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Seeing the pain of others while being in pain: A laser-evoked potentials study

Massimiliano Valeriani,[a] Viviana Betti,[b,c,*] Domenica Le Pera,[d] Liala De Armas,[d] Roberto Miliucci,[a] Domenico Restuccia,[e] Alessio Avenanti,[b,f] and Salvatore Maria Aglioti[b,f,*]

[a] *Division of Neurology, IRCCS Bambino Gesù, Paediatric Hospital, Piazza Sant' Onofrio 4, I-00165 Rome, Italy*
[b] *Department of Psychology, University of Rome 'La Sapienza', Via dei Marsi 78, I-00185 Rome, Italy*
[c] *AFaR, Fatebenefratelli Hospital, Isola Tiberina, Rome, Italy*
[d] *Motor Rehabilitation, IRCCS San Raffaele Pisana, Rome, Italy*
[e] *Department of Neurology, Università Cattolica del Sacro Cuore, L.go A.Gemelli 8, I-00168 Rome, Italy*
[f] *Centro Ricerche Neuropsicologia, IRCCS Fondazione Santa Lucia, Via Ardeatina 306, I-00179 Rome, Italy*

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Seeing actions, emotions and feelings of other individuals may activate resonant mechanisms that allow the empathic understanding of others' states. Being crucial for implementing pro-social behaviors, empathy is considered as inherently altruistic. Here we explored whether the personal experience of pain make individuals less inclined to share others' pain. We used laser-evoked potentials (LEPs) to explore whether observation of painful or non-noxious stimuli delivered to a stranger model induced any modulation in the pain system of onlookers who were suffering from pain induced by the laser stimuli. After LEPs recording, participants rated intensity and unpleasantness of the laser pain, and of the pain induced by the movie in themselves and in the model. Mere observation of needles penetrating the model's hand brought about a specific reduction of the N1/P1 LEP component, related to the activation of somatic nodes of the pain matrix. Such reduction is stronger in onlookers who rated the pain intensity induced by the pain movie as higher in themselves and lower in the model. Conversely, the N2a-P2 component, supposedly associated to affective pain qualities, did not show any specific modulation during observation of others' pain. Thus, viewing 'flesh and bone' pain in others specifically modulates neural activity in the pain matrix sensory node. Moreover, this socially-derived inhibitory effect is correlated with the intensity of the pain attributed to self rather than to others suggesting that being in pain may bias the empathic relation with stranger models towards self-centred instead than other-related stances.

Introduction

Empathy refers to the ability to understand the subjective experience of other individuals by vicariously sharing their desires, beliefs, emotions and feelings. The intrinsically altruistic nature of empathy is suggested by social psychology studies indicating that empathic individuals tend to help people in need even when lending a hand implies specific risks of psychological distress or physical danger (Batson, 1991). However, higher order emotional variables, such us for example the type of social bond between individuals, may modulate empathic behavioral and neural reactions in less altruistic directions. Relevant to this issue is an fMRI study demonstrating that empathic responses to the pain of others' are dramatically lower for unfair than fair individuals (Singer et al., 2006). Learning about the conditions that allow humans to empathize with others may help understand social and clinical conditions characterized by a lack or an excess of empathy. For example, it has been suggested that pain-induced distress may be prohibitive of empathy (Preston and de Waal, 2002); yet, it is still largely unknown whether and at which neural level suffering from physical pain modulates the way we perceive and understand others' pain.

Recent fMRI (Morrison et al., 2004; Singer et al., 2004; Botvinick et al., 2005; Jackson et al., 2005, 2006; Saarela et al., 2007) and neurophysiological studies (Avenanti et al., 2005, 2006; Bufalari et al., 2007) explored the mechanisms and the neural underpinnings of empathy for pain in humans. Most of the above fMRI studies reported changes in the neural activity of the anterior cingulate cortex (ACC) and the anterior insula (AI) when subjects observed pictures of painful stimuli delivered to other individuals (Morrison et al., 2004, 2007; Jackson et al., 2005, 2006) or imagined their partners feeling pain (Singer et al., 2004). Thus,

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* Corresponding authors. Department of Psychology, University of Rome "La Sapienza", Via dei Marsi 78, 00185 Rome, Italy. Fax: +39 06 4991 7635.

E-mail addresses: salvatoremaria.aglioti@uniroma1.it (S.M. Aglioti), viviana.betti@afar.it (V. Betti).

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most of the fMRI studies converge to indicate that mainly the affective nodes of the pain matrix are called into play during empathy for pain. However, single pulse Transcranial Magnetic Stimulation (TMS) (Avenanti et al., 2005, 2006) and Somatosensory Evoked Potentials (SEPs) (Bufalari et al., 2007) studies found that the neurophysiological modulations contingent upon observation of "flesh and bone" painful stimuli delivered to a stranger model triggers an automatic mapping of the noxious stimulus onto the observer's body, a phenomenon we called sensorimotor contagion. Interestingly, this effect was correlated with the observer's subjective empathetic rating of the sensory qualities of the pain supposedly felt by the model but not with self-centered state-or trait-empathy measures.

Here we sought to add a new dimension to current knowledge by exploring whether an observer suffering from physical pain is still prone to the basic form of empathy for the pain of strangers called sensorimotor contagion. To this aim, we used the emergent, high-temporal resolution, neurophysiological technique of CO_2 laser-evoked potentials (LEPs), which offers the unique opportunity to induce acute pain on the body part stimulated by the laser beam and at the same time to explore non-invasively and specifically neural activity in sensory (secondary somatosensory area, SII) and emotional (cingulate cortex) nodes of the pain matrix (Bromm and Lorenz, 1998).

Materials and methods

Subjects

Twelve right-handed, healthy subjects (5 women), mean age (±SD) = 25.75 (±5.53) years, range 22–41, participated in the study. Participants gave their written informed consent and were naive as to the purposes of the experiment. The procedures were approved by the local ethics committee and were in accordance with the standards of the 1964 Declaration of Helsinki.

LEP recording

Cortical potentials were evoked by means of a CO_2 laser stimulation device (El.En., Florence, Italy). 32 recording electrodes were used. 31 electrodes were placed according to the positions of the 10-20 International System (excluding Fpz and Oz); the remaining electrode was placed above the right eyebrow for electro-oculogram (EOG) recording. The reference was at the nose, and the ground at Fpz. Electrode impedance were kept below 5 KΩ. The electroencephalographic (EEG) signal was amplified and filtered (bandpass 0.3–70 Hz). For each laser stimulation trial the time analysis lasted 1000 ms, with a bin width of 2 ms (500 Hz sampling rate). An automatic artifact rejection algorithm excluded from the average all runs containing transients exceeding ±65 μV at any recording channel, including the EOG. LEPs were acquired, processed and analyzed by MYOQUICK System Plus (Micromed, Treviso, Italy). Microneurographic studies demonstrated that CO_2 laser pulses delivered on hairy skin specifically activate thin nociceptive Aδ and C fibers, without any concurrent stimulation of non-nociceptive Aβ afferents (Bromm and Treede, 1984). In our study, LEP components evoked by CO_2 laser stimulation showed latencies consistent with activation of Aδ fibers (Bromm and Lorenz, 1998). LEP components were identified on the basis of their latency and polarity and they were labeled according to Valeriani et al. (1996). Two main components were recorded: (i) middle-latency (about 160 ms after hand stimulation) responses recorded over the temporal electrode (T3, Jasper, 1958) following right hand laser stimulation) controlateral to the stimulation side (N1) and over the frontal electrode Fz (P1). To identify the N1 component and dissociate it from the partially overlapping N2 component, we used a frontal median reference electrode (Fz). N1/P1 amplitude was measured with respect to the isoelectric line after referring the T3 to Fz electrode (Kunde and Treede, 1993). Note that the N1/P1 complex originates from SII (Garcia-Larrea et al., 2003); (ii) long-latency responses (about 200–350 ms following laser hand stimulation) consisting of a large biphasic N2a-P2 complex, recorded over Fz, Cz, Pz, C3, C4 electrodes. This complex has maximal distribution over the vertex region (Cz electrode) and is thought to originate from the ACC (Garcia-Larrea et al., 2003). Peak-to-peak amplitudes of the N2a-P2 complex were computed. Grand averages of LEP components were obtained for each observational condition. Finally, to analyze LEP distribution, color maps calculated by spline interpolation (Perrin et al., 1987) were used.

Visual stimuli

In different experimental blocks, different types of video clips were presented on a 17-in. screen located 80 cm from the subjects. Each subject was tested in six observational blocks. In the first and the sixth block the dorsal view of a still right hand was shown (Static Hand). In the remaining four observational blocks the following types of video clips were presented in a counterbalanced order: (1) a needle penetrating the dorsum of a hand depicted from a first person perspective ("Needle in Hand"); (2) a Q-tip gently touching the same hand ("Q-tip on Hand"); (3) a needle penetrating the dorsum of a foot depicted from a first person perspective ("Needle in Foot"); (4) a tomato penetrated by a needle ("Needle in Tomato"). Only right body parts were presented in the videos so as to achieve complete congruency between the onlookers' laser stimulated hand and the body part penetrated or touched in the model. To minimize habituation effects, different videos, with one out of three possible sites of stimulation, and one out of three possible sizes or colours of the syringe or Q-tip were randomly presented in each block. In order to avoid activation of the motor mirror system due to the observation of an action (Rizzolatti et al., 2001) which may also modulate the activity of somatosensory cortices (Avikainen et al., 2002), in none of the videos was the holder of the syringe or the Q-Tip visible.

Experimental procedure

During LEP recording the subjects were seated in a comfortable armchair and were asked to stay awake and relax their muscles. Laser pulses were delivered to the dorsum of the right hand in blocks of 27 stimuli. The locus of laser hand stimulation was changed on each trial. To avoid nociceptor fatigue or sensitization the location of the laser on the skin was slightly shifted after each stimulus. An area of about 9 cm^2 on the radial side of the hand dorsum was stimulated. Moreover, 9–11 s interstimulus intervals allowed us to minimize central habituation effects. The distance between the laser stimulator and the hand was kept constant. The laser pulses used in the study (coaxial He-Ne beams, 10.6 μm wavelength, 2 mm diameter, 10 ms pulse duration, 18 mJ/mm^2) were perceived as painful pinpricks by all subjects.

The interval between each dynamic observation block was 2 min. The interval between the first and the second and between the next to last and the last block was 10 min. Each video-clip lasted 7 s. Laser stimuli were delivered from 3 to 4 s after the beginning of each video. On each trial, the subjects were asked to watch carefully and pay attention to the events in the video clips. Moreover, subjects were asked to imagine that the observed body parts belonged to them.

Subjective reports

Effects of laser stimuli

Immediately after each block the subjects rated the intensity and unpleasantness of the laser pain using 100-points visual analogue scales (VAS) in which 0 indicates no pain (intensity or unpleasantness) and 100 the maximum pain that can be imagined.

Measures of state- and trait- empathy

At the end of each block, after the evaluation of laser stimuli, four *state-empathy measures* were obtained by asking subjects to evaluate along a VAS: i) the intensity of the pain felt by themselves during observation of the experimental stimuli (sensory, self-referred); ii) the unpleasantness of the pain felt by themselves during observation of the experimental stimuli (emotional, self-referred); iii) the intensity of the pain sensation supposedly felt by the model when penetrated or touched (sensory, other-referred); iv) the unpleasantness of the pain sensation felt by the model when penetrated or touched (emotional, other-referred). Four independent ratings were obtained. The order of the four ratings was randomized to avoid any influence of non specific variables (e.g. memory recall effects). While other-referred measures iii) and iv) express the empathic inference about the qualities of the pain ascribed to the observed model, self-referred measures i) and ii) express the qualities of the pain mentally simulated and felt by the onlooker, and thus refer to the process of coding others' pain in a more self-centred perspective.

Trait-empathy measures were obtained at the end of the experiment by asking subjects to complete the Italian version (Bonino et al., 1998) of the Interpersonal Reactivity Index (IRI) (Davis, 1983, 1996). This 28-item self-report survey consists of four subscales, namely, Empathic Concern (EC, which assesses the tendency to experience feelings of sympathy and compassion for

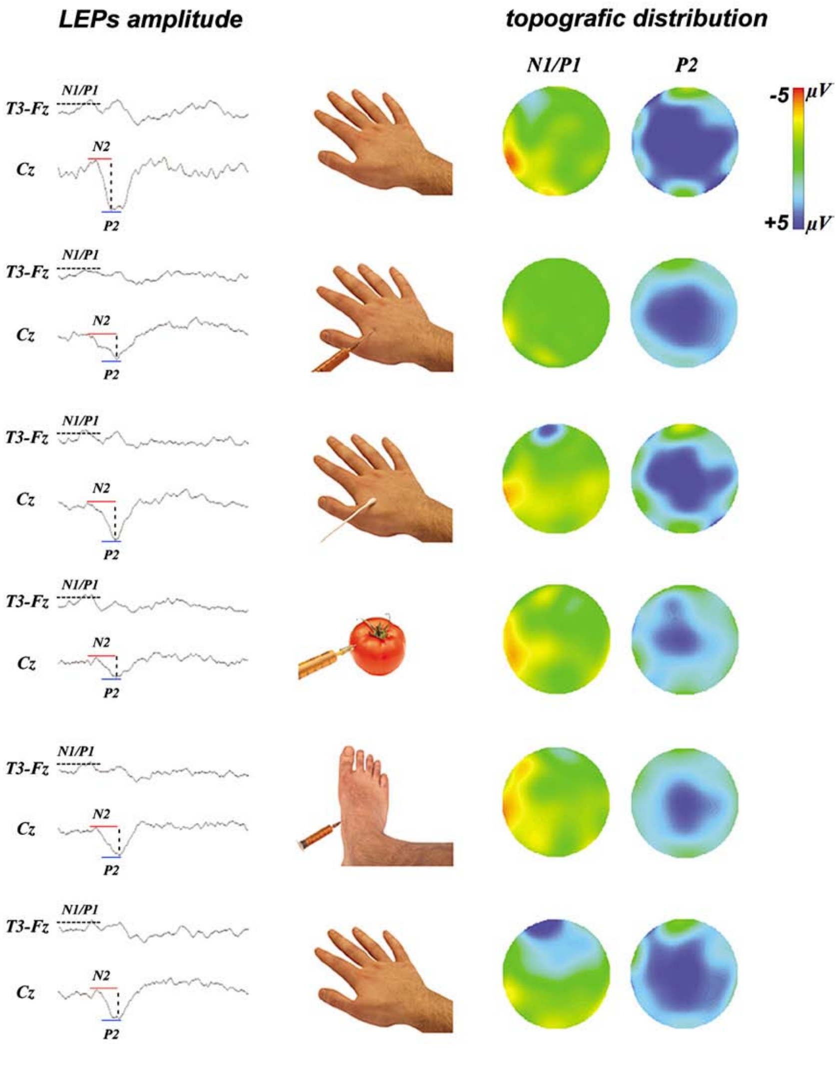

Fig. 1. Electrophysiological data. Grand-averages (left part) of the N1/P1 (recorded at contralateral temporal electrode referred to the central frontal electrode, T3-Fz) and N2a-P2 (recorded at the vertex electrode, Cz) in the different observational conditions (central part). Spherical spline interpolation maps (right part) show the distribution of the two LEP components. The positive component of the N2a-P2 complex (P2) is reported. The "first Static Hand" observational condition (used as baseline for normalizing LEP amplitudes) is reported at the top.

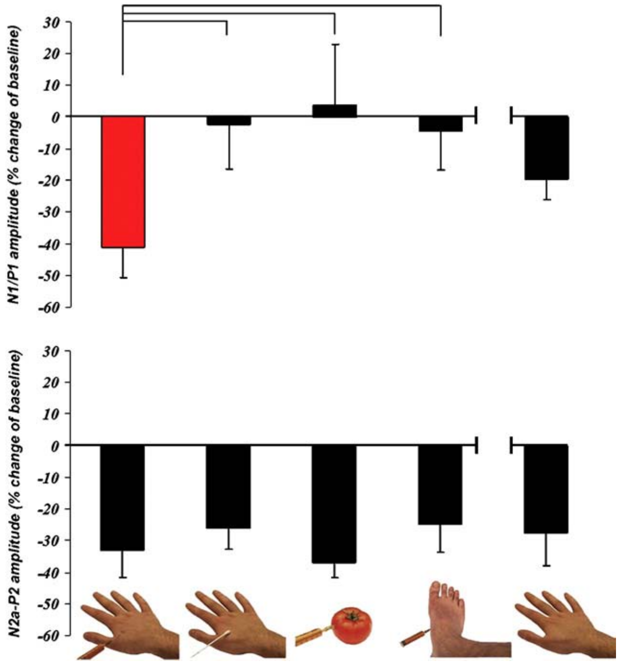

Fig. 2. N1/P1 and N2a-P2 LEPs components. Normalized amplitude of N1/P1 (top row) and N2a-P2 (bottom row) LEP components induced by right hand laser stimulation. Columns refer to the four dynamic observation conditions. The x-axis interruption emphasizes that the “last Static Hand” observation block (fifth column) is considered a control condition of the habituation effects of the laser *per se*. The icons refer to the movie presented in the relative observational condition.

others in need), Personal Distress (PD, which assesses the extent to which an individual feels distress as a result of witnessing another’s emotional distress), Perspective taking (PT, which assesses the disposition tendency of an individual to adopt another’s perspective) and Fantasy scale (FS, which assesses an individual’s propensity to become imaginatively involved with fictional characters and situations) (Davis, 1983, 1996). Current social psychology interpretations of the different subscales posit that the first two refer to the affective components of empathy and the last two to the cognitive components. High scores on the IRI indicate high capability of empathizing (for EC, PT e FS) and feeling distress in interpersonal situations (for PD).

Statistical analysis

Electrophysiological data

The raw N1/P1 and N2a-P2 were clearly recognizable in each subject and in each observation block. Because of the inter-individual variability in raw LEPs amplitudes we expressed N1/P1 and N2a-P2 components for each observational block (“Needle in Hand”; “Q-tip on Hand”; “Needle in Tomato”; “Needle in Foot”; “Static Hand, last block”) as percentage of the “first Static Hand” observation block. Normalized LEPs amplitudes were used for the statistical analysis. Furthermore, normalized values in each dynamic observational condition and in the last static hand observation block were compared against the first static hand by means of one sample *t*-tests.

N1/P1 normalized LEP amplitudes were analyzed by means of repeated measure one-way ANOVA with Condition as the main factor with five levels. Since N2a-P2 components are recorded on several electrodes we first carried out a 5 X 5 two-way ANOVA with Electrode and Condition as main factors. The five levels of the Electrode factor were: Fz, Cz, Pz, C3, C4. Normalized amplitudes of N2a-P2 component recorded from the most representative electrode, namely Cz, were also analyzed by means of a repeated-measure one-way ANOVA with Condition as main factor. Finally, normalized LEP amplitudes in each dynamic observational condition and in the “last Static Hand” observation block were compared against the value of 100 (baseline) by means of one sample *t*-tests.

Raw N1/P1 latencies were analyzed by means of two repeated-measure one-way ANOVAs with Condition (six levels: “first Static Hand”; “Needle in Hand”; “Q-tip on Hand”; “Needle in Tomato”; “Needle in Foot”; “Static Hand last block”) as main factor. Raw N2a and P2 latencies were analyzed by means of two ANOVAs with Condition (six levels) and Electrode (Fz, Cz, Pz, C3, C4) as main factors. For both amplitude and latency *post-hoc* analysis was carried out by using the Newman–Keuls test.

Subjective measures

VAS ratings for pain intensity and unpleasantness induced by the laser stimuli were analyzed using two repeated-measure one-way ANOVAs with the observation Condition as main factor. VAS scores concerning self or other-referred intensity and unpleasantness of the pain induced by observation of the different types of video-clips were analyzed by means of repeated measure one-way ANOVAs with the observation Condition as main factor. *Post-hoc* analysis was carried out by means of the Newman–Keuls test. Laser pain scores and self and other-referred pain qualities derived from observation of “Needle in Hand” and “Needle in Foot” movies were compared by means of Bonferroni corrected, paired *t*-tests.

Correlation analysis

To assess whether the pain-related modulation of N1/P1 and N2a-P2 was linked to the resonant mapping of sensory or affective qualities of the pain felt by the onlooker or ascribed to the model, we performed a series of correlation analyses between normalized N1/P1 and N2a-P2 amplitudes in the different observation conditions and *state*- and *trait-empathy* scores and laser-pain scores. To explore whether subjects who rated their pain as most intense (or most unpleasant) and the models’ pain as less intense (or less unpleasant) we combined self (s) and other (o) ratings, according to the following formula: $(s-o/s+o)$. The resulting index referring to intensity (or unpleasantness) ratings was used for correlation with the LEPs component amplitude changes. Pearson coefficients were computed. Correlations between subjective scores concerning the

Table 1
Effects of laser stimuli

	Static Hand (first)	Needle in Hand	Q-tip on Hand	Needle in Tomato	Needle in Foot	Static Hand (last)
Intensity	41.0 (18.6)	41.4 (22)	39.4 (19.6)	36.4 (18.7)	43.3 (24.4)	41.7 (23.6)
Unpleasantness	39.3 (20.9)	43.2 (24.5)	38.4 (21.1)	38.7 (20.5)	41.5 (22.8)	42.3 (25.2)

Mean (±SD) subjective ratings of intensity and unpleasantness of the pain induced by laser pulses in the different observation conditions.

Table 2
Measures of state-empathy

	Self-referred			Other-referred		
	Needle in Hand	Needle in Tomato	Needle in Foot	Needle in Hand	Needle in Tomato	Needle in Foot
Intensity	27.0 (21.4)	4.3 (8.9)	26.0 (19.1)	75.0 (21.9)	0 (0)	75.4 (19.4)
Unpleasantness	25.9 (22.2)	1.8 (5.7)	24.8 (19.1)	75.3 (29.2)	0 (0)	76.8 (29.8)

Mean (±SD) subjective ratings of intensity and unpleasantness of the pain derived from observation of needle movies, attributed to self (self-referred) or attributed to the model (other-referred) in the different observation conditions.

laser-induced and the movie-derived, self- or other-referred sensations were also carried out.

Results

Electrophysiological data

Inspection of Fig. 1 shows that the amplitude of the N1/P1 component evoked by laser stimuli delivered to the observer's right hand is specifically reduced during viewing of needles penetrating the model's right hand. Amplitude modulations of the N2a-P2 component are also visible during pain observation. However, these modulations seem comparable in the different observational conditions.

The ANOVA performed on normalized N1/P1 amplitudes showed a significant main effect of Condition ($F(4,44)=3.14$, $p=0.023$), which is entirely accounted for by the lower amplitude in the "Needle in Hand" condition with respect to "Q-tip on Hand" ($p=0.047$), "Needle in Tomato" ($p=0.026$) and "Needle in Foot" ($p=0.037$) conditions. The insignificance ($p=0.143$) of the comparison between "Needle in Hand" and the second "Static Hand" observation block (which was carried out as the last block in all subjects), is likely attributable to the cumulative habituation effect of several laser stimuli (Valeriani et al., 2003a). One sample t-tests analysis showed that N1/P1 amplitudes in the first "Static hand" observation block (baseline) were higher than in the "Needle in Hand" ($p=0.003$) and the second "Static Hand" observation block ($p=0.007$). Again, this last effect likely reflects habituation to the laser stimulation *per se* (see Fig. 2 top row).

ANOVA performed on N2a-P2 component did not show any significance of Condition ($F(4,44)=1.26$, $p=0.30$) or Electrode

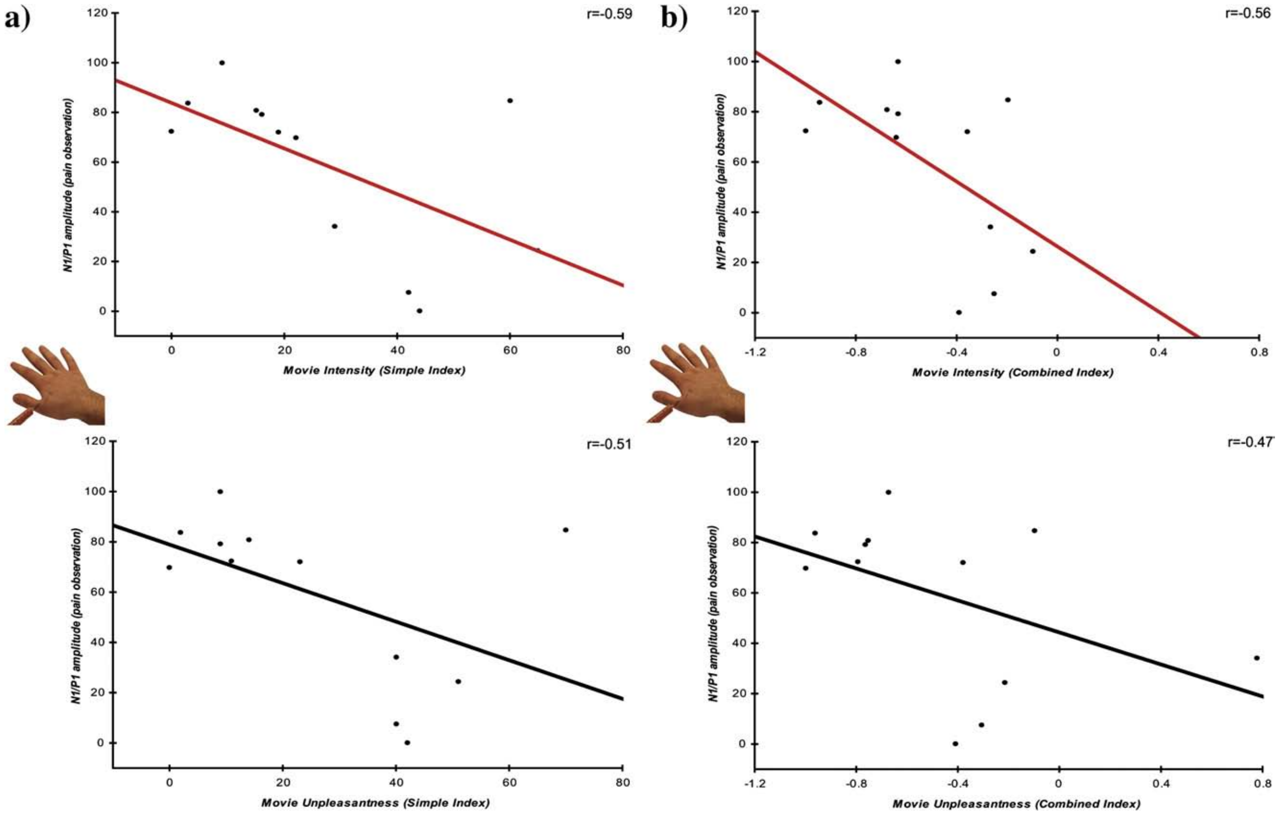

Fig. 3. Correlation analyses. Part a) shows scatter plots of normalized N1/P1 amplitude and VAS subjective ratings of Intensity (upper part) and Unpleasantness (lower part) of the pain derived from observation of needle in hand videos and referred to the self. The N1/P1 suppression was maximal in subjects who rated as most intense their pain related to needle in hand movie. Part b) shows scatter plots of normalized N1/P1 amplitude and an index that combines subjective ratings of pain intensity (upper part) and unpleasantness (lower part) derived from observation of needle in hand videos and referred to self (s) or to others (o) ($s-o/s+o$). Red lines indicate significant correlations (self referred index $p=0.04$; combined self and other referred index, $p=0.056$). Importantly, the suppression of N1/P1 amplitude resulted maximal in the subjects who rated as most intense their pain and less intense the pain of the model.

Table 3
Correlation analysis between the N1/P1 and state-empathy measures

	Needle in Hand	Q-tip on Hand	Needle in Tomato	Needle in Foot
Self-referred				
Intensity	**−0.59 ($p=0.04$)**	− (−)	−0.15 ($p=0.64$)	−0.19 ($p=0.54$)
Unpleasantness	−0.51 ($p=0.09$)	− (−)	−0.15 ($p=0.63$)	−0.12 ($p=0.72$)
Other-referred				
Intensity	−0.16 ($p=0.62$)	− (−)	− (−)	0.27 ($p=0.39$)
Unpleasantness	0.04 ($p=0.90$)	− (−)	− (−)	0.37 ($p=0.24$)

Correlation between the N1/P1 LEP component and subjective scores concerning the movie-derived, self- or other-referred pain qualities. Significant r and p values are reported in bold.

($F(4,44)=0.52$, $p=0.72$) main effects nor of their interaction ($F(16,176)=1.09$, $p=0.36$). Furthermore, no significant effect of Condition for N2a-P2 component recorded from Cz ($F(4,44)=0.68$, $p=0.61$) was found. This result does not imply the absence of modulation with respect to the “first Static hand” observation block. Indeed, one sample t-test performed on Cz amplitudes showed that the N2a-P2 values were higher in the “first Static hand” (baseline) than in the “Needle in Hand” ($p=0.004$), “Q-tip on Hand” ($p=0.004$), “Needle in Tomato” ($p<0.0001$), “Needle in Foot” ($p=0.022$), or in the “last Static Hand“ block ($p=0.028$) (see Fig. 2, bottom row).

ANOVA on N1/P1 latencies did not show a main effect of Condition ($F(5,55)=0.89$, $p=0.49$). ANOVA on N2a latencies revealed a significant main effect of Electrode ($F(4,44)=3.45$, $p=0.015$) entirely accounted for by the different latencies between Fz (218.7 ms) and C3 (213.0 ms) electrodes ($p=0.008$), but no main effect of Condition ($F(5,55)=0.97$, $p=0.44$). As attested by the non significant Condition × Electrode interaction ($F(20,220)=1.03$, $p=0.42$), the main effect of Electrode was completely independent from the observational condition. ANOVA on P2 latencies showed no effect of Condition ($F(5,55)=0.93$, $p=0.47$), Electrode ($F(4,44)=1.16$, $p=0.34$) or of their interaction ($F(20,220)=0.65$, $p=0.87$).

Subjective reports

Intensity and unpleasantness ratings of the pain induced by laser stimuli for each observational condition are reported in Table 1. Laser pain intensity and unpleasantness scores were comparable in the different observation conditions ($F(5,55)=0.80$, $p=0.55$) and ($F(5,55)=0.55$, $p=0.74$) respectively.

While laser pain intensity and unpleasantness were not modulated in the different observational conditions, the self- or other-referred sensations derived from movie observation reflected the impact of the different movies on the onlookers. VAS scores of self- and other-referred intensity and unpleasantness of the pain induced by the needle movies in the different stimulation blocks are reported in Table 2.

Subjective ratings concerning pain intensity and unpleasantness during observation of Static hand and Q-tip movies were 0 and are not reported for table clarity. ANOVA on pain intensity scores showed a significant main effect of the observational conditions [self-referred $F(5,55)=18.28$, $p<0.0001$; other-referred $F(5,55)=152.72$, $p<0.0001$]. The same pattern of results was found for pain unpleasantness scores [self-referred $F(5,55)=16.87$, $p<0.0001$; other-referred $F(5,55)=75.17$, $p<0.0001$]. *Post-hoc* analysis showed that the main effects were entirely accounted for by the fact that both self- and other-referred judgments of pain intensity and unpleasantness during observation of “Needle in Hand” and “Needle in Foot” resulted significantly higher than during observation of the other movies (all $ps<0.001$).

Scores of pain intensity and unpleasantness of the laser stimuli delivered to the hand were significantly higher than scores of self-referred pain, and lower than scores of other-referred pain qualities. This was true for both observation of “Needle in Hand” and “Needle in Foot” movies (all $ps<0.02$) (see Tables 1 and 2). The higher rating of the pain qualities of others would rule out that any lack of correlation between neurophysiological and subjective effects is due to lack of empathy. Scores on the different IRI subscales were as follows (mean ± SD): FS = 13.2 ± 5.6; PT = 17.5 ± 5.6; EC = 18.1 ± 33; PD = 9.1 ± 6.0.

Correlation analyses

The correlation analysis shows that normalized N1/P1 amplitude during the “Needle in Hand” observation block was negatively correlated with intensity but not with unpleasantness of the pain felt during observation of the same movie (self-referred pain intensity: $r=-0.59$, $p=0.044$; self-referred pain unpleasantness: $r=-0.51$, $p=0.09$) (see Fig. 3a).

No correlation between normalized N1/P1 amplitude in the remaining dynamic observation conditions and self- or other-referred ratings of pain intensity or unpleasantness was found (Table 3).

Importantly, the correlation analysis between the normalized N1/P1 amplitude and the self-other combined index of pain intensity and unpleasantness shows that only for pain intensity we found that LEP

Table 4
Correlation analysis between the different subjective reports

		Laser		Self-referred		Other-referred	
		Intensity	Unpleasantness	Intensity	Unpleasantness	Intensity	Unpleasantness
Laser	Intensity		**0.93 ($p=0.000$)**	**0.72 ($p=0.008$)**	**0.68 ($p=0.014$)**	0.06 ($p=0.84$)	0.09 ($p=0.76$)
	Unpleasantness			**0.78 ($p=0.002$)**	**0.75 ($p=0.004$)**	0.02 ($p=0.96$)	0.16 ($p=0.63$)
Self-referred	Intensity				**0.90 ($p=0.000$)**	0.17 ($p=0.60$)	0.000 ($p=0.99$)
	Unpleasantness					0.01 ($p=0.97$)	0.17 ($p=0.60$)
Other-referred	Intensity						**0.84 ($p=0.001$)**
	Unpleasantness						

Correlation between the subjective scores concerning the laser-induced and the movie-derived, self- or other-referred pain qualities. Significant r and p values are reported in bold.

inhibition was higher in subjects who scored their pain as most intense and the pain of others as less intense (r=-0.56, p=0.056). No significant correlation was found for pain unpleasantness (r=-0.47, p=0.13) (see Fig. 3b). No other significant correlation was found between normalized LEPs components and subjective measures concerning laser pain and state- or trait- empathy scores (all $ps > 0.05$). Interestingly, laser pain scores were positively correlated with self- but not with other-referred scores of the pain derived from vision of "Needle in Hand" movies (see Table 4). This result concurs to suggest a relationship between actual pain and self-centered pain-qualities derived from observation of others' pain.

Discussion

Empathy allows us to share and comprehend the feelings and the intentions of other individuals and it is thus fundamental for social interactions and for shaping pro-social behaviour (Eisenberg, 2007). Far from being an all-or-nothing phenomenon, empathy is quite a multifarious construct ranging from low-level mechanisms such as emotional contagion to higher order processes such as perspective taking and mentalizing (Preston and de Waal, 2002; Decety and Lamm, 2006; Lamm et al., 2007). Empathy is clearly called into play when we observe others suffering either from psychological (e.g. social rejection) or physical pain (e.g. being penetrated by a needle). The reactions of an onlooker to the pain of a model can became quite complex depending on the feelings experienced by the former and the onlooker–model relationships. Empathy for pain can for example mainly deal with emotional sharing and with the evaluation of social bonds and interpersonal relations or may be mainly concerned with a comparatively simple, observational mapping onto an onlooker's body of the stimuli delivered to a model in the absence of any inter-individual relationship. Our study revolves around this latter type of empathic mapping of others' pain. A possible mechanism on which different forms of empathy do rely has to do with the notion of mirror resonant systems. This notion implies that a given neural substrate reacts similarly to a similar experience in self and other. Considering the wide range of possible vicarious experiences, future studies are needed to try and understand which aspects of a given experience are derived from observing others. Based on current knowledge, both affective (Singer et al., 2004, 2006) and sensory (Avenanti et al., 2005, 2006; Bufalari et al., 2007) qualities of the social pain can be internally simulated in different circumstances.

The pain of a model in the sensory node of the pain matrix of an onlooker

One main result of the present study is that mere observation of others' pain brings about a decrease in amplitude of the N1/P1 LEP component. This reduction is found specifically when the supposedly painful stimulus is delivered to the model's hand that corresponds to the onlooker body part stimulated by the laser. Although the brain sources of the different LEPs components are not fully understood, there is large agreement that the N1/P1 is generated in the suprasylvian region corresponding to the secondary somatosensory area (SII) contralateral to the stimulated side (Frot et al., 1999; Garcia-Larrea et al., 2003; Vogel et al., 2003). Studies exploring the neural underpinnings of the personal experience of pain processing indicate that, like the primary somatosensory cortex (SI), SII is crucially involved in sensory-discriminative aspects of the pain experience and contains neurons that code spatial, temporal and intensive aspects of noxious stimuli (Peyron et al., 2000; Hofbauer et al., 2001; Peyron et al., 2002; Craig, 2003; Bingel et al., 2004). The N1/P1 LEP component derives from excitation of SII neurons by laser stimulation of peripheral nociceptors. The amplitude reduction of N1/P1 found in the present study may reflect the competitive influence of the observed pain stimuli upon the laser-induced activation of SII nociceptive neurons. It is possible for example that, due to the slow conduction time of the nociceptive pathway, visually inferred sensations about the model's pain pre-activate SII nociceptive neurons and thus reduce the excitation power of laser pulses. Whatever the mechanism may be, this result highlights, for the first time, the pain-related mirror properties of specific neuronal pools in SII.

Previous studies showed that observing touching stimuli brought about the activation of frontal, temporal and parietal regions (Keysers et al., 2004; Blakemore et al., 2005). Therefore, SII may play a role in mirroring pain thanks to the heavy reciprocal connections between this area and the posterior parietal lobe and the F5 area where action-related mirroring seems to be common (Gallese et al., 1996; Rizzolatti et al., 2001; Fogassi et al., 2005). Whether specific neurons are committed to mirroring specific processes (e.g. action, touch, pain) is an open question. Importantly, our data indicate that the laser-pain activated SII neurons linked to the N1/P1 LEP component that are not modified by the observation of a Q-tip touching a hand thus suggesting these neurons are selectively triggered by the inferred painful sensations of others. This may suggest that specific neuronal pools within SII code both perceived (Frot et al., 2001) and observed (Keysers et al., 2004; Blakemore et al., 2005) nociceptive and innocuous stimuli. However, another possibility is that intensity-related effects occur in the same population of SII neurons and that their sensitivity to observed pain is simply higher than their sensitivity to observed touch. These findings extend significantly studies on somatic empathy (Keysers et al., 2004; Blakemore et al., 2005) by showing that SII may be of crucial importance in the neural circuit for sharing perceived and observed pain. Furthermore, our study shows that the inhibitory effect was specific for observation of needles penetrating the model's right hand but not the right foot. This effect seems in keeping with the somatotopic mapping of sensations and actions reported in previous TMS (Avenanti et al., 2005) and fMRI studies (Buccino et al., 2001; Hauk et al., 2004) and it may suggest that the process of mapping the sensory features of others' pain in SII may derive from matching the body part supposedly in pain in the model with the representation of the onlookers' very same body part.

That pain processing induces opposite polarity changes in SEP (Bufalari et al., 2007) and LEP studies (present results) may be puzzling in that the mechanisms underlying the P45 and the N1/P1 complex may be similar. Note however, the SEP study provides information on the effect of pain observation on somatic processing while the LEP study provides information on nociceptive processing during observation of others' pain. A possible explanation may have to do with the fact the onlookers were in pain in the LEP but not in the SEP study. It may be plausible that subjects who are not in pain while seeing the pain of others try and learn about the effects of pain from what they see. This process may have an adaptive value in that one can learn about pain without the risk of being exposed to it and may imply an increase of responsiveness of the primary somatosensory cortex (SI) (which is the main information one can get with SEP). Note also that a similar increase of SI activity has been found during pain perception in patient (Peyron et al., 2004) and healthy (Baron et al., 2000) subjects. In the present LEP study, subjects are exposed to the laser pain and they have to compare what they derive from observation with what they are already experiencing. This may ensue in a suppression of neural activity in the pain system that is reminiscent of what happens when subjects feel pain in the absence of any observational task (e.g. in conditions of neuropathic pain or experimental pain where amplitude of LEPs may be reduced, Garcia-Larrea et al., 2002; Valeriani et al., 2003b, 2005). In a similar vein, the amplitude of SEP components originating from SI is suppressed both when subjects feel (Cheron and Borenstein, 1991; Gandevia et al., 1983) and observe touch in others (Bufalari et al., 2007). Taken together our SEP and LEP studies support the notion that social touch and pain specifically modulate somatic and nociceptive neural processing.

Being in pain and seeing the pain of strangers: Self-centred resonance with others' pain

In keeping with our previous TMS (Avenanti et al., 2005, 2006) and SEP (Bufalari et al., 2007) studies, we show that seeing painful stimuli delivered to a stranger model induces specific modulations of the onlookers' pain matrix sensory node. Moreover, the inhibitory modulation of the N1/P1 LEP component correlated with subjective measures of sensory but not of emotional qualities of the sensations derived from observing stimuli delivered to others. Iannetti and colleagues (2005) demonstrated that amplitude of LEP components, likely originating from activation in the bilateral operculo-insular cortices, correlated significantly with the subjective pain ratings while the amplitude of the LEP components, likely originating from the cingulate cortex, provided less consistent results. This indicates that coding of pain intensity occurs already at the earliest stage of nociceptive processing. Our finding that others' pain specifically modulated a LEP component related to the sensory but not the affective node of the pain matrix, together with the finding that such modulation was specifically linked to the intensity but not the unpleasantness of pain, expands on the results of Iannetti and colleagues (2005) by suggesting that intensity coding of observed pain and actual pain may rely on largely overlapping neural structures. The correlation between sensorimotor neurophysiological effects and sensory qualities of the pain attributed to the model is also in keeping with our previous research (Avenanti et al., 2005, 2006; Bufalari et al., 2007). However, a novel result of the present study is the demonstration that individuals who are in pain map the pain of others according to what they feel more than to what they think the other is feeling. Thus, the SII system for mirroring others' pain recruited in our experimental conditions seems to make a self-related code of the observed pain intensity. This is different from what we have found in our previous studies (Avenanti et al., 2005, 2006; Bufalari et al., 2007) where neurophysiological modulations contingent upon observation of pain stimuli delivered to a stranger model correlated with the observer's subjective rating of the sensory qualities of the pain attributed to the model. Studies suggest that adopting a first-person viewpoint perspective of the stimuli (Lloyd et al., 2006; Jackson et al., 2006; Ogino et al., 2007) influences parietal activity related to empathic modulation of pain. It is in principle possible that the modulation of SII activity during pain observation and the self-related coding of the intensity of others' pain found in our study may be related to the fact that the subjects took an egocentric perspective. However, the results of the present study do not allow us to exclude that different neural structures may be primarily involved in different representations of others' pain (e.g. preferentially 'allocentric' representation in primary sensorimotor cortices vs. preferentially 'egocentric' representation in SII). Relevant to the present results is that, using similar stimuli (Avenanti et al., 2005, 2006; Bufalari et al., 2007) and instructions (Avenanti et al., 2006) we have demonstrated that neurophysiological modulations in the motor and somatic system were correlated with subjective ratings of the intensity of the pain attributed to the model (Avenanti et al., 2005, 2006; Bufalari et al., 2007). By contrast, in the present LEP study modulations of the neurophysiological component linked to neural activity in SII correlated with the intensity of the pain referred to the self. We posit that this effect is linked to the direct experience of the laser pain in addition to the observation of pain in others. This would indicate that the personal painful experience may lead to a more self-related representation of others' pain. Exploring how the perspective taken by 'in-pain onlookers' influences their brain reaction to the pain of other individuals is an important issue that deserves further studies.

Modulations of neural activity in the cingulate cortex during observation of painful and non painful events hint at the complex functions of this area

Most fMRI studies carried out so far suggest that only emotional aspects of empathy for pain are mapped in the affective nodes of the pain matrix (Morrison et al., 2004; Singer et al., 2004; Botvinick et al., 2005; Jackson et al., 2005). Moreover, more recent fMRI studies demonstrate that observing faces which imply strong pain (Saarela et al., 2007) induces neural activity in both the sensorimotor (mainly supplementary motor and premotor areas and inferior parietal gyrus) and the affective nodes (mainly anterior cingulate cortex and insular cortices) of the pain matrix. Since the N2a-P2 LEP component recorded in the present study is thought to originate in the mid-portion of the ACC, corresponding to Brodmann's area 24 (Garcia-Larrea et al., 2003) we focus our discussion on this structure. It is worth noting that this area is specifically activated during the personal experience of pain (Peyron et al., 2002; Vogt, 2005) as well as during imagination or observation of painful stimuli delivered to other individuals (Hutchison et al., 1999; Singer et al., 2004, 2006; Morrison et al., 2004; Botvinick et al., 2005; Jackson et al., 2006; Saarela et al., 2007). Moreover ACC is also involved in different higher-order functions such as attentional shifts and response selection (Paus, 2001). It is held that the N2a-P2 component evoked by painful stimulation may also reflect different processes ranging from shifts of attention towards different aspects of the potentially noxious stimulus to selection of appropriate motor reactions to the pain stimuli (Lorenz and Garcia-Larrea, 2003). In keeping with this view is the demonstration that N2a-P2 amplitudes are reduced by modifications of attention levels during laser stimulation (Lorenz and Garcia-Larrea, 2003). In particular, paying attention to visual stimuli strongly reduced the amplitude of the N2a-P2 component, an effect attributed to the involuntary shift of attention from painful to visual events (Legrain et al., 2005). In our study N2a-P2 amplitude in the first static hand observation condition was significantly higher than in the needle in hand, foot, tomato and in the Q-tip on hand conditions. Since the laser pain was comparable in the different observation conditions, the suggestion is made that the amplitude reduction of the N2a-P2 component is likely due to the fact that observing highly dynamic visual stimuli captures attention and diverts it from the laser pain. This result does not imply that our stimuli do not elicit any emotional resonance. The non-specific N2a-P2 LEP modulation may indicate that attentional salience of the stimuli mask emotional modulations in ACC. It is also possible that the condition of being in pain may reduce the emotional response to observation of strangers' pain. Relevant to this issue is the recent SEPs study (Godinho et al., 2006) showing an increased perception of electrical pain stimuli in subjects who observed images of burned, amputated, or wounded human models. In all these conditions both affective and sensory properties of the pain experience were at play. Interestingly, temporal and source analysis of SEP components showed that emotional modulation of pain perception occurred very late and in cortical areas possibly upstream the sensory and affective nodes of the pain matrix (Godinho et al., 2006). This result would support the notion that observation of different pain scenarios trigger different forms of empathy for pain (Avenanti et al., 2006).

Conclusion

In summary, we have demonstrated that viewing "flesh and bone" painful stimuli delivered to a stranger model modulates the pain system of onlookers suffering from acute pain induced by the laser stimuli. The modulation consisted of the inhibition of the N1/P1 LEP component that originates in the SII area and likely reflects the sensory qualities of pain. Previous studies of empathy for pain show that neural modulations are linked to sensory or affective pain qualities attributed to the model (Morrison et al., 2004; Singer et al., 2004, 2006; Botvinick et al., 2005; Avenanti et al., 2005, 2006; Jackson et al., 2005, 2006; Bufalari et al., 2007; Saarela et al., 2007). However, we demonstrate that suffering individuals map the observed pain according to their feelings rather than to the feelings attributed to a stranger model. This may suggest that the personal experience of pain influences social interactions by inducing the sufferer to evaluate the others according to an egocentric stance. This result paves the way to future studies aimed at clarifying the extent to which this default tendency to self-centered empathy in individuals who are in pain may be amended by different types of social bonds.

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