Efficacy of motor cortex stimulation in the treatment of neuropathic pain: a randomized double-blind trial

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Object. In this study the authors used a double-blind protocol to assess the efficacy of motor cortex stimulation (MCS) for treating neuropathic pain.

Methods. Eleven patients with unilateral neuropathic pain (visual analog scale [VAS] score 8–10) of different origins and topography were selected for MCS. A 20-contact grid was implanted through a craniotomy centered over the motor cortex contralateral to the painful area. The motor cortex strip was identified using neuroimages, somatosensory evoked potentials, acute electrical stimulation, and corticocortical evoked potentials. Subacute therapeutic stimulation trials allowed the authors to determine the most efficient pair of contacts to use for long-term MCS. The grid was replaced with a 4-contact electrode connected to an internalized stimulator. Bipolar stimulation at a 40-Hz frequency, 90-μsec pulse width, amplitude 2–7 V, and 1 hour in “ON” and 4 hours in “OFF” mode was used. Pain was evaluated using the VAS, Bourhis, and McGill pain scales applied each month for 1 year. At Day 60 or 90, the stimulators were turned to OFF mode for 30 days in a randomized, double-blind fashion. The statistical tool used was the Wilcoxon test.

Results. Three patients did not report improvement in the subacute trial and were excluded from long-term MCS; the remaining patients underwent long-term stimulation. Significant improvement of pain was induced by MCS (p < 0.01); this persisted during the follow-up period. Turning stimulation to OFF mode increased pain significantly (p < 0.05). Improvement at 1 year was ≥ 40% (40–86%) in all cases.

Conclusions. Motor cortex stimulation is an efficient treatment for neuropathic pain, according to an evaluation facilitated by a double-blind maneuver. Subacute stimulation trials are recommended to determine the optimum motor cortex area to be stimulated and to identify nonresponders. (DOI: 10.3171/JNS/2008/108/4/0698)

Key Words • chronic pain • electrical stimulation • localization • motor cortex • neuropathic pain • pain control • sensory response

Electrical stimulation of the motor cortex was initially proposed to treat cases of central neuropathic pain caused by thalamic and suprathalamic lesions, mainly of vascular origin.⁴³–⁴⁵ These lesions could not be treated by dorsal column, periaqueductal, or thalamic stimulation. Since that time, MCS has been attempted and frequently reported as successful in treating neuropathic pain syndromes involving practically any body segment and pain syndromes of the most diverse origins. To date, indications for MCS, including the central poststroke syndromes,⁷,⁸,¹¹,¹⁶,¹⁸,²³,²⁴,²⁷,⁴⁰ have not been well established, mainly because numerous failures in patients with apparently good indications have been reported.¹³,²²,²⁸,²⁹,³¹,³⁶,⁴⁴ In fact, on reviewing 67 publications on MCS published in the English language, all studies report failures, including in a group of > 5 patients followed up for > 6 months, and even studies presenting few cases (2 or 3 patients) also report failures.²⁷

A number of factors have been proposed to account for these failures, including the following: poor case selection; flaws in the electrode implantation technique; inadequate neurostimulator programming; loss of efficacy due to plastic changes in the motor cortex organization;²⁶ and excessive deafferentation of the painful territory, among others.⁵,⁹,⁴⁸ However, despite the fact that these factors have been well recognized and described, the manner in which patients continue to be selected and surgically treated, their devices programmed, their outcomes evaluated, and follow-up conducted is extremely heterogeneous. For example, although the majority of reports stress the importance of precise placement of electrodes used for stimulation, the electrode placement technique is far from being standardized.
Motor cortex stimulation for pain

To predict MCS outcome from the beginning, a number of tests have been proposed and include the following: analgesic response to morphine, ketamine, and amytal; determination of the abnormal threshold of some sensory modalities and its normalization during a therapeutic stimulation trial; and analgesic response to magnetic transcranial stimulation over the frontal cortex. These techniques continue to be evaluated and are not available to the clinician in daily practice. In the present report, we analyze a number of cases with incapacitating deafferentation-related pain of different origins and affecting unilateral body segments in face, neck, arm, and chest.

After a therapeutic stimulation trial to separate responders from nonresponders, the responders were successfully treated with MCS. Patients were evaluated by means of a set of conventional international pain scales throughout a 1-year follow-up period and underwent a randomized double-blind trial. The purpose was to analyze critically the efficacy of MCS and to determine some predictors that are readily available to the clinician and that may help to differentiate responders from nonresponders for this therapeutic modality.

Clinical Materials and Methods

Patient Population

Table 1 summarizes our patients’ clinical data. Eleven patients (4 men and 7 women) ranging from 29 to 80 years of age (mean age ± standard deviation, 56 ± 17.7 years) were considered for MCS. All suffered from chronic deafferentation pain syndromes that had started from 8 months to 15 years (5.8 ± 4.9 years [mean ± standard deviation]) prior to their entering the study protocol. One patient experienced hemifacial thalamic infarct–associated pain that restricted opening of the mouth and swallowing; these actions induced excruciating pain and compromised feeding, so this individual had an early indication for MCS. Five patients suffered from postherpetic neuralgia involving the following areas: left V1 territory (1 patient), right C2–3 territory (1 patient), left brachial plexus (1 patient), and left intercostal roots (2 patients). One patient had traumatic injury of the brachial plexus with partial deafferentation of the painful territory. Two patients had cervical root avulsion, one with no motor or sensory residual function. One patient had painful arteriovenous malformations (hemangiectasia) related to a complex regional pain syndrome in her left arm, and another patient experienced scleroderma and had left-arm pain thought to be related to microvascular lesions in nerves associated with this entity. Both hemangiectasia and scleroderma were associated with vasomotor disturbances. All patients experienced disturbances in the painful territory, such as allodynia, hyperalgesia, and hypalgesia, and 2 had anesthesia dolorosa.

All patients had been treated with multiple analgesics, antiepileptic drugs, nerve and sympathetic blocks, and other specific forms of therapy according to their disease. Patients with pain in the arms, chest, and neck (Cases MC4, -5, -6, -8, -10, and -11) were not considered good candidates for dorsal column stimulation in view of the extension of painful territory, which might have required a combination of electrodes to cover 6 or 7 dermatomes of the painful area. A therapeutic trial with dorsal column stimulation failed in the patients in Cases MC1 and -4. Despite these therapies, patients considered their pain to be severe to extreme. Pain was evaluated using the VAS, in a 10-cm rule-like scale in which the left end was represented by 0, indicating no pain, and the right end was represented by 10, indicating maximum imaginable pain; the median value for the group was 9.4. Despite this, patients felt at least some temporary relief with high doses of analgesics. All of them were too severely incapacitated to work and to perform ADL. The extended version of the MPQ cites 170 as the maximum score; the MPQ is used to evaluate pain type and severity, analgesic consumption, and ADL.

For preoperative scores the median value was 8.5, based on the scale developed by Bourhis et al. for evaluating the severity of pain. This behavioral scale is divided into 3 sections: a) speech interruption by pain; b) ability to perform spontaneous ADL; and c) daily analgesic requirements. To evaluate analgesic consumption, the scale uses equivalent doses for different analgesic types. Each item has 5 ranks, with a minimum value of 0 to a maximum score of 4; the highest possible score is 12.

The study protocol was reviewed and approved by the Research and Ethical Committee at our institution. In their signed consent, patients authorized medical staff to discontinue stimulation as part of the protocol, to evaluate the efficacy of the treatment. However, patients and evaluators were blinded as to when and for how long this would happen. A third party, who performed the readings and adjusted stimulation parameters, kept the double-blind code in secrecy. She was instructed to decrease pulse amplitude to 0 during the “OFF” period, while leaving the stimulator turned to “ON.” Because the evaluations with pain scales were scheduled every month throughout the follow-up, the OFF period lasted for 1 month, to avoid letting the patients suspect when the OFF period had occurred. Because there was no objective or subjective sensation induced by therapeutic MCS and because the examiner was unaware of the double-blind protocol timing, the maneuver was considered valid.

Motor Cortex Localization

The motor cortex localization was performed according to the technique previously described. Prior to surgery, the rolandic fissure trajectory was estimated by means of cranial landmarks, drawing a line from a point 4 cm behind the vertex to a point 0.5 cm above the pterion. At the middle point of that line, a vitamin E capsule was glued to the skin. An MR imaging study was performed using oblique sections with a plane parallel to a line between the sylvian and interhemispheric fissures, beginning at the skin where the vitamin E capsule was visible. A cursor mark was placed above the center of the vitamin E capsule and maintained in a visible location in subsequent sections. The cursor was found to lie from 0 to 7 mm from the rolandic fissure trajectory (mean 1.6 mm) in the AP direction. After induction of general anesthesia, a 5-cm-diameter craniotomy centered on the rolandic fissure was performed to place an epidural 20-contact platinum grid embedded in a 4 × 5-cm Silastic plate (AD-Tech Instruments) in the epidural space (Fig. 1). The grid was oriented toward maintaining the rows of contacts perpendicular to the rolandic fissure trajectory in the AP direction. The craniotomy was closed, and during the following days with the patient awake and unre-
strained, the following studies were performed to localize the painful territory’s cortical representation.

1) The SEPs were assessed by the stimulation of contralateral median nerve, according to the technique described elsewhere.\(^\text{27}\) In cases with a median nerve peripheral lesion below the shoulder, the SEP may be obtained by stimulating at the Erb-point level. The N/P20 phase-reversal component indicates the transition between sensory and motor cortices.

2) Bipolar stimulation between 2 adjacent contacts was performed using 1–5-second trains, 1-msec duration, 1-Hz frequency, and increasing current intensity in 0.5-mA steps up to 15 mA, while a chart was maintained for localized motor-response occurrence. Stimulation frequency from 40

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**TABLE 1**
Clinical characteristics of 11 patients with neuropathic pain, including sensory deficits in the painful territory

<table>
<thead>
<tr>
<th>Case No.*</th>
<th>Age (yrs), Sex</th>
<th>Source &amp; Painful Territory</th>
<th>Duration</th>
<th>VAS Score</th>
<th>Sensory Changes</th>
</tr>
</thead>
<tbody>
<tr>
<td>MC1 74, F</td>
<td>postherpetic neuralgia, T5–6 lt</td>
<td>4 yrs</td>
<td>9</td>
<td>allodynia, hyperalgesia, hypesthesia, anesthesia</td>
<td></td>
</tr>
<tr>
<td>MC2 68, M</td>
<td>postherpetic neuralgia, C2–3 rt</td>
<td>5 yrs</td>
<td>8</td>
<td>allodynia, hyperalgesia</td>
<td></td>
</tr>
<tr>
<td>MC3 52, F</td>
<td>thalamic infarct, CN V2–3 lt</td>
<td>8 mos</td>
<td>10</td>
<td>allodynia, hyperalgesia, hypesthesia</td>
<td></td>
</tr>
<tr>
<td>MC4 29, F</td>
<td>brachial plexus trauma, C2–T3 lt</td>
<td>14 yrs</td>
<td>10</td>
<td>allodynia, hyperalgesia</td>
<td></td>
</tr>
<tr>
<td>MC5 33, F</td>
<td>hemangiectasia syndrome, C4–6 lt</td>
<td>6 yrs</td>
<td>10</td>
<td>allodynia, hyperalgesia</td>
<td></td>
</tr>
<tr>
<td>MC6 42, M</td>
<td>cervical root avulsion, C5–T1 lt</td>
<td>1.5 yrs</td>
<td>9</td>
<td>anesthesia dolorosa, hyperalgesia</td>
<td></td>
</tr>
<tr>
<td>MC7 43, M</td>
<td>postherpetic neuralgia, CN V1 lt</td>
<td>7 yrs</td>
<td>10</td>
<td>allodynia, hyperalgesia, hypesthesia</td>
<td></td>
</tr>
<tr>
<td>MC8 80, F</td>
<td>scleroderma, C4–T1 lt</td>
<td>15 yrs</td>
<td>10</td>
<td>allodynia, hyperalgesia, hyperesthesia</td>
<td></td>
</tr>
<tr>
<td>MC9 67, M</td>
<td>postherpetic neuralgia, T4–6 lt</td>
<td>4 yrs</td>
<td>8</td>
<td>allodynia, hyperalgesia, hypesthesia, anesthesia</td>
<td></td>
</tr>
<tr>
<td>MC10 55, F</td>
<td>cervical root avulsion, C4–T1 rt</td>
<td>4 yrs</td>
<td>10</td>
<td>anesthesia dolorosa</td>
<td></td>
</tr>
<tr>
<td>MC11 73, F</td>
<td>postherpetic neuralgia, C4–T2 lt</td>
<td>3 yrs</td>
<td>9</td>
<td>allodynia, hyperalgesia</td>
<td></td>
</tr>
</tbody>
</table>

* The last 3 patients listed were those rejected for permanent stimulator implantation, although these were not the last patients studied chronologically. Abbreviation: CN = cranial nerve.

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**Fig. 1.** External landmarks used to localize the trajectory of the rolandic fissure (RF). A: Drawing showing measurements taken from a vitamin E capsule (VEC) that is glued midway along a line running from a point 4 cm behind the vertex (V) to a point 0.5 cm above the pterion (P). B: An MR imaging study is obtained using oblique sections oriented parallel to a line between the sylvian and interhemispheric fissures, starting at the level of the skin, to identify the center of the vitamin E capsule. An X cursor is placed over the vitamin capsule and maintained in a visible position in subsequent sections. The rolandic fissure is readily recognized for being the only sulcus that has no perpendicular sulci in its trajectory, that reaches the interhemispheric fissure, and that extends deeper. The superior frontal sulcus (SFS), inferior frontal sulcus (IFS), prefrontal sulcus (PFS), precentral sulcus, and post-central sulcus (PCS), as well as motor cortex (MC) and somatosensory cortex (SC) are identified. The cursor usually remains within 2 mm of the rolandic fissure, and minor corrections to center the craniotomy are necessary. C: Photograph of the 20-contact grid used for electrophysiological localization and therapeutic trial. Contacts are numbered starting in the upper left corner (number 1) and ending in the lower right corner (white contact). EAM = external auditory meatus; I = inion; N = nasion; SF = sylvian fissure. (Modified from Velasco et al: Motor cortex stimulation in the treatment of deafferentation pain. Localization of the motor cortex. Stereotact Funct Neurosurg 79:146–167, 2002. Reprinted with permission from S. Karger AG, Basel.)
to 130 Hz, 1-msec pulse width, and amplitudes of 1–5 mA most frequently induced sensory response as a tingling sensation.

3) Corticocortical evoked responses were induced by bipolar stimulation of adjacent contacts at 6–8 Hz, 1 msec, and intensities ranging from 0.3 to 1.5 mA. High-frequency parameters were 60–130 Hz, 1 msec, ranging from 0.4 to 1.3 mA. Scalp EEG recordings were obtained through a conventional 10- to 20-electrode montage with ipsilateral ear-referred leads. Corticocortical responses were obtained by stimulating through frontally placed contacts at low frequency from ipsilateral frontal leads (FP1–FP2 and –F3), whereas they were recorded in ipsilateral occipitoparietal leads (P2–O2) when stimulating through parietally placed contacts (arrows in tracings on the left). The DC shifts had similar distribution as corticocortical evoked potentials; they were negative in frontal leads and positive in parietal leads (arrows in tracings on the right). (Modified from Velasco et al: Motor cortex stimulation in the treatment of deafferentation pain. Localization of the motor cortex. Stereotact Funct Neurosurg 79:146–167, 2002. Reprinted with permission from S. Karger AG, Basel.)

Fig. 2. Tracings showing corticocortical responses. The diagram represents potentials induced by low- (left) and high-frequency (right) stimulation of pairs of contacts placed in front of the rolandic fissure. Plotting of a different pair of contacts on the cortex surface is represented by black circles. Low-frequency stimulation parameters were 6–8 Hz (denoted in the charts as cycles per second [cps]), 1 msec, and intensities ranged from 0.3 to 1.5 mA. High-frequency parameters were 60–130 Hz, 1 msec, ranging from 0.4 to 1.3 mA. Scalp EEG recordings were obtained through a conventional 10- to 20-electrode montage with ipsilateral ear-referred leads. Corticocortical responses were obtained by stimulating through frontally placed contacts at low frequency from ipsilateral frontal leads (FP1–FP2 and –F3), whereas they were recorded in ipsilateral occipitoparietal leads (P2–O2) when stimulating through parietally placed contacts (arrows in tracings on the left). The DC shifts had similar distribution as corticocortical evoked potentials; they were negative in frontal leads and positive in parietal leads (arrows in tracings on the right). (Modified from Velasco et al: Motor cortex stimulation in the treatment of deafferentation pain. Localization of the motor cortex. Stereotact Funct Neurosurg 79:146–167, 2002. Reprinted with permission from S. Karger AG, Basel.)

4) A subacute therapeutic stimulation trial was performed using different pairs of adjacent contacts that according to postoperative MR imaging and the tests described previously would be located on the painful territory’s motor cortex representation. Stimulation of a given pair of contacts using a frequency of 40 Hz, pulse width of 90 μsec, and intensities ranging from 2 to 7 V was continued for up to 24 hours. The analgesic effect was detected by the patient within the first hour; although there were 2 or 3 pairs of contacts that when stimulated induced analgesia, 1 of these induced a better effect at the lowest threshold. Should stimulation not induce analgesia in a range of 2.1–10.0 V, the pair of contacts was considered OFF target. In cases in which patients were considered nonresponders, we conducted an exhaustive stimulation trial that lasted up to 15 days and that used many combinations of contacts and parameters.

**Long-Term Stimulation**

Three patients reported no improvement in pain during subacute therapeutic stimulation and were rejected from the study protocol. The remaining 8 patients underwent a repeated operation after induction of general anesthesia, and the grid was replaced with a 4-contact plate electrode (Resume, Medtronic, Inc.) that was exactly oriented to place 2 contacts in the same position as those that had induced the best therapeutic response in the subacute trial. In 7 cases, contacts were perpendicular to and in 1 case parallel to the motor cortex trajectory. Electrodes were connected to an internalized stimulation system (Soletra, Medtronic, Inc.) placed in the chest below the clavicle. Stimulation was initiated with parameters that had been efficient for decreasing pain in the subacute therapeutic trial. All patients who received the implants have shown improvement with stimulation at 40 Hz, pulse width 90 μsec, and amplitudes ranging from 2.0 to 3.5 V. During the following 2 weeks, amplitude and frequency were increased up to 6.5 V and 130 Hz in 2 cases in which the analgesic response was less satisfactory. Thereafter, the parameters were maintained for the...
The cycling stimulation mode, which has been successfully used in the treatment of pain either by spinal cord stimulation or MCS, was adopted in our protocol because in addition to being efficient, it saves stimulator battery charges.

Patients were discharged from the hospital with the stimulators turned to the ON mode and were seen at monthly appointments as outpatients, with repetition of testing using preoperative pain scales at each visit, as well as reading of therapy charges.

Patients were assigned to each group by lottery numbers. Because neurostimulation parameters and electrode impedance readings with the aid of a transcutaneous programmer (8840 N’Vision Programmer, Medtronic, Inc.), Patients entered a double-blind protocol, turning the stimulator to OFF mode during 30 days, starting at Day 60 in half of the patients and at Day 90 in the remaining half. Patients were assigned to each group by lottery numbers. Because neurostimulation parameter and electrode impedance readings were performed at the patients’ monthly visits, the individual maintaining the double-blind protocol code simply decreased the neurostimulation amplitude to 0 at the beginning of the OFF period. The readings and the code were maintained in a blinded fashion; thus, neither the patient nor the examiner was aware of the stimulators’ ON/OFF condition at any time.

We compared scores for pain on tests performed before and at 1, 6, and 12 months after initiation of MCS, as well as scores from the month prior to turning the stimulator to OFF mode (Month 2–3) for the double-blind period and scores after 1 month OFF stimulation (Month 3–4). The significance of changes was determined by nonparametric, one-tailed Wilcoxon test, and significance was established with an alpha level of 0.05 and a beta level of 0.20.

**Results**

**Motor Cortex Localization**

In general, rolandic fissure localization by external landmarks was satisfactory, because the error varied from 0 to 7 mm (mean 1.6 mm) and was readily recognized and adjusted to center the incision and cranial flap. The SEP from median nerve stimulation could be recorded in 8 of 11 patients; in the remaining 3 cases (MC6, -10, and -11), the median nerve was severely damaged. In 1 of these cases, nerve stimulation at the Erb point evoked cortical SEP. The N20 component was easily identified, whereas the P20 was identified in only 5 patients, with reliable phase reversal between the 2 components in only 4 cases. Electrical stimulation evoking motor responses in the painful area was obtained in 6 patients, and sensory responses were reported as tingling sensations when stimulating at > 60 Hz in 8 patients. Although sensory responses were obtained from contacts of the grid placed posterior to the rolandic fissure and motor responses from contacts in front of the rolandic fissure, in 3 cases both motor and sensory responses were obtained from the same contacts. In all cases, 6- to 8-Hz frequency–threshold stimulation through a pair of contacts placed anterior to the rolandic fissure elicited corticocortical evoked responses only in frontal EEG leads. Pairs of electrodes with the cathode placed anterior and the anode posterior to the rolandic fissure evoked the most prominent responses in central (CZ–A1, A2) leads. In all but 1 case, pairs of contacts placed behind the rolandic fissure elicited evoked potentials in parietal leads; 60-Hz stimulation induced regional DC shifts in the EEG readings, with a distribution similar to 6- to 8-Hz potentials.

**Therapeutic Trial**

Eight of the 11 patients experienced evident—and in the majority of cases, dramatic—analgesic responses during the therapeutic stimulation trial. Although analgesic responses were reported when stimulating ≥ 2 pairs of contacts, there was always a pair of contacts that induced the best analgesic response at the lowest threshold. The remaining 3 patients reported no improvement of pain, even when stimulation voltage and frequency were increased several-fold and numerous combinations of contacts were used. Two of these patients (Cases MC10 and -11) had extensive sensory changes in the painful territory, one of them (Case MC10) with paralysis of muscles innervated by the brachial plexus and anesthesia dolorosa. The remaining patient (Case MC9) reported a tingling sensation when the pulse amplitude was increased up to 8–10 V, and this occurred around but never on the painful chest area during the stimulation trial.

**Long-Term Stimulation**

Table 2 and Figs. 1–3 present the results of MCS in the 8 patients during the 1-year follow-up period. All patients

![Table 2](https://example.com/table2.png)

**TABLE 2**

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Stimulation Parameters</th>
<th>%ΔVAS</th>
<th>Sensory Modifications</th>
</tr>
</thead>
<tbody>
<tr>
<td>MC1</td>
<td>40–130 Hz, 2.0–6.0 V, 90 μsec</td>
<td>456</td>
<td>allodynia disappeared, hyperalgesia decreased, hyposthesia &amp; anesthesia unchanged</td>
</tr>
<tr>
<td>MC2</td>
<td>40 Hz, 2.0–6.5 V, 90 μsec</td>
<td>475</td>
<td>allodynia &amp; hyperalgesia disappeared</td>
</tr>
<tr>
<td>MC3</td>
<td>40–130 Hz, 2.0–3.5 V, 90 μsec</td>
<td>460</td>
<td>allodynia disappeared, hyperalgesia decreased, hyposthesia unchanged</td>
</tr>
<tr>
<td>MC4</td>
<td>40 Hz, 2.0–5.0 V, 90 μsec</td>
<td>440</td>
<td>allodynia &amp; hyperalgesia disappeared</td>
</tr>
<tr>
<td>MC5</td>
<td>40 Hz, 2.0–5.0 V, 90 μsec</td>
<td>460</td>
<td>allodynia &amp; hyperalgesia disappeared</td>
</tr>
<tr>
<td>MC6</td>
<td>40 Hz, 2.0–3.5 V, 90 μsec</td>
<td>450</td>
<td>anesthesia dolorosa unchanged, hyperalgesia disappeared</td>
</tr>
<tr>
<td>MC7</td>
<td>40 Hz, 2.0–3.5 V, 90 μsec</td>
<td>480</td>
<td>allodynia &amp; hyperalgesia disappeared, hyposthesia unchanged</td>
</tr>
<tr>
<td>MC8</td>
<td>40 Hz, 2.0–3.5 V, 90 μsec</td>
<td>485</td>
<td>allodynia &amp; hyperalgesia disappeared, hyposthesia unchanged</td>
</tr>
</tbody>
</table>

* Range of improvement was 40–85%, and allodynia and hyperalgesia disappeared or decreased in all patients, whereas hyposthesia and anesthesia remained unchanged. Pulse frequency was increased in 2 patients from 40 to 130 Hz, without evident benefit.
Motor cortex stimulation for pain

Fig. 3. Bar graph showing pain decrements according to VAS-estimated values from baseline (basal) to final scores for each patient who received long-term stimulation. The patient in Case MC4 had an initial decrease of VAS score from 10 to 2–3, and remained at 3–4 up to the 11th month of follow-up. At 1 year, this score had increased to 6, and 2 months later it had risen to 9, with increased electrode impedance. On surgical review extensive fibrosis of the contacts was revealed, and when these were cleaned the efficacy of MCS was restored.

Presented with a decrease in VAS score that was more prominent during the first 2 months with stimulation ON prior to their entering the double-blind trial. By the end of the year, the decrement of pain ranged from 40 to 85% of the prestimulation score, with a median for the group of 63.25% (Table 2 and Fig. 3). During the ON-stimulation period, the Bourhis scale and MPQ scores for the group decreased from 8.5 to 4.5 and from 133 to 40, respectively, for statistically significant improvement (p < 0.01). It was remarkable that, in all patients, areas of allodynia disappeared (p < 0.001) and hyperalgesia decreased (p < 0.001) in intensity and extension, decreasing in 5 patients (p < 0.001); in contrast, hypesthesia and anesthesia were not modified. Although pulse amplitude and frequency were increased as the follow-up period progressed, and particularly in cases in which they had less analgesic effect, the efficacy of stimulation changed very little with these incremental increases. The analgesic effect remained fairly stable throughout the follow-up period.

During the double-blind period, pain intensity increased in all patients and VAS and Bourhis scores reached 93% of prestimulation levels. The difference in scores between ON- and OFF-stimulation periods was significant (p < 0.05; Figs. 4 and 5), whereas baseline and OFF-period changes were not significant (p = 0.85). Complications did not occur in this group during the follow-up period considered in this study, and no seizures were elicited at any time during the stimulation trial.

Discussion

In studying this small group of patients, we gained experience with regard to adequate identification and placement of stimulating electrodes over cortical representations of the painful territory in the motor cortex as well as with respect to selection of cases, with patients who would represent good outcomes in the long term.

Motor Cortex Localization

Correct placement of epidural electrodes for stimulation requires identifying the motor cortex in relation to sensory cortex and the rolandic fissure in the AP direction, and subsequently identifying the cortical representation of the painful territory along the motor cortex trajectory. As discussed in previous papers, initial localization of the motor cortex and its posterior limit marked by the rolandic fissure is easy when using an oblique section-guided neuronavigator guided by MR imaging or computed tomography scanning or initially guided by external landmarks and confirmed by oblique MR imaging sections, or by using external fiducial markers and 3D surface MR imaging.

Electrophysiological confirmation of the limits between motor and sensory cortices by studying phase-reversal polarity of N20 and P20 components is not always possible. The P20 component may not be identified due to volume-conduction peculiarities or because a severe brachial plexus lesion prevents any response to stimulation, as in some of our cases (MC6, -10, and -11). However, when reverse polarity occurs, one has a precise location of the sensory/motor transition at cortical representation levels of muscles innervated by the stimulated nerve to evoke the responses. Actually, all reports refer to stimulation of the median nerve and therefore identify the hand area. A more reliable method to determine the transition between somatosensory cortex and motor cortex seems to be the corticocortical potentials induced by stimulation of different pairs of grid contacts, because in practically all cases it was.
possible to determine such transition along the trajectory of the rolandic fissure.46

Motor compared with sensory responses to electrical stimulation do not precisely determine sensory and motor cortical limits because both may be obtained by stimulating either motor or sensory cortices. Nonetheless, the motor and sensory response locations in the contralateral hemis- body are helpful to determine cortical representation of the painful territory over the motor cortex area. Our observations in this regard confirm the cortical organization recently reported in motor cortex mapping by electrical stimulation.33 Somatotopic distribution has been studied and is well established. The face is represented below the level of the inferior frontal sulcus, the neck representation is placed immediately behind this sulcus, arm and hand representa- tion extends over the motor cortex from the inferior to the superior frontal sulci, the chest is represented in a small area at the level of the superior frontal sulcus, and the abdomen and hip are immediately above it. In this report, we do not show patients treated for pain in the lower extremi- ties, but it has been reported that leg representation extends over the convexity near the interhemispheric fissure.17,34,35

After using all of these techniques in localizing the motor cortex position, it is our impression that there is no single technique that guarantees correct electrode placement. In papers in which several localization methods have been combined, better results have been reported in treating cases similar to those in which electrophysiological exploration has been limited and the therapeutic stimulation trial has been obviated.29,31

**Efficacy of MCS**

Given the heterogeneous information that one gathers from the literature on MCS, it is impossible at present to draw a conclusion concerning candidates for this treatment. In a survey of the literature on MCS efficacy in pain control, we found that in > 60 clinical reports fewer than half have used international pain scales to evaluate results. Six-teen reports used a self-rating scale in which patients render a verbal estimation of pain improvement expressed as a percentage.5,9,38 In 12 reports the VAS scale alone was used, in 5 the MPQ was used,4,31,32,39,41 and in 3 the Bourhis ques- tionnaire was used.33–35 Follow-up periods ranged from 4 to 74 months, and some reports include only an initial evalu- ation.14,15 In practically all papers, there have been failure rates fluctuating between 12%14 and 84%31 of MCS-treated cases. The majority of the reports list as treatment failures cases improving by < 30–40%.20

In our series, we had no patients with < 40% improvement in the long term, and the overall group improvement was 63.25% for VAS and 70% for the MPQ score, which is used to evaluate the patient’s ability to perform ADL. The Bourhis scale, which is used to evaluate speech disturbances by pain, spontaneous ADL, and analgesic consumption, had a decrement of 53%. These values are considerably better than those in the majority of reports that covered the long-term outcome.

To account for this success in treating neuropathic pain by using MCS, we presume a number of factors, such as meticulous mapping of cortical pain territory representa- tion, which was exceedingly time-consuming. The most important maneuver, however, comprised elimination of nonresponders to subacute therapeutic stimulation from the group receiving long-term stimulation. In fact, if these non-responding patients had received long-term stimulation and their treatment had failed, our degree of success would have been comparable to that in the majority of the reports.

Rejected cases possessed certain peculiarities that may
serve as negative predictors for future case selection. Two of these patients (MC10 and -11) had extensive deafferentation zones, with anesthesia dolorosa areas covering the entire arm in one patient and areas in the arm and chest in the other. These sensory deficits remained unchanged during the therapeutic trial. As reported by Drouot et al.\textsuperscript{13} in 2002, an abnormal threshold for certain sensory modalities such as temperature that are not modified by MCS is associated with poor responders. In contrast, all of our patients who received long-term stimulation experienced significant modification of sensory abnormalities such as allodynia (which disappeared in all) and hyperalgesia; this is the same observation reported by Drouot et al. in their study of 31 patients. In other reports, severe deafferentation of the painful territory is considered an unfavorable response to MCS.\textsuperscript{3,10,48} Therefore, severe sensory changes not modified by MCS represent a predictor of unfavorable outcome, whereas improvement in sensory deficits that appears at the subacute therapeutic trial accompanies a favorable outcome.

In the remaining case (MC9), which was deemed unsuitable for permanent neurostimulator implantation, the problem was localization of the cortical representation of such a small painful territory covering the T2–4 dermatomes that we were never able to induce paresthesias anywhere in that territory during the acute and subacute trials. Therefore, we hypothesize that pain problems covering a restricted territory with small cortical representation may be more difficult to treat with MCS. Nevertheless, another patient (Case MC1) with similar postherpetic neuralgia over dermatomes T5–6 was successfully treated with MCS; in these cases, the subacute therapeutic trial may aid in predicting poor outcomes. It must be mentioned that 2 of the rejected cases (MC9 and -10) were treated successfully with dorsal root entry zone microsurgery (termed DREZotomy), which is proposed as a more invasive therapeutic alternative.

**Stimulation Parameters and the Double-Blind Trial**

The majority of reports on MCS describe a cycling mode of stimulation, from 10 minutes\textsuperscript{5} to 9 hours\textsuperscript{56} ON stimulation, repeated every 4–6 hours. Frequencies ranged from 15 to 130 Hz,\textsuperscript{2} pulse width from 60 to 450 μsec,\textsuperscript{10} and pulse amplitude from 2.0 to 9.5 V.\textsuperscript{9} Experience in adjusting the stimulation program and parameters in our cases showed that the initial improvement obtained at 90 μsec, 40 Hz, 2.5–3.5 V, 1 hour ON and 4 hours OFF stimulation/24 hours remained fairly stable at the 1-year follow-up evaluation. Increasing any of these parameters did not result in additional improvement.

When stimulation was discontinued during the double-blind trial, pain increased in 1–4 days. Because the patient had no sensation when the stimulator was ON at therapeutic parameters, the maneuver was valid. One of our patients (MC7) realized that the stimulator was turned off because the pain intensity increased, and he insisted on having the stimulator turned on; thus, he was the sole patient with a 7-day OFF-stimulation period. On the other hand, it was remarkable that after the double-blind trial period, pain improvement never reached the levels of the period ON-stimulation prior to the double-blind maneuver (Fig. 4). This was true in all patients and perhaps represents a placebo effect when patients meet their expectation in the therapeutic maneuver at the initial ON-stimulation period, which was lost when pain returned in the OFF period, with patients remaining skeptical thereafter.

**Conclusions**

The use of MCS induces significant improvement in pain syndromes of different origins, as demonstrated in this double-blind protocol. Correct electrode placement in the cortical representation of pain territory over the motor cortex appears to be the most important factor for good outcome, and is better achieved by combining several imaging and electrophysiological techniques. In contrast, stimulation parameters and cycling modes are not as critical. Patients with severe or complete deafferentation of the painful territory frequently exhibit poor analgesic response and no modification of allodynia and hyperalgesia by MCS. These patients are probably not good candidates for MCS, and a subacute therapeutic trial aids in identifying these individuals.

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**References**


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