ARTICLE

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Transcranial magnetic stimulation highlights the sensorimotor side of empathy for pain

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Supplementary Fig. 1
Examples of raw MEP amplitudes for each observation condition in a representative subject of experiment 1.

Supplementary Fig. 2
Sensory and affective qualities of the pain supposedly felt by the model during observation of the different types of video clips in experiments 1, 2 and 3.

Supplementary Fig. 3
Self-oriented emotional reactions during observation of the different movies of experiment 1 measured by means of VAS.

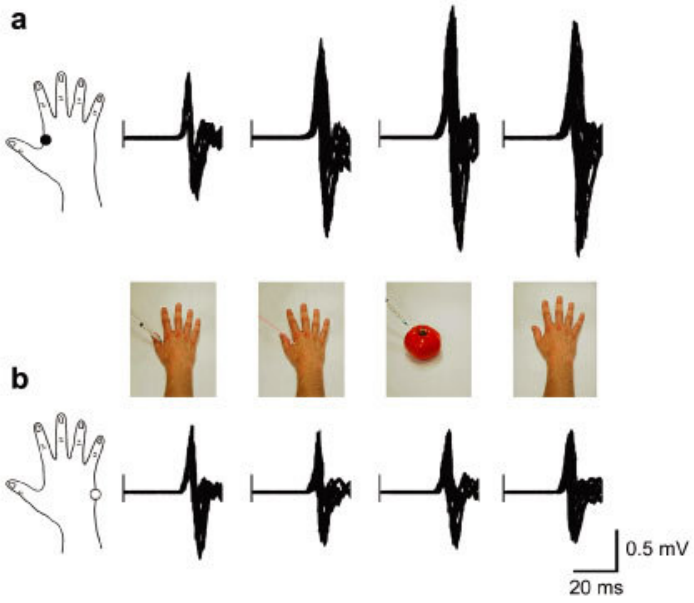
Supplementary Fig. 4
MEP amplitude recorded from the FDI (black bars) and the ADM (white bars) muscles during the observation of 'Needle in FDI' condition of experiment 5 (expressed with respect to the correspondening static condition).

Supplementary Table 1
Mean amplitude (± s.e.m.) of F and M waves recorded from the FDI muscle in experiment 4.

Supplementary Table 2
Simple correlations between MEP amplitude changes recorded from FDI and ADM muscles and subjective ratings of 'Needle in FDI' video clips of experiment 1 and 5, and 'Needle in ADM' video clips of experiment 3.

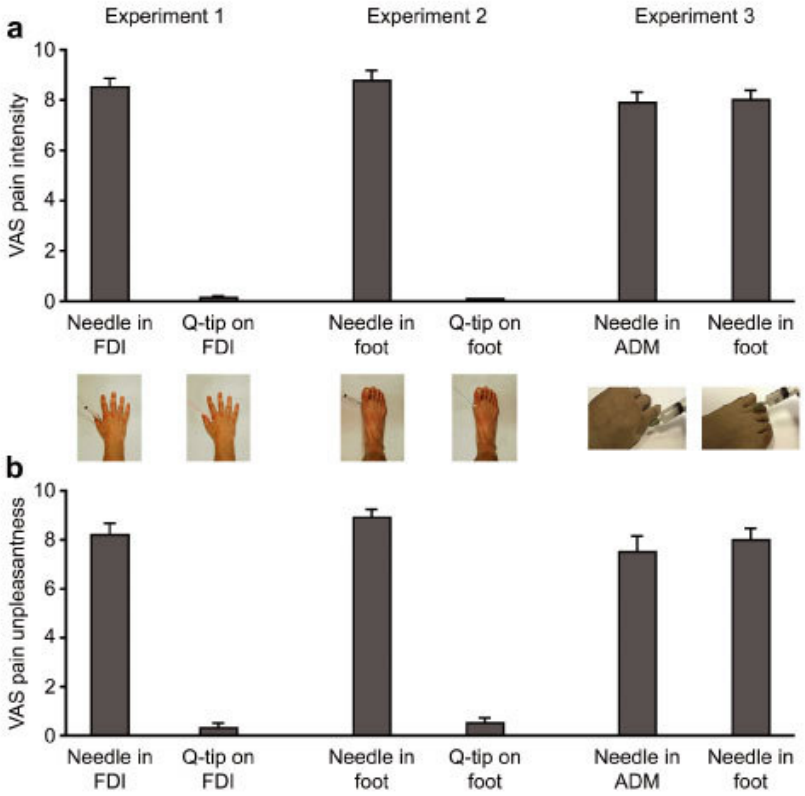
Supplementary Note

Supplementary Figure 1 Examples of raw MEP amplitudes for each observation condition in a representative subject of experiment 1.



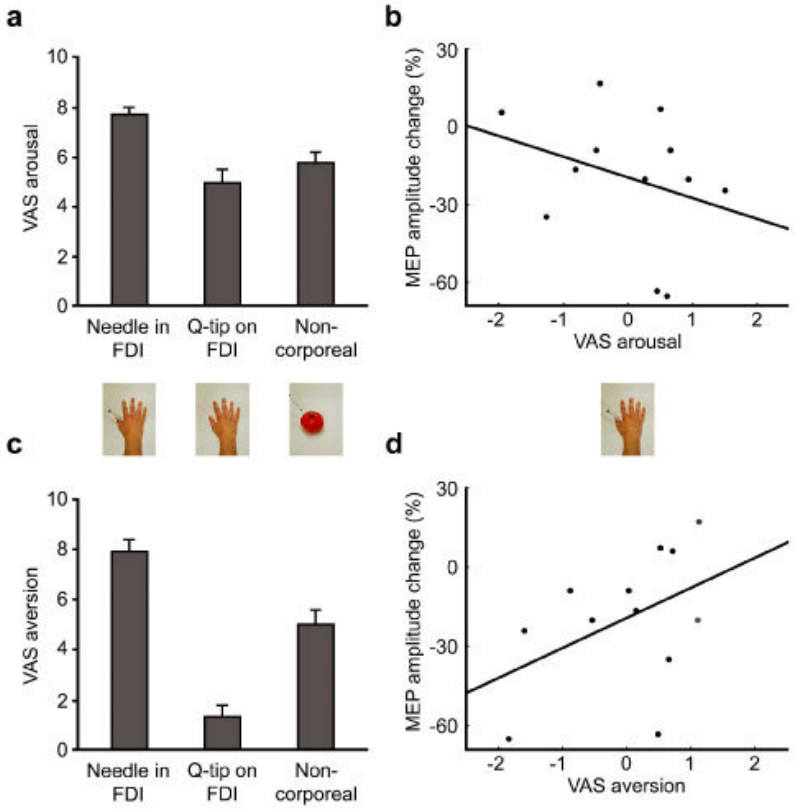
(a) MEPs recorded from FDI. (b) MEPs recorded from ADM. For the baseline condition, 36 overlying traces are shown. For each of the dynamic observation conditions 18 overlying traces are presented.

Supplementary Figure 2 Sensory and affective qualities of the pain supposedly felt by the model during observation of the different types of video-clips in experiment 1, 2 and 3.



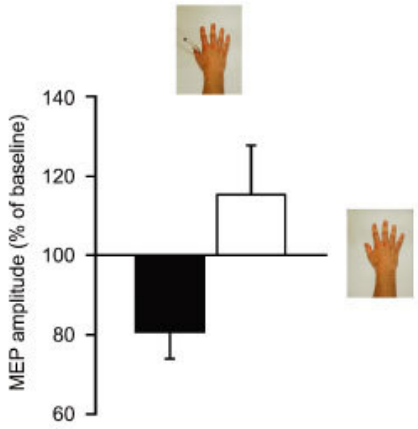
(a) Mean (± s.e.m.) VAS pain intensity ratings. Significant type of movie effect: $F_{5,58} = 146.26$, $P < 0.0001$.
(b) Mean (± s.e.m.) VAS pain unpleasantness ratings. Significant type of movie effect: $F_{5,56} = 83.98$, $P < 0.0001$.
For both sensory and affective judgements, the type of movie effect was entirely accounted for by the higher ratings of needle penetration with respect to tactile stimulation movies. Importantly, there were no differences in pain ratings of the different needle penetration (hand or foot) video-clips. Thus, absence of modulation of MEPs during observation of painful foot stimulations in experiment 2 and 3, cannot be ascribed to the different 'painfulness' of the experimental stimuli. Rather, the inhibition found in experiment 1 and 3 may be related to the somatotopic mapping of others' pain.

Supplementary Figure 3 Self-oriented emotional reactions during observation of the different movies of experiment 1 measured by means of VAS.



(a) Mean (± s.e.m.) arousal scores. The significance of the type of movie effect ($F_{2,22} = 12.53$, $P < 0.001$) is due to the fact that 'Needle in FDI' movies were rated as more arousing than 'Q-Tip on FDI' ($P < 0.001$) and 'Non-Corporeal' movies ($P = 0.004$), which in turn did not differ from one another. (b) A negative, but non-significant correlation between VAS arousal (z-scores) and MEP amplitude changes recorded from FDI during 'Needle in FDI' ($r = -0.31$, $P = 0.32$) was found. (c) Mean (± s.e.m.) aversion scores. A significant type of movie effect ($F_{2,22} = 47.70$, $P < 0.001$) was found. 'Needle in FDI' movies were judged as significantly more aversive than 'Q-Tip on FDI' ($P < 0.001$) and 'Non-Corporeal' ($P < 0.001$) movies. Moreover, the 'Non-Corporeal' movies were rated as more aversive than the 'Q-Tip on FDI' movies ($P = 0.001$). (d) A positive but non significant correlation between VAS aversion (z-scores) and MEP amplitude changes recorded from FDI during 'Needle in FDI' ($r = 0.44$, $P = 0.15$) was observed. This pattern of results suggests that inhibition of the FDI representation during 'Needle in FDI' condition was not related to self-oriented emotional reactions (arousal and aversion).

Supplementary Figure 4



MEP amplitude recorded from the FDI (black bars) and the ADM (white bars) muscles during the observation of 'Needle in FDI' condition of experiment 5 (expressed with respect to the correspondent static condition). One-sample t-tests showed that amplitude of MEPs recorded from FDI were significantly different from the baseline ($t15 = -3.09$, $P = 0.008$). By contrast, MEPs recorded from ADM did not significantly differ from the corresponding baseline ($t15 = 1.28$, $P = 0.22$). Error bars indicate s.e.m.

Supplementary Table 1 Mean amplitude (± s.e.m.) of F and M waves recorded from the FDI muscle in experiment 4.

Experiment 4

	'Static Hand' (mV)	'Needle in FDI' (mV)	'Needle in FDI' (% Static Hand)
M wave amplitude	19.81 (± 4.63)	19.46 (± 4.24)	98.64 (± 1.44)
F wave amplitude	0.32 (± 0.13)	0.35 (± 0.16)	107.65 (± 4.80)

One-sample t-tests showed that 'Needle in FDI' was not different respect to the 'Static Hand' condition for both normalized F waves ($t7 = 1.59$, $P = 0.16$) or M waves ($t7 = -0.95$, $P = 0.38$). Since M and F waves reflect activity of muscle or peripheral nerve and of spinal motoneurons respectively, the inhibition found in experiment 1 likely occurs upstream the spinal cord.

Supplementary Table 2

Experiment 1: observation of 'Needle in FDI'			
	Amplitude changes of MEP recorded from		Subjective Evaluation
	FDI muscle: *r* value	ADM muscle: *r* value	Mean (St. Dev.)
MPQ sensory scale	**-0.76*****	-0.28	20.58 (6.14)
VAS Pain Intensity	**-0.71****	-0.42	8.51 (1.28)
MPQ affective scale	-0.26	-0.29	3.25 (2.38)
VAS Pain Unpleasantness	0.22	-0.30	8.21 (1.59)
VAS Arousal	-0.31	-0.01	7.72 (1.07)
VAS Aversion	0.44	0.01	7.92 (1.81)

Experiment 3: observation of 'Needle in ADM'			
	Amplitude changes of MEP recorded from		Subjective Evaluation
	FDI muscle: *r* value	ADM muscle: *r* value	Mean (St. Dev.)
VAS Pain Intensity	-0.37	**-0.58***	7.89 (1.33)
VAS Pain Unpleasantness	-0.07	-0.07	7.53 (2.09)

Experiment 5: observation of 'Needle in FDI'			
	Amplitude changes of MEP recorded from		Subjective Evaluation
	FDI muscle: *r* value	ADM muscle: *r* value	Mean (St. Dev.)
VAS Pain Intensity	**-0.50***	0.14	6.83 (2.32)
VAS Pain Simulation	**-0.56***	-0.17	6.48 (2.68)
VAS Empatich Concern	0.06	0.06	2.93 (1.96)
VAS Personal Distress	0.15	0.32	5.94 (2.80)
IRI Empathic Concern	-0.24	0.11	20.63 (4.33)
IRI Personal Distress	-0.11	0.29	9.31 (4.61)

* $p<0.05$
** $p<0.01$
*** $p<0.005$

Supplementary notes online

We believe that the modulation of MEPs amplitude during observation of pain in others is best explained by the hypothesis of pain resonance systems activation. In principle, at least three additional mechanisms may influence the MEP modulation found in our study. Thus, it is important to emphasise here that none of them can explain our main experimental finding.

Activation of motor mirror system due to observation of tool-use. It has been demonstrated that action observation elicits in humans a clear MEPs facilitation[1-3]. Moreover, observation of a hand using tools use may elicit an activation of the primary motor cortex[4]. Our participants were presented with videos showing painful or tactile stimulations performed by means of syringes or Q-tips (exp 1-5). Although, in none of the videos the holder of the syringe or of the Q-Tip was visible, it is still possible to find a motor mirror system activation due to observation of tool-use. However, the possibility that the observers' motor system simply simulates the inferred actions of the syringe or Q-tip holder is ruled out by the inhibitory rather than facilitating sign of the effect, by the specificity of the effect for pain stimuli only, and by the muscle selectivity (exp 1-5).

Predictive simulation of a defensive reflex response. TMS studies report that nociceptive hand stimulation induces a strong reduction of cortico-spinal excitability[5-13] that affects several, mainly distal, muscles and is likely to be related to the implementation of a protective withdrawal reflex. Recent findings indicate that the motor mirror system may play an important role in setting up an anticipatory model of others' movements[14]. Although there were no movements of the model during hand needle penetration (exp 1,3,5), the predictive properties of the motor mirror system may evoke the simulation of a subsequent withdrawal reflex in the model which can explain hand motor inhibition[5-13]. Given the somatotopic organization of motor mirror system[1-3,15-17], finding no modulation during observation of needles penetrating a remote body part (foot stimulation in exp 2, 3) may also be in keeping with this hypothesis. However, the inhibition contingent upon pain observation is limited to the muscles corresponding to those pinpricked in the model (e.g. FDI in exp 1 and 5, ADM in exp 3) and is absent in nearby muscles which have a contiguous motor representation[18] (e.g. ADM in exp 1 and 5, FDI in exp 3). Thus, the high selectivity of our pain-related observational effect speaks against the simulation of a massive retraction reflex.

Observation of painful stimuli induces selective shifts of attention to a given muscle. Our study shows that vision of needles entering body parts resulted more arousing than vision of other stimuli (exp 1). This higher salience may in principle trigger a selective shift of attention to the observer's muscle corresponding to that pinpricked in the model. It is worth noting, however, that the instruction

to voluntarily attend a given muscle brings about a selective MEPs facilitation rather than inhibition[19]. Thus, our pain-related observational MEPs inhibition cannot be accounted for by a mere shift of attention.

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