). In both subjects MEPs to stimulation of the left M1 were recorded from the right hand. Top: MEPs recorded from the FDI muscle. Bottom: MEPs recorded from TE. Data from different trials are superimposed.

TABLE 2
Pearson coefficients (*p*-levels) between pain qualities and amplitude change of MEP

	MEP amplitude change (both hemispheres), recorded from:		*MEP amplitude change (left sensorimotor cortex), recorded from:*		*MEP amplitude change (right sensorimotor cortex), recorded from:*	
	FDI	*TE*	*FDI*	*TE*	*FDI*	*TE*
MPQ Sensory	$r = -.34$ ($p = .08$)	$r = -.20$ ($p = .32$)	$r = -.64$ ($p = .01$)	$r = -.42$ ($p = .13$)	$r = -.12$ ($p = .68$)	$r = -.07$ ($p = .82$)
MPQ Affective	$r = -.05$ ($p = .80$)	$r = -.04$ ($p = .85$)	$r = -.25$ ($p = .39$)	$r = -.05$ ($p = .88$)	$r = .13$ ($p = .65$)	$r = -.04$ ($p = .89$)
MPQ Sensory-mix	$r = -.24$ ($p = .23$)	$r = -.02$ ($p = .91$)	$r = -.58$ ($p = .03$)	$r = -.09$ ($p = .76$)	$r = -.01$ ($p = .97$)	$r = -.09$ ($p = .75$)
MPQ Affective-mix	$r = .21$ ($p = .29$)	$r = -.14$ ($p = .47$)	$r = -.16$ ($p = .58$)	$r = -.17$ ($p = .56$)	$r = -.27$ ($p = .36$)	$r = .12$ ($p = .67$)

intensity or unpleasantness of the pain ascribed to the model. Indeed, pain qualities were comparable in the two groups of subjects (Table 1) and ANOVAs on subjective measures failed to detect any significant difference ($p > .05$).

For each muscle, we computed an index of MEP amplitude change by subtracting normalized MEP ratios during ''Static Hand'' from MEP ratios during ''Needle in FDI'' condition. Such indices were entered in a correlational analysis with subjective measures (MPQ). No significant correlation was found when we merged data from the two hemispheres for either the FDI or the TE muscle (Table 2).

In a further correlational analysis we explored the relation between MEP and subjective measures separately for each hemisphere. We found significant correlations between MEP amplitude changes recorded from the right FDI muscle (left hemisphere) and sensory qualities of the pain ascribed to the model measured by the MPQ sensory ($r = -.64$, $p = .01$) and MPQ sensory-mix scales ($r = -.58$, $p = .03$; Figure 3, Table 2).

Notably, using a combined index of sensory qualities (MPQ sensory+MPQ sensory-mix) the relation with neurophysiological index was stronger ($r = -.68$, $p = .008$). No correlation was found with a combined index of affective qualities (MPQ affective+MPQ affective mix; $r = -.10$, $p = .72$).

No significant correlation was found for MEP amplitude changes recorded from the left FDI muscle (TMS over the right hemisphere) and the sensory qualities of pain. No other significant correlation between either FDI or TE MEPs and subjective measures was found (see Table 2).

DISCUSSION

The present study expands our previous research on the ''sensorimotor contagion'' triggered by the direct observation of ''flesh and bone'' painful stimulation delivered to another person (Avenanti et al., 2005, 2006) in two main ways. First, the somatotopic reduction of MEPs amplitude during pain observation was strictly dependent on the onlooker's mental representations of the sensory qualities (spread and intensity of the sensation) attributed to the model. Second, the two cerebral hemispheres seem to be differentially involved in the somatomotor modulation contingent upon pain observation. Indeed, the

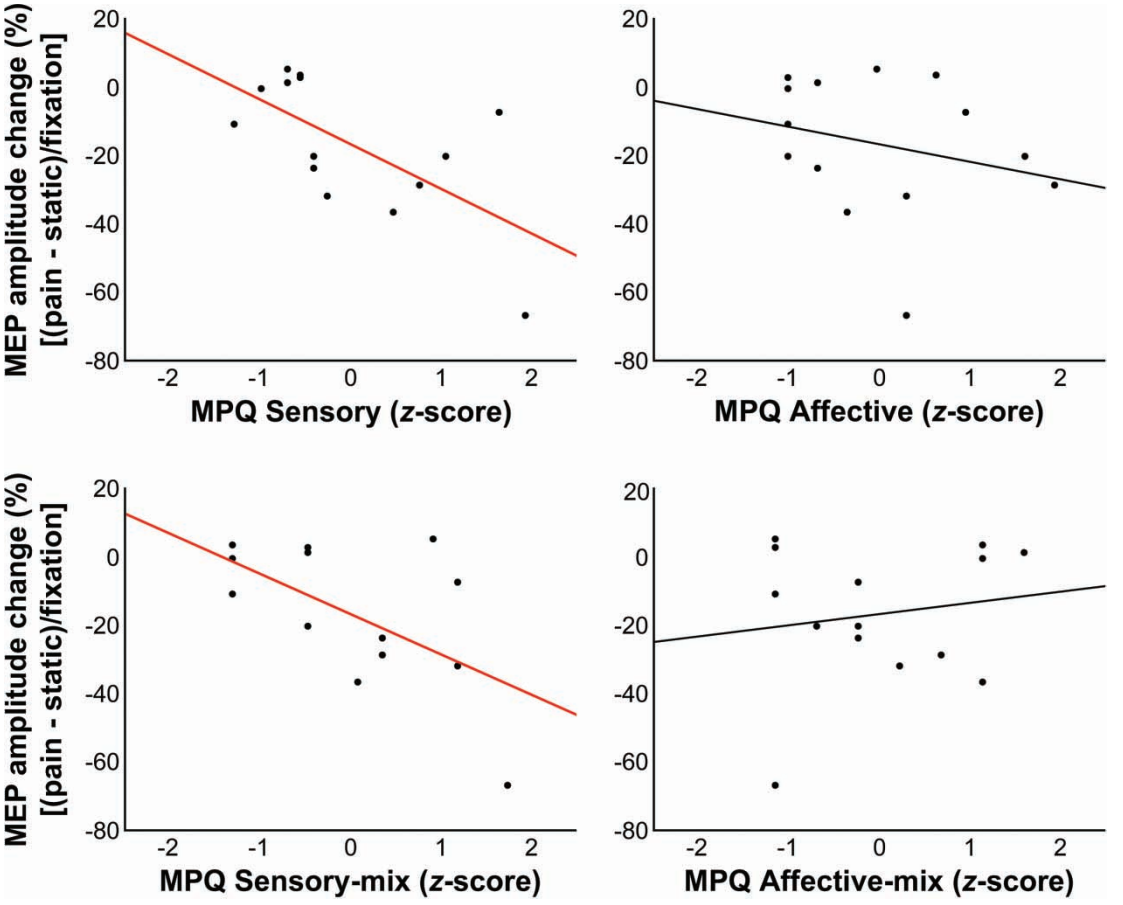

Figure 3. Correlations between MEP amplitude change (static–pain) recorded from right FDI (left M1) and pain qualities. The four panels show the relation between MEP induced by stimulation of left M1 and the four subscales of the McGill Pain Questionnaire: (A) Sensory; (B) Sensory-mix; (C) Affective; and (D) Affective-mix scale.

left hemisphere provides a more detailed reading of the imagined sensory qualities of others' pain.

Somatotopic pain motor mapping

In the present study we confirmed the basic features of the motor inhibition linked to the direct observation of others' pain (Avenanti et al., 2005, 2006; Fecteau et al., 2006). Observing needles entering specific body parts of a stranger model brought about a reduction of excitability that was specific to the muscle the subjects observed being penetrated. This effect correlated with sensory (intensity) but not affective (unpleasantness) qualities of the pain ascribed to the model (although this effect is ascribable more to the left than the right hemisphere, see below). We have proposed that this reduction of excitability of specific corticospinal representations may be due to a *mirror-like* ''resonance'' mechanism that extracts basic *sensory* qualities of another person's painful experience (location and intensity of the noxious stimulus) and maps them onto the observers' motor system according to somatotopic rules (Avenanti et al., 2005, 2006). This interpretation is supported by the inhibitory sign of the effect, by the muscle specificity and by the correlation of MEP inhibition with the intensity of the pain attributed to the model (Avenanti et al., 2005, 2006; Avenanti & Aglioti, 2006; Fecteau et al., 2006).

An alternative interpretation may invoke the activation of the *motor* mirror system. In principle, motor inhibition during pain observation may reflect the simulation of a defensive motor reaction to pain similar to the suppression of distal muscle activity observed during the upper limb withdrawal reflex (Farina et al., 2003; Inghilleri, Cruccu, Argenta, Polidori, & Manfredi, 1997). However, actual motor reactions to pain result in suppression of MEPs amplitude from all distal

hand muscles (Farina et al., 2001, 2003; Svensson et al., 2003; Urban et al., 2004). Thus, the high selectivity of the pain-related observational effect speaks against the simulation of a massive retraction reflex (for further discussions see Avenanti et al., 2005, 2006; Avenanti & Aglioti, 2006).

The notion that empathy for pain may also imply the simulation of the sensory qualities of others' pain may seem at odds with most of the fMRI studies carried out so far. Indeed these studies show that only the affective division of the pain matrix (ACC, AI) is involved in empathy for pain thus suggesting that only emotional representations of pain are shared between self and others (Botvinick et al., 2005; Morrison et al., 2004; Singer et al., 2004, 2006). However, the pattern of modulation of the pain matrix sensorimotor and affective nodes seems more complex. On the one hand, recent evidence suggests that several neural structures do participate in the extraction of intensity of others' pain, including sensorimotor cortex (Avenanti et al., 2005, 2006), parietal structures (Saarela et al., 2006), ACC and insula (Jackson et al., 2005, 2006; Saarela et al., 2006). This suggests that sensory representations of others' pain may be shared in both sensorimotor and affective nodes of the pain matrix. By contrast, high-level emotional empathy-related reactions (empathic concern, personal distress) are crucially encoded into ACC and AI (Singer et al., 2004, 2006; Saarela et al., 2006). On the other hand, it is possible that a lack of sensorimotor activation in fMRI studies is due to the experimental paradigm employed. Current data suggest that the crucial variables in evoking sensorimotor activations are: (1) the instruction to imagine others' pain onto one's own body (first-person perspective), when the visual stimuli employed for inducing empathy are not particularly effective in evoking a strong pain (e.g., pain-implying static pictures) (Jackson et al., 2006; Ogino et al., 2006); and (2) the direct observation of particularly intense or shocking visual stimuli, even in passive observation condition (Avenanti et al., 2006; Saarela et al., 2006). For example, a recent fMRI study in which participants observed pictures of chronic pain patients whose faces expressed long-lasting suffering augmented by a transient intensification of the pain, showed activation of several sensorimotor structures (Saarela et al., 2006). Thus, even passive observation of visual stimuli that are particularly effective in evoking pain is sufficient to induce activity in sensorimotor regions. In a similar vein, we recently demonstrated that inhibitory modulations of the somatomotor system occurred only during observation of needles deeply penetrating but not lightly pinpricking body parts (Avenanti et al., 2006).

Empathic inference of the sensory qualities of others' pain modulates pain motor mapping

The present study further indicates that motor mapping of others' pain is strictly dependent upon the sensory qualities ascribed to the observed person in pain. We explored whether the subjective representation about the localization of pain attributed to the model was linked to specific patterns of corticospinal excitability. We found different motor modulations in subjects who attributed different sensory states to the model. When the model's pain was considered to be diffused to TE, the motor inhibition of FDI muscle underneath the skin region penetrated by the needle was large. When pain was imagined to be localized to the FDI region, only a weak nonsignificant inhibition was detected in the FDI muscle. These findings indicate that the major contribution to the observational pain-related inhibitory effect is ascribable to those participants who judged the pain of the model as diffused to the thenar eminence. It is worth noting that the TE region is located on the palm of the hand in correspondence with the dorsal FDI region. It is thus likely that the ''spread'' group evaluated others' pain as more ''deep,'' rather than spatially diffused. This may have caused the motor inhibition effect to be larger in the ''spread'' group. In keeping with this interpretation, is our previous result that only the observation of deep needle penetrations, but not of superficial pinpricks, elicited corticospinal motor inhibition (Avenanti et al., 2006). These findings may suggest that the relation between visual features of the observed stimuli and somatomotor response is mediated via top-down influence of mental representation of specific sensory qualities of the pain evoked by the observed stimulus and attributed to the observed person. No main effect of observational condition was found in the control muscle (TE), which was not directly penetrated by the needle, thus confirming previous reports (Avenanti et al., 2005, 2006; Fecteau et al., 2006). Interestingly, however, we found that judgments about the localization of the observed pain had an effect

on TE excitability. When pain was imagined as being localized on the FDI muscle, TE was strongly facilitated. Intriguingly, subjects who judged the pain as being spread to the TE tended to show a weak inhibition of TE. It is entirely plausible that in these subjects, TE corticospinal representation was influenced ''as if'' TE were affected by the noxious sensation. Although the functional significance of TE modulation in the two groups of subjects (strong facilitation vs. weak inhibition) is not clear cut, the general pattern of MEPs modulation implies a top-down modulatory role of subjective representations of sensory qualities of others' pain experience (i.e., the spatial localization of the sensation) on the empathic pain motor mapping. This further suggests that empathic inferences about specific sensory qualities of others' pain can modulate somatomotor response in a fine-grained somatotopic manner (Avenanti et al., 2005, 2006; Avenanti & Aglioti, 2006).

How were model's sensory and affective qualities of pain inferred by participants? Did they adopt the model's perspective or their own? The present study does not separate these two alternatives. We can only speculate that, given that the subjects did not know the model and his personal characteristics (e.g., sensitivity to pain), it is more likely that they used a first-person perspective. In other words, they may have judged the model's pain according to what they imagined they would have felt if they were penetrated by the needle. Further studies investigating the influence of perspective taking in empathizing with the pain of familiar or stranger models are needed to better understand brain response to others' pain.

Are left and right somatomotor cortices differently involved in mapping the pain of others?

Brain lesion studies highlighted a preferential role of the right hemisphere in empathic and ToM abilities (Shamay-Tsoory, Tomer, Berger, Goldsher, & Aharon-Peretz, 2005; Shamay-Tsoory, Tomer, Goldsher, Berger, & Aharon-Peretz, 2004). Further, right hemisphere plays an essential role in sympathy (Decety & Chaminade, 2003) and the ability to identify with another individual, which is a prerequisite to empathy (Decety & Chaminade, 2003b).

Pain (Schlereth et al., 2003; Symonds et al., 2006) and empathy for pain studies (Avenanti et al., 2005, 2006; Jackson et al., 2006; Morrison et al., 2004; Saarela et al., 2006) are in line with the notion of a superiority of left hemisphere in coding sensory qualities of pain and a superiority of right hemisphere in coding emotional qualities of pain; this idea is also supported by the evidence in favor of right hemisphere superiority in emotion processing (Demaree et al., 2005).

In the present study we investigated the role of left and right sensorimotor cortices during the direct observation of others' pain. We found that left sensorimotor cortex was strongly inhibited during pain observation. By contrast, right sensorimotor cortex was only slightly inhibited. Correlational analyses also indicated that only left somatomotor system neural activity is tightly linked to subjective judgments of the intensity of the pain supposedly felt by the model. Indeed left somatomotor cortex inhibition correlated with sensory but not affective qualities of the pain attributed to the model whereas no correlation was found for the right hemisphere. Accordingly, fMRI data indicate that sensory qualities are mainly encoded in left-sided neural structures (e.g., left infero-parietal cortex, left ACC, left but also right insula; Saarela et al., 2006). Taken together, these findings suggest a crucial role of left hemisphere in encoding sensory qualities of others' pain.

However, it should be noted that both left and right somatomotor cortices were comparably involved in the extraction of the locus of others' pain. First, both left and right sensorimotor cortices were somatotopically inhibited during the observation of others' pain. Indeed, inhibition contingent upon pain observation was confined to the same muscle penetrated in the model (i.e., the FDI) and was absent in nearby muscles (thenar eminence), which have a contiguous motor representation (Krings, Naujokat, & von Keyserlingk, 1998). Second, localization judgments comparably affected both left and right sensorimotor systems, thus suggesting that mental representation of pain localization is similarly processed in the two hemispheres.

Overall our data suggest that left somatomotor cortex is linked to a detailed inner simulation of the sensory-discriminative qualities of others' pain, including the locus and the intensity of others' pain; by contrast, right somatomotor cortex maps others' pain only according to where the other person is feeling pain. Neither left nor right somatomotor cortices seem involved in encoding emotional qualities of others' pain.

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