

Predictive Value of rTMS in the Identification of Responders to Epidural Motor Cortex Stimulation Therapy for Pain

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Abstract: This study was designed to assess the value of repetitive transcranial magnetic stimulation (rTMS) to predict the efficacy of epidural motor cortex stimulation (EMCS) to treat neuropathic pain. We have included 59 patients treated by EMCS for more than 1 year and in whom active and sham 10Hz-rTMS sessions were performed as preoperative tests, targeted over the cortical representation of the painful area. Analgesic effects were rated on a visual analogue scale. The real rTMS efficacy was determined by subtracting the effect of the sham stimulation on pain scores from that of the active stimulation (active-sham calculation). Pain scores were significantly reduced by active rTMS and EMCS, but not by sham rTMS. Twenty-six of the 33 patients (79%) who responded to active rTMS and all the 21 patients (100%) who responded for active-sham calculation also responded to EMCS. The response observed in active-sham calculation had a positive predictive value of 1.0, but a negative predictive value of .6 regarding EMCS outcome. The analgesic effect of rTMS or EMCS was not influenced by the side, origin, or duration of pain or by the presence of motor or sensory deficit in the painful area. Poorer results were observed in case of lower limb pain for rTMS and in older patients for EMCS. This study confirms that neuropathic pain can be significantly relieved by motor cortex rTMS or EMCS. A positive outcome of EMCS can be predicted by a real response to rTMS, but not on clinical grounds.

Perspective: Single sessions of sham-controlled preoperative rTMS tests can be used to confirm the indication of EMCS therapy but have no value to exclude patients from this therapy. New rTMS protocols remain to be assessed to improve the usefulness of preoperative rTMS in EMCS practice.

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Key words: Epidural stimulation, motor cortex, neuropathic pain, neurostimulation therapy, predictive factor, transcranial magnetic stimulation.

Implanted epidural motor cortex stimulation (EMCS) was first proposed in 1991 as a neurostimulation therapy for chronic, drug-resistant neuropathic pain.³⁵ The efficacy of EMCS was initially reported for thalamic pain and then confirmed for neuropathic pain syndromes of other etiologies.^{2,4,13,26,28,34,36} Recent meta-analyses showed that EMCS has positive therapeutic effects on pain in 55 to 64% of patients.^{7,25} However, criteria

predicting the outcome of EMCS are lacking. Some studies have reported a positive association between EMCS efficacy and preserved sensory⁶ or motor^{3,11} function in the painful area during preoperative clinical examination, but a larger series failed to confirm these findings.³⁰ Various drug challenge tests have also been proposed, including preoperative sensitivity to anesthetic drugs such as ketamine and propofol.^{2,33} In particular, sensitivity to barbiturates (thiopental) associated with insensitivity to opioids (morphine) was initially considered to be a favorable profile for EMCS therapy,³⁸ but this result was subsequently invalidated.³³

Besides EMCS results, it was shown that neuropathic pain could also be relieved by repetitive transcranial magnetic stimulation (rTMS) applied at high frequency (5–20 Hz) over the primary motor cortex.¹⁴ A correlation

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between the analgesic effects produced by high-frequency rTMS in preoperative testing and the efficacy of subsequent EMCS therapy has been described in few case reports or small open studies without placebo control.^{1,10,20} Herein, we report our experience in 59 patients who underwent preoperative rTMS tests before EMCS implantation.

Methods

Between September 1999 and September 2006, 82 patients were implanted by Prof. J. P. Nguyen in Henri Mondor hospital (APHP, Créteil, France) for the treatment of chronic refractory neuropathic pain by EMCS. We have reviewed the course of all these patients to determine if they had performed preoperative rTMS tests during this period. To be included in our study, patients had to: 1) have undergone both active and sham preoperative rTMS sessions, targeted over the cortical representation of the painful area, with clearly defined, standardized parameters of stimulation (frequency, 10 Hz; intensity, 90% of rest motor threshold (RMT); total number of pulses per session, 2,000 pulses); 2) have been stimulated for at least 1 year with implanted EMCS; and 3) have rated their mean daily pain on a 0 to 10 visual analogue scale (VAS) during the week preceding and following both active and sham rTMS sessions and a week before and 1 year after EMCS implantation.

From the whole series of 82 patients, 23 patients have been excluded from this study because of: 1) impossible rTMS targeting due to absent motor evoked potentials (MEPs) in painful area in the context of amputation ($n = 1$), perineal pain ($n = 2$), or lower limb pain ($n = 3$); 2) specific research protocol that did not include preoperative rTMS test ($n = 6$); 3) preoperative screening outside Henri Mondor hospital ($n = 5$); 4) reintervention with repositioning of epidural electrode ($n = 2$); and 5) unavailable EMCS data at 1 year after surgery due to explantation for infection ($n = 1$), trauma ($n = 2$), or psychological intolerance to the stimulator shortly after implant (fear of electromagnetic interference due to the implanted pulse generator) ($n = 1$).

Therefore, 59 patients were retrospectively included in this study (Fig 1). Among these 59 patients, 32 had initially received the active rTMS condition. The active and sham sessions were always separated by more than 3 weeks. All patients had given their informed consent for the preoperative rTMS tests, which were made in the context of research programs on the treatment of chronic neuropathic pain by EMCS approved by the local ethics committee. All preoperative rTMS tests were performed by the same operators (JPL, IML) using the same stimulus material and the same experimental procedure.

Patients

The patients were 35 men and 24 women, aged from 28 to 80 years (mean [SD]: 55.0 [12.6]). They presented chronic pain syndrome (average pain level ≥ 5 on a 0 to

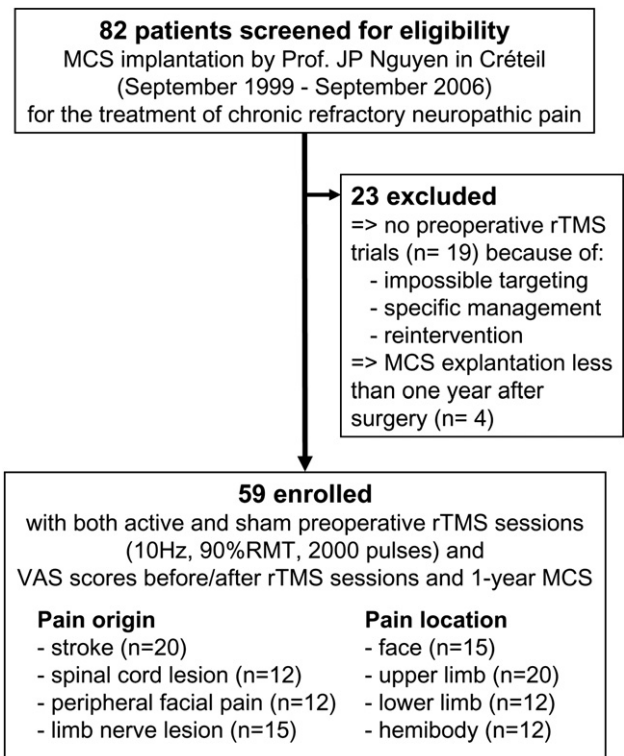


Figure 1. Flow chart diagram showing the number of patients at the stage of screening and inclusion.

10 visual analogue scale (VAS) over 7 days of self-assessment) for more than 2 years. Pain was refractory to at least 3 different types of analgesic medical treatments, including antiepileptics and antidepressants. They were therefore eligible for EMCS therapy.⁵

Pain duration ranged between 2 and 30 years (mean [SD]: 8.3 [5.9]). Pain origin was related to: 1) stroke ($n = 20$: 34.0%), affecting the thalamus ($n = 9$), the brainstem ($n = 7$), or the cortex ($n = 4$); 2) spinal cord lesion ($n = 12$: 20.3%) related to syrinx ($n = 5$), following surgery for spondylotic myelopathy ($n = 4$), or posttrauma ($n = 3$); 3) peripheral facial pain ($n = 12$: 20.3%) related to trigeminal neuralgia refractory to surgical treatment ($n = 7$), tooth avulsion ($n = 3$), or secondary to surgical lesion of the trigeminal nerve ($n = 2$); and 4) limb nerve lesion ($n = 15$: 25.4%), due to lesion of the brachial plexus secondary to trauma ($n = 6$), irradiation ($n = 1$), or thoracic outlet surgery ($n = 1$), or due to traumatic lesion of a nerve trunk at upper ($n = 4$) or lower ($n = 3$) limb.

Pain was unilateral, on the right side ($n = 28$: 47.5%) or on the left side ($n = 31$: 52.5%), localized or predominant in the face ($n = 15$: 25.4%), upper limb ($n = 20$: 34.0%), lower limb ($n = 12$: 20.3%), or hemibody ($n = 12$: 20.3%). In a number of patients, clinical examination revealed a deficit in the painful area of the body, regarding strength ($n = 22$: 37.3%), mechanical sensitivity ($n = 33$: 55.9%), or thermal sensitivity ($n = 38$: 64.4%).

Repetitive Transcranial Magnetic Stimulation

Both rTMS sessions, active and sham, were conducted identically.

First, RMT was assessed by recording MEPs in the first dorsal interosseus muscle of the hand on pain side, regardless of pain location. Determining RMT for only this muscle was designed to standardize the procedure, but the choice of this strategy was in fact arbitrary. RMT is defined as the minimal intensity of stimulation required to elicit MEPs of more than 50 μ V in amplitude in at least 5 out of 10 trials performed during complete muscle relaxation.³² Stimulation was delivered using the single-pulse program of a Super-Rapid Magstim magnetic stimulator (The Magstim Co., Whitland, UK) with a figure-of-eight shaped coil (70-mm Double Coil, #9925-00, Magstim). The coil was placed tangentially to the scalp and angled at 45° relative to the interhemispheric fissure, approximately perpendicular to the central sulcus, for optimal activation of the corticospinal pathways. The MEPs were recorded using a standard EMG machine (Phasis II, EsaOte, Florence, Italy) and pre-gelled self-adhesive disposable surface electrodes (#9013S0241, Alpine Biomed, Skovlunde, Denmark).

Second, the rTMS target was determined as the scalp site where single-pulse TMS was able to generate contralateral MEPs of maximal amplitude in a muscle located in the painful area of the body. The MEPs were recorded in nasalis or orbicularis oris muscle for facial pain; deltoid, biceps brachii, extensor carpi radialis, or first dorsal interosseus muscle for upper limb pain; vastus medialis, tibialis anterior, or soleus muscle for lower limb pain. In patients with hemibody pain, the pain area always included the hand and therefore, MEPs were recorded in the first dorsal interosseus muscle.

Third, rTMS was performed using the Super-Rapid Magstim magnetic stimulator with a figure-of-eight shaped coil centered over the rTMS target, as defined above. The coil was oriented postero-anteriorly, parallel to the interhemispheric fissure, the handle pointing backwards. Pulses of biphasic waveform were delivered and therefore the initial direction of the current induced into the brain was posterior to anterior. Each rTMS session consisted of a series of 20 trains of 10 seconds in duration (30-second intertrain interval) at a stimulation rate of 10 Hz (2,000 pulses) and an intensity set at 90% of RMT. The frequency of 10 Hz was chosen because significant pain relief was obtained when using this frequency (and not lower frequencies) in all our previous studies.^{15,19,21,24} An active figure-of-eight coil (#9925-00, Magstim) was used for one session and a placebo figure-of-eight coil (#1730-23-00, Magstim) was used for the other. The placebo coil looks the same as the active coil and produces discharge noise and slight sensory stimulation of the scalp, but does not induce any substantial current in the cortical tissue. The patients were not instructed about the existence of a sham condition, but they were informed that 2 sessions using different parameters would be tested for their respective efficacy in relieving pain.

Surgical Procedure

All leads and stimulators were implanted under general anesthesia using a surgical procedure previously

described.^{17,27} Briefly, 1 or 2 quadripolar leads (Resume® electrode, Medtronic, Inc., Minneapolis, MN) were attached to the dura mater in the cortical region corresponding to the painful area of the body. Electrode arrays were placed, perpendicular to the central sulcus, according to neuroradiological navigation and intraoperative neurophysiological mapping using somatosensory and motor evoked potentials. The leads were connected, via an extension, to a neurostimulator (implanted pulse generator). In almost all patients, the stimulator was a Synergy model (#7427, Medtronic) placed subcutaneously in the subclavicular region. The mean parameters of chronic stimulation were as follows: number of active contacts, 2.3 (range: 2–4); voltage, 2.5V (range: 1–7); pulse duration, 68 μ sec (range: 60–150); frequency, 41 Hz (range: 25–60); stimulation mode, 80% continuous versus 20% cyclic 12 hour-12 hour.

Pain Level Assessment

The patients were instructed to self-rate the averaged intensity of their pain on a 0 to 10 VAS (0 = no pain, 10 = highest imaginable pain) once a day. Since analgesic effects can be observed up to 8 days after an rTMS session,²² daily pain was recorded for 1 week after each session. Daily scores were averaged and the resulting mean score was retained for analysis. Pain scores were also recorded for 1 week before each rTMS session, and before and 1 year after EMCS implantation. Baseline EMCS scores were obtained before any preoperative rTMS trial was conducted.

The percent change from baseline in mean pain scores was calculated by dividing the difference score (after score subtracted from the before score) by the before score and multiplying this ratio by 100 [(pre–post) \times 100/(pre)] for active rTMS, sham rTMS, and EMCS. Regarding rTMS, the percent change calculated for the sham session was subtracted from that calculated for the active session (active-sham) to determine the real effect of motor cortex rTMS on pain. A good responder to rTMS was defined by an active-sham percentage of pain relief equal or greater than 30%.^{19,21} A good responder to EMCS was defined by a percentage of pain relief equal or greater than 50%.⁷

Statistical Analyses

All mean pain scores (averaged from each week of assessment) recorded before and after active rTMS, sham rTMS, and EMCS were analyzed using repeated measures ANOVA under 6 conditions that resulted from the combination of 2 nominal variables as within-subject factors: Stimulation, with 3 group levels (active rTMS, sham rTMS, EMCS), and Time, with 2 group levels (before, after). A *P* value of less than .05 was considered as significant. In case of significant ANOVA, Bonferroni post hoc tests were performed including a correction for multiple comparisons (level of significance set at *P* < .0033).

Percentage changes in pain scores (analgesic effects) produced by active or sham rTMS, or observed in active-sham calculation, and following EMCS, were

compared using the Kruskal-Wallis ANOVA test with Dunn's multiple comparisons post hoc tests. The correlation between the analgesic effect produced by EMCS and that produced by each rTMS condition (active or sham) or observed in active-sham calculation was studied using the Spearman test. The influence of age and pain duration on the analgesic effect observed in active-sham calculation or following EMCS was also studied using the Spearman test. The influence of the first performed rTMS condition (active or sham) on the analgesic effect observed in active-sham calculation and the influence of pain side (right or left) and motor, mechanical, or thermal sensory deficit (present or absent) on the analgesic effect observed in active-sham calculation or EMCS were studied using the Mann-Whitney test. The influence of pain origin (stroke, spinal cord lesion, peripheral facial or limb pain) and pain location (face, upper or lower limb, or hemibody) on the analgesic effect observed in active-sham calculation or following EMCS was studied using the Kruskal-Wallis ANOVA test with Dunn's multiple comparisons post hoc tests. All these tests were nonparametric because most data failed to pass the normality test using the Kolmogorov-Smirnov method. A 2-tailed P value of less than .05 was considered as significant.

Finally, results were analyzed in terms of responders. The relationship between the rate of responders versus nonresponders to active rTMS or observed in active-sham calculation compared to that obtained by EMCS was analyzed using the Fisher's Exact Test. We also calculated the positive and negative predictive values of rTMS for EMCS outcome.

Results

The mean pain scores varied with the conditions ($F(5,58) = 42.69$, $P < .0001$, repeated measure ANOVA) (Fig 2). Effects of Stimulation ($F(2,58) = 3.10$, $P = .0489$) and Time ($F(1,58) = 130.42$, $P < .0001$) were significant, as well as Stimulation \times Time interaction ($F(2,58) = 30.71$, $P < .0001$). Post hoc tests did not show significant differences in pain scores at baseline (before scores) between conditions. By contrast, pain scores were lower after active rTMS or EMCS than after sham rTMS ($P < .0001$, Bonferroni test). Actually, pain scores were reduced by active rTMS or EMCS, but not by sham rTMS (Fig 2).

The percentage changes in pain scores (analgesic effects) also varied with the conditions ($P < .0001$, Kruskal-Wallis ANOVA test) (Fig 2). The analgesic effect of active rTMS or EMCS was greater than that of sham rTMS ($P < .0001$, Dunn test). Pain score reduction did not differ between active rTMS condition and EMCS, but was greater for EMCS than observed in active-sham calculation ($P < .0001$) (Fig 2).

Correlates of EMCS or rTMS Analgesic Effects

The analgesic effect of EMCS positively correlated with that of active rTMS ($r = .31$, $P = .0156$, Spearman test)

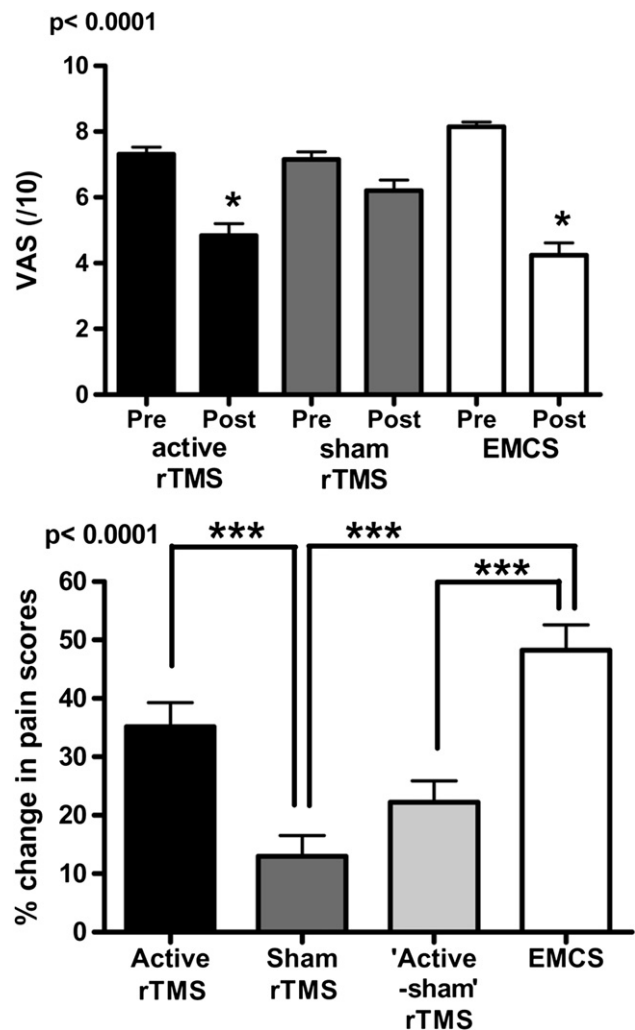


Figure 2. Upper part: mean (+sem) pain scores (on a 0–10 visual analogue scale, VAS) measured before (pre) and after (post) a single session of active or sham repetitive transcranial magnetic stimulation (rTMS) or implanted epidural stimulation (EMCS) of the motor cortex corresponding to the pain area. Pain scores were significantly lower after active rTMS or EMCS than in other conditions (* = $P < .0001$, Bonferroni test). Lower part: mean (+sem) percentage changes in pain scores produced by rTMS or EMCS. Pain reduction was greater for active rTMS or EMCS than for sham rTMS and also for EMCS than for active-sham calculation (***) = $P < .0001$, Dunn test).

or that observed in active-sham calculation ($r = .42$, $P = .0010$), but not with that of sham rTMS ($r = -.09$, $P = .4882$) (Fig 3).

The analgesic effect observed in active-sham calculation did not differ whether the first rTMS test was the active or the sham one ($P = .2797$, Mann-Whitney test). There was also no difference in the analgesic effects observed in active-sham calculation and following EMCS according to the side of pain ($P = .1041$ and $.8673$, respectively, Mann-Whitney test) or to the presence of motor deficit ($P = .7124$ and $.3630$), mechanical sensory deficit ($P = .3435$ and $.8307$), or thermal sensory deficit ($P = .1169$ and $.5009$) (Fig 4).

Pain duration did not correlate with the analgesic effect observed in active-sham calculation ($r = .12$, $P = .3508$, Spearman test) or following EMCS ($r = .18$,

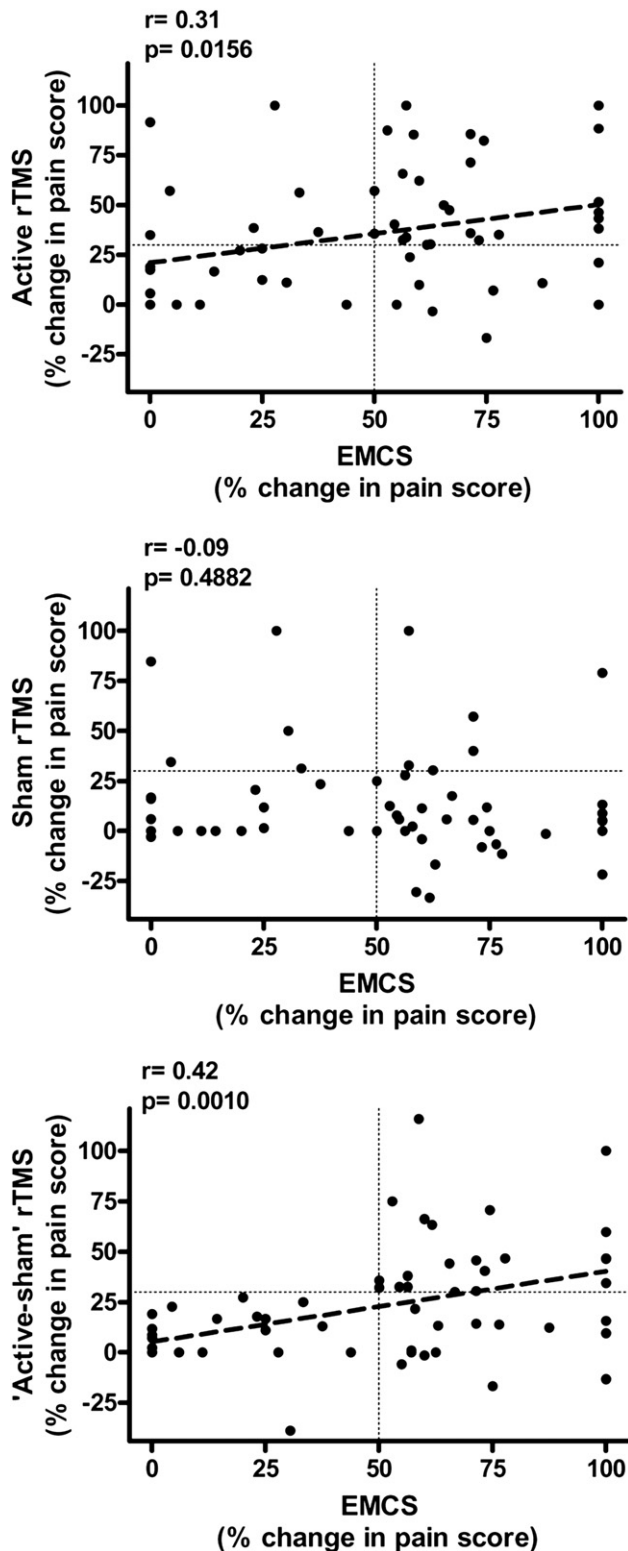


Figure 3. Relationship between the analgesic effect of epidural motor cortex stimulation (EMCS) and that of active or sham repetitive transcranial magnetic stimulation (rTMS) of the motor cortex corresponding to the pain area, or active-sham calculation. Significant correlations were found between EMCS efficacy and the efficacy observed following active rTMS or for active-sham calculation.

$P = .1611$) (Fig 5). Patient's age also did not correlate with the analgesic effect observed in active-sham calculation ($r = .00$, $P = .9812$), but negatively correlated with that

of EMCS ($r = -.31$, $P = .0188$) (Fig 5). Pain origin (stroke, spinal cord lesion, peripheral trigeminal, or limb pain) did not influence the analgesic effects observed in active-sham calculation and following EMCS ($P = .2431$ and $.6382$, respectively, Kruskal-Wallis test) (Fig 6). Finally, pain location (face, upper or lower limb, or hemibody) did not influence the analgesic effect of EMCS ($P = .5541$), in contrast to that which was observed in active-sham calculation ($P = .0151$) (Fig 6). Dunn's post hoc tests showed that the analgesic effect observed in active-sham calculation was lower in case of lower limb pain than in case of facial or upper limb pain ($P < .05$).

EMCS and rTMS Responders and Predictive Values

In terms of responders, 33 patients (56%) responded to active rTMS, 11 (19%) to sham rTMS, 21 (36%) in case of active-sham calculation, and 35 (59%) to EMCS.

Among the 33 patients who responded to active rTMS, 26 patients (79%) responded to EMCS and 7 (21%) did not respond. Among the 26 patients who did not respond to active rTMS, 9 patients (35%) responded to EMCS and 17 (65%) did not respond. The association between active rTMS and EMCS responses was very significant ($P = .0011$, Fisher's Exact Test) with positive predictive value of .7879 (95% Confidence Interval: .6113–.9102), and negative predictive value of .6538 (.4431–.8277).

All of the 21 patients who were responders in case of active-sham calculation also responded to EMCS. Among the 38 patients who did not respond in case of active-sham calculation, 14 patients (37%) responded to EMCS and 24 (63%) did not respond. The association between the response observed in active-sham calculation and following EMCS responses was extremely significant ($P < .0001$, Fisher's Exact Test) with positive predictive value of 1.000 (95% Confidence Interval: .8390–1.000), and negative predictive value of .6316 (.4599–.7816).

Discussion

This study confirms that rTMS and EMCS are effective in relieving chronic neuropathic pain and describes the factors that may influence such an efficacy. This study also shows that the analgesic effect of preoperative rTMS correlates to that of subsequent EMCS at 1-year postoperative, a positive response to preoperative rTMS tests predicting good EMCS efficacy. These 2 different aspects of the study will be treated successively in the discussion.

First, we found that precentral cortical stimulation, using rTMS or EMCS, was able to produce analgesic effects in patients with chronic refractory neuropathic pain. Regarding rTMS, we had the opportunity to compare an active to a sham procedure: active rTMS significantly reduced pain scores, but not sham rTMS. By contrast, the EMCS procedure was not controlled (we did not perform a comparative study between on-stimulation and off-stimulation conditions) and therefore the results

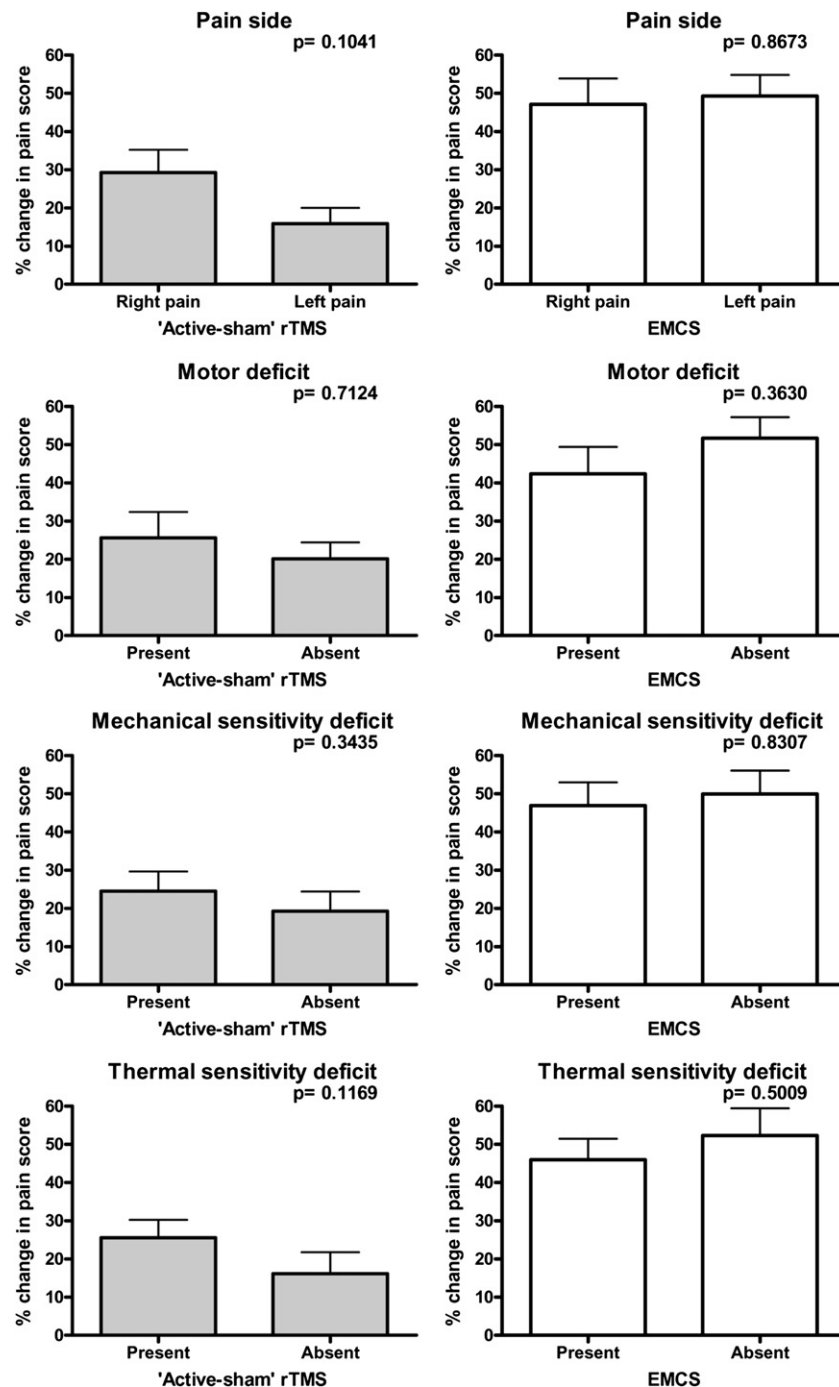


Figure 4. The analgesic effect produced by repetitive transcranial magnetic stimulation (rTMS) (according to the difference of efficacy between active and sham conditions) or by implanted epidural stimulation (EMCS) of the motor cortex corresponding to the pain area did not differ with the side of pain or the presence or absence of motor or sensory deficit.

incorporate the placebo effect. However, the efficacy of EMCS on neuropathic pain is supported by several controlled crossover trials.^{18,29,31,37}

We studied the potential influence of various factors on the analgesic effect of rTMS or EMCS. We found that the side, origin, or duration of pain or the presence of motor or sensory deficit in the painful area did not influence the efficacy of cortical stimulation. By contrast, rTMS was influenced by pain location (poorer results were observed in case of lower limb pain) and EMCS by

patient's age (poorer results were observed in older patients).

Poorer rTMS results in case of lower limb pain could be explained by the fact that the motor cortical representation of the lower limb (in the mesial wall of each frontal lobe) is farther from the scalp than the representation of the upper limb or the face (in the lateral part of precentral gyrus convexity). However, if the distance to the stimulating source was the key factor of treatment efficacy, then EMCS should similarly be affected by pain location

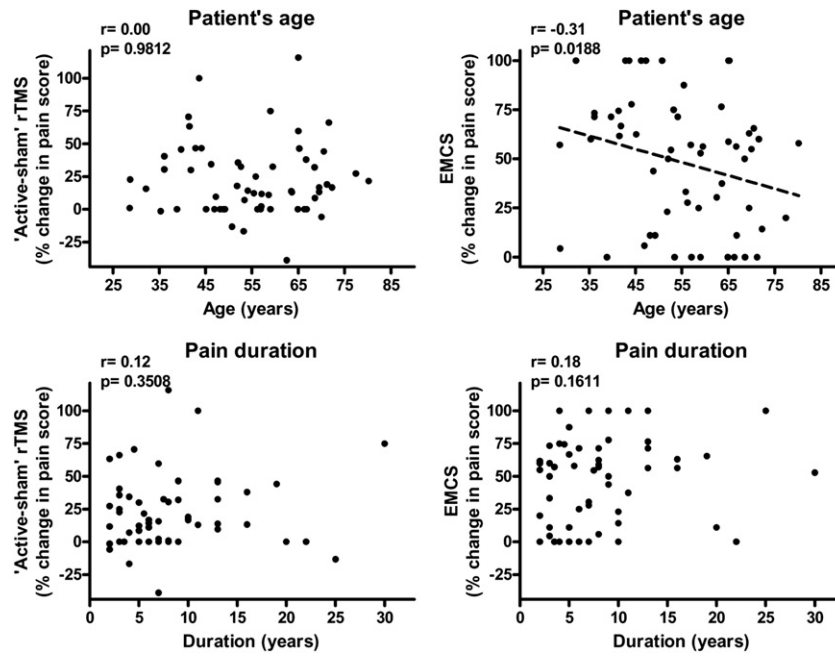


Figure 5. Relationship between patient's age or pain duration and the analgesic effect produced by repetitive transcranial magnetic stimulation (rTMS) (according to the difference of efficacy between active and sham conditions) or by implanted epidural stimulation (EMCS) of the motor cortex corresponding to the pain area. Patient's age negatively correlated with the analgesic effect of EMCS.

in the lower limb. Actually, pain relief provided by EMCS was slightly lower for lower limb pain than other pain locations, but the difference did not reach statistical significance. EMCS could be better than rTMS to act on such a distant target, because EMCS (performed with a quadripolar lead) can activate a larger cortical area than rTMS and because rTMS intensity (expressed as a percentage of RMT assessed in hand muscle regardless of pain location)

may be suboptimal for reaching the cortical representation of the lower limb.

In fact, it is thought that rTMS and EMCS share almost the same mechanisms of action for pain relief, and, for example, it was recently demonstrated that both techniques produced the same descending volleys at the spinal level.²³ Both types of stimulation can probably activate common neural circuits, modulating various

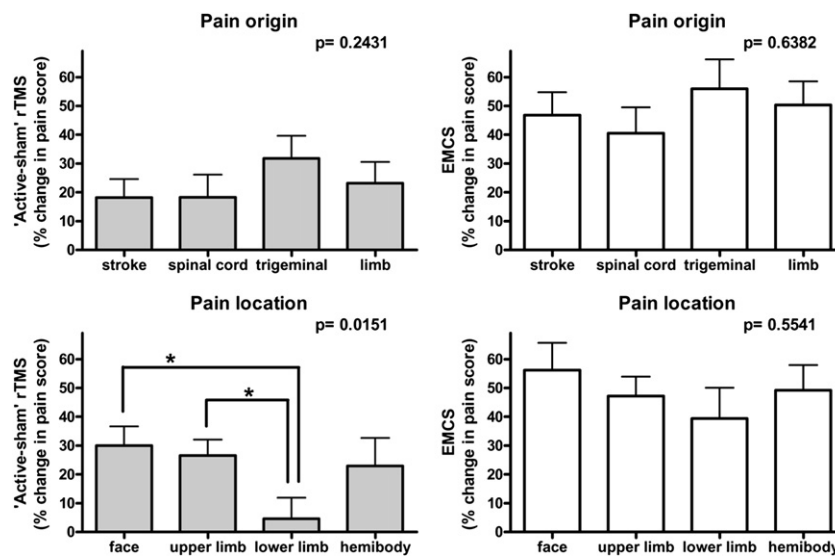


Figure 6. The analgesic effect produced by repetitive transcranial magnetic stimulation (rTMS) (according to the difference of efficacy between active and sham conditions) or by implanted epidural stimulation (EMCS) of the motor cortex corresponding to the pain area did not vary with pain origin (stroke, spinal cord lesion, or peripheral trigeminal or limb nerve pain). Pain location (face, upper or lower limb, or hemibody) influenced the analgesic effect observed in the calculation of active-sham rTMS, but not that of EMCS. The analgesic effect observed in the calculation of active-sham rTMS was lower in case of lower limb pain than in case of facial or upper limb pain (* = $P < .05$, Dunn test).

structures of the central nervous system distant from the site of stimulation and involved in pain processing, including a top-down inhibition of dorsal horn neurons via the activation of brainstem structures.¹⁴

The second factor associated with the analgesic effect of cortical stimulation was patient's age, which was negatively correlated with EMCS efficacy. Age should be taken into account before considering EMCS therapy, particularly with respect to cortical atrophy, because the amount of current reaching the cortical layers could be less effective for epidural stimulation in this context. However, in the 15 oldest patients of this series (more than 65 years old), there was a majority of EMCS responders (8 patients, 53%) with a percentage of pain relief produced by EMCS equal or greater than 50%. In addition, increasing age did not affect rTMS efficacy. For all these reasons, the influence of age does not appear to be a key factor for treatment efficacy and it is probably not justified to set a limit of age for selecting good candidates for EMCS implantation.

In contrast to previous EMCS^{3,6,11} or rTMS^{19,21} studies, we did not find an association between the analgesic effect of cortical stimulation and pain origin or preserved sensorimotor function in the painful area. This confirms the negative results previously reported in a large series of 31 patients with refractory neuropathic pain treated by EMCS.³⁰ On the whole, preoperative clinical examination cannot provide reliable predictive factors for EMCS outcome. Therefore, the correlation found between rTMS and EMCS efficacy was particularly appealing.

This correlation was found for the active rTMS condition or in case of active-sham calculation, but not for the sham rTMS condition. This strongly suggests that the analgesic effect of EMCS at 1 year after implantation is not a placebo effect. This also means that placebo responders are not good candidates for implantation.

The positive predictive value of active rTMS for positive response to EMCS was high (.7879), but among the 33 patients who responded to active rTMS, 7 patients (21%) did not respond to subsequent implantation. By contrast, the positive predictive value observed in active-sham calculation was optimal, since all the 21 patients who responded in case of active-sham calculation, also responded to EMCS. The value of high-frequency rTMS to predict EMCS outcome has previously been described in a few case reports or small series.^{1,10,21} This is the first large, controlled series of patients reported in this regard. One of the main new areas of information provided by the present study is that the analgesic effect produced by sham rTMS has to be subtracted

from that produced by active rTMS to reliably appraise the positive predictive value of rTMS.

However, the negative predictive value of rTMS was suboptimal: 9/26 patients (35%) who did not respond to active rTMS and 14/38 patients (37%) who did not respond in case of active-sham calculation were found to respond to implanted EMCS. This may be explained by some limitations of the rTMS procedure used in this study. First, we chose to stimulate the motor cortical region corresponding to the painful area, whereas rTMS applied to an adjacent cortical area may be more effective in relieving localized pain.²⁴ Second, rTMS was performed using a standard procedure of targeting based on MEP mapping, whereas the reliability of rTMS targeting can improve by using image-guided navigation.¹⁶ Indeed, the value of navigated motor cortex rTMS have recently been reported in patients with neuropathic pain.^{8,9} Unfortunately, at the time of this study (1999–2006), we were not yet equipped with such a system. Finally, the analgesic effect of rTMS was assessed after a single session, whereas it may be valuable to increase the number of sessions to obtain more reliable, prolonged, and consistent efficacy.¹²

Thus, our data indicate that even if the rTMS fails, patients might well still respond to EMCS. Based on this fact, it is not reasonable to restrict EMCS procedure only to those patients who respond to rTMS for fear of denying several other patients a chance at substantial pain relief, especially in case of lower limb pain.

Using the standard, non-navigated method described in this study, preoperative rTMS testing can confirm the indication for surgical EMCS implantation in case of positive response to rTMS. A positive response is defined by a percentage of pain relief equal or greater than 30% in the difference of efficacy between active and sham rTMS. Patients who respond to rTMS should have a high likelihood of getting some pain relief in case of subsequent EMCS therapy. But for now, preoperative rTMS tests cannot be used to exclude patients from EMCS therapy. This may seem, at first, of limited interest, but in fact it can be a great help in practice, given the absence of any other selection criteria validated to date. Further study should be designed to assess the value of other rTMS procedures, such as iterative image-guided rTMS sessions, to better predict EMCS efficacy, but also its potential ineffectiveness.

Disclosures

The authors had no conflict of interest related to this study.

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