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Transcranial magnetic stimulation highlights the sensorimotor side of empathy for pain

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Pain is intimately linked with action systems that are involved in observational learning and imitation. Motor responses to one's own pain allow freezing or escape reactions and ultimately survival. Here we show that similar motor responses occur as a result of observation of painful events in others. We used transcranial magnetic stimulation to record changes in corticospinal motor representations of hand muscles of individuals observing needles penetrating hands or feet of a human model or noncorporeal objects. We found a reduction in amplitude of motor-evoked potentials that was specific to the muscle that subjects observed being pricked. This inhibition correlated with the observer's subjective rating of the sensory qualities of the pain attributed to the model and with sensory, but not emotional, state or trait empathy measures. The empathic inference about the sensory qualities of others' pain and their automatic embodiment in the observer's motor system may be crucial for the social learning of reactions to pain.

Empathy helps us to understand feelings and inner states of mind of others and to share experiences, needs, beliefs and goals[1–3]. Current neuroscientific models of empathy postulate that a given motor, perceptual or emotional state of an individual activates corresponding representations in another individual observing that state[1–3]. Single-cell recording studies in monkeys show that premotor neurons become active both during execution of a given action and during observation of the same action performed by another human or monkey (mirror neurons)[3–5]. In a similar vein, studies in humans demonstrate that observation of other individuals acting, being touched or showing facial emotions induces activity in neural networks that are also activated when observers act[6–9], are touched[10] or display the same emotions[9,11,12]. Thus, empathy may be based on 'mirror-matching' simulation of others' state[3].

Various painful personal experiences, ranging from being pin-pricked to feeling an aching phantom limb[13] or suffering from social loss[14], are represented in a complex neural network referred to as the 'pain matrix'. Affectively distressing components (such as unpleasantness) and sensory components (such as localization and intensity) of the experience of pain are encoded in different nodes of the pain matrix[15,16]. Although pain is an essentially private subjective experience[17], the ability to understand and to experience indirectly the pain of others is fundamental to social ties[18]. Thus, pain is an interesting model for testing theories of empathy based on the notion of shared representations. An empathic matching of others' pain is suggested by (i) the observation that a neuron in the human cingulate cortex increases its firing rate both when pain is inflicted on the observing subject and when it is inflicted on another person[19] and (ii) the anecdotal report of a patient in whom genuine pain was evoked by observation of potentially hurtful stimuli applied to his wife[20]. Recent fMRI (functional magnetic resonance imaging) studies indicate that only affective components of the pain matrix are crucial for the empathic matching of others' pain[21–23], suggesting that only emotional representations of pain are shared between self and others.

Neurophysiological and neuroimaging studies indicate that pain systems are tightly linked to action systems that can be considered as the part of the pain matrix[16,24–27] involved in the implementation of appropriate reactions to actual or potential noxious stimuli. Transcranial magnetic stimulation (TMS) studies, for example, have demonstrated that actual painful stimuli delivered to the hand bring about a massive inhibition of corticospinal excitability that affects upper limb muscles[25,28–30].

Despite this intimate relationship between pain and action systems, knowledge about the possible motor mapping of others' pain is lacking. Here we explored whether pain and action systems are linked also at a social level by looking for possible motor correlates of watching and empathizing with others' pain. We used single-pulse TMS in healthy individuals to assess the functional modulation of the corticospinal system during the observation of painful or non-noxious events shown on the body of a model. During each observation condition, motor-evoked potentials (MEPs) to focal TMS of the left motor cortex were recorded simultaneously from two muscles of the observers' right hand: namely, the first dorsal interosseus (FDI) and the abductor digiti minimi (ADM).

RESULTS

Specific motor mapping of others' pain

In the first experiment, subjects observed different categories of stimuli: (i) a needle penetrating the FDI muscle at the dorsal surface of the right hand between the thumb and index finger ('Needle in FDI'),

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(ii) a Q-tip gently moving over and pressing the same region where the painful stimuli were delivered ('Q-tip on FDI') and (iii) a needle penetrating a tomato ('Non-corporeal'; **Supplementary Video 1**).

We found a significant main effect of condition for MEPs recorded from the FDI muscle ($F_{2,22} = 5.64$, $P = 0.01$; **Fig. 1a**, **Supplementary Fig. 1**) underlying the region where painful or touch stimuli were delivered to the model. MEPs amplitudes recorded from FDI were significantly lower in the 'Needle in FDI' condition than in the 'Q-tip on FDI' ($P = 0.01$), 'Non-corporeal' ($P = 0.02$) and baseline ($t_{11} = -3.17$, $P = 0.009$) conditions, indicating a decrease of motor excitability during the observation of pain. By contrast, we found no modulation of MEPs recorded from the ADM muscle ($F_{2,22} = 0.56$, $P = 0.58$; **Fig. 1b**, **Supplementary Fig. 1**), which was not involved in the pain or touch stimulation.

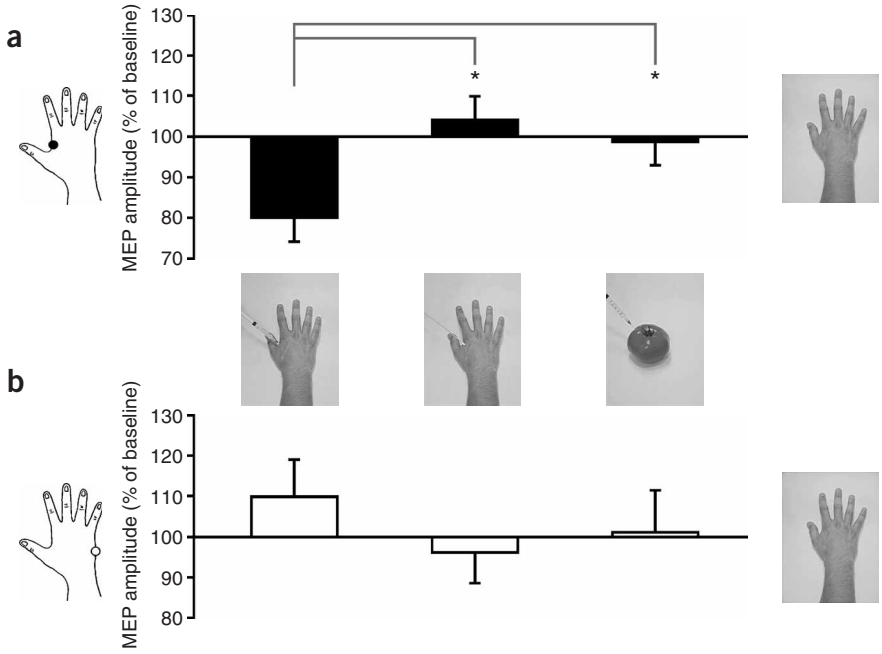

Figure 1 MEP amplitude with respect to the baseline during observation of 'Needle in FDI', 'Q-tip on FDI' and 'Non-corporeal' conditions of experiment 1. (**a**) MEPs recorded from the FDI muscle (black bars). (**b**) MEPs recorded from ADM (white bars). Error bars indicate s.e.m. Asterisks (*) indicate significant post-hoc comparisons ($P < 0.02$).

Somatotopic motor mapping of others' pain

In the second experiment, we further investigated the issue of muscle selectivity by recording MEPs while participants observed a needle entering the dorsum of a right foot ('Needle in foot') or a Q-tip touching the same region ('Q-tip on foot'). There was no significant modulation of MEP amplitude recorded from FDI ($F_{1,7} = 0.04$, $P = 0.85$) or ADM muscles ($F_{1,7} = 0.01$, $P = 0.91$) when the observers viewed foot stimulations (**Fig. 2**).

In a third experiment, we recorded MEPs during observation of painful stimuli delivered to the ADM region of a right hand ('Needle in ADM'), and to the dorsum of a right foot ('Needle in foot'). The results are consistent with the topographic selectivity seen in experiment 1 and 2 (**Fig. 3**). MEPs recorded from the ADM muscle during the observation of 'Needle in ADM' were significantly lower with respect to the corresponding baseline ($t_{11} = -3.50$, $P = 0.005$) and to 'Needle in foot' ($F_{1,11} = 5.09$, $P = 0.045$). We did not find any modulation in MEPs recorded from FDI ($F_{1,11} = 0.02$, $P = 0.88$) (**Fig. 3**).

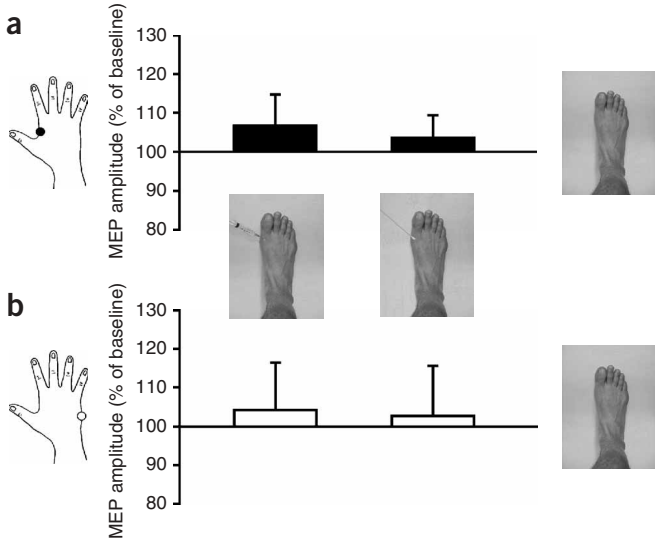

Figure 2 MEPs amplitude with respect to the baseline during observation of 'Needle in foot' and 'Q-tip on foot' conditions of experiment 2. (**a**) MEPs recorded from the FDI muscle (black bars). (**b**) MEPs recorded from the ADM muscle (white bars). Error bars indicate s.e.m.

Comparisons of subjective ratings in experiments 2 and 3 showed that 'painfulness' of the observed stimuli did not differ between hand and foot stimulations. Thus, the selectivity of the motor inhibition cannot reflect differences in the perceived painfulness of the observed events (**Supplementary Fig. 2**).

A fourth experiment suggested that the inhibition of hand representations were likely to have a cortical origin: the observation of painful stimuli delivered to the FDI region did not induce changes in excitability at the muscle or peripheral nerve levels and spinal cord segments controlling the same muscle (**Supplementary Table 1**).

Motor mapping of sensory qualities of others' pain

To explore whether the observed reduction of corticospinal excitability was related to an empathic mapping of different components of the pain experience attributed to the model, we analyzed the subjective judgments about the sensory and affective qualities of the pain ascribed to the model during needle penetration. These judgments were obtained in experiment 1 by means of Sensory and Affective subscales of the McGill Pain Questionnaire[31,32] (MPQ) and two visual analogue scales (VAS), one for pain intensity and the other for pain unpleasantness. We found that amplitude changes of MEPs recorded from the FDI muscle were negatively correlated with sensory aspects of the pain purportedly felt by the model during the 'Needle in FDI' condition, both for the Sensory scale of MPQ ($r = -0.76$, $P = 0.004$) and for pain intensity VAS ($r = -0.71$, $P = 0.01$; **Fig. 4a,c**). In contrast, we found no significant correlation with affective qualities of others' pain (MPQ Affective scale: $r = -0.26$, $P = 0.42$; VAS pain unpleasantness: $r = 0.22$,

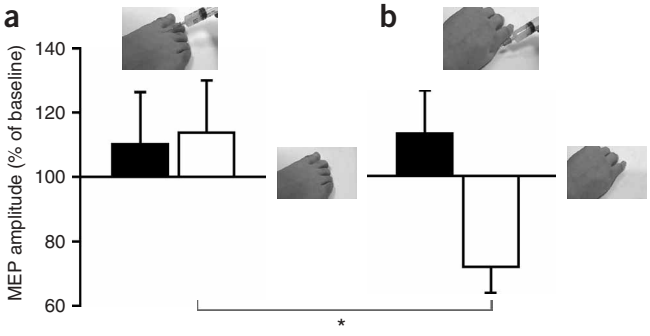

Figure 3 MEP amplitude recorded from the FDI (black bars) and the ADM (white bars) muscles during the observation conditions of experiment 3. (**a**) Observation of 'Needle in foot'. (**b**) Observation of 'Needle in ADM'. Each painful condition was expressed with respect to the corresponding static condition (baseline). Error bars indicate s.e.m. Asterisks (*) indicate significant comparisons ($P < 0.05$).

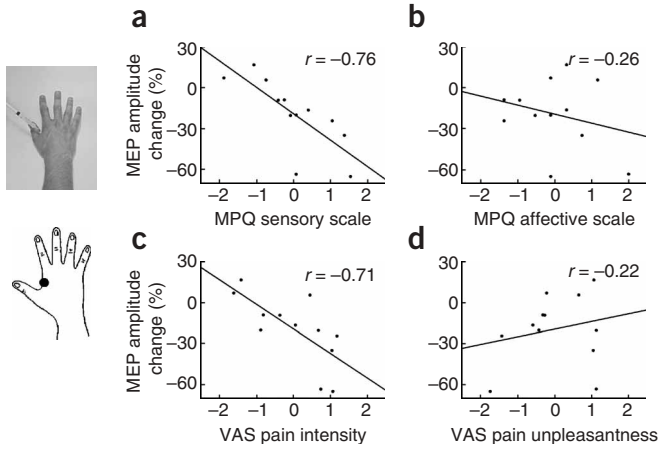

Figure 4 Amplitude changes of MEPs recorded from the FDI muscle and subjective ratings (*z*-scores) of the pain ascribed to the model during the 'Needle in FDI' condition in experiment 1. (**a**,**c**) MEP amplitude changes were negatively correlated with sensory ratings. (**b**,**d**) No significant correlation between MEP amplitude change and affective scores was found. Details in **Supplementary Table 2**.

$P = 0.49$; **Fig. 4b**,**d**). We did not find any correlations between amplitude changes of MEPs recorded from the ADM muscle and qualities of the pain ascribed to the model (**Supplementary Table 2**).

Seeing painful or unpleasant stimuli may elicit arousal or aversion (personal distress) reactions[18]. Subjects used VAS to rate arousal and aversion induced by the different movies presented in experiment 1. We found no correlation between these self-oriented emotional reactions and MEP amplitude changes (**Supplementary Fig. 3**, **Supplementary Table 2**).The selective motor mapping of sensory qualities of others' pain is further suggested by experiment 3 where amplitude changes of MEPs recorded from the pricked ADM muscle correlated with intensity ($r = -0.58$, $P = 0.046$; **Fig. 5**) but not unpleasantness ($r = -0.07$, $P = 0.83$) VAS scores of the pain attributed to the model. We did not find any correlations between amplitude changes of MEPs recorded from the FDI muscle and qualities of the pain ascribed to the model (**Supplementary Table 2**).

State and trait empathy during observation of others' pain

We carried out a fifth experiment to explore whether MEP inhibition was related to inter-individual differences in specific aspects of empathy. Subjects were delivered TMS pulses during observation of 'Needle in FDI'. After TMS sessions, four measures of state empathy, either 'sensory' or emotional, were acquired. In particular, subjects were asked to evaluate along VAS (i) how much they simulated the pain of the model in their mind (self-oriented), (ii) how intense the pain of the model was (other-oriented), (iii) how much aversion they felt (self-oriented) and (iv) how much compassion for the model they felt (other-oriented). Moreover, we obtained two measures of trait empathy by asking subjects to complete two subscales of the Interpersonal Reactivity Index (IRI)[33,34], namely Personal Distress (PD) and Empathic Concern (EC), each of which corresponds to the notion of self-oriented and other-oriented empathic emotional reactions.

Results confirmed the specific MEP inhibition ($t_{15} = -3.09$, $P = 0.008$) contingent upon observation of pain found in experiment 1 (**Supplementary Fig. 4**). We found it important that scores on the two measures of 'sensory' empathy were correlated with the amplitude changes of MEPs recorded from the FDI muscle during the observation of 'Needle in FDI' (VAS pain simulation: $r = -0.56$, $P = 0.02$; VAS pain intensity: $r = -0.50$, $P = 0.05$; **Fig. 6a**,**b**; **Supplementary Table 2**).

We did not find any significant correlation between MEP amplitude change and emotional state (VAS aversion: $r = 0.06$, $P = 0.84$; VAS compassion: $r = 0.15$, $P = 0.57$; **Fig. 6c**,**d**) or trait (IRI Empathic Concern: $r = -0.24$, $P = 0.37$; IRI Personal Distress: $r = -0.11$, $P = 0.67$) empathy scores (**Fig. 6e**,**f**). Nor did we find any correlations between amplitude changes of MEPs recorded from the ADM muscle and 'sensory' or emotional empathy measures (**Supplementary Table 2**).

DISCUSSION

Only three studies, all using fMRI, have so far explored the neural underpinnings of empathy for pain in humans[21–23]. Despite several differences in the experimental protocols, all the previous studies indicate that only affective nodes in the pain network are concerned with empathy for pain[21–23]. Here we highlight the sensorimotor side of empathy for pain by showing a consistent reduction of excitability of hand muscles during the mere observation of 'flesh and bone' painful stimuli delivered to a model. The observational pain-related inhibition was robust and conspicuous on several fronts. First, it was specific for the observation of a needle entering the hand and absent during the observation of a needle entering feet or non-corporeal objects. Second, it was confined to the observation of pain and absent during the observation of harmless tactile stimulation. Third, it was selective for MEPs recorded from the hand muscle underlying the skin region penetrated by the needle, and absent for MEPs recorded from a nearby hand muscle. Fourth, the effect was clearly related to the observer's

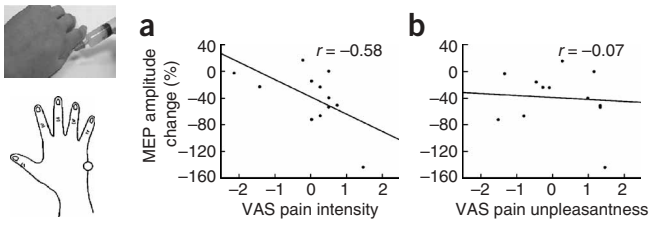

Figure 5 Amplitude changes of MEPs recorded from the ADM muscle and subjective ratings (*z*-scores) of the pain attributed to the model during the 'Needle in ADM' condition in experiment 3. (**a**) Changes in MEP amplitude negatively correlated with sensory ratings (**b**) but not with affective scores. Details in **Supplementary Table 2**.

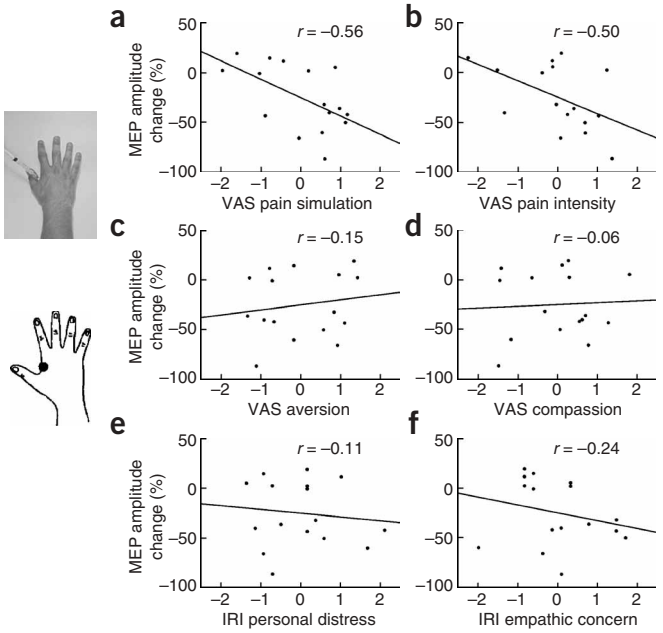

Figure 6 Amplitude changes of MEPs recorded from the FDI muscle during 'Needle in FDI' observation and state (**a**,**b**,**c**,**d**) and trait (**e**,**f**) empathy measures (*z*-scores) in experiment 5. (**a**,**b**) MEPs amplitude changes were negatively correlated with VAS pain simulation and VAS pain intensity. Moreover, both 'sensory' state empathy measures independently predict the inhibition (**Supplementary Table 2**). (**c**,**d**,**e**,**f**) No significant correlation between MEP amplitude change and emotional state or trait empathy scores was found. Details in **Supplementary Table 2**.

subjective empathetic rating of the sensory, but not affective, qualities of the pain ascribed to the model. Fifth, the inhibition was related to measures of state 'sensory' empathy scores but not to emotional state empathy or trait empathy scores.

We suggest the effect may be due to activation of a pain resonance system[3,20] (**Supplementary Note**) that extracts basic sensory aspects of the model's painful experience (such as source or intensity of a noxious stimulus) and maps them onto the observer's motor system according to topographic rules. This hypothesis is further strengthened by the high correlations found in experiments 1, 3 and 5 indicating that the strongest motor inhibition was found in the observers who rated as most intense the model's pain.

The evidence presented here for a direct 'mirror-matching' simulation of sensory but not of affective features of others' pain may seem in sharp contrast with a previous fMRI study. In that study, empathy for pain was induced by means of arbitrary visual cues signaling an impending painful stimulus to a loved one[21]. Empathy for pain brought about an increase of the BOLD (blood oxygen level–dependent) signal in anterior insula and anterior cingulate cortices, which are part of the affective division of the pain matrix. We find it important that there was a positive correlation between neural activity and emotional empathy scores[21]. Neural activity in the affective pain network was also reported in fMRI studies where subjects observed pictures[22] or movies[23] in which potentially painful stimuli were delivered to hands or other human body parts. Our study does not indicate the absence of activity in the affective nodes of the pain matrix during observation of 'flesh and bone' stimuli. Rather, it indicates that empathy for pain may rely not only on affective-motivational[21–23] but also on fine-grained somatic representations. Indeed, our results suggest a link between the visual representation of others' painful experiences and the somatomotor representation of feeling the same experience[35]. The results also suggest that the functional mechanism that allows linkage of visual and somatomotor representations may rely on the inner simulation of specific attributes of the observed stimulus.

Evidence for a somatic resonance system has been provided by a fMRI study in which an increase of the BOLD signal in the secondary somatosensory cortex (SII) was found both when the participants were touched and when they observed someone else being touched[10]. Moreover, additional structures that may be involved in somatic processing such as the thalamus, brainstem, parietal cortex and cerebellum are active when seeing or imagining others' pain[21,22].

Notably, affective and sensorimotor nodes of the pain matrix may not be involved only in processing actual painful stimuli[15,16] but also in anticipation of somatosensory and painful events administered to the self[24,36,37]. According to shared representation models[1,2,22], it is entirely possible that the somatomotor contagion that may underlie the corticospinal inhibition reported in our study implies pain anticipation in oneself.

As our subjects were informed that no painful stimulus would actually be delivered at any time, we suggest that the anticipatory quality of the sensorimotor mapping may be automatic. Moreover, we posit that the selective embodiment of others' pain, sensitively more than emotionally denoted, may be crucial for the social learning of reactions to painful stimuli in that it may help the observer's corticospinal system to implement escape or freezing reactions before painful stimuli are actually experienced.

It may thus be possible to think of at least two forms of empathy linked to one another in an evolutionary and developmental perspective. A comparatively simple form of empathy, based on somatic resonance, may be primarily concerned with mapping external stimuli onto one's own body[3–10,38]. A more complex form of empathy, based on affective resonance, may deal with emotional sharing[11,12,21–23] and with the evaluation of social bonds and interpersonal relations[21,39]. All in all, our results indicate that the motor system is an important node in the complex neural network, recruited not only during the personal experience of pain[16,21,24–30,36] but also during empathy for others' pain. We propose that a direct matching of specific sensory aspects of others' pain occurs in sensorimotor structures of the pain matrix, whereas emotional components of others' painful experiences are coded in the affective division of the network[21]. Hence, empathy for pain may take different forms in different nodes of the complex neural network that represent sensations, feelings and emotions linked to the experience of pain. Philosophers have emphasized that our bodily sensations are intrinsically private[17]. However, our findings suggest that, at least in humans, the social dimension of pain extends even to the very basic, sensorimotor levels of neural processing.

METHODS

Subjects. For experiments 1–5 there were 12, 8, 12, 8 and 16 participants, respectively (6, 4, 6, 4 and 8 men). Ages ranged between 20–28, 21–27, 20–27, 20–29 and 19–30. All subjects were right-handed, according to a standard handedness inventory[40]. Subjects gave written informed consent and were paid for their participation. The protocol was approved by the ethics committee of the Fondazione Santa Lucia, Rome and was carried out in accordance with the ethical standards of the 1964 Declaration of Helsinki. None of the participants had neurological, psychiatric or other medical problems or had any contraindication to TMS[41].

EMG and TMS recording. In experiments 1, 2, 3 and 5, MEPs were recorded simultaneously from first right dorsal interosseus (FDI) and abductor digiti minimi (ADM) by means of a Viking IV (Nicolet Biomedical)

electromyograph. EMG signals were band-pass filtered (20 Hz–2.5 kHz, sampling rate 10 kHz), digitized and stored on a computer for offline analysis. Pairs of Ag/AgCl surface electrodes were placed over the muscle belly (active) and over the associated joint or tendon (reference). A circular ground electrode with a diameter of 30 mm was placed on the dorsal surface of the right wrist. A figure-eight coil connected to a Magstim Super Rapid Transcranial Magnetic Stimulator was placed over the left motor cortex. The intersection of the coil was placed tangentially to the scalp with the handle pointing backward and laterally at a 45° 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[42,43]. The coil was moved over the left hemisphere to determine the optimal position from which maximal amplitude MEPs were elicited in FDI. The intensity of magnetic pulses was set at 130% of the resting motor threshold, defined as the minimal intensity of the stimulatory output that produces MEPs with an amplitude of at least 50 μV with 50% probability[44]. The complete muscle relaxation before TMS was verified by means of visual and auditory monitoring of the EMG signal. F and M waves were elicited by supramaximal electric square-wave pulses (duration, 0.3 ms) at 5-s intervals and were recorded from the FDI muscle. The electric stimuli were delivered to the right ulnar nerve at the wrist. Whereas the F wave is considered an index of spinal cord excitability, the M wave is considered an index of nerve and muscle excitability[45,46].

Visual stimuli. In each experiment, different blocks of video clips were presented on a 19-inch screen located 80 cm from the subjects. In experiment 1, the video clips showed (i) the dorsal view of a right hand ('Static Hand'), (ii) a needle penetrating the FDI muscle region ('Needle in FDI'), a Q-tip touching the same region ('Q-tip on FDI') and (iii) a needle penetrating a tomato ('Non-corporeal'; **Supplementary Video 1**). In experiment 2, video clips of (i) the dorsal view of a right foot ('Static foot'), (ii) a needle penetrating a foot ('Needle in foot') and (iii) a Q-tip touching the same region ('Q-tip on foot') were shown. In experiment 3, the video clips showed (i) a static view of the ADM region of a right hand ('Static ADM'), (ii) a static view of the dorsal surface of a right foot ('Static foot'), (iii) a needle penetrating the ADM muscle of a right hand ('Needle in ADM') and (iv) a needle entering the dorsal surface of a right foot ('Needle in foot'). In experiments 4 and 5, the video clips showed the 'Needle in FDI' and the 'Static Hand' conditions used in experiment 1. Previous neurophysiological studies report that observation of moving body parts brings about an increase of corticospinal excitability[6,47,48] and that observation of a hand using tools elicits an activation of primary motor cortex[49]. To avoid such effects in the present study, we checked that no movements of hand, foot or tomato were evoked by pinprick or touch stimuli. In a similar vein, we checked that in none of the videos was the holder of the syringe or of the Q-tip visible.

Procedure. The experiments were programmed using Psychophysics Toolbox (http://www.psychotoolbox.org) and Matlab (http://www.mathworks.com) software to control sequence and duration of video clips and to trigger TMS and EMG recording. Each type of video clip was presented in separate blocks. Five (18 trials), four (18 trials), four (15 trials) and two (18 trials) blocks were performed in experiments 1, 2, 3 and 5, respectively. On 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 blank screen was shown for 7.2 s in the intertrial intervals. The choice of long intertrial intervals was based on a study demonstrating that TMS delivered for 1 h at 0.1 Hz frequency did not induce any change of excitability[50]. In experiments 1 and 2, the first and the last block served as baseline and consisted of video clips showing 'Static Hand' and 'Static foot', respectively. The order of the other blocks was counterbalanced. In experiment 3, 'Static ADM' and 'Static foot' served as baseline for 'Needle in ADM' and 'Needle in foot', respectively. In experiment 4, 20 F and M waves were recorded in two blocks. In experiment 5, 'Static Hand' served as baseline for 'Needle in FDI'. The order of the different blocks in experiments 3–5 was counterbalanced. In all the experiments, a central cross (1,000 ms) indicated the begin of a trial and initiated EMG recording. The duration of each video was 1,800 ms. 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.

Subjective reports. After TMS sessions of experiment 1, subjects were presented with all movies and asked to judge the arousal and aversion (personal distress) induced by each movie by marking a vertical, 10-cm visual analogue scale (VAS) with 0 cm indicating 'no effect' and 10 cm 'maximal effect imaginable'. In experiments 1, 2, 3 and 5, VAS were used to rate the intensity and unpleasantness of the pain purportedly experienced by the model when being injected or touched on the hand or the foot. In experiment 1, qualities of the pain ascribed to the model were also measured by means of the Italian version[32] of the McGill Pain Questionnaire (MPQ)[33]. Sensory and Affective subscales of MPQ were used.

Measures of state and trait empathy. After TMS sessions of experiment 5, four measures of state empathy (sensory or emotional, self-oriented or other-oriented) were acquired. Subjects were shown the 'Needle in FDI' movies and asked to evaluate along a VAS (i) their inner mental simulation of the model's pain (sensory, self-oriented), (ii) the intensity of the pain they attributed to the model (sensory, other-oriented), (iii) the aversion they felt (emotional, self-oriented) and (iv) the compassion they felt for the model (emotional, other-oriented). Two measures of emotional trait empathy were obtained by asking subjects to complete two subscales of the Italian version[33] of the Interpersonal Reactivity Index (IRI)[34], namely Empathic Concern and Personal Distress. The Empathic Concern subscale assesses the tendency to experience feelings of sympathy and compassion for others in need, and the Personal Distress subscale assesses the tendency to experience distress and discomfort in response to extreme distress in others.

Neurophysiological measures analysis. Data were processed offline. Trials with EMG activity before TMS (less than 5%) were discarded from analysis. In experiments 1, 2, 3 and 5, mean MEP amplitude in each condition was measured peak-to-peak (in mV). In experiment 1, MEP amplitude in the first and last block was comparable for both FDI ($t_{11} = 0.51$, $P = 0.62$) and ADM ($t_{11} = -0.18$, $P = 0.86$) muscles. The same result was obtained in experiment 2 (FDI: $t_7 = 1.02$, $P = 0.34$; ADM: $t_7 = 1.40$, $P = 0.20$). Therefore, in both experiments, the baseline was obtained by averaging MEP values from the first and the last block. In experiments 1, 2, 3 and 5, mean MEP amplitude in each dynamic observation condition was expressed as percentage of the corresponding baseline ('Static Hand' in experiment 1 and 5, 'Static foot' in experiment 2, and 'Static ADM' and 'Static foot' in experiment 3). For each muscle, normalized MEP values were analyzed by means of repeated-measure one-way ANOVAs with Condition as the main factor with three levels ('Needle in FDI', 'Q-tip on FDI', 'Non-corporeal') in experiment 1, two levels ('Needle in foot', 'Q-tip on foot') in experiment 2 and two levels ('Needle in foot', 'Needle in ADM') in experiment 3. Post-hoc comparisons were carried out by means of the Newman-Keuls test. In experiment 4, mean amplitudes of F and M waves (in mV) were measured peak-to-peak. F and M waves recorded during 'Needle in FDI' condition were normalized using 'Static Hand' condition. Normalized MEP (experiments 1, 2, 3 and 5) and F and M wave (experiment 4) values were compared against the value of 1 (baseline) by means of one-sample *t*-tests.

Subjective measures analysis. In experiment 1, mean VAS ratings for arousal and aversion induced by the different types of video clip were analyzed by means of two repeated-measure one-way ANOVAs with type of movie as main factor ('Needle in FDI', 'Q-tip on FDI', 'Non-corporeal'; **Supplementary Fig. 3**). We compared the VAS ratings of pain qualities ascribed to the model by means of two one-way ANOVAs with type of movie as main factor ('Needle in FDI', 'Q-tip on FDI' in experiment 1; 'Needle in foot', 'Q-tip on foot', in experiment 2; 'Needle in ADM', 'Needle in foot' in experiment 3), one for pain intensity and one for pain unpleasantness (**Supplementary Fig. 2**). Post-hoc comparisons were carried out by means of the Newman-Keuls test.

Correlation analysis. In each experiment, a correlation analysis between neurophysiological and subjective measures (experiments 1, 2, 3 and 5) and state and trait empathy scores (experiment 5) was performed for observation conditions in which MEP amplitude was significantly different from the

baseline. An index of MEP amplitude change with respect to the baseline was computed. The only two conditions significantly different from the baseline were 'Needle in FDI' in experiments 1 ($t_{11} = -3.17$, $P = 0.009$) and 5 ($t_{15} = -3.09$, $P = 0.008$) and 'Needle in ADM' in experiment 3 ($t_{11} = -3.50$, $P = 0.005$). Indices of MEP amplitude change were computed as follows: amplitude during observation of the pain condition minus amplitude during observation of the static hand condition divided by the average of the same two conditions. Pearson correlation coefficients between indices of amplitude change of MEPs recorded from each muscle and subjective reports were computed in each experiment. In experiment 5, we carried out a standard regression analysis to test whether sensory state empathy scores were independent predictors of amplitude change of MEPs recorded from FDI during the observation of 'Needle in FDI'.

Note: Supplementary information is available on the Nature Neuroscience website.

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COMPETING INTERESTS STATEMENT

The authors declare that they have no competing financial interests.

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