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# Corticospinal excitability during painful self-stimulation in humans: a transcranial magnetic stimulation study☆

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**Abstract**

We investigated changes in the corticospinal pattern of activity in healthy volunteers during sustained noxious and non-noxious mechanical stimulation of the first hand digit, resulting from active (self-stimulation) or passive (externally-induced) pressing against a sharp or blunted tip. The results indicate that, in order to press a finger onto a noxious stimulus with the same force generated to press onto a non-noxious one, the motor cortex adopts a peculiar strategy in terms of recruitment of motor units. This is reflected by an increase of corticospinal excitability (as revealed by motor potentials evoked by transcranial magnetic stimulation of the contralateral primary motor cortex) and EMG activity of agonist muscles, possibly related to an increase of motor unit synchronization.


*Keywords:* Motor cortex; Mechanical stimulation; Pain; Hand; Transcranial magnetic stimulation; Electromyography

The pain system and the motor system are functionally linked at multiple levels of the neuraxis, including the cerebral cortex [10,11,18]. Stimulation of the motor cortex can induce suppression of noxious-evoked activity in somatosensory relay stations [8,12,19], and exerts a powerful analgesic effect in some central pain syndromes [16]. Conversely, motor and premotor cortical areas often display increases of regional blood flow during somatic pain in humans. These hemodynamic changes could however reflect either excitation or inhibition of corticospinal networks [1,7]. Recent transcranial magnetic stimulation (TMS) studies found decreased primary motor cortex (MI) excitability at rest, both during phasic [9,15,17] and tonic [5,10] noxious stimulation of the hand or of the trigeminal territory. These effects may be related to protective reflexes acting at both spinal and supraspinal sites [6,9,10,15].

Under natural circumstances, noxious stimulation often results from active movements, and it may be necessary to maintain willed muscle contraction even if this induces pain. Available data on the effects of noxious input on cortical motor excitability during active muscle contraction are, however, limited to the trigeminal territory [14]. To further address this issue, we hereby investigated, using TMS, changes in MI excitability during sustained noxious and non-noxious mechanical stimulation of the first hand digit, either resulting from active muscle contraction (self-stimulation) or from passive (externally-induced) stimulation.

Twelve (six male, six female) right handed [13] normal subjects (mean age 23 years) participated in the experiment after giving their informed consent. The experimental procedure was approved by the local University Ethical Committee. The experiment took place in a sound attenuated room, dimly illuminated. Participants were seated on a motorized dental armchair with both elbows flexed and their hands supinated in a relaxed position. Participants' head was laying on a headrest and the backrest was regulated at about 45° to maintain a comfortable and stable head position. Participants underwent two different sessions during the same day: a mapping session and an experimental session that consisted of four experimental conditions and two control conditions. The experimental conditions consisted in: (1) active noxious stimulation; (2) passive noxious stimulation; (3) active non-noxious stimulation; and (4) passive non-noxious stimulation of the right thumb. Noxious and non-noxious stimuli were applied to the

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pulpar surface of the thumb by using the specially designed manipulandum shown in Fig. 1.

In brief, the apparatus consisted in a solid plastic cylinder (30 × 150 mm) with a grove in which subjects inserted their right thumb (Fig. 1B). A longitudinal hole was drilled along the cylinder hosting a sharpened aluminum stick (Fig. 1A, 2). At the basis of the stick, a transverse hole in the cylinder hosted a latex bulb (Fig. 1A, 3) connected to a 50 cm silicon tube, graduated at the end (which was left open) and acting like a manometer. The end of the tube was located in front of the subject at about 60 cm of distance from its frontal plane and the system was filled with ink colored fluid. During stick lowering, the elastic resistance of the latex bulb acted as a spring, the fluid was pushed inside the tube and its level raised proportionally to the force applied to the stick, thus giving to the subject a visual feedback on the amount of applied pressure.

During both active conditions, subjects were asked to exert a pressure of about 350 g and to continuously monitor the fluid level in order to maintain constant their effort. During active noxious stimulation, pressure was exerted on the sharpened tip, whereas during active non-noxious stimulation the tip of the stick was covered by a flat metallic cap. During passive conditions, subjects were instructed to relax their thumb and the finger pulpar surface was pressed against the stick tip (either sharpened or covered) by lowering the uppermost screw (Fig. 1A, 1). The screw position was adjusted to generate a pressure of the finger on the stick tip equal to that exerted during active conditions. There were two control conditions. In the first, subjects stay at rest, totally relaxed. In the second, the left thumb, ipsilateral to the stimulated cortex, was actively pressed on the sharpened tip. In all the experimental and the control conditions, participants were required to fixate the graduated scale printed on the tubing located in front of them.

The intensity of perceived pain was evaluated in a preliminary psychophysical investigation on a different group of ten subjects (five males, five females; mean age, 24 years). They were requested to judge the painfulness of noxious experimental stimuli (during active and passive conditions, five repetitions for each condition), by scoring them on a 0–100 scale (0 = no pain; 100 = maximal imaginable pain intensity). Condition order was balanced between subjects. Scores assigned to passive noxious stimuli (mean ± SEM, 63.5 ± 6.1) were significantly higher than those of active noxious stimuli (48.0 ± 5.5) ($F(1,9) = 7.27$, $P < 0.05$).

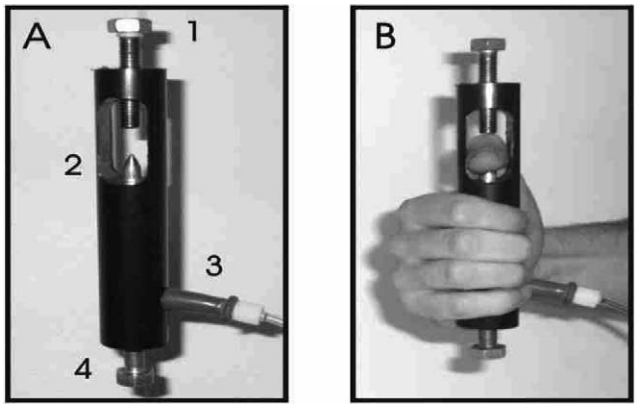


Fig. 1. The manipulandum used in the experiment. Explanations are in the text.

During mapping and experimental sessions, participants' left motor cortex was stimulated by using a Magstim Rapid magnetic stimulator (Magstim Co., UK). Biphasic magnetic stimuli were delivered through an eight shaped coil placed tangentially to the skull, with the handle pointing upwards in a medio-lateral orientation. During the mapping session, magnetic stimuli were applied on predetermined positions of a one-centimeter grid drawn on a latex swimming cap worn by participants. The coordinate origin was located at the Cz reference point determined according to the International 10–20 EEG system. Motor-evoked potentials (MEPs) were recorded from the right hand opponens pollicis muscle (OP, acting as an agonist during the task) by using 6 mm Ag-AgCl surface electrodes (Kendall GmbH, Germany) glued to the participants' skin according to a tendon-belly bipolar disposition. The cortical representation of OP was initially assessed with the stimulator intensity regulated at 70% of its maximum power. After detecting the point showing the highest evoked OP response (hot-spot), the intensity of stimulation was gradually reduced and the OP motor threshold (presence of detectable MEPs in five out of ten stimuli) was established.

During the experimental session, the coil was positioned at the center of the previously determined OP hot-spot and was kept in a stable position by means of an articulated arm (Manfrotto, Italy). The stimulus intensity was adjusted at about 110% of the OP motor threshold and corticospinal excitability was assessed during the four experimental and the two control conditions. For each condition, each subject underwent 12 TMS stimulations during two 45 s periods separated by a brief rest (about 30 s). The whole procedure took approximately 45 min.

MEPs evoked from 100 ms before to 100 ms after TMS were band-pass filtered (50–1000 Hz), digitized (2000 Hz) and stored on a computer. After EMG rectification, the area underlying each MEP was calculated and used for subsequent analyses.

A one-way analysis of variance (ANOVA) was performed on MEPs' area after intrasubject normalization ($z$-scores, Fig. 2). The considered factor was Condition with six levels (the four experimental and the two control conditions). The main effect was significant ($F(4,44) = 86.99$, $P < 0.0001$). Post hoc analysis (Newman–Keuls test, $P < 0.05$) revealed that MEPs recorded during active noxious stimulation were significantly higher than those recorded during all other conditions. MEPs recorded during active non-noxious stimulation were significantly higher than those recorded during the two controls and the two passive stimulation conditions. Passive

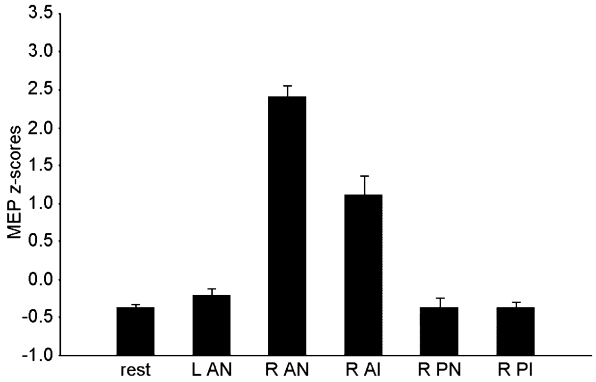


Fig. 2. Mean values of MEPs $z$-scores evoked by left motor cortex TMS. The two control conditions were rest and left thumb active noxious stimulation (L AN). The four experimental conditions were right thumb active noxious (R AN) and non-noxious (R AI) stimulations and right thumb passive noxious (R PN) and non-noxious (R PI) stimulations. See text for further explanations.

noxious and non-noxious stimulation and the two control conditions did not statistically differ one from each other.

To further investigate the presence of MEP modulation due to active/passive and noxious/non-noxious conditions, a two-ways ANOVA was performed on MEPs $z$-scores recorded during the four experimental conditions only (Motor Task: active and passive; Stimulus: noxious and non-noxious). The results showed that both main effects and the interaction between the two factors were significant (Motor Task, $F(1, 11) = 291.73$, $P < 0.0001$; Stimulus, $F(1, 11) = 35.38$, $P < 0.0001$; interaction, $F(1, 11) = 11.81$, $P < 0.01$).

The fact that MEPs recorded from the right OP muscle after TMS of the contralateral motor cortex were not influenced by *passive* noxious or non-noxious stimulation of the thumb is at odds with previous data showing that corticospinal excitability is modulated by brief thermal [17] or electrical [9,15] noxious stimuli. Possible reasons at the basis of this discrepancy include the type (mechanical) and duration of noxious stimulation. Moreover, in our paradigm, a pressure was applied on the finger dorsal surface to push the subject's thumb onto the sharpened tip. Tactile stimulation of the dorsal surface of the hand may elicit complex reflex actions influencing the excitability of flexor reflex afferent system [2]. In our paradigm, this might have masked the underlying noxious-induced modulation.

During *active* thumb pressing on the noxious tip, MEPs recorded from the right OP muscle after TMS of the left motor cortex significantly increased with respect to *active* thumb pressing on a non-noxious tip. The absence of MEPs increase during active noxious stimulation of the left thumb (ipsilateral to the stimulated cortex) rules out the possibility of unspecific modulation of corticospinal excitability (e.g. arousal effects).

Considering that in both noxious and non-noxious active conditions the same degree of force was exerted, one could argue that OP MEPs facilitation in the painful condition results from a larger muscle activation generated to overcome the spinal inhibition (and/or the facilitation of antagonist muscles) resulting from protective reflexes. Indeed, brief noxious finger stimulation is known to exert strong post-synaptic inhibition, related to A-delta afferents, of the C7-T1 motoneurons [6]. To investigate the role played by antagonist muscles, we performed an additional experiment in six normal subjects (four females, two males; mean age, 28 years) while they executed the same tasks. We recorded surface EMG from OP (agonist for thumb pressing), extensor pollicis and abduttor pollicis brevis muscles (EP and APB, antagonists for thumb pressing) and from flexor digitorum superficialis (FDS, which participates in manipulandum holding). Statistical analysis (ANOVA + Newman–Keuls pairwise comparison, $P < 0.05$) performed on normalized EMG root mean squares (RMS) showed that, apart from obvious differences between active and passive conditions, OP was significantly more active during active noxious than non-noxious stimulation (+139.5%). However, EP and APB (antagonist muscles) were similarly active during noxious and non-noxious conditions. Surprisingly, FDS was significantly more active (approximately + 200%) during active noxious stimulation with respect to the other three conditions, which did not differ one from each other. This unexpected result suggests that during active noxious stimulation subjects held the manipulandum with more force than during active non-noxious one. One possible interpretation is that during noxious self-stimulation the force pattern applied by subjects' thumb onto the tip was somehow different from that applied during non-noxious stimulation, because of additional components (directed anteriorly or posteriorly) which could be counteracted by FDS. This hypothesis seems quite unlikely because the total measured force did not vary in the two conditions. Alternatively, it may be hypothesized that EMG increases of both OP and FDS during prolonged painful self-stimulation reflect a change in motor strategy. For instance, during a sustained non-noxious contraction of hand muscles (10% of maximum voluntary contraction for several minutes) an increase of RMS values *without force variation* could be due to a synchronization of motor units recruitment and is accompanied by a decrease in frequency of EMG power spectrum [3]. Although in the present study trial duration was considerably shorter, it is possible that painful self-stimulation shares (in a broad sense) some features with fatigue. Indeed, also in the present experiment, the increment of RMS activity observed during active noxious vs. non-noxious stimulation was paralleled by a significant shift of power spectra towards lower frequency values (data not shown).

In conclusion, the present results indicate that, in order to press a finger onto a noxious stimulus with the same force generated to press onto a non-noxious one, the motor cortex adopts a peculiar strategy in terms of recruitment of motor units. This is reflected by an increase of corticospinal excitability and of RMS activity of agonist muscles,

possibly due to an increase of motor unit synchronization. Furthermore, this recruitment strategy is accompanied by a synergic activation of hand muscles participating in holding the manipulandum. This increase in holding force is not directly serving the finger task, but could be necessary to contrast the natural tendency to release the painful stimulus. Moreover, giving the pain-alleviating effects of motor cortex stimulation [4], the observed increase in motor output might reflect an antalgic strategy.

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