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The pain of a model in the personality of an onlooker: Influence of state-reactivity and personality traits on embodied empathy for pain

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ABSTRACT

The study of inter-individual differences at behavioural and neural levels represents a new avenue for neuroscience. The response to socio-emotional stimuli varies greatly across individuals. For example, identification with the feelings of a movie character may be total for some people or virtually absent for others. Inter-individual differences may reflect both the on-line effect (state) of the observed stimuli and more stable personal characteristics (trait). Here we show that somatomotor mirror responses when viewing others' pain are modulated by both state- and trait-differences in empathy. We recorded motor-evoked potentials (MEPs) induced by Transcranial Magnetic Stimulation (TMS) in healthy individuals observing needles penetrating a model's hand. We found a reduction of corticospinal excitability that was specific for the muscle that subjects observed being penetrated. This inhibition correlated with sensory qualities of the pain ascribed to the model. Moreover, it was greater in subjects with high trait-cognitive empathy and lower in subjects with high trait-personal distress and in those with high aversion for the observed movies. Results indicate that somatomotor responses to others' pain are influenced by specific onlookers' personality traits and self-oriented emotional reactions. Our findings suggest that multiple distinct mechanisms shape mirror mapping of others' pain.

Introduction

Empathy enables us to share the emotions and the sensations of others. Current neuroscientific models of empathy postulate that watching, hearing or imagining another person in a particular mental state automatically activates a representation of that state in the observer (Preston and de Waal, 2002; Decety and Jackson, 2004; Gallese, 2006; Avenanti and Aglioti, 2006). Recent studies provide evidence for common neural modulations elicited when feeling disgust (Wicker et al., 2003), touch (Keyser et al., 2004; Blakemore et al., 2005; Bufalari et al., 2007) or pain (Singer et al., 2004; Morrison et al., 2004; Avenanti et al., 2005; Jackson et al., 2006; Bufalari et al., 2007) in oneself, and when observing others having a corresponding experience. These empathic '*mirror-matching*' responses to the observation of others' feelings may be related to the simulation of different somatomotor and emotional aspects of others' experience (Gallese, 2006; Keysers and Gazzola, 2006; Avenanti and Aglioti, 2006; Avenanti et al., 2007).

Pain is a complex feeling with separate sensory (intensity, localization) and emotional (unpleasantness) components that are represented in distinct sensorimotor and affective nodes of a cortico-subcortical network called 'pain matrix' (Peyron et al., 2000; Rainville, 2002). This neural segregation makes pain an extraordinary model for testing theories of empathy based on the notion of resonant mirror systems.

Transcranial magnetic stimulation (TMS) studies show that direct observation of 'flesh and bone' painful stimulations delivered to the body of a human model elicits inhibitory responses in the observers' corticospinal motor system (Avenanti et al., 2005, 2006; Minio-Paluello et al., 2006, 2008; Fecteau et al., 2008) similar to those found during pain perception (Farina et al., 2003; Svensson et al., 2003; Urban et al., 2004). These onlookers' '*mirror-like*' inhibitory corticospinal responses are specific to the body part stimulated in the model and correlate with the evaluation of spread and intensity (but not of the unpleasantness) of the pain ascribed to the model (Avenanti et al., 2005, 2006; Minio-Paluello et al., 2006); thus, the inhibition likely reflects the simulation of basic sensory features of others' pain (intensity, diffusion, localization of pain) (Avenanti et al., 2005). In a similar vein, somatosensory-evoked potentials (SEPs, Bufalari et al., 2007), laser-evoked potentials (LEPs, Valeriani et al., 2008), magnetoencephalography (MEG, Cheng et al., 2008a) and neuroimaging

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studies (Jackson et al., 2006; Saarela et al., 2007; Moriguchi et al., 2007; Cheng et al., 2007; Lamm et al., 2007a; Lamm et al., 2007b; Benuzzi et al., 2008) indicate specific pain-related activity into the observers' somatomotor system during empathy for pain.

In addition to somatomotor responses, a number of studies consistently showed neural response to others' pain in the affective division of the pain matrix, including the anterior cingulate cortex (ACC) and the anterior insula (AI) (Singer et al., 2004; Morrison et al., 2004; Jackson et al., 2006; Saarela et al., 2007; Lamm et al., 2007a,b; Benuzzi et al., 2008), suggesting that perceiving pain in others induces the sharing of emotional components of pain. Taken together, these findings suggest that our ability to understand and empathize with the pain of others relies on neural systems that underpin our own bodily and emotional states.

However, responses to others' pain are likely to go beyond a simple mapping of sensory or emotional components of others' painful experience. For example, emotional reactions derived from the recognition of others' pain may be *other-oriented* and/or *self-oriented* (Batson, 1991; Davis, 1996; Eisenberg, 2000; Goubert et al., 2005; Lamm et al., 2007a). Two main fundamental components of 'emotional empathy' namely the feeling of sorrow or concern for others in pain (*other-oriented* sympathy responses) (Singer et al., 2004; Saarela et al., 2007; Lamm et al., 2007a) and distress for the unpleasant scene (*self-oriented* emotional reactions) (Saarela et al., 2007; Lamm et al., 2007a) have been described in social and developmental psychology and neuroscience (Batson, 1991; Davis, 1996). Although these two empathy dimensions may act together, they are qualitatively distinct (Batson, 1991; Davis, 1996; Goubert et al., 2005) and imply different effects on implementing prosocial behavior (Davis, 1996; Eisenberg, 2000). *Other-oriented* responses may instigate an altruistic motivation to help the other, whereas *self-oriented* responses may imply an egoistic motivation to reduce personal distress (Batson, 1991). Studies also suggest that personal distress may counteract empathic responses and helping behavior (Hoffman, 1984; Eisenberg et al., 1989; Eisenberg, 2000).

Another key component of empathy is the ability to adopt and understand the psychological perspective of others (Hoffman, 1984; Davis, 1996). This type of empathy is generally viewed as cognitive in nature: for example one can voluntarily think about or imagine another person's feelings without an affective response to them (Davis, 1996). Importantly, inter-individual differences in cognitive and emotional components of empathy may result in different responses to others' actions and experiences (Davis, 1996). Behavioral studies indicate that people with high levels of cognitive empathy show the tendency to mimic the postures, mannerisms, and facial expressions of others (the so called 'chameleon effect') to a greater extent than low-empathic individuals (Chartrand and Bargh, 1999). While the chameleon effect is specifically linked to cognitive rather than to emotional empathy (Chartrand and Bargh, 1999), the automatic mimicking of others' emotional facial expressions has been linked to emotional empathy (Sonnby-Borgström, 2002).

Psychological research thus postulates multiple independent but interacting mechanisms at the base of empathy (Davis, 1996; Eisenberg, 2000; Decety and Jackson, 2004). From a neuroscientific perspective this implies that distinct neural mechanisms may underpin different types of empathy-related responses. Preliminary evidence suggests that cognitive empathy may modulate sensorimotor brain responses to hearing the sound of others' actions, suggesting a close link between motor mirror systems and empathy (Gazzola et al., 2006). Moreover, pain empathy studies indicate that affective neural response to others' pain is modulated by emotional empathy-related personality traits (both *self-* and *other-oriented*) (Singer et al., 2004; Saarela et al., 2007; Lamm et al., 2007a). However, to date little is known about the role of empathy traits in the modulation of the somatomotor response to others' pain (Cheng et al., 2008a).

Using single-pulse TMS in healthy subjects, we show that separate empathy-related dimensions influence the somatomotor response to the direct observation of others' pain. By demonstrating that different psychological dimensions are independent predictors of empathic neural response, we provide psychological and neural evidence in favor of the models that acknowledge the influence of multiple distinct mechanisms at the base of empathy (Davis, 1996; Eisenberg, 2000; Decety and Jackson, 2004; Keysers and Gazzola, 2006).

Methods

Participants

Seventy-eight (48 men, mean age 25 years, range 19–34) subjects, all recruited at the IRCCS Fondazione Santa Lucia Rome, participated in the study. We used a large sample in order to have sufficient power to assess effects of individual differences in empathy. All subjects were right handed according to a standard handedness inventory (Oldfield, 1971) and gave their written informed consent. A reimbursement for their time was provided. None of the participants had neurological, psychiatric, or other medical problems, or had any contraindication to TMS (Wasserman, 1998). The protocol was approved by the ethics committee at 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 in any of the subjects.

EMG and TMS recordings

MEPs induced by TMS were recorded simultaneously from first right dorsal interosseus (FDI, in the region of the index finger) and abductor digiti minimi (ADM, in the region of little finger) by means of a Viking IV (Nicolet biomedical, U.S.A.) 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. 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 right wrist. A figure-of-8 coil connected to a Magstim Super Rapid Transcranial Magnetic Stimulator (Magstim, Whitland, Dyfed, U.K.) was placed over the left M1. 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 (Brasil-Neto et al., 1992; Mills et al., 1992). By using a slightly suprathreshold stimulus intensity, the coil was moved over the left hemisphere 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 130% of the resting motor threshold (rMT), defined as the minimal intensity of the stimulator output that produces MEPs with amplitude of at least 50 μV in both muscles with 50% of probability (using about 20–30 pulses) (Rossini et al., 1994). In each subject, the rMT was determined in reference to the higher threshold muscle (in most cases the ADM). This way a stable signal could be recorded in both muscles. Importantly, previous studies suggest that modulations due to pain observation are independent from the chosen OSP (Avenanti et al., 2005, 2006), at least when the two recording muscles have a contiguous motor representation in the cortex (Krings et al., 1998). The absence of voluntary contraction was continuously verified visually and, prior to the recording session, by auditory monitoring of the EMG signal.

Visual stimuli

Two types of video clips were presented on a 19-inch screen located 80 cm from the subjects. Video clips showed: (i) the static view of the dorsal surface of a right hand of a stranger male model depicted from a first-person view point; (ii) a needle deeply penetrating the FDI muscle of the same hand (Avenanti et al., 2005, 2006; Minio-Paluello et al., 2006). To minimize habituation, three different versions of the stimuli were presented. Previous TMS studies report that observation of moving body parts brings about an increase of corticospinal excitability (Fadiga et al., 1995) and that observation of a hand using tools elicits an activation of primary motor cortex (Järveläinen et al., 2004). To avoid such effects in the present pain study, we checked that no movements of hand were evoked by penetrating stimuli. In a similar vein, we checked that in none of the videos the holder of the syringe was visible.

Procedure

The experiment was programmed using Psychophysics Toolbox (www.psychotoolbox.org/) and Matlab (www.mathworks.com) software to control sequence and duration of the video clips, and to trigger TMS and EMG recording. 'Static hand' and 'needle in FDI' video clips were presented in separate blocks. Each type of clip was presented for 6 times (18 trials in total for each block). The order of the two blocks was counterbalanced across subjects. In each block, a central cross (1000 ms) indicated the beginning of the trial, and initiated EMG recording. The duration of each video was 1800 ms. 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 black screen was shown for 7.2 s in the intertrial intervals. The choice of long intertrial interval was based on a study demonstrating that TMS delivered for 1 h at 0.1 Hz frequency did not induce any change of excitability (Chen et al., 1997). Subjects were instructed to pay attention to the video clips and to focus on what the stimulated individual may have felt, as used in our previous studies (Avenanti et al., 2005; Minio-Paluello et al., 2006, in press). At the end of each block in order to verify and encourage attention, participants were asked to answer questions concerning the videos (e.g. "How old do you think the model is?", "Were different syringes used to pierce the hand?").

State empathy measures

After the TMS session, subjects were presented with the three versions of the needle in FDI clips and asked to judge different aspects of the "on-line" experience linked to the observation of the model's pain. These 'state' measures consisted in: i) *empathic inferences* of others' pain; and ii) *self-oriented* emotional reactions. *Empathic inferences* measures included sensory and affective qualities of the pain ascribed to the model. Subjects were asked to judge the intensity and the unpleasantness of the pain supposedly felt by the model by marking a vertical, 10-cm visual analogue scale (VAS) with 0 cm indicating "no effect" and 10 cm "maximal effect imaginable". Different qualities of the pain ascribed to the model were also measured by means of the Italian version (Maiani and Sanavio, 1985) of the McGill Pain Questionnaire (MPQ) (Melzak, 1975) that includes four scales: Sensory (items 1–10), Affective (items 11–15), Sensory-mixed (items 17–19) and Affective-mixed subscale (item 20) (Maiani and Sanavio, 1985). *Self-oriented* emotional reactions to the observation of others' pain were assessed by asking to report on 10-cm VAS the Arousal and Aversion induced by each movie. To avoid building up artificial correlations between the different judgments, each state-empathy rating was collected separately during successive presentation of the whole set of stimuli. The order of the different measures was randomized across subjects.

Trait empathy

While 'state' measures are more directly linked to the observed experimental painful stimuli, 'trait' empathy measures reflect participants' stable dispositions that may generalize to different types of situations. These measures were obtained at the end of the experiment by asking subjects to complete the Italian version (Bonino et al., 1998) of the Davis' Interpersonal Reactivity Index (IRI) (Davis, 1996), a 28-item self-report survey that consists of four subscales, namely Perspective Taking (PT, that assess the tendency to spontaneously imagine and assume the cognitive perspective of another person), Fantasy scale (FS, that assess the tendency to project oneself into the place of fictional characters in books and movies), Empathic Concern (EC, that assess the tendency to feel sympathy and compassion for others in need) and Personal Distress (PD, that assess the extent to which an individual feels distress as a result of witnessing another's emotional distress). PT and FS assess cognitive components of empathy, while EC and PD correspond to the notions of *other-oriented* and *self-oriented* empathy-related emotional reactions (Davis, 1996). The PD subscale reflects a primitive form of empathy that may interfere with more mature forms of empathy; thus it tends to drop as the other scales rise and is negatively related to measures of overall social functioning. Higher scores on the PT, FS, and EC scales are associated with a more highly developed capacity for empathy (Davis, 1996).

Data analysis

Neurophysiological data were processed off-line. Trials with EMG activity prior to TMS were discarded from the analysis. Participants with more than 20% of motor artifacts were replaced in the data set (N=8). Mean MEP amplitude values in each condition were measured peak-to-peak (in mV). Outliers (±2.5 SD of the mean) were identified for each muscle in each condition and the data removed. Logarithmic transformation was applied to amplitude values [log (mean MEP amplitude value + 1)] in order to normalize data distribution. MEP amplitude values were analyzed by a two-way repeated measures ANOVA with Muscle (FDI, ADM) and Condition (Static, Pain) as within-subjects factors.

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 $[(m_1-m_2)/\sigma]$. 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 et al., 1996; Morris and DeShon, 2002). MEP values were transformed into z-scores to avoid correlations due to inter-individual difference in amplitude size (Rossini et al., 1994) and Cohen's d

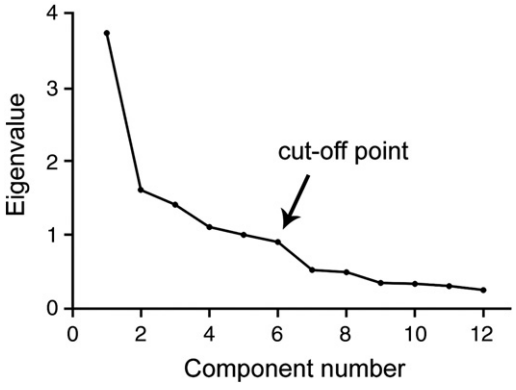

Fig. 1. Scree plot. A six component solution was considered acceptable based on slope change.

Table 1
Mean (St. Dev.) of the subjective ratings and results (factor loading and communalities) of PCA

Original variables	Mean (St. dev.)	PCA factor loadings (rotated solution)						h^2
		PC1	PC2	PC3	PC4	PC5	PC6	
		'State-Pain sensory'	'State-Personal distress'	'Trait-Cognitive Empathy'	'Trait-Sympathy'	'Trait-Personal distress'	'State-Pain affective'	
a) VAS pain intensity	7.01 (2.19)	**0.61**	0.50	0.01	−0.05	0.03	0.40	0.79
b) MPQ sensory scale	15.50 (6.86)	**0.80**	0.07	0.17	0.05	−0.03	0.27	0.75
c) MPQ sensory-mix scale	7.33 (3.22)	**0.89**	0.02	0.08	0.05	0.10	0.10	0.81
d) VAS pain unpleasantness	7.11 (2.35)	0.41	0.46	−0.18	0.00	0.11	**0.55**	0.72
e) MPQ affective scale	2.52 (2.42)	0.32	−0.02	0.01	0.26	0.18	**0.75**	0.76
f) MPQ affective-mix scale	1.91 (1.90)	0.12	0.06	0.16	−0.16	−0.10	**0.87**	0.84
g) VAS arousal	6.07 (2.26)	0.10	**0.86**	−0.10	0.04	−0.11	−0.04	0.77
h) VAS aversion	5.77 (2.80)	0.01	**0.87**	0.14	0.01	0.19	0.11	0.82
i) IRI fantasy scale	17.35 (5.68)	0.28	−0.05	**0.87**	−0.14	0.08	0.04	0.87
j) IRI perspective taking	19.45 (3.66)	−0.14	0.15	**0.59**	0.56	−0.27	0.16	0.80
k) IRI emotional concern	19.51 (3.91)	0.10	−0.01	−0.10	**0.91**	0.01	−0.03	0.85
l) IRI personal distress	11.03 (5.10)	0.06	0.07	0.00	−0.04	**0.97**	0.05	0.95
Explained variance		2.20	2.00	1.25	1.26	1.13	1.91	

Six principal components were extracted accounting for 81% of the variance of the twelve original subjective measures. Each of the original variables was adequately represented in the final solution as attested by the high communalities (h^2). Factors were rotated to simple structure using varimax rotation. For each of the original variables the highest factor loading is represented in bold. Based on factor loadings the principal components were interpreted. PC1 and PC6 were mainly related to the sensory (variables a–c) and the affective (variables d–f) qualities of pain ascribed to the model and were thus labeled 'State-Pain sensory' and 'State-Pain affective' respectively. PC2 was principally related to self-oriented emotional reactions elicited by observation of pain stimuli (variables g, h) and was interpreted as 'State-Personal distress'. PC3 was linked to IRI cognitive scales (variable i, j) and was thus labeled 'Trait-Cognitive empathy'. PC4 and PC5 were linked to IRI other- and self-oriented emotional empathy scales and were thus labeled 'Trait-sympathy' and 'Trait-Personal distress' respectively.

was computed on standardized MEP scores. 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 a large $d=0.8$ (large) is clearly larger than medium.

An exploratory factor analysis of the subjective measures was performed by using standard procedures (Harris, 1967). 'State' (VAS, MPQ) and 'Trait' (IRI subscales) subjective measures were analyzed by principal component analysis (PCA) to reduce dimensionality of the data. Based on scree plot (Fig. 1) we extracted six components which accounted for 81.16% of the total variance (Table 1). Examination of other solutions involving 1–5 factors confirmed that a six-factor solution provided the best conceptual clustering of variables.

A varimax rotation was applied in order to obtain independent components to submit to further analyses (Harris, 1967). The six PCA components were interpreted based on the correlations (factor loadings) with the original measures (Table 1) and were entered as predictors in a standard regression model to analyze the relation between subjective measures and sensorimotor response to others' pain (indexed as the a MEP amplitude change: (pain−static)/(pain+static)). The regression model was significant ($R=0.52$, $F_{6,71}=4.30$, $P=0.0008$) and it strongly improved ($R=0.72$, $F_{6,62}=11.60$, $P<0.000001$) after the removal of 9 outliers with standard residuals>±2sigma. For regression analyses, we computed the Cohen's f^2: $R^2/(1-R^2)$, as an index of effect size. Cohen's f^2 was computed on the adjusted R^2 ($adjR^2$). By convention, f^2 effect sizes of 0.02, 0.15, and 0.35 are considered small, medium, and large, respectively (Cohen, 1988).

Results

Participants were delivered TMS pulses over the left primary motor cortex during the observation of (i) a static hand, and (ii) a needle deeply penetrating the FDI muscle. MEPs to single-pulse TMS were simultaneously recorded from the FDI and ADM muscle of the right hand. MEP amplitude values were analyzed by a two-way repeated measures ANOVA with Muscle (FDI, ADM) and Condition (Static, Pain) as within-subjects factors. ANOVA on MEP amplitude revealed a significant main effect of muscle ($F_{1,77}=41.92$, $P<0.00001$, $d=1.77$) with higher amplitude in the FDI muscle than in the ADM and a significant main effect of Condition ($F_{1,77}=7.57$, $P=0.007$, $d=0.81$) with lower amplitude during the observation of pain. Importantly, a significant Condition×Muscle interaction was found ($F_{1,77}=50.12$, $P<0.00001$; Fig. 2). In keeping with previous findings (Avenanti et al., 2005, 2006; Minio-Paluello et al., 2006, 2008; Fecteau et al., 2008) we found a selective suppression of corticospinal excitability of the onlooker muscle that corresponded to the one penetrated in the

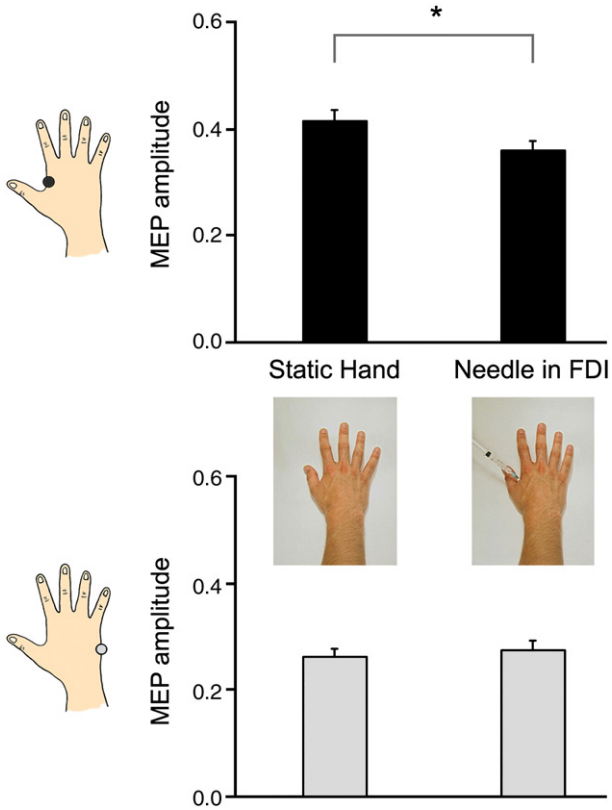

Fig. 2. MEP amplitudes [log (mean MEP amplitude value in mV+1)] recorded from the FDI (top) and the ADM muscle (bottom) during the observation of a static hand (left) and painful stimulations on the FDI region of that hand (right). Error bars denote s.e.m. Asterisks indicate significant comparisons ($P<0.0001$).

model. Indeed, watching painful stimulations delivered to the FDI region of the model brought about a strong reduction of amplitude of MEPs recorded from the FDI muscle of the observer (P=0.0001; d=1.05); by contrast, a small, non-significant trend toward facilitation was found in the ADM muscle (P=0.09, d=0.21). The specific inhibition of the muscle vicariously involved in the painful stimulation indicates that empathic mapping of others' pain occurred according to somatotopic rules. Examples of MEPs recorded from the FDI and ADM muscles in the two observation conditions are provided in Fig. 3.

After the TMS session, visual stimuli were evaluated by means of four visual analogue scales (VAS) ('state' measures). Participants were asked to report specific *empathic* and *self-oriented* subjective experiences related to observation of the model's pain. Self-oriented measures included the arousal and the aversion felt by the subjects during the observation of the movies, whereas empathic inference of the mental state of the observed model included the sensory (intensity) and affective (unpleasantness) qualities of the pain attributed to him. Qualities of the pain supposedly felt by the model were also evaluated by means of the four subscales of the Italian version (Maiani and Sanavio, 1985) of the Mc Gill Pain questionnaire (MPQ) (Melzack, 1975) (Table 1). In order to assess 'Trait' empathy, participants were also asked to fill out the four subscales of the IRI test (Davis, 1996; Bonino et al., 1998) which measure cognitive (FS, PT) and emotional (EC, PD) aspects of reactivity to others. Table S1 reports the inter-correlations between 'state' and 'trait' empathy measures.

We submitted 'state' and 'trait' measures to varimax-rotated principal component analysis (PCA) for data reduction (see methods). PCA extracted six independent factors accounting for 81% of the variance of the original twelve measures (Fig. 1). Table 1 shows factor loadings which were used to interpret the extracted components. Loadings of VAS Pain Intensity, MPQ Sensory and MPQ Sensory-mix on the first factor revealed a common component accounting for variance due mainly to sensory-evaluative qualities of the pain ascribed to the model ('State-Pain sensory'). State-measures of VAS Arousal and VAS Aversion loaded heavily and almost exclusively on the second factor that was interpreted as *self-oriented* emotional reactions of personal distress triggered by the observation of the pain scene ('State-Personal distress'). The third factor was labeled 'Trait-Cognitive empathy' as it was accounted for by the variance of PT and FS of the IRI. IRI EC and PD loaded specifically on the fourth ('Trait-Sympathy') and fifth ('Trait-Personal distress') factor respectively. The sixth factor appeared to be related to the emotional qualities of the pain supposedly felt by the model, with high loadings of VAS Pain Unpleasantness, MPQ Affective and MPQ Affective-mix scales ('State-Pain affective').

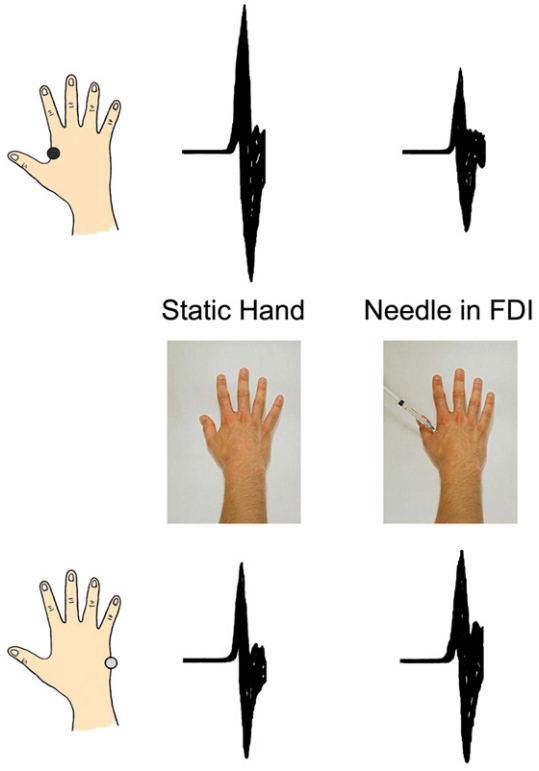

Fig. 3. Raw MEPs amplitudes recorded from the FDI (top) and ADM muscle (bottom) in one representative subject during the observational conditions.

To explore possible relations between somatomotor response to others' pain and empathy, the six principal components were entered in a standard multiple regression model as predictors, with MEP amplitude change (pain−static)/(pain+static) recorded from the FDI muscle as dependent variable. The regression model was significant (R=0.52, $adjR^2$=0.21, f^2=0.27, $F_{6,71}$=4.30, P=0.0008). 'State-Pain sensory' (β=−0.39, t_{71}=−3.84, P=0.0003) and 'Trait-Cognitive empathy' (β=−0.27, t_{71}=−2.62, P=0.011) were independent predictors of MEP amplitude changes. Negative relations between subjective and neurophysiological measures indicate that greatest somatomotor inhibitory responses were found in those subjects: i) who judged the pain of the model as most intense and with most pronounced sensory qualities (high 'State-Pain sensory' score) (Avenanti et al., 2005, 2006; Minio-Paluello et al., 2006, in press) and; ii) who had greater tendency to identify with others and adopt their psychological perspective (high 'Trait-Cognitive empathy' score).

The model strongly improved after outliers removal (R=0.73, $adjR^2$=0.48, f^2=0.92, $F_{6,62}$=11.60, P<0.000001). 'State-Pain sensory' (β=−0.39, t_{62}=−4.65, P=0.00002, Fig. 4A) and 'Trait-Cognitive empathy' (β=−0.44, t_{62}=3.64, P=0.0006, Fig. 4C) remained the strongest negative independent predictors of MEP amplitude change. Interestingly, somatomotor response to others' pain was also predicted by measures of self-oriented emotional reaction, which were both dispositional and generalized to different interpersonal situations ('Trait-Personal distress': β=0.27, t_{62}=3.05, P=0.003, Fig. 4D) and more specifically linked to the observed painful stimuli ('State-Personal distress': β=0.31, t_{62}=3.57, P=0.0007, Fig. 4B). Notably, the relations between MEP amplitude change and measures of personal distress were positive, with higher level of state- or trait-personal distress associated with a reduced somatomotor response to others' pain. Fig. 4 shows linear relations between MEP amplitude change and the four significant predictors.

The same regression model was applied to MEP amplitude change recorded from the ADM muscle. The model was not significant (R=0.34, $adjR^2$=0.04, f^2=0.002, $F_{6,71}$=1.59, P=0.16).

Discussion

Empathic resonant neural responses to others' pain may be related to the simulation of different somatomotor and emotional aspects of others' experience (Singer et al., 2004; Morrison et al., 2004; Avenanti et al., 2005; Jackson et al., 2006; Minio-Paluello et al., 2006; Saarela et al., 2007; Bufalari et al., 2007; Benuzzi et al., 2008). In keeping with previous TMS studies (Avenanti et al., 2005, 2006; Minio-Paluello et al., 2006, 2008; Fecteau et al., 2008) the present findings further indicate that the mere observation of strong 'flesh and bone' painful events elicits pain-related inhibitory activity in the observers' corticospinal motor system. Observing painful stimulations delivered to the body of a stranger selectively reduced the excitability of the corticospinal representation of the muscle vicariously involved in the noxious stimulation. Moreover, this inhibition was strongly correlated to the intensity but not the unpleasantness of the pain ascribed to the observed individual, suggesting that this inhibitory response may reflect the simulation of sensory but not affective qualities of others' pain (Avenanti et al., 2005, 2006; Minio-Paluello et al., 2006, in press).

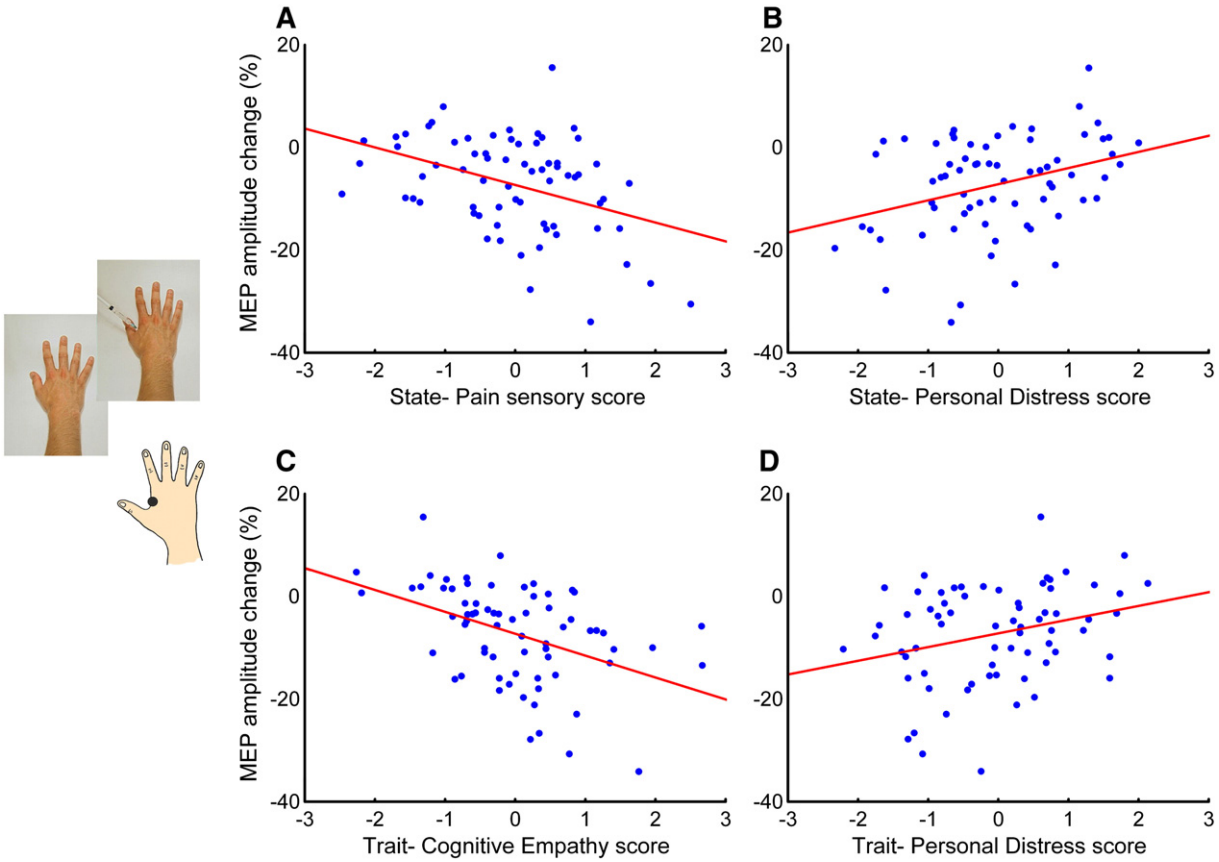

Fig. 4. Linear relations between MEP amplitude change [(pain−static/pain+static)] and empathy measures. (A) State-Pain sensory: $r=-0.40$, $P=0.0007$; (B) State-Personal distress: $r=0.34$, $P=0.005$; (C) Trait-Cognitive empathy: $r=-0.43$, $P=0.0002$; (D) Trait-Personal distress: $r=0.28$, $P=0.019$.

The most novel finding of our study is the demonstration that both trait- and state-empathy-related dimensions are closely associated with the amount of inhibitory corticospinal response to others' pain. Indeed, the somatomotor response was higher in subjects with high trait-cognitive empathy and lower in subjects with high state- and trait-personal distress. Importantly all these subjective measures independently predicted the somatomotor response, suggesting that separate mechanisms may influence the sensorimotor activity during empathy for pain.

Inhibition of corticospinal representations during pain observation

In the present study we confirm the basic features of the motor inhibition linked to the observation of others' pain reported in previous research (Avenanti et al., 2005, 2006; Minio-Paluello et al., 2006, in press; Fecteau et al., 2008). Watching needles deeply entering the FDI region of a model's hand brought about a suppression of MEPs recorded from the FDI muscle of the observer, without inhibiting the ADM control muscle which has a contiguous motor representation (Krings et al., 1998). It is worth noting that a similar inhibition of motor representations has also been reported during the direct experience of pain (Farina et al., 2003; Svensson et al., 2003; Urban et al., 2004). This suggests that the inhibition of corticospinal excitability during pain observation may reflect a 'resonant' activation of pain mechanisms in the observer, an effect which is reminiscent of the activation called into play when sharing motor (Rizzolatti and Craighero, 2004), emotional (Wicker et al., 2003) and somatic representations (Keysers et al., 2004; Blakemore et al., 2005; Bufalari et al., 2007; Moriguchi et al., 2007; Benuzzi et al., 2008).

Current knowledge strongly suggests that the somatotopic inhibition of corticospinal representations during the direct observation of others' pain reflects the activity of a *mirror-like* 'resonance' mechanism that extracts basic *sensory* qualities of another person's painful experience (location, diffusion and intensity of the noxious stimulus) and maps them onto the observers' corticospinal system according to somatotopical rules (Avenanti et al., 2005; Minio-Paluello et al., 2006, 2008). This hypothesis is supported by the inhibitory sign of the effect (others' pain is encoded as real pain), by the muscle specificity (others' pain is encoded in terms of its location) and by the correlation between MEP inhibition and sensory (but not affective) qualities of the pain attributed to the model (others' pain is encoded in terms of its intensity, not unpleasantness).

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

The notion of a fine-grained simulation of sensory qualities of others' experience is in line with the recent evidence of parietal somatic and multisensory activations during the observation of painful (Jackson et al., 2006; Bufalari et al., 2007; Moriguchi et al., 2007; Saarela et al., 2007; Cheng et al., 2007; Lamm et al., 2007b; Benuzzi et al., 2008; Valeriani et al., 2008) and non-painful tactile

experiences (Keyser et al., 2004; Blakemore et al., 2005; Bufalari et al., 2007). For example, observing painful stimuli delivered to the hand modulated a positive short-latency component (P45) of SEPs induced by median nerve stimulation, whose origin is ascribed to primary somatosensory cortex (Bufalari et al., 2007); in a similar vein, observing pain on the hand selectively modulated the amplitude of the N1/P1 component (originating from the secondary somatosensory cortex) of LEPs induced by painful stimulations of the hand (Valeriani et al., 2008). Importantly, in both studies observational pain-related modulation of P45 and N1/P1 components were strictly correlated with evaluations of sensory but not affective components of pain (Bufalari et al., 2007; Valeriani et al., 2008), indicating an important role of the somatosensory cortices not only in analyzing the intensity of one's own pain experience (Peyron et al., 2000; Rainville, 2002) but also in extracting sensory qualities of others' pain from social interaction. In keeping, neuroimaging and MEG studies indicate that a complex network including somatic, insular and inferior parietal cortices may participate in this process (Jackson et al., 2006; Saarela et al., 2007; Lamm et al., 2007b; Cheng et al., 2007, 2008a; Benuzzi et al., 2008). Further studies combining repetitive TMS (to perturb and disrupt the activity of a cortical area) and single-pulse TMS paradigms (to probe corticospinal excitability) (Avenanti et al., 2007) may test the crucial role of these structures in the modulation of MEPs during pain observation.

In the present study, needle-in-hand stimuli were contrasted with static hands. In principle, using this low level control for pain may be considered a potential limitation of the present study. However, it should be noted that MEPs recorded from hand muscles are comparable during the observation of static hand stimuli and during the observation of several higher-level control conditions including Q-tips touching the hand or the foot, and needles entering other body parts or non corporeal objects (Avenanti et al., 2005, 2006; Fecteau et al., 2008). While all the above mentioned categories of stimuli can be considered equivalent to static hand stimuli in terms of MEP modulation, the inclusion of static hand stimuli may allow a better comparison with previous studies (Avenanti et al., 2005, 2006; Fecteau et al., 2008) in which correlations were computed by considering the conditions used in this study (pain on hand, static hand).

Multiple mechanisms affecting somatomotor response to others' pain

As in the personal experience of pain (Coghill et al., 2003), humans show a large inter-individual variability in the reaction to others' pain (Williams, 2002; Boothby et al., 2004; Singer et al., 2004; Saarela et al., 2007). In the present study we have dealt with this variability by showing how specific aspects of the subjective experiences of others' pain and specific personality traits can modulate somatomotor mapping of others' pain.

In addition to the pain sensory qualities attributed to the model's, the inhibition of MEPs contingent upon the observation of others' pain was *independently* predicted by (i) participants' ability to adopt the psychological perspective of others and tendency to imaginatively transpose themselves into fictional situations (dispositional cognitive empathy); and by (ii) situational and (iii) stable tendencies to experience personal distress. While the relation between pain intensity and MEP modulation is in keeping with the view that the corticospinal system is involved in the internal simulation of basic sensory features of others' pain, the pattern of relations between somatomotor mapping and other empathy measures suggests that distinct – non purely 'sensory' – functional mechanisms may modulate the somatomotor mapping of others' pain.

A first important factor that seems to favor the corticospinal mapping of others' pain is trait-cognitive empathy: in our study the strongest mirror inhibitory responses to others' pain were found in the subjects with high scores on both IRI PT and FS. Cognitive empathy as measured by the two cognitive subscales of the IRI has been characterized as the ability to adopt the point of view of others and identify with them, in both real and fictional situations (such as during the observation of a movie) (Davis, 1996). Considered in these terms, cognitive empathy seems closely linked to a concept of simulation that goes beyond the notion of mirroring and that have been metaphorically described as the (effortful) process of imaginary putting in others' mental shoes (Goldman and Sebanz, 2005; Goldman, 2006).

Our data may indicate that high-empathic subjects, who are prone to imaginatively transpose into others' feelings and inner states, tend to be more profoundly engaged in the painful scenario compared to low-empathic subjects. Higher levels of the cognitive disposition to simulate others' mental states may strengthen the simulative somatomotor response to others' pain. This suggests that cognitive empathy exerts a top-down influence on the somatomotor mapping of others' pain further and independently from the supposedly more-basic intensity-related mechanisms (Avenanti et al., 2005).

The present findings may seem at odds with a previous report of no difference in MEP inhibition in three small groups of subjects (N=9) who were either asked to passively observe the stimuli or to adopt first- or third-person perspective (Avenanti et al., 2006). Our current results suggest that during pain observation, inter-individual differences in cognitive empathy modulate the corticospinal system much more than the explicit instruction to take the perspective of others. Further studies on large samples where inter-individual differences in cognitive empathy are controlled, will allow to investigate the role of active perspective taking during pain observation.

The important role exerted by cognitive empathy inter-individual differences on the somatomotor response to others' pain has been evidenced by a MEG study in which observing pain brought about a suppression of somatosensory oscillations (an index of activation of the somatic cortex) that correlated with the ability to take another person's perspective (Cheng et al., 2008a). The link between somatomotor responses to others' pain and cognitive empathy is also in line with a recent TMS study reporting lack of empathic corticospinal mapping of others' pain in individuals with Asperger syndrome (Minio-Paluello et al., in press). All these evidences support the notion that cognitive empathy may shape sensorimotor mirroring phenomena (Gazzola et al., 2006; Keysers and Gazzola, 2006). Social psychology studies indicate that subjects with high cognitive empathy show high levels of automatic mimicry of postures, mannerism and facial expression during interpersonal communications (Chartrand and Bargh, 1999). Moreover, in a recent fMRI study, Gazzola et al. (2006) showed that hearing the typical sound of actions brought about the resonant activation of sensorimotor systems involved in the action execution; importantly, mirror activity in premotor and somatosensory areas was strongly related to the participants' perspective taking abilities, suggesting a link between cognitive empathy and sensorimotor mirror activity.

These findings parallel and complement the results of recent fMRI studies on emotional aspects of empathy for pain in which imagination or observation of others' pain activated the pain matrix and neural activity in its affective division (including ACC and AI) correlated with emotional empathy-related traits (empathic concern, personal distress, and emotional contagion) (Singer et al., 2004; Saarela et al., 2007; Lamm et al., 2007a). Taken together, these studies hint at the differential contribution of cognitive and emotional empathy-related reactivity in modulating the resonant activation of the pain matrix sensorimotor and affective nodes respectively.

Personal distress may reduce somatomotor response to others' pain

Two additional independent mechanisms affecting somatomotor response to others' pain are linked to situational self-oriented emotional reactions induced by pain observation ('State-Personal distress') and to the stable tendency to experience personal distress as a consequence of perceiving distress in others ('Trait-Personal distress'). We find

important that while higher levels of both state-pain sensory and trait-cognitive empathy scores were associated to greater somatomotor response to others' pain, state- or trait-measures of personal distress showed an opposite relation with such somatomotor response. Thus, situational or stable tendencies to experience negative emotional reactions to others' distress seem to be linked to a facilitation of the corticospinal system rather than to inhibition. In keeping, recent TMS evidence shows that corticospinal excitability is increased during the observation of emotional stimuli (Hajcak et al., 2007). This corticospinal facilitation is likely to be mediated by a neural circuit that encompasses the ACC, amygdala and supplementary motor area (SMA) and that is involved in emotional processing in both human and nonhuman primates (Morecraft and Van Hoesen, 1992; Luppino et al., 1993; Devinsky et al., 1995). Emotional stimuli may trigger activity in motor areas (Bremner et al., 1999) and there is direct evidence for a crucial role of SMA in mediating corticospinal facilitation contingent upon observation of emotionally unpleasant visual stimuli (Oliveri et al., 2003). Importantly, subjective feelings of aversion, anxiety and personal distress have been found to correlate with activity in limbic areas during physical pain and social pain (the experience of being rejected) as well as during observation of highly unpleasant visual stimuli (Rainville, 2002; Eisenberger et al., 2003; Straube et al., 2007). Our study adds to previous knowledge by showing that self-oriented negative feelings induced by observing others' pain are linked to corticospinal modulation.

The link between dispositional measures of personal distress and the tendency toward motor facilitation found in our study is in line with a recent EEG study in which the suppression of mu rhythm (an index of motor cortex facilitation) induced by observing others' actions positively correlated with participants' trait-personal distress (Cheng et al., 2008b). The relation between trait-personal distress and motor facilitation may be linked to the evidence of a relation between anxiety-related personality traits and the excitability of intracortical facilitatory mechanisms in the primary motor cortex (Wassermann et al., 2001).

In light of neuroimaging studies on empathy for pain, it is possible that the link between corticospinal facilitation and trait-personal distress may be mediated by the activity in the insula and the inferior frontal gyrus (Saarela et al., 2007; Moriguchi et al., 2007). Further studies combining TMS and neuroimaging will directly investigate the role of different brain circuits in mediating the relation between state- and trait-measures of personal distress and corticospinal modulation contingent upon watching others' pain. Whatever the precise circuits involved in such corticospinal modulation may be, our study clearly demonstrates that personal distress may reduce or even prevent somatomotor mapping of others' pain.

Taken together all these findings provide a neural basis to psychological theories of empathy positing that personal distress may reduce empathy-related responding e.g. emotional concern and helping behavior (Batson, 1991; Davis, 1996; Eisenberg, 2000). Based on the present data, it could be suggested that reduced empathy responses due to extreme personal distress may be functionally linked to a reduced *mirror-matching* with others' mental states.

Conclusion

All in all, in keeping with current neuroscientific models of empathy (Preston and de Waal, 2002; Decety and Jackson, 2004; Gallese, 2006; Keysers and Gazzola, 2006; Avenanti and Aglioti, 2006) the present study shows that the direct observation of 'flesh and bone' stimuli purportedly able to induce pain in a model elicits pain-related activity into the observers' nervous system. The present findings further highlight the role of the corticospinal system in the empathic mapping of specific sensory aspects of others' painful experiences (locus, intensity) (Avenanti et al., 2005; Minio-Paluello et al., 2006). An entirely novel result of the present study is that observers' cognitive empathy traits, likely reflecting their tendency to mentally simulate others' experiences, may increase empathic sensorimotor mapping. By contrast, state or trait emotional *self-oriented* personal distress tends to reduce sensorimotor response to others' pain. These findings may add to a recent empathy for pain TMS study in which the corticospinal inhibition contingent upon the observation of others' pain was greater in those (healthy) subjects who scored high on a scale of psychopathology (Fecteau et al., 2008). Clinical studies indicate that psychopaths show cognitive empathy and mentalizing abilities in the normal range (if not higher) but they lack emotional reactivity and sympathy responses (Blair, 2005). It is thus likely that individuals with relatively high scores on psychopathology questionnaires may have reduced emotional reactions (including personal distress) to the observation of others in pain (Herpertz et al., 2005). Our result that low personal distress in response to the observation of others' pain is linked to higher corticospinal inhibition is in keeping with (and may help to interpret) the result that individuals with psychopathic traits show higher corticospinal inhibition (Fecteau et al., 2008).

Empathy for pain may take different forms in different sensorimotor and emotional nodes of the pain neural network (Singer et al., 2004; Morrison et al., 2004; Avenanti et al., 2005; Jackson et al., 2006; Minio-Paluello et al., 2006, 2008; Bufalari et al., 2007; Lamm et al., 2007a,b; Cheng et al., 2007; Valeriani et al., 2008). Our study sheds further light on the nature of the somatomotor mapping of others' pain that occurs during the direct observation of strong 'flesh and bone' painful stimuli delivered to the body of others (Avenanti et al., 2005, 2006; Minio-Paluello et al., 2006, in press; Fecteau et al., 2008). This mapping appears to be strengthened by state-sensory and trait-cognitive empathy dimensions and reduced by state- and trait-*self-oriented* emotional reactions. Whether these different psychological dimensions are represented in different sensorimotor and affective nodes of the pain neural network recruited during empathy for pain, remains to be investigated.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.neuroimage.2008.08.001.

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