ELSEVIER

NeuroImage

www.elsevier.com/locate/ynimg
NeuroImage 32 (2006) 316 – 324

Stimulus-driven modulation of motor-evoked potentials during observation of others' pain

Alessio Avenanti, Ilaria Minio Paluello, Ilaria Bufalari, and Salvatore M. Aglioti*

Dipartimento di Psicologia, Università degli studi di Roma "La Sapienza", Via dei Marsi 78, I-00185 Rome, Italy
Centro Ricerche Neuropsicologia, IRCCS Fondazione Santa Lucia, Via Ardeatina 306, I-00179 Rome, Italy

Received 5 November 2005; revised 7 March 2006; accepted 7 March 2006
Available online 3 May 2006

Empathy may allow interindividual sharing not only of emotions (e.g., joy, sadness, disgust) but also of sensations (e.g., touch, itching, pain). Although empathy for pain may rely upon both sensory and affective components of the pain experience, neuroimaging studies indicate that only the affective component of the pain matrix is involved in empathy for pain. By using transcranial magnetic stimulation (TMS), we highlighted the sensorimotor side of empathy for pain by showing a clear motor inhibition during the mere observation of needles penetrating body parts of a human model. Here, we explored stimulus-specific and instruction-specific influences on this inhibition by manipulating task instructions (request to adopt first- or third-person perspective vs. passive observation) and painfulness of the experimental stimuli (presentation of videos of needles deeply penetrating or simply pinpricking a hand). We found a significant reduction in amplitudes of motor-evoked potentials (MEPs) specific to the muscle the subjects observed being penetrated that correlated with the intensity of the pain attributed to the model. Crucially, this motor inhibition was present during observation of penetrating but not of pinpricking needles. Moreover, no MEPs modulation contingent upon different task instructions was found. Results suggest that the motor inhibition elicited by the observation of 'flesh and bone' pain stimuli is more stimulus-driven than instruction-driven.

Introduction

Empathy refers to the reactions of one individual to the observed experiences of another (Davis, 1996; Decety and Jackson, 2004). Current neuroscientific models of empathy postulate that a given motor, perceptual, or emotional state of one individual activates corresponding neural representations in another individual observing that state (Preston and de Waal, 2002; Decety and Jackson, 2004; Gallese, 2003). In keeping with this *mirror-like* mechanism, neuropsychological, neurophysiological, and brain imaging studies indicate that the neural structures underlying sensation and emotion processing are also involved when the same sensations and emotions are observed in others (Hutchison et al., 1999; Adolphs et al., 2000; Calder et al., 2000; Carr et al., 2003; Wicker et al., 2003; Pourtois et al., 2004; Hennenlotter et al., 2005; Keysers et al., 2004; Blakemore et al., 2005). For example, viewing another person's facial emotional reactions to unpleasant odorants activates parts of the anterior insula (AI) that are also activated when the subject himself inhales the same odorants (Wicker et al., 2003).

Pain is a complex and enigmatic feeling with sensory-discriminative (e.g., intensity, duration, localization of the noxious stimulus) and affective-motivational (e.g., unpleasantness) components. These different components are mapped in two separate nodes of a complex neural network referred to as the 'pain matrix' (Ingvar, 1999; Peyron et al., 2000; Rainville, 2002). Converging lines of evidence indicate that the sensory dimension of pain is mainly coded in sensorimotor neural structures (Porro et al., 1998; Bushnell et al., 1999; Hofbauer et al., 2001), while the affective component is mapped in several limbic areas including the anterior cingulate cortex (ACC) and AI (Rainville et al., 1997; Peyron et al., 2000). The neural segregation of sensory and affective components makes pain an interesting model for testing theories of empathy based on the notion of shared neural representations.

Previous functional magnetic resonance (fMRI) studies indicate that only the affective components of the pain matrix are involved in empathy for pain. This suggests that only emotional representations of pain are shared between the self and others (Singer et al., 2004; Morrison et al., 2004; Jackson et al., 2005; Botvinick et al., 2005). Activation of ACC and AI was reported when participants imagined others' pain (Singer et al., 2004), watched facial pain-related behavior (Botvinick et al., 2005) or observed potentially painful situations (Jackson et al., 2005; Morrison et al., 2004). In a recent transcranial magnetic stimulation (TMS) study, however, we provided evidence that empathy for pain may imply the sharing of

* Corresponding author. Department of Psychology, University of Rome "La Sapienza", Via dei Marsi 78, I-00185 Rome, Italy. Fax: +39 06 4991 7635.
E-mail address: salvatoremaria.aglioti@uniroma1.it (S.M. Aglioti).
Available online on ScienceDirect (www.sciencedirect.com).

1053-8119/$ - see front matter © 2006 Elsevier Inc. All rights reserved.
doi:10.1016/j.neuroimage.2006.03.010

fine-grained somatomotor representations (Avenanti et al., 2005). Indeed, the direct observation of painful stimuli delivered to specific body parts of a human model brought about a reduction of corticospinal excitability (Avenanti et al., 2005) similar to that found in subjects who actually received painful stimulations (Farina et al., 2001, 2003; Le Pera et al., 2001; Svensson et al., 2003; Urban et al., 2004). Moreover, this reduction of motor excitability was specific for the muscle being penetrated and correlated with the sensory (intensity) instead of the emotional (unpleasantness) qualities of the pain attributed to the model.

It has been suggested that the mental attitude of the participants when thinking about the pain of others may account for by the differences in sensorimotor activity in pain empathy studies (Singer and Frith, 2005). One may posit that specific sensorimotor neural responses occur only when observers are explicitly asked to mentally simulate specific sensory qualities (e.g., intensity, locus of the stimulus) of others' sensations. This may help to explain (i) the muscle-specific reduction of corticospinal excitability found in our study when the observing subjects were instructed to focus on the sensations purportedly felt by the model (Avenanti et al., 2005); (ii) the somatotopic sensorimotor activation found during observation of touch stimuli in conditions in which subjects were instructed to rate the intensity of the touching stimuli (Blakemore et al., 2005). If explicit instructions to mentally simulate sensory features of others' pain are crucial for triggering empathic sensorimotor responses, no specific modulation of corticospinal excitability should be observed during passive observation of painful events.

However, it is entirely possible that not only instruction-based but also stimulus-based factors may induce simulation of specific qualities of others' pain and thus may modulate sensorimotor or emotional nodes of the pain matrix. Only the direct observation of shocking or intensely painful stimulations may, for example, elicit activity in the sensorimotor node of the pain matrix. Indeed, in most fMRI studies on empathy for pain, participants were not allowed to see others' painful stimulations directly (Singer et al., 2004; Botvinick et al., 2005) or observe static pictures of potentially painful situations (Jackson et al., 2005). In an fMRI study, Morrison et al. (2004) employed dynamic videos, similar to those used in our previous TMS study (Avenanti et al., 2005). However, an important difference between these two studies was the observation of light pinpricks (Morrison et al., 2004) instead of deep needle penetrations into specific body parts (Avenanti et al., 2005).

In this study, we set out to explain the seeming discrepancy between fMRI (Singer et al., 2004; Morrison et al., 2004; Jackson et al., 2005) and TMS studies (Avenanti et al., 2005). In particular, we carried out two single-pulse TMS experiments to test whether sensorimotor neural activity underlying empathy for pain is modulated by instruction-based factors, stimulus-based factors or by both. In the first experiment, we sought to determine whether the reduction of corticospinal excitability found in our previous study (Avenanti et al., 2005) was different in passive observation conditions and when the experimental subjects received the explicit instruction to focus on the qualities of the model's pain and to mentally simulate sensory features of others' pain by adopting a first-person perspective. The role of stimulus-based factors was assessed in a second experiment by testing whether the cortico-spinal inhibition contingent upon pain observation was modulated by different strength in evoking 'painfulness' of the stimuli to be observed (needles pinpricking vs. deeply penetrating body parts of a model).

Material and methods

Participants

Eighteen (9 men, mean age 25 years, range 20–28) and nine (4 men, mean age 26 years, range 19–32) subjects, all recruited at the IRCCS Fondazione Santa Lucia Rome, were tested in experiments 1 and 2 respectively. All subjects were right handed according to a standard handedness inventory (Oldfield, 1971). They gave their written informed consent to participate in the study. None of the participants had neurological, psychiatric, or other medical problems or had any contraindication to TMS (Wassermann, 1998). The protocol was approved by the ethics committee of the Fondazione Santa Lucia and was carried out in accordance with the ethical standards of the 1964 Declaration of Helsinki.

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, USA) electromyograph. EMG signals were band-pass filtered (20 Hz–2.5 kHz, sampling rate fixed at 10 kHz), digitized and stored on a computer for off-line analysis. Pairs of silver/silver chloride surface electrodes were placed over the muscle belly (active electrode) and over the associated joint or tendon of the muscle (reference electrode). A circular ground electrode with a diameter of 30 mm was placed on the dorsal surface of the right wrist. A figure-of-8 coil connected to a Magstim Super Rapid Transcranial Magnetic Stimulator (Magstim, Whitland, Dyfed, UK) 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 ADM (experiment 1) or FDI (experiment 2) 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, defined as the minimal intensity of the stimulator output that produces MEPs with an amplitude of at least 50 μV with a 50% probability (Rossini et al., 1994). The absence of voluntary contraction was continuously verified visually and, prior to the recording session, by auditory monitoring of the EMG signal.

Visual stimuli

In each experiment, different types of video clips were presented on a 19-in. screen located 80 cm from the subjects. In experiment 1, the video clips showed the following: (i) the dorsal static view of a right foot; (ii) the dorsolateral static view of the FDI and (iii) of the ADM region of a right hand; (iv) a needle deeply penetrating the dorsal surface of a right foot; (v) a needle deeply penetrating the FDI muscle; and (vi) the ADM muscle of a right hand. In experiment 2, the video clips included (i) the static view of the dorsal surface of a right hand; (ii) a needle deeply

penetrating the FDI muscle of a right hand; (iii) a needle pricking the same muscle.

Previous TMS studies report that observing moving body parts brings about an increase in corticospinal excitability (Fadiga et al., 1995, 2005), and that observing a hand using tools elicits activation of the primary motor cortex (Järveläinen et al., 2004). To avoid such effects in the present pain study, we checked that no hand or foot movements were evoked by pinprick stimuli. We also checked that the syringe holder was not visible in any of the videos.

Procedure

The experiments were programmed using Psychophysics Toolbox (www.psychotoolbox.org) and Matlab (www.mathworks.com) software to control sequence and duration of video clips, and to trigger TMS and EMG recording. Each type of video clip was presented in a separate block. Six (15 trials) and four (18 trials) observational blocks were performed in experiments 1 and 2 respectively. In all experiments, a central cross (1000-ms duration) indicated the beginning of a trial and initiated EMG recording. The duration of each video was 1800 ms. In each trial, a magnetic pulse was randomly delivered between 200 and 600 ms before the end of the movie to avoid any priming effects that could affect MEP size. A black screen was shown for 7.2 s in the intertrial intervals. The choice of a 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 in excitability (Chen et al., 1997).

In experiment 1, the 18 volunteers received two different kinds of instructions. Nine participants were specifically instructed to pay attention to the displayed events and were explicitly asked to adopt a first-person perspective during the observation of painful stimuli applied to the model. They were asked to "imagine feeling the same pain as the model, in the same body part" and to focus on what they "would have felt on that body part" if being stimulated (first-person instruction) (Table 1). Following these instructions should imply that the voluntary first-person mental simulation induces a precise spatial mapping of the model's feelings onto the observer's body. The remaining nine participants were told to simply watch the movie clips attentively (passive observation) (Table 1). The order of the six different blocks was randomized.

In experiment 2, participants were asked to adopt a third-person perspective during the observation of the model's pain, and as they were instructed to "focus on what the stimulated individual may have felt" (third-person instruction) (Table 1), as used in our previous study (Avenanti et al., 2005). Blocks of videos depicting deep needle penetrations or pinpricks were presented in two different sessions separated by 24–48 h. In each session, participants observed static and deep penetration videos or static and pinprick videos (Table 1). The order of the different sessions and blocks was counterbalanced. After each TMS session in experiment 2, subjects were presented with all videos and asked to judge the pain qualities supposedly felt by the model in each condition. Subjects were asked to rate the intensity and the unpleasantness of the pain ascribed to the model during deep needle penetrations and pinpricks, by marking a vertical, 10-cm visual analogue scale (VAS) with 0 cm indicating 'no effect' and 10 cm 'maximal effect imaginable'.

Data analysis

Neurophysiological data were processed off-line. Trials with EMG activity prior to TMS were discarded from the analysis. Three participants in experiment 1 (two in the passive observation group, one in the first-person group) were replaced due to high number of

Table 1
Detailed information about subjects, task instructions and stimuli employed in experiments 1 and 2

	Task instructions:	Blocks of visual stimuli:
Passive observation $N = 9$ (5 men) mean age 25 years range 20–27	"Try to keep your arm relaxed throughout the experiment. Watch and pay attention to the video-clip"	–Static foot –Needle penetrating the foot –Static hand (FDI region) –Needle penetrating the FDI –Static hand (ADM region) –Needle penetrating the ADM
First-person $N = 9$ (4 men mean age 25 years range 20–28	"Try to keep your arm relaxed throughout the experiment. Watch and pay attention to the video-clip. Assume the model's point of view so as to observe the displayed body parts from an egocentric, first person perspective. If you see a needle penetrating a body part, imagine feeling the same pain as the model, in the same body part. Focus on what you would have felt in that body part"	–Static foot –Needle penetrating the foot –Static hand (FDI region) –Needle penetrating the FDI –Static hand (ADM region) –Needle penetrating the ADM
Third-person $N = 9$ (4 men) mean age 26 years range 19–32	"Try to keep your arm relaxed throughout the experiment. Watch and pay attention to the video-clip. If you see a needle penetrating or pinpricking a body part, try to focus on what the stimulated individual may have felt"	Session A (TMS): –Static hand (dorsal view) –Needle penetrating the FDI Session B (TMS): –Static hand (dorsal view) –Needle pricking the FDI Session C (movie evaluation): –Needle penetrating the FDI –Needle pricking the FDI

motor artefacts (more than 30% of the trials). In both experiments, 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 were removed. Logarithmic transformation was applied to amplitude values [log (mean MEP amplitude value + 1)] to normalize data distribution.

In experiment 1, we subtracted MEP amplitudes recorded during each static condition (Foot, FDI, and ADM region) from the MEP amplitude recorded during each correspondent pain condition to emphasize the possible somatotopic modulation contingent upon pain observation. Thus, we obtained three normalized MEP difference values for each muscle ('Pain–Foot'; 'Pain–FDI'; 'Pain–ADM'); each value indicated the contrast between the painful and neutral (static) view of a given body part. For each muscle, normalized MEP differences were analyzed by mixed model two-way ANOVAs, with Instruction (explicit instruction, passive observation) as between-subjects and Condition ('Pain–Foot', 'Pain–FDI', 'Pain–ADM') as within-subjects factors. Post hoc comparisons were made by means of the Newman-Keuls test.

In experiment 2, we calculated normalized MEP differences by subtracting the mean MEP amplitude recorded during the static conditions from the mean MEP amplitude recorded during the painful conditions. Each painful condition (deep penetration, pinprick) was contrasted with the static condition recorded in the same session. For each muscle, normalized MEP differences were analyzed by repeated measures one-way ANOVA with Condition ('Penetration–FDI', 'Pinprick-FDI') as within-subjects factor.

In both experiments, for each condition and for each muscle separately, normalized MEP differences were compared against the value of 0 (no modulation) by means of one-sample t tests. An additional between groups one-way ANOVA on MEPs differences (pain-static) recorded from FDI during observation of deep needle penetration in the FDI muscle was performed across experiments to compare directly the effect of the three types of (passive observation, first-person, third-person) on corticospinal excitability during observation of pain.

In experiment 2, the pain qualities attributed to the model during deep needle penetrations or pinpricks were rated by means of two VAS (pain intensity, pain unpleasantness). We compared the ratings in the two observational conditions by means of paired t tests. We carried out a correlation analysis between neurophysiological and subjective measures for observation conditions in which MEP amplitude contrasts were significantly different from 0. One-sample t test indicated that the only MEP amplitude difference significantly different from 0 was recorded from the FDI muscle during 'Penetration–FDI' ($t_8 = -3.51$, $P = 0.003$). Thus, Pearson correlation coefficients between MEP amplitude difference recorded in 'Penetration–FDI' and subjective reports (VAS pain intensity, VAS pain unpleasantness) were computed.

Results

In the first experiment, ANOVA on MEPs contrasts (pain-neutral) recorded from FDI revealed a main effect of observational Condition ($F_{2,32} = 4.33$, $P = 0.022$) (Fig. 1). This effect was entirely accounted for by the lower amplitude recorded during 'Pain–FDI', compared to 'Pain–Foot' ($P = 0.021$) or 'Pain–ADM' ($P = 0.032$). Moreover, one-sample t test revealed that the 'Pain–FDI' contrast was significantly different from 0 ($t_{17} = -2.61$, $P = 0.018$). This indicates that there was a specific decrease in excitability of the observers' FDI muscle corticospinal representation when they viewed deep needle penetrations in the FDI with respect to when they observed the neutral view of the same body part. Examples of MEPs recorded from the FDI muscle in different observation conditions of experiment 1 are provided in Fig. 2A.

ANOVA on MEPs contrasts recorded from ADM showed a main effect of condition ($F_{2,32} = 3.69$, $P = 0.036$) accounted for by the lower amplitude recorded during observation of pain in ADM region compared to foot ($P = 0.046$) or FDI ($P = 0.037$) region (Fig. 1). Again, 'Pain–ADM' contrast was significantly different from 0 ($t_{17} = -2.48$, $P = 0.024$).

The two groups of participants that received the two types of instructions (first-person, passive observation) presented very similar patterns of corticospinal excitability modulation (Table 2). We found no main effect of Instructions or interaction with

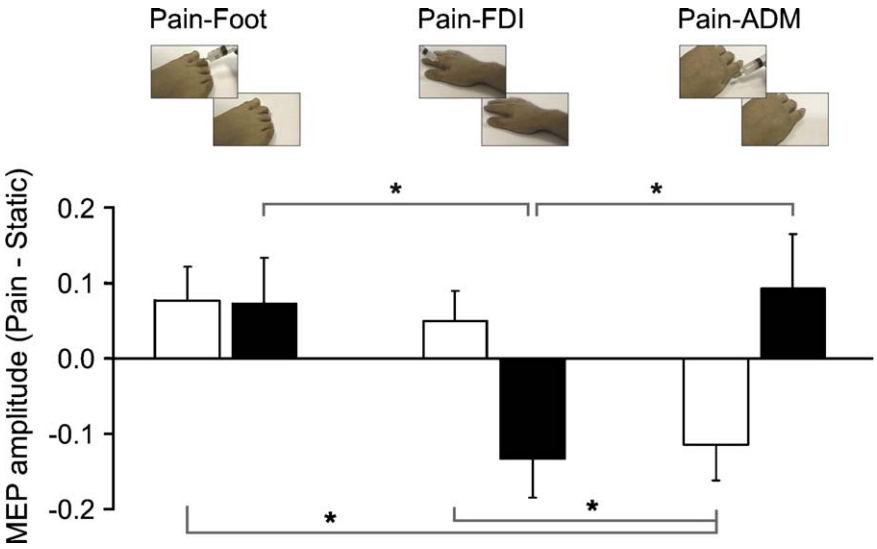

Fig. 1. MEP amplitude contrasts between pain and neutral conditions of experiment 1. Left, middle, and right columns indicate foot, FDI, and ADM regions respectively. MEPs recorded from FDI are indicated in black; MEPs recorded from ADM in white. Error bars denote SEM. Asterisks indicate significant post hoc comparisons ($P < 0.05$).

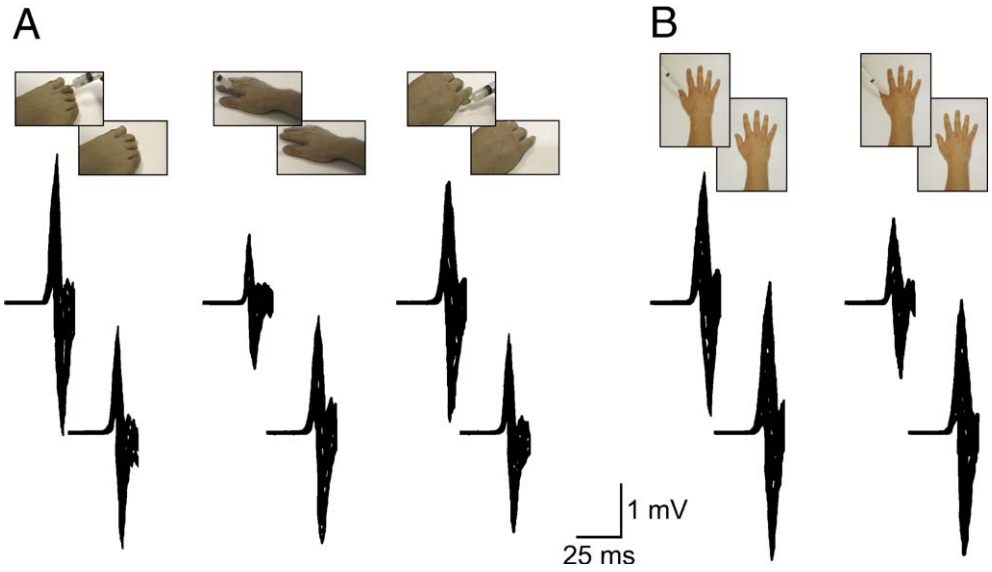

Fig. 2. Raw MEPs amplitudes recorded from the FDI muscle in one representative subject from experiment 1 (passive observation instruction) (A) and one from experiment 2 (third-person instruction) (B).

Condition for either muscle ($P > 0.6$). Critically, the MEPs inhibition effect showed no differences between the two groups.

In the second experiment, subjects were instructed to focus on the model's sensation (third-person instruction) during observation of deep and superficial needle penetrations of the FDI muscle. MEPs recorded from FDI during observation of 'Penetration–FDI' were reduced with respect to the 'Pinprick-FDI' contrast ($F_{1,8} = 6.49$, $P = 0.034$) (Fig. 3).

Only MEPs recorded from the FDI muscle during observation of needles deeply penetrating the model's FDI were significantly different from 0 ($t_8 = -3.51$, $P = 0.003$), indicating a selective motor inhibition during the observation of deep painful penetrations. Fig. 2B shows examples of MEPs recorded from the FDI muscle in the different observation conditions of experiment 2. No modulation of ADM muscle activity was found ($F_{1,8} = 0.007$, $P = 0.94$).

The videos depicting needles deeply penetrating the FDI muscle were quite similar in experiments 1 and 2. By contrast, three experimental groups were defined according to the different types of instruction (passive observation and first-person instructions in experiment 1, third-person instruction in experiment 2). Thus, in a further analysis, we directly tested the effect of instructions by comparing the MEP contrasts (pain-static) recorded from the FDI during observation of deep needle penetration in the FDI muscle with the three different types of experimental instructions. ANOVA revealed no differences between the three groups of participants ($F_{2,21} = 0.03$, $P = 0.97$).

After TMS sessions in experiment 2, subjects used VAS to judge sensory and affective qualities of the pain presumably felt by the model in the two conditions. The pain ascribed to the model during deep penetrations was evaluated as more intense ($t_8 = 4.60$, $P = 0.002$) and unpleasant ($t_8 = 3.08$, $P = 0.015$) than during pinpricks (see Fig. 4A). Importantly, we found that MEP amplitude contrast (pain-static) recorded from the FDI muscle during observation of needles deeply penetrating the model's FDI correlated with the sensory qualities of the pain ascribed to the model during penetration (VAS pain intensity: $r = -0.69$, $P = 0.041$) but not with the emotional

Table 2
MEP amplitude contrasts between pain and static conditions in the two groups of participants in experiment 1

	MEPs contrasts recorded from FDI Mean (SEM)		MEPs contrasts recorded from ADM mean (SEM)	
	First-person	Passive observation	First-person	Passive observation
Pain–Foot	0.09 (0.07)	0.06 (0.07)	0.14 (0.10)	0.02 (0.10)
Pain–FDI	−0.15 (0.07)	−0.12 (0.07)	0.04 (0.06)	0.07 (0.06)
Pain–ADM	0.08 (0.10)	0.10 (0.10)	−0.10 (0.07)	−0.13 (0.07)

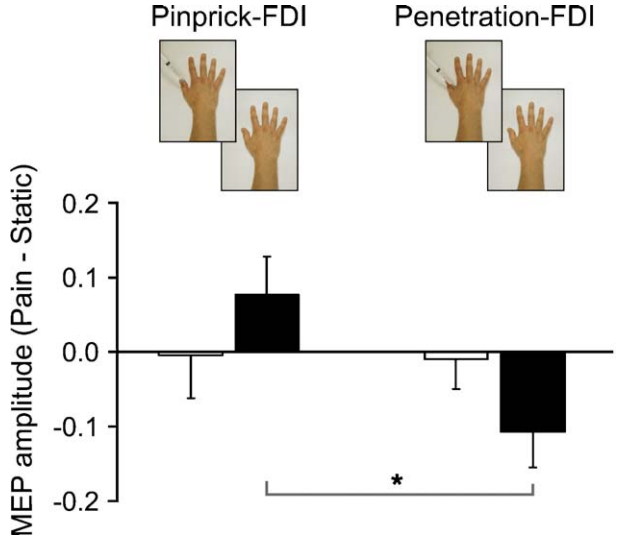

Fig. 3. MEP amplitude contrasts between pain and neutral conditions of experiment 2. Left and right columns indicate observation conditions of pinpricks and deep penetrations of the FDI muscle respectively. MEPs recorded from FDI are indicated in black; MEPs recorded from ADM in white. Error bars denote SEM. Asterisks indicate significant post hoc comparisons ($P < 0.05$).

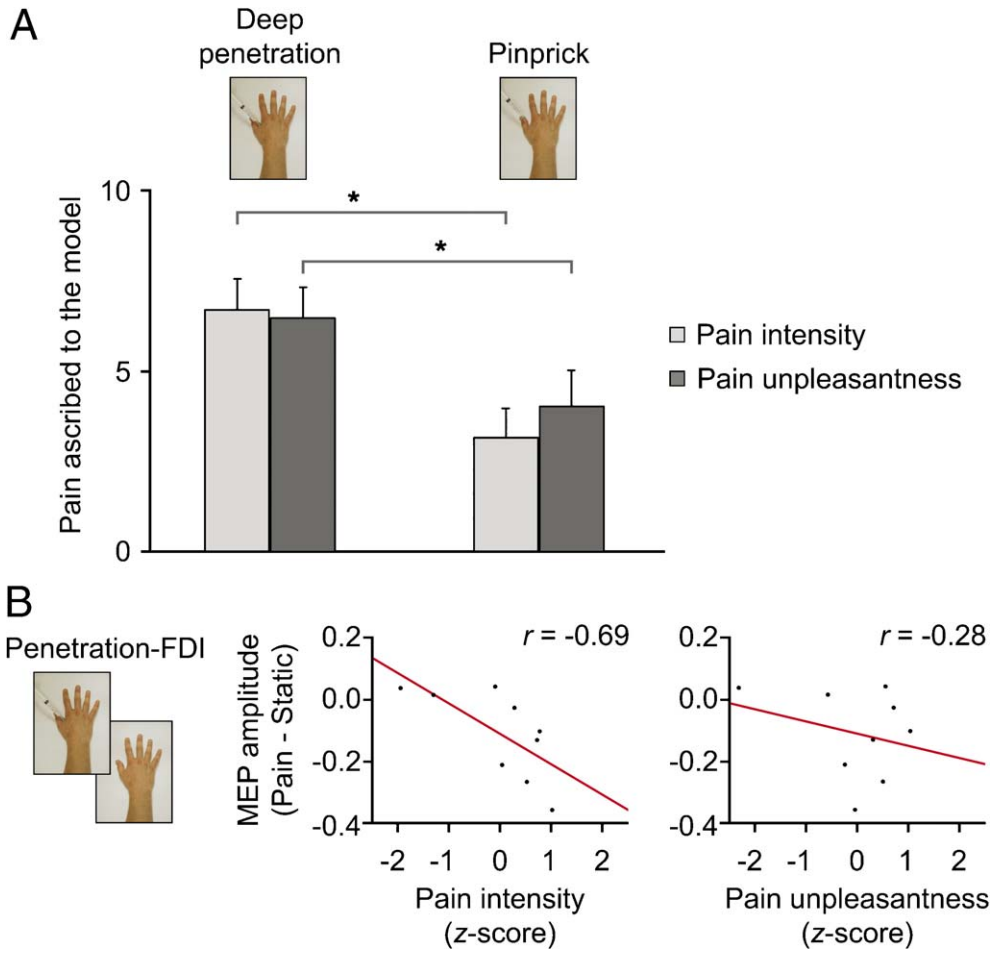

Fig. 4. Subjective evaluations and correlation analysis in experiment 2. (A) Qualities of the pain attributed to the model during observation of deep penetrations and pinpricks. Error bars denote SEM. (B) Correlation between amplitude of MEPs recorded from FDI during 'Penetration–FDI' and pain qualities ascribed to the model (pain intensity and unpleasantness).

qualities (VAS pain unpleasantness: $r = -0.28$, $P = 0.47$) (Fig. 4B). Negative correlations indicated that the largest MEP inhibition was found in the subjects who evaluated the model's pain as most intense.

Discussion

In a previous TMS study, we reported that observation of 'flesh and bone' painful events elicited pain-related activity in the observers' motor system (Avenanti et al., 2005). In particular, we demonstrated that observing needles penetrating different body parts of a human model unknown to the observer induced a somatotopic inhibition of the corticospinal system of the observers, who were instructed to focus on the model's feelings. Importantly, the inhibitory effect correlated with the intensity, but not the unpleasantness, of the pain attributed to the model, suggesting that inhibitory motor mapping may reflect simulation of sensory, rather than affective, qualities of others' pain (Avenanti et al., 2005). It is worth noting that a similar inhibition of motor representations has also been reported during the personal experience of pain (Farina et al., 2001, 2003; Le Pera et al., 2001; Svensson et al., 2003; Urban et al., 2004). The correspondent mapping of pain on self and others hints at the existence of a pain 'resonant' activation similar to that called into play during sharing of motor (Rizzolatti et al., 2001; Rizzolatti and Craighero, 2004), emotional (Carr et al., 2003; Wicker et al., 2003; Hennenlotter et al., 2005), and somatic representations (Keysers et al., 2004; Blakemore et al., 2005).

Somatotopic inhibition of motor representations during observation of others' pain

In the present study, we confirm all the basic features of the motor inhibition linked to pain observation. In particular, we demonstrate that the observation of 'flesh and bone' painful stimuli inflicted to another person's hand muscle inhibits the corticospinal representation of the very same muscle in the observer. This effect may be due to activation of the *motor* mirror system. In principle, our motor inhibition may reflect the simulation of a defensive motor reaction to pain similar to the suppression of distal muscle activity observed during the upper limb withdrawal reflex (Inghilleri et al., 1997; Farina et al., 2003). However, actual motor reactions to pain result in suppression of MEPs amplitude from all distal hand muscles (Farina et al., 2001, 2003; Le Pera et al., 2001; Svensson et al., 2003; Urban et al., 2004). Thus, the high selectivity of our pain-related observational effect speaks against the simulation of a massive retraction reflex (for further discussions, see Avenanti et al., 2005).

We suggest, rather, that the effect may be due to a *mirror-like* 'resonance' mechanism that extracts basic *sensory* qualities of another person's painful experience (location and intensity of the noxious stimulus) and maps them onto the observers' motor system according to somatotopic rules (Avenanti et al., 2005). This view is supported by the inhibitory sign of the effect, by the muscle specificity found in experiments 1 and 2 and by the correlation of MEP inhibition with the intensity of the pain attributed to the model (see experiment 2).

The correlation of motor inhibition with sensory aspects of others' pain may seem at odds with fMRI studies showing that only the affective division of the pain matrix is involved in empathy for pain and thus suggesting that only emotional representations of pain are shared between self and others (Singer et al., 2004; Morrison et al., 2004; Jackson et al., 2005; Botvinick et al., 2005). The discrepancy between TMS (Avenanti et al., 2005) and fMRI (Singer et al., 2004; Morrison et al., 2004; Jackson et al., 2005) studies may be partially explained by the possibly higher sensitivity in detecting subtle sensorimotor changes of TMS with respect to fMRI (Farina et al., 2003). However, it is also possible that different empathic phenomena are likely called into action in different studies (Singer and Frith, 2005). In the present study, we have dealt with this discrepancy by exploring whether the so-called *somatomotor contagion* described in our previous research (Avenanti et al., 2005) is an instruction-based or stimulus-based phenomenon. Two key results will be discussed.

Instructions to focus on pain qualities have little influence on somatomotor contagion

It is plausible that the different task instructions employed in previous pain empathy studies account for the different results (Singer and Frith, 2005). An entirely 'instruction-based' hypothesis predicts that specific sensorimotor neural activity is mainly found in paradigms in which participants are asked to attend to specific sensory qualities (e.g., intensity, locus) of others' pain or touch feelings (Singer and Frith, 2005; Blakemore et al., 2005; but see Jackson et al., 2005).

In contrast with predictions of instruction-based effects, the results of experiment 1 demonstrate that even the passive observation of others' pain can elicit somatotopic motor inhibition. Furthermore, the three experimental groups in experiments 1 and 2 had very similar patterns of corticospinal excitability regardless of whether the instruction was to simply pay attention to the displayed movie (passive observation, experiment 1), to focus on what the participant would have felt during a similar stimulation on the same body part (first-person perspective, experiment 1), or to focus on what the stimulated individual may have felt in the observed stimulation (third-person perspective, experiment 2).

We cannot of course exclude that the instructions used in the present study may modulate other nodes of the pain matrix, e.g., emotional neural structures. The explicit instruction to imagine experiencing the pain personally may lead, for example, to an increase in personal distress (Underwood and Moore, 1982; Batson et al., 1997; Jackson et al., 2006) and thus to a higher activation in limbic areas. In a similar vein, it is entirely possible that first-person instructions similar to those used in the present study would disclose modulation of somatomotor areas in different experimental conditions (e.g., during observation of comparatively non-painful or less involving stimuli such as pain-implying static pictures) (Jackson et al., 2006). Although, as discussed in the next session, *somatomotor contagion* may be mainly influenced by the properties of the observed stimuli, manipulations of task instructions different from those used in the present study may influence the somatomotor response to others' pain. For example, verbal or non-verbal cues indicating high–low intensity of the pain felt by the model may increase–decrease the size of the motor inhibition effect found in passive observation conditions. Future research is needed to directly test this hypothesis.

Stimulus-driven somatomotor contagion during observation of 'flesh and bone' painful stimulations

Experiment 2 shows clearly different patterns of corticospinal excitability during observation of videos depicting our 'flesh and bone' stimuli with needles deeply penetrating the hand of a model (Avenanti et al., 2005) and during observation of videos depicting needles lightly pinpricking the same hand. Interestingly, the latter movies were purposely made very similar to those used in an fMRI study where only the affective but not the somatomotor part of the pain matrix was activated (Morrison et al., 2004). In view of the similarity of the experimental stimuli, this discrepancy was particularly puzzling. However, results of experiment 2 provide a plausible explanation. Indeed, an inhibitory modulation of specific motor representations was elicited only by observation of the former type of movie, which was also subjectively rated as more painful. It is also important that the inhibitory effect correlated with the sensory, but not affective, qualities of the pain attributed to the model.

Thus, the second main result is that motor inhibition may be crucially dependent upon the painfulness of the observed scenes and in particular, on the intensity of the sensation evoked by the visual stimuli and ascribed to the model. This result hints at the important role of visual features of the observed painful stimulations in evoking sensorimotor neural response to others' pain. We do not exclude, however, that other types of peripheral information, such as for example auditory or even gustatory or olfactory stimuli, could modulate this type of response. It is also possible that re-enacting specific painful memory traces might modulate this effect. We believe that all of these issues are potentially important, and we plan to address them in future studies.

In summary, the present study suggests that the key variables modulating sensorimotor responses to others' pain are mainly related to the visual features of the observed scene and thus to stimulus-based factors. This hypothesis may explain the absence of specific sensorimotor neural activity in previous brain imaging studies of empathy for pain. In a first fMRI study, for example, empathy for pain was induced by means of arbitrary visual cues signaling an impending painful stimulus to the participants' romantic partner (Singer et al., 2004). In these conditions, an increase in the BOLD signal was found mainly in AI and ACC cortices, which are part of the affective division of the pain matrix. Neural activity in the affective pain network was also reported in fMRI studies in which experimental subjects viewed videos of facial expressions of pain in human models they did not know (Botvinick et al., 2005) or static pictures of potentially painful stimuli delivered to the model's hands or feet (Jackson et al., 2005). Importantly, Jackson et al. (2005) looked specifically for somatotopic activations by asking subjects to rate the intensity of the pain attributed to the model. The absence of somatotopic activation in sensorimotor structures during attention to sensory qualities of

others' pain further contrasts the prediction of an entirely 'instruction-based' hypothesis.

Conclusion

All in all, the present study shows that the direct observation of 'flesh and bone' stimulations purportedly able to induce pain in a model elicits pain-related activity in the observers' motor system. In keeping with our previous study (Avenanti et al., 2005), the present findings highlight the role of the sensorimotor node of the 'pain matrix' in the empathic matching of specific sensory aspects of others' painful experiences. An entirely novel result of the present study is that the visual features of the observed stimuli modulate the inhibitory effect much more than the instruction to simulate the pain of others. Thus, the mere observation of 'flesh and bone' stimuli that profoundly engage the onlookers in the painful scenario seems per se adept to induce them to automatically map the model's supposed pain onto their somatomotor system. This is important insofar as it sheds light on the apparent discrepancy between TMS (Avenanti et al., 2005) and fMRI studies (Singer et al., 2004; Morrison et al., 2004; Jackson et al., 2005; Botvinick et al., 2005) in which the observed stimuli likely elicited different types of empathy for pain than the *somatomotor contagion* explored in our research. Further studies using neuroimaging (fMRI) and neurophysiological (somatosensory- and laser-evoked potentials, magnetoencephalography) techniques are currently being conducted in our laboratories with the aim of investigating the critical variables that supposedly affect the different nodes of the complex neural network underlying 'flesh and bone' empathy for pain.

Acknowledgments

This research was supported by grants from the Ministero Istruzione Università e Ricerca (PRIN 2005) and Finanziamento Italiano Ricerca di Base (FIRB), Italy, both awarded to Salvatore M. Aglioti. The TMS experiments were conducted at Centro di Neuropsicologia, IRCCS Fondazione Santa Lucia, Rome, Italy.

References

Adolphs, R., Damasio, H., Tranel, D., Cooper, G., Damasio, R., 2000. A role for the somatosensory cortices in the visual recognition of emotion as revealed by three-dimensional lesion mapping. J. Neurosci. 20, 2683–2690.

Avenanti, A., Bueti, D., Galati, G., Aglioti, S.M., 2005. Transcranial magnetic stimulation highlights the sensorimotor side of empathy for pain. Nat. Neurosci. 8, 955–960.

Batson, C.D., Early, S., Salvarini, G., 1997. Perspective taking: imagining how another feels versus imagining how you would feel. Pers. Soc. Psychol. Bull. 23, 751–758.

Blakemore, S.J., Bristow, D., Bird, G., Frith, C., Ward, J., 2005. Somatosensory activations during the observation of touch and a case of vision–touch synaesthesia. Brain 128, 1571–1583.

Botvinick, M., Jha, A.P., Bylsma, L.M., Fabian, S.A., Solomon, P.E., Prkachin, K.M., 2005. Viewing facial expressions of pain engages cortical areas involved in the direct experience of pain. NeuroImage 25, 312–319.

Brasil-Neto, J.P., Cohen, L.G., Panizza, M., Nilsson, J., Roth, B.J., Hallett, M., 1992. Optimal focal transcranial magnetic activation of the human motor cortex: effects of coil orientation, shape of the induced current pulse, and stimulus intensity. J. Clin. Neurophysiol. 9, 132–136.

Bushnell, M.C., Duncan, G.H., Hofbauer, R.K., Ha, B., Chen, J.-I., Carrier, B., 1999. Pain perception: is there a role for primary somatosensory cortex? Proc. Natl. Acad. Sci. 96, 7705–7709.

Calder, A.J., Keane, J., Manes, F., Antoun, N., Young, A.W., 2000. Impaired recognition and experience of disgust following brain injury. Nat. Neurosci. 3, 1077–1078.

Carr, L., Iacoboni, M., Dubeau, M.C., Mazziotta, J.C., Lenzi, G.L., 2003. Neural mechanisms of empathy in humans: a relay from neural systems for imitation to limbic areas. Proc. Natl Acad. Sci. U. S. A. 100, 5497–5502.

Chen, R., Classen, J., Gerloff, C., Celnik, P., Wassermann, E.M., Hallett, M., Cohen, L.G., 1997. Depression of motor cortex excitability by low-frequency transcranial magnetic stimulation. Neurology 48, 1398–1403.

Davis, M.H., 1996. Empathy: A Social Psychological Approach. Westview Press, Madison.

Decety, J., Jackson, P.L., 2004. The functional architecture of human empathy. Behav. Cogn. Neurosci. Rev. 3, 71–100.

Fadiga, L., Fogassi, L., Pavesi, G., Rizzolatti, G., 1995. Motor facilitation during action observation: a magnetic stimulation study. J. Neurophysiol. 73, 2608–2611.

Fadiga, L., Craighero, L., Olivier, E., 2005. Human motor cortex excitability during the perception of others' action. Curr. Opin. Neurobiol. 15, 213–218.

Farina, S., Valeriani, M., Rosso, T., Aglioti, S.M., Tamburin, S., Fiaschi, A., Tinazzi, M., 2001. Transient inhibition of the human motor cortex by capsaicin-induced pain. A study with transcranial magnetic stimulation. Neurosci. Lett. 314, 97–101.

Farina, S., Tinazzi, M., Le Pera, D., Valeriani, M., 2003. Pain-related modulation of the human motor cortex. Neurol. Res. 25, 130–142.

Gallese, V., 2003. The manifold nature of interpersonal relations: the quest for a common mechanism. Philos. Trans. R. Soc. Lond. Biol. 358, 517–528.

Hennenlotter, A., Schroeder, T.U., Erhard, P., Castrop, F., Haslinger, B., Stoecker, D., Lange, K.W., Ceballos-Baumann, A.O., 2005. A common neural basis for receptive and expressive communication of pleasant facial affect. NeuroImage 26, 581–591.

Hofbauer, R.K., Rainville, P., Duncan, G.H., Bushnell, M.C., 2001. Cortical representation of the sensory dimension of pain. J. Neurophysiol. 86, 402–411.

Hutchison, W.D., Davis, K.D., Lozano, A.M., Tasker, R.R., Dostrovsky, J.O., 1999. Pain-related neurons in the human cingulate cortex. Nat. Neurosci. 2, 403–405.

Inghilleri, M., Cruccu, G., Argenta, M., Polidori, L., Manfredi, M., 1997. Silent period in upper limb muscles after noxious cutaneous stimulation in man. Electroencephalogr. Clin. Neurophysiol. 105, 109–115.

Ingvar, M., 1999. Pain and functional imaging. Philos. Trans. R. Soc. Lond. Biol. 354, 1347–1358.

Jackson, P.L., Meltzoff, A.N., Decety, J., 2005. How do we perceive the pain of others? A window into the neural processes involved in empathy. NeuroImage 24, 771–779.

Jackson, P.L., Brunet, E., Meltzoff, A.N., Decety, J., 2006. Empathy examined through the neural mechanisms involved in imagining how I feel versus how you feel pain. Neuropsychologia 44, 752–761.

Järveläinen, J., Schürmann, M., Hari, R., 2004. Activation of the human primary motor cortex during observation of tool use. NeuroImage 23, 187–192.

Keysers, C., Wicker, B., Gazzola, V., Anton, J.L., Fogassi, L., Gallese, V., 2004. A touching sight: SII/PV activation during the observation and experience of touch. Neuron 42, 335–346.

Le Pera, D., Graven-Nielsen, T., Valeriani, M., Oliviero, A., Di Lazzaro, V., Tonali, P.A., Arendt-Nielsen, L., 2001. Inhibition of motor system excitability at cortical and spinal level by tonic muscle pain. Clin. Neurophysiol. 112, 1633–1641.

Mills, K.R., Boniface, S.J., Schubert, M., 1992. Magnetic brain stimulation with a double coil: the importance of coil orientation. Electroencephalogr. Clin. Neurophysiol. 85, 17–21.

Morrison, I., Lloyd, D., di Pellegrino, G., Roberts, N., 2004. Vicarious responses to pain in anterior cingulate cortex: is empathy a multisensory issue? Cogn. Affect. Behav. Neurosci. 4, 270–278.

Oldfield, R.C., 1971. The assessment and analysis of handedness: the Edinburgh inventory. Neuropsychologia 9, 97–113.

Peyron, R., Laurent, B., Garcia-Larrea, L., 2000. Functional imaging of brain responses to pain. A review and meta-analysis. Clin. Neurophysiol. 30, 263–288.

Porro, C.A., Cettolo, V., Francescato, M.P., Baraldi, P., 1998. Temporal and intensity coding of pain in human cortex. J. Neurophysiol. 80, 3312–3320.

Pourtois, G., Sander, D., Andres, M., Grandjean, D., Reveret, L., Olivier, E., Vuilleumier, P., 2004. Dissociable roles of the human somatosensory and superior temporal cortices for processing social face signals. Eur. J. Neurosci. 20, 3507–3515.

Preston, S.D., de Waal, F.B.M., 2002. Empathy: its ultimate and proximate bases. Behav. Brain. Sci. 25, 1–71.

Rainville, P., 2002. Brain mechanisms of pain affect and pain modulation. Curr. Opin. Neurobiol. 12, 195–204.

Rainville, P., Duncan, G.H., Price, D.D., Carrier, B., Bushnell, M.C., 1997. Pain affect encoded in human anterior cingulate but not in somatosensory cortex. Science 277, 968–971.

Rizzolatti, G., Craighero, L., 2004. The mirror-neurons system. Annu. Rev. Neurosci. 27, 169–192.

Rizzolatti, G., Fogassi, L., Gallese, V., 2001. Neurophysiological mechanisms underlying the understanding and imitation of action. Nat. Rev., Neurosci. 2, 661–670.

Rossini, P.M., Barker, A.T., Berardelli, A., Caramia, M.D., Caruso, G., Cracco, R.Q., Dimitrijevic, M.R., Hallett, M., Katayama, Y., Lucking, C.H., Maertens de Nordhout, A.L., Marsden, C.D., Murray, N.M.F., Rothwell, J.C., Swash, M., Tomberg, C., 1994. Non-invasive electrical and magnetic stimulation of the brain, spinal cord and roots: basic principles and procedures for routine clinical application. Report of an IFCN committee. Electroencephalogr. Clin. Neurophysiol. 91, 79–92.

Singer, T., Frith, C.D., 2005. The painful side of empathy. Nat. Neurosci. 8, 845–846.

Singer, T., Seymour, B., O'Doherty, J., Kaube, H., Dolan, R.J., Frith, C.D., 2004. Empathy for pain involves the affective but not sensory components of pain. Science 303, 1157–1162.

Svensson, P., Miles, T.S., McKay, D., Ridding, M.C., 2003. Suppression of motor evoked potentials in a hand muscle following prolonged painful stimulation. Eur. J. Pain 7, 55–62.

Underwood, B., Moore, B., 1982. Perspective-taking and altruism. Psychol. Bull. 91, 143–173.

Urban, P.P., Solinski, M., Best, C., Rolke, R., Hopf, H.C., Dieterich, M., 2004. Different short-term modulation of cortical motor output to distal and proximal upper-limb muscles during painful sensory nerve stimulation. Muscle Nerve 29, 663–669.

Wassermann, E.M., 1998. Risk and safety of repetitive transcranial magnetic stimulation: report and suggested guidelines from the International Workshop on the Safety of Repetitive Transcranial Magnetic Stimulation, June 5–7, 1996. Electroencephalogr. Clin. Neurophysiol. 108, 1–16.

Wicker, B., Keysers, C., Plailly, J., Royet, J.P., Gallese, V., Rizzolatti, G., 2003. Both of us disgusted in My insula: the common neural basis of seeing and feeling disgust. Neuron 40, 655–664.