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## Freezing or escaping? Opposite modulations of empathic reactivity to the pain of others

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### ABSTRACT

Perceiving pain in others may induce the covert simulation of both sensory and emotional components of others' pain experience. Previous transcranial magnetic stimulation (TMS) studies have investigated the motor counterpart of this resonant mapping by showing suppression of motor-evoked potentials (MEPs) during the observation of a needle entering body parts of another person. Here we explored whether MEPs recorded from an onlooker's hand (e.g., the right hand, TMS to the left motor cortex) are differentially influenced by the observation of painfully stimuli delivered to the same (right) or the opposite (left) hand in a model. Congruency between observed (model) and recorded (onlooker) hand brought about a reduction of MEPs amplitude. This resonant inhibitory response in the onlooker was specific for the muscle penetrated in the model. In contrast, observing pain on the model's hand opposite to that from which MEPs were recorded brought about a generalized increase of hand corticospinal excitability. Corticospinal inhibition and facilitation effects were comparable in the two hemispheres and specific for the corresponding and opposite hand. Results suggest that observing pain in another person's hand automatically induces the covert simulation of potentially adaptive freezing and avoidance responses in the onlooker's corticospinal system.

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### 1. Introduction

Studies suggest that observing or imagining the pain of others activates neural circuits largely overlapping with those involved in the first-hand experience of pain (Avenanti and Aglioti, 2006). These circuits comprise both regions processing the affective dimension of pain (e.g., the unpleasantness of a noxious stimulus), such as the anterior insula and the anterior cingulate cortex (Singer et al., 2004), and regions processing the sensory dimension of pain (e.g., intensity, localization of a noxious stimulus) including the somatosensory cortices (Bufalari et al.,

2007; Lamm et al., 2007; Cheng et al., 2008; Benuzzi et al., 2008; Valeriani et al., 2008). Using single-pulse transcranial magnetic stimulation (TMS) it has been demonstrated that the direct observation of ‘flesh and bone’ painful stimulations delivered to the body of a stranger human model brings about a decrease of amplitude of motor-evoked potentials (MEPs) in the onlooker (Avenanti et al., 2005; Fecteau et al., 2008). Importantly, this inhibition was specific to the muscle the subjects observed being painfully stimulated and correlated with the evaluations of the intensity (Avenanti et al., 2006, 2009) and spread (Minio-Paluello et al., 2006) of the pain ascribed to the observed model,

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suggesting that corticospinal inhibition may reflect a ‘sensorimotor contagion’, i.e., an automatic embodiment of sensory qualities of pain onto the observers’ motor system.

What remains unclear is whether observing painful stimuli on the body of another person may induce a more complex modulation of the onlooker’s motor system in addition to the resonant freezing response of the muscle vicariously involved in the painful stimulation. In principle, feeling pain on one hand may be associated to a higher reactivity of the opposite hand that can be used to try and reduce the effect of the noxious stimulus (Melzack and Casey, 1968; Williams, 2002). Therefore, it is possible that the sensorimotor contagion contingent upon the vicarious feeling of others’ pain may involve not only corticospinal inhibition of the hand corresponding to that painfully stimulated in the other person (freezing) but also corticospinal facilitation of the hand opposite to the one stimulated in the model (implementation of reactions aimed at reducing pain, escaping).

We explored this issue in two groups of participants who undergone single-pulse TMS over the left or right motor cortex (M1) while they observed needles entering both the right and the left hand of a stranger model. Corticospinal reactivity to the model’s pain was recorded from both the left and the right hand of the experimental subjects in order to explore the relationship between the model and the onlookers’ hands and hemispheres.

## 2. Methods

### 2.1. Participants

Twenty-four right-handed subjects (10 men, mean age 25 y, range 21–32) free from any contraindication to TMS gave their written informed consent to take part in the study and were paid for their participation. The study was approved by Fondazione Santa Lucia ethics committee 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.

### 2.2. Visual stimuli

Different types of video-clips were presented on a 19-inch screen located 80 cm away from the participants. Video-clips showed the following: (i) fixation cross; the static view of the dorsal surface of (ii) a right or (iii) a left hand of a stranger male model depicted from a first-person view point; needle deeply penetrating the first dorsal interosseus (FDI) muscle of the same (iv) right or (v) left hand. To minimize habituation, three different versions of the stimuli were presented. All the videos had been already used in our previous studies (Avenanti et al., 2005; Minio-Paluello et al., 2006).

### 2.3. TMS and electromyographic (EMG) recording

MEPs were recorded simultaneously from the FDI muscle (in the dorsal region of the hand between the index finger and the thumb) and the thenar eminence (TE, on the palm region just beneath the thumb) by means of a Viking IV (Nicolet biomedical,

U.S.A.) electromyograph. EMG signals were band-pass filtered (20–2.5 kHz, sampling rate fixed at 10 kHz), digitized and stored on a computer for off-line analysis. Twelve subjects (6 men, mean age 25 y) received TMS over their left M1 and twelve subjects (4 men, mean age 25 y) over their right M1 while MEPs were recorded from the contralateral FDI and TE muscles. Thus, in subjects who received TMS over the left M1, MEPs were recorded from the right hand during presentation of right (congruent) and left (opposite) hand stimuli. By the same token, in the subjects who received TMS over the right M1 MEPs were recorded from the left hand during presentation of left (congruent) and right (opposite) hand stimuli.

Pairs of Ag–AgCl surface electrodes were placed in a belly-tendon montage on each muscle, with further ground electrodes on the wrist. A figure-of-8 coil connected to a Magstim Super Rapid Transcranial Magnetic Stimulator (Magstim, Whitland, U.K.) was placed over the motor cortex (with the handle pointing backward at 45° from the midline) contralateral to the recorded muscles. The optimum scalp position (OSP) was chosen so as to produce maximum amplitude MEPs in the FDI muscle. Pulse intensity was set at 120% of the resting motor threshold (rMT), defined as the lowest level of stimulation able to induce MEPs of at least 50  $\mu$ V in both muscles with 50% probability. Thus, in each subject, the rMT was based on the higher threshold muscle. This way a stable signal could be recorded from 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. The absence of voluntary contraction before the TMS pulse was continuously verified visually and, prior to the recording session, by auditory monitoring of the EMG signal.

### 2.4. Procedure

The experiment was programmed using Matlab software to control video-clips, and to trigger EMG and TMS. Each type of video-clip was presented in separate blocks. This block-design paradigm has been proved to be adept to explore the corticospinal response to others’ pain in previous research (e.g., Avenanti et al., 2005; Fecteau et al., 2008). The first and the last block served as baseline and consisted of video-clips showing the fixation cross. The order of the other four blocks (congruent static hand, pain on congruent hand, opposite static hand, pain on opposite hand) was counterbalanced. The fixation blocks consisted of 15 trials each, the static hand and pain blocks consisted of 18 trials each.

In each block, a central cross (1000 msec duration) indicated the beginning of a trial and initiated EMG recording. The duration of each video was 1800 msec. In each trial, a magnetic pulse was randomly delivered between 200 and 600 msec before the end of the movie to avoid any priming effects that could affect MEP size. A black screen was shown for 7.2 sec in the intertrial intervals.

In all observation conditions, participants were asked to pay attention to the events shown in the video-clips and to focus on what the stimulated individual may have felt. After each TMS session, subjects were presented with all pain videos and asked to rate the intensity of the pain ascribed to

the model during needle penetrations, by marking a vertical, 10-cm visual analogue scale (VAS) with 0 cm indicating 'no effect' and 10 cm 'maximal effect imaginable'.

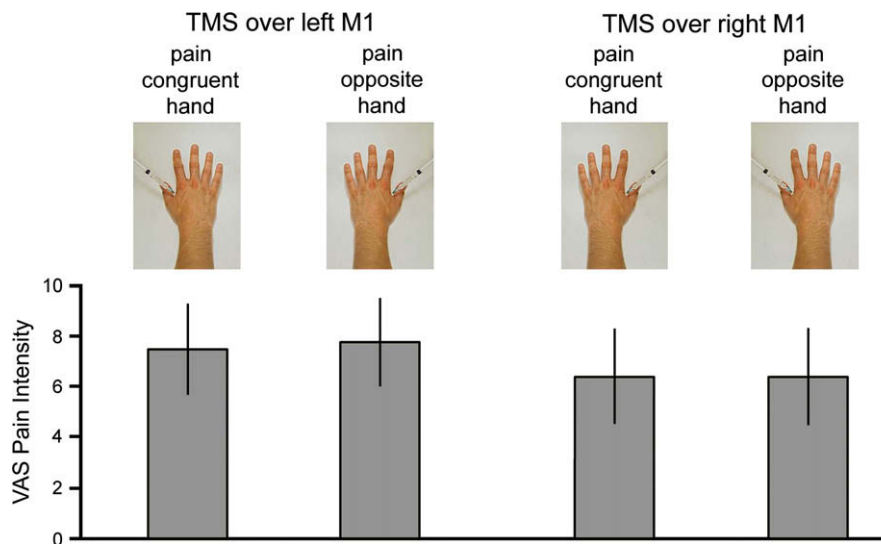
### 2.5. Data analysis

Neurophysiological data were processed off-line. Trials with EMG activity prior to TMS were discarded from the analysis (less than 10% in each subject). Mean MEP amplitude values in each condition were measured peak-to-peak (in mV). MEPs amplitude values recorded during the four experimental conditions were divided by MEP amplitude values recorded during the fixations blocks (MEP ratios). MEP ratios were entered into a mixed-model four-way ANOVAs, with Hemisphere (left M1, right M1) as between-subjects factor and Hand (congruent, opposite), Condition (static, pain) and Muscle (FDI, TE) as within-subjects factors. Pain judgements were entered into a mixed-model two-way ANOVA with Hemisphere (left M1, right M1) as between-subjects factor and Hand (congruent, opposite) as within-subjects factors. Post-hoc analysis was performed by means of Tukey HSD test.

## 3. Results

Participants were presented with stimuli depicting left or right static hands or left or right hands being penetrated by a needle. Subjects were divided in two groups according to the stimulated hemisphere (left M1, right M1). In the left M1 group, MEPs were recorded from the right hand during presentation of right hand (congruent) and left hand (opposite) stimuli. In the right M1 group MEPs were recorded from the left hand during presentation of left hand (congruent) or right hand (opposite) stimuli.

ANOVA on pain intensity evaluations showed no effect of Hemisphere, hand congruency nor their interaction ( $F_s < 2.82$ ,  $p_s > .11$ , Fig. 1). This indicates that pain inflicted on congruent and opposite hand was similarly judged in the two groups.



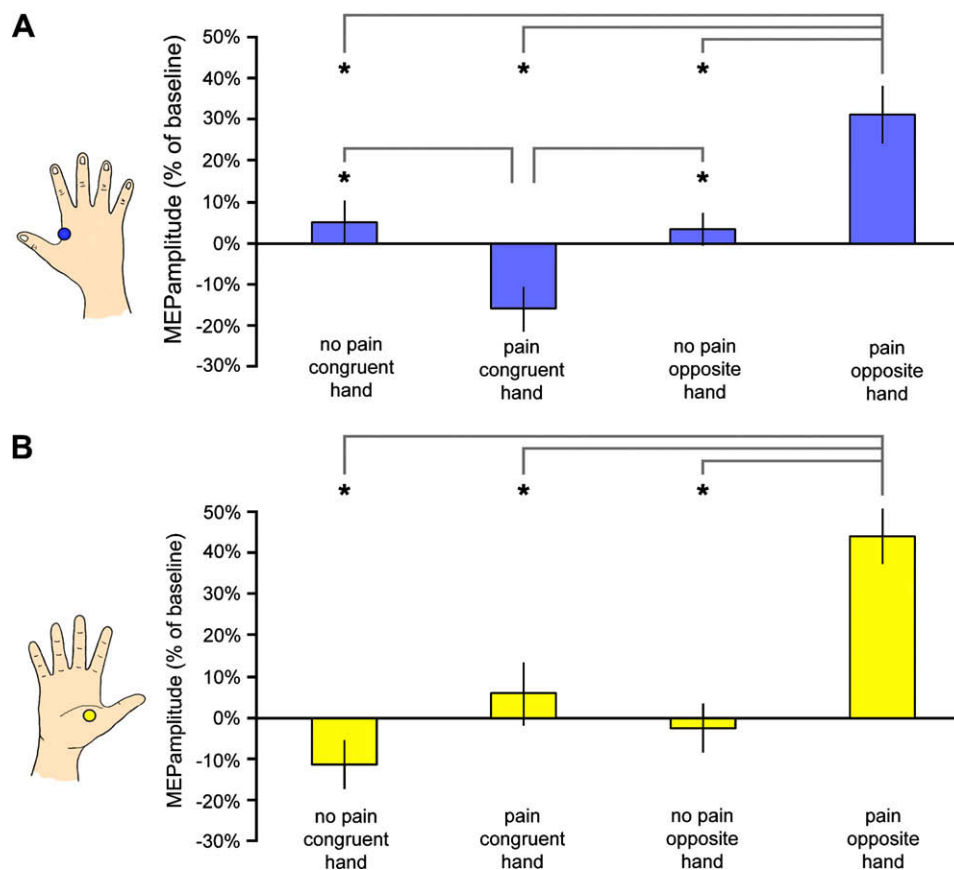
**Fig. 1 – Pain intensity judgements in the two groups of subjects who received TMS pulses over the left or right M1. Error bars indicate s.e.m.**

In contrast to the similarity in subjective evaluations, pain on congruent and opposite hand was associated to different patterns of corticospinal excitability (Fig. 2). ANOVA on MEP ratios revealed a significant triple interaction Muscle  $\times$  Hand  $\times$  Condition ( $F_{1,22} = 4.86$ ,  $p = .038$ ). To analyze this interaction two separate ANOVAs, one for each muscle, were performed.

Analysis of MEPs recorded from the FDI muscle revealed a significant main effect of Hand ( $F_{1,22} = 47.42$ ,  $p = .000001$ ) which was accounted for by the higher MEPs amplitude during observation of opposite hand (mean  $\pm$  s.e.m.:  $117\% \pm 6\%$ ) than congruent hand ( $95\% \pm 6\%$ ) corresponding to that from which MEPs were recorded (Fig. 2A).

Importantly, a significant interaction Hand  $\times$  Condition was found ( $F_{1,22} = 25.17$ ,  $p = .00005$ ). Post-hoc analysis revealed that amplitudes of MEPs recorded during the observation of painful stimulation on the congruent hand ( $84\% \pm 5\%$ ) were lower than those recorded when watching the static view of the congruent hand ( $105\% \pm 5\%$ ,  $p = .027$ ) or opposite hand ( $103\% \pm 4\%$ ,  $p = .046$ ) and when watching pain on the opposite hand ( $131\% \pm 7\%$ ,  $p = .0002$ ). Moreover MEPs recorded during the observation of pain on the opposite hand were higher than MEPs recorded during the observation of opposite ( $p = .003$ ) and congruent ( $p = .005$ ) static hand. MEPs were comparable for the two static hand stimuli with no painful stimulation ( $p = .81$ ). Thus, observing pain on the congruent hand reduced the excitability of the FDI corticospinal representation while observing pain on the opposite hand facilitated the FDI. These two different effects hold true also with respect to the fixation baseline ( $t_{23} = -2.97$ ,  $p = .007$ ;  $t_{23} = 4.80$ ,  $p = .00008$  respectively). No other significant effect was found for MEPs recorded from the FDI muscle ( $F_s < 2.06$ ,  $p_s > .16$ ).

ANOVA on MEPs recorded from the TE showed a main effect of Hand ( $F_{1,22} = 28.25$ ,  $p = .00002$ ) with higher amplitudes during observation of opposite ( $121\% \pm 8\%$ ) than congruent hand stimuli ( $98\% \pm 7\%$ ) and a main effect of Condition ( $F_{1,22} = 28.98$ ,  $p = .00002$ ) with higher amplitudes during the observation of painful ( $125\% \pm 8\%$ ) than during static stimuli with no painful stimulations ( $93\% \pm 6\%$ ). Importantly,



**Fig. 2 – Normalized MEP amplitude (% of fixation baseline) recorded from the FDI (A) and the TE (B) during the observation of the experimental stimuli. Error bars indicate s.e.m. Asterisks (\*) indicate significant post-hoc comparisons ( $p < .05$ ). Icons on the left show the position of the active electrodes on right hand for exemplificative purpose. Note that MEPs were recorded from the right hand in the group receiving the TMS over the left M1, and from the left hand in the group receiving the TMS over the right M1.**

a significant interaction Hand  $\times$  Condition was found ( $F_{1,22} = 7.74$ ,  $p = .011$ ). Post-hoc analysis shows that MEP amplitudes were higher during observation of pain on the opposite hand ( $145 \pm 6\%$ ) compared to observation of opposite ( $98 \pm 6\%$ ,  $p = .0002$ ) or congruent static hand stimuli ( $89 \pm 6\%$ ,  $p = .0004$ ) or pain on congruent hand ( $106 \pm 8\%$ ,  $p = .0002$ ), which in turn did not differ from one another ( $ps > .13$ ) (Fig. 2B). MEP amplitudes during the observation of pain on the opposite hand were higher also with respect to the fixation baseline ( $t_{23} = 4.10$ ,  $p = .0004$ ). No other significant effects were found for MEPs recorded from the TE ( $F_s < .67$ ,  $ps > .42$ ).

#### 4. Discussion

We explored the possible complexity of the corticospinal reactivity to the pain of others, by investigating the modulation of MEP amplitude contingent upon observation of painful stimuli inflicted to the left or the right hand of a model. We found that observing needles entering the FDI muscle of one hand brought about a suppression of MEP amplitude recorded from the observers' FDI muscle of the corresponding hand, confirming previous studies on sensorimotor contagion

(Avenanti et al., 2005, 2006, 2009; Avenanti and Aglioti, 2006; Minio-Paluello et al., 2006, in press; Fecteau et al., 2008). No modulation was found in the TE which has a contiguous representation in the motor cortex, suggesting that resonant corticospinal mapping of others' pain occurred according to fine-grained somatotopic rules.

Importantly, we found that observing pain on one hand brought about a strong increase in the amplitude of MEPs recorded from both the TE and FDI muscles of the opposite hand, indicating that sensorimotor contagion may also involve corticospinal facilitation. Therefore, inhibitory and facilitatory changes in corticospinal excitability were specific for congruent and opposite hands respectively. Moreover, inhibitory and facilitatory effects were comparable for left and right motor cortex stimulation. Subjective evaluations of the visual stimuli indicate that pain on the correspondent and opposite hand were similarly judged by the two groups of subjects, ruling out that inhibition and facilitation effects may be linked to any difference in the perceived painfulness of the stimuli.

The corticospinal inhibition found during pain observation confirms previous pain observation TMS studies where only complete compatibility between the observers' and the model's hand was assessed. In such conditions, a selective corticospinal inhibition of the muscle corresponding to that stimulated in the

model was found during the observation of deep needle penetrations, but not of touching stimuli (Avenanti et al., 2005; Fecteau et al., 2008) or light pinpricks (Avenanti et al., 2006). It is worth noting that a similar inhibition of motor representations has also been reported during first-person experience of pain (Farina et al., 2003). The inhibitory freezing responses to real pain may have the functional role of relaxing the body part that are in contact with the painful stimulus in order to reduce possible noxious consequences of this interaction (Farina et al., 2003). According to current models of empathy (Preston and De Waal, 2002; Decety and Jackson, 2004; Avenanti and Aglioti, 2006) the observational muscle-specific pain-related inhibition of the corticospinal system would suggest that watching pain in others triggers the resonant activation of correspondent somatotopic pain representations in the onlooker's sensorimotor system (Avenanti et al., 2005). That the sensorimotor node of the pain network is involved in encoding others' pain is also supported by the specific modulation of activity in sensory and motor areas that has been found with different techniques, including functional magnetic resonance imaging (fMRI) (Lamm et al., 2007; Benuzzi et al., 2008), magnetoencephalography (MEG) (Cheng et al., 2008) and somatosensory-evoked potentials (SEPs) (Bufalari et al., 2007) and laser-evoked potentials (LEPs) (Valeriani et al., 2008).

Pain is tightly linked to the motor system that, moreover, can be regarded as the division of the pain network involved in the implementation of appropriate reactions to actual or potential noxious stimuli. Nociceptive stimuli can elicit a series of defensive or reactive responses, like freezing and escaping, emotional-motor reactions or complex avoidance behaviours that may involve different sectors of the motor system (Melzack and Casey, 1968; Inghilleri et al., 1997; Williams, 2002; Farina et al., 2003). Observing painful stimuli on one hand facilitates corticospinal motor representations of the opposite hand. This facilitation cannot be accounted for by a general attentional or arousal effect linked to observing pain, since observing comparable painful and arousing stimuli i.e., needles entering in the foot, does not change hand corticospinal excitability (Avenanti et al., 2005, 2006). We posit that the increase of corticospinal excitability may be specifically linked to the functional relation between the two hands when perceiving pain. While receiving a painful stimulus on one hand may induce a freezing reaction in that hand, the opposite hand may be more involved in actively reacting to the painful stimulus, e.g., removing the source of pain (Melzack and Casey, 1968; Williams, 2002; Farina et al., 2003). We suggest that similar complex motor reactions may occur as a consequence of observing pain in others. These reactions may be embodied into the onlookers' sensorimotor system and may be automatically triggered by observing pain in others. Notably, no actual body movement was presented in our visual stimuli, suggesting that the putative covert simulation of a defensive motor response to pain may be anticipatory in nature. Predictive motor responses have been reported in action observation studies. For example Kilner et al. (2004) demonstrated that electroencephalographic (EEG) responses comparable to the readiness potential may be recorded also during action observation before an observed predictable movement. Moreover, Urgesi et al. (2006) showed that observing static snapshots depicting implied hand actions facilitate hand corticospinal motor circuits in the observer. Importantly, this type of facilitation is maximal when the

observed static image depicts an ongoing movement and not when observing completed actions. Our data add to previous studies by showing that facilitation of hand corticospinal motor circuits, putatively linked to the inner simulation of a defensive motor response, can be triggered by the observation of pain inflicted to a functionally complementary body part, namely the opposite hand.

In conclusion, the main finding of the present study is that perceiving others' pain may be linked not only to the covert simulation of affective (Singer et al., 2004) or sensory (Bufalari et al., 2007; Valeriani et al., 2008) qualities of others' pain, but also to a set of complex responses in the onlooker's corticospinal system that may underpin adaptive freezing or escaping reactions.

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