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Motor cortex stimulation for chronic non-malignant pain: current state and future prospects

B. Cioni and **M. Meglio**

Neurochirurgia Funzionale e Spinale, Università Cattolica, Roma, Italy

Summary

Motor cortex stimulation (MCS) was proposed by Tsubokawa in 1991 for the treatment of post-stroke thalamic pain. Since that time, the indications have been increased and included trigeminal neuropathic pain and later other types of central and peripheral deafferentation pain. The results reported in the literature are quite good; the mean long-term success rate is 80% in facial pain and 53% in non-facial pain. Our own results are less impressive: 4 of 14 patients (28%) experienced a greater than 40% pain relief, but in 2 of them the effect faded with time. Only few minor complications have been reported. The accurate placement of the epidural electrode over the motor cortex that somatotopically corresponds to the painful area is believed to be essential for pain relief. Predictive factors included the response to pharmacological tests, the relative sparing from the disease process of the cortico-spinal tract and the sensory system, and the analgesic response achieved during the test period of MCS. A possible predictive factor might be a test of repetitive transcranial magnetic stimulation (rTMS) of the motor cortex. MCS may act by rebalancing the control of non-nociceptive sensory inputs over nociceptive afferents at cortical, thalamic, brainstem and spinal level. In addition, it may interfere with the emotional component of nociceptive perception. Biochemical processes involving endorphins and GABA may also be implicated in the mechanism of MCS. It is time for a large multicenter prospective randomized double blind study evaluating not only the effect of MCS on pain (based on the available guidelines for assessment of neuropathic pain), but also the optimal electrode placement and stimulation parameters, and the possible relationship with the response to rTMS. New electrode design and a new generation of stimulators may help in improving the results.

Keywords: Neuromodulation; epidural motor cortex stimulation; chronic non-malignant pain; neuropathic pain; central pain; intraoperative neurophysiological monitoring.

Introduction

Motor cortex stimulation (MCS) was introduced in the treatment of central and neuropathic pain in the early nineties. This type of pain is defined by the International Association for the Study of Pain (IASP) as pain initiated or caused by a lesion (or dysfunction) of the central or peripheral nervous system; in spite of the advances in pharmacological treatment, it still represents a challenge to pain specialists and particularly to neurosurgeons. Tsubokawa and colleagues [27, 28] observed hyperactivity of low threshold mechanoreceptor thalamic neurons after spino-thalamic tractotomy in a cat model, and found that MCS inhibited the abnormal firing whereas sensory cortex stimulation (SCS) had no effect. On this basis, they proposed MCS for the treatment of thalamic pain. They treated 11 patients with epidural MCS and reported the long-term results [28]. Eight patients obtained an excellent pain relief during the one week test period and, hence, they underwent chronic stimulation. At 2 years, in 5 cases the results were unchanged (greater than 80% pain relief), while, in the remaining 3 cases, the effect of MCS decreased gradually over several months. The stimulation was subthreshold for muscle contraction and no complications were described. In 1993, Meyerson published his experience on ten patients [16]. Five of them complained of trigeminal neuropathic pain and all achieved more than 50% pain relief. Stimulation was subthreshold for movement in these cases as well, and it was used for 20–30 minutes, one to six times a day. Since then, an exponentially increasing number of cases have been described over the following years, supporting the use of MCS in the treatment of central and peripheral neuropathic pain syndromes.

Clinical indications

MCS has been used so far for central and peripheral neuropathic pain; there is no experience on chronic benign nociceptive pain. The indications have increased

from the original post-stroke central pain and trigeminal neuropathic pain, and include postherpetic neuralgia, peripheral deafferentation pain syndromes such as brachial plexus and roots avulsions, spinal cord injury pain, phantom limb and stump pain, and complex regional pain syndrome (CRPS) [2–4, 7, 10, 14, 17–19, 22, 23, 26]. The best results were obtained in trigeminal pain (more than 80% of successful results); the large somatotopic facial representation on the motor cortex compared to the other body regions, may be an explanation for these particularly good results in facial neuropathic pain.

Surgical technique

The key point of surgery is the accurate placement of the electrode over the motor cortex that somatotopically corresponds to the painful area [17]. A multicontact strip electrode is usually placed in the epidural space; subdural placement has been used in the interhemispheric fissure for lower limbs pain and was advocated by Saitoh for a more stable motor cortex activation [24]. There is general agreement that the best electrode orientation is perpendicular to the central sulcus. The location of the motor cortex has been identified by morphological craniometer landmarks, using fiducial markers and MRI neuronavigation, integrating functional MRI (fMRI) into the targeting plan [21]; however, a precise neurophysiological localisation is mandatory. We use the phase reversal technique to identify the central sulcus. We stimulate the controlateral median nerve at the wrist and record from each contact of the strip electrode. A cortical N20 potential is recorded over the sensory cortex and a cortical P20 potential is recorded over the motor cortex; the central sulcus is found between the two contacts showing the phase reversal. The motor mapping is obtained by motor cortex focal anodal stimulation through two adjacent contacts of the same strip electrode with a short train of stimuli (5 stimuli, 0.5 ms, ISI 4 ms, 10–30 mA). Muscle responses are recorded from muscle bellies of the controlateral hemibody, with needle electrodes. This mapping technique allows the use of general anaesthesia (totally intravenous anaesthesia with Propofol and Remifentanyl, and no muscle relaxants after intubation) and has a very low rate of inducing epileptic seizures (less than 4%) compared to the classical so called ''Penfield's technique'' for motor cortex mapping. In contrast to other authors [1], we feel that a neurophysiological precise localisation of the motor cortex is essential. In the past, we placed the electrode through a simple burr hole, but with experience we prefer a small craniotomy; it allows an easier and more extensive cortical mapping and the placement of 2 electrode paddles when the region of pain is extensive and, consequently, the cortical area to be covered is wide.

Stimulation parameters

An empirical approach is used to select the optimal stimulation parameters by adjusting the combination of contacts, polarity, frequency, pulse width and, to a lesser extent, amplitude, according to the patient's pain relief. Stimulation is always subthreshold for muscle contraction or any sensation. This makes possible double blind studies. Manola *et al.* published the results of a computer modelling study on MCS [13]. They studied the electrical potential field characteristics and the initial response of single fibre models to stimulation of the precentral gyrus by an epidural multicontact electrode. They concluded that the amount of the cerebrospinal fluid (CSF) between the dura and the cortex underneath the stimulating electrode is the most important factor affecting the distribution of the electrical field; when the CSF layer increases in thickness from 0 to 2.5 mm, the load impedance decreases by 28%, and the stimulation amplitude increases by 6.6 V for each mm of CSF. Both anode and cathode should be considered active because of the large anode-cathode distance (<10 mm). Anodal fields preferentially excite fibres perpendicular to the electrode surface, whereas cathodal fields excite fibres running parallel to the electrode surface. Therefore, anodal stimulation over the precentral gyrus preferentially activates pyramidal axons; cathodal precentral stimulation, used in most of the published clinical reports, preferentially excites fibres parallel to the brain surface, i.e. connecting interneurons or horizontal braches of cortical afferents and efferents.

Assessment of the results

Guidelines have been published for the assessment of neuropathic pain and its response to treatment [5]. The most reliable assessment measures are the visual analogue scale (VAS) (not the percentage of pain relief) and the global impression of change (GIC), which can be implemented utilizing multidimensional scales such as the SF-36 or the Owenstry questionnaire. Many articles report only the percentage of pain relief, some report the VAS score and a few utilize multidimensional scales. A pain relief of 50% is the usual cut-off for success, but

recently also pain relief of 40% or even 30% during medical treatment, has been considered sufficient to define a treatment as effective for neuropathic pain.

Clinical results

The clinical results in patients complaining of trigeminal neuropathic pain are reported in Table 1 [3, 7, 15, 17, 18, 22]. The long-term success rate (greater than 40% pain relief) ranged from 40 to 100%. In these 7 published series, 47 patients were submitted to MCS and 38 (80%) reported a fair to excellent pain relief. The clinical results in patients complaining of central or peripheral deafferentation pain are reported in Table 2; six published series are analysed [4, 9, 18, 19, 24, 28]. The long-term success rate ranged from 40 to 77%. Overall, 56 of 104 patients (53%) experienced long-term fair to excellent pain relief. Our personal results are less impressive. We submitted to MCS 14 patients (Table 3); in 8 cases, the pain was due to trigeminal neuropathy (4 post-traumatic, 2 post-herpetic, 1 post-trigeminal surgical lesion, and 1 multiple sclerosis), in 4 to an ischemic stroke (3 thalamic, 1 bulbar), and in the remaining 2 to a spinal cord lesion. Only 2 patients (14%) reported a stable long-term pain relief (greater than 50%); one patient reported a 40% pain relief for a few months, but then the effect gradually faded; another patient initially was a failure, then gained a 50% pain relief after an aggressive reprogramming of the stimulator, but the effect decreased over few weeks. Ten patients are considered as failures.

Table 1. *Effect of MCS on facial neuropathic pain*

Author	Patients	Acute responders (%)	Long-term responders (%)	Follow up
Meyerson *et al.* [16]	5	100	100	
Herrengodts *et al.* (1995)	5		80	
Nguyen *et al.* [17]	7	100	100	
Rainov *et al.* [22]	2	100	100	18 months
Ebel *et al.* [7]	7		43	
Nguyen *et al.* [18]	12		83	27 months
Brown and Barbaro [2]	9	88	75	10 months

Recently, commenting on an article published in Neurosurgery [3], Kanpolat wrote ''We are reluctant to mention our hesitation regarding the effectiveness of MCS, but it seems that only series with good results have been reported . . . and most of the failures seem to remain unreported''. Regarding the same article, Broggi commented [3]: ''My experience with MCS has been that patients with neuropathic facial pain . . . experience poor and transient results as measured by quality of life''. The same sort of scepticism is expressed by Meyerson in his editorial published in Pain [15]: ''MCS . . . should not be considered an established method of pain control . . . . It may seem that the results of MCS are not impressive but it must be remembered that the forms of pain for which MCS may be effective, . . . are those for which there are no or little other treatment''

Complications

Complications such as haematomas either epidural or subdural, infections and other minor problems, are reported in a small percentage of patients, but they do not produce neurological deficits. Epileptic seizures occasionally occurred during the motor mapping, but chronic seizures have never been reported.

Table 2. *Effect of MCS on central and peripheral neuropathic pain (non-trigeminal)*

Author	Patients	Type/cause of pain	Acute responders (%)	Long-term responders (%)	Follow up
Tsubokawa *et al.* [28]	11	thalamic	73	45	24 months
Katayama *et al.* [19]	31	post-stroke		48	>24 months
Carrol *et al.* [4]	10	5 post-stroke 3 phantom limb 2 various	50	40	1–31 months
Nguyen *et al.* [18]	13	central pain		77	27 months
Saitoh *et al.* [24]	8	4 thalamic 4 peripheral deafferentation	75	75	6–26 months
Nuti *et al.* [19]	31	22 poststroke 4 brachial plexus 5 variuos		52	48 months

Table 3. *Personal experience*

Type/cause of pain	Patients	Long-term results
Trigeminal neuropathy	8	1 S 1 F, then S, then F 6 F
Post-stroke	4	1S then F 3 F
Spinal cord lesion	2	1S 1F

S Success (>40% pain relief), *F* failure (<40% pain relief).

Predictive factors

Pharmacological tests have been proposed in order to predict the efficacy of MCS. Yamamoto *et al.* correlated the percentage of pain relief obtained with different drugs with that of MCS in post-stroke patients [29]. The regression analysis showed a significant correlation between the MCS effect and the effect of the Thiamytal test or the Ketamine test, but not with the Morphine test. These results have not been duplicated [24]. Katayama stressed the importance of a relative integrity of the cortico-spinal tract [9]; only 15% of 13 patients reported a satisfactory pain relief when a moderate to severe motor weakness was present, and only 9% reported a benefit when motor contraction could not be elicited. The success rate was 73% when a mild or absent motor impairment was present [9]. Drouot *et al.* [6] noticed that the antalgic efficacy of MCS was related to sensory changes in the painful zone. Favourable prognostic factors were the absence of alteration of non-nociceptive sensory modalities within the painful area, or an abnormal sensory threshold that could be improved by MCS (a better sensory discrimination by switching on the stimulator). Katayama *et al.* [9] on the other hand, reported no correlation between sensory symptoms, somatosensory evoked potentials (SEPs) and the MCS effect.

Nuti *et al.* published the 4-years outcome in 31 patients and studied the possible predictors of efficacy [19]. There was no statistical correlation between the long-term outcome and any of the following variables: pre-operative motor status, pain semeiology, type or site of the lesion that causes pain, quantitative sensory testing, and SEPs. Notably, the patients who had a normal motor function showed a tendency towards a significantly decreased analgesic drug intake; this finding is in agreement with the observations of Katayama. The pain relief obtained at the end of the first month of MCS was the only factor that had a strong statistical correlation with the long term pain relief [19]. There are many reports on the analgesic effect of repetitive transcranial magnetic stimulation (rTMS) over the motor cortex at subthreshold intensities [11, 12], but so far there is no evidence of a significant correlation of the response to rTMS with the efficacy of MCS. The parameters used for rTMS are very different from those used for MCS, apart from the intensity, which is subthreshold for muscle contraction in both electrical and magnetic stimulation.

Mechanisms of action

According to Tsubokawa's hypothesis [28], under normal conditions noxious and non-noxious inputs from the thalamus converge at cortical level and the non-noxious stimulus is able to inhibit the noxious afferences. When such an inhibitory mechanism is lost as a consequence of a thalamic lesion, MCS can antidromically and orthodromically activate large fibres reciprocal connections between the motor and the sensory cortex, and then activate non-noxious, fourth order sensory neurones restoring the inhibitory control over the nociceptive inputs. PET studies demonstrated a significant increase in cerebral blood flow in the ipsilateral lateral thalamus, but also in the brainstem, cingulate gyrus, anterior insula, and orbito-frontal cortex, during MCS, in patients reporting a good pain relief [8, 20, 23]. MCS may reinforce the control of non-nociceptive sensory inputs on nociceptive systems not only at the thalamic level, but also at the brainstem and at the spinal cord level. Indeed, in experimental models of deafferentation pain, MCS reduces the hyperactivity of thalamic neurones as well as the hyperactivity at dorsal columns nuclei. An attenuation of flexion reflexes (R III) has been shown during MCS in cases of good analgesic effect [8]. The changes in these polysynaptic reflexes during MCS suggest that a descending inhibitory mechanism at spinal level may be involved in mediating the effect of MCS. A recent experimental study in rats by Senapati *et al.* [25], has shown that MCS produced significant inhibition of wide dynamic range dorsal horn neuron activity in response to high intensity mechanical painful stimuli but not to innocuous stimuli. MCS may also reduce the emotional component of chronic pain by activating the anterior cingulate cortex and the anterior insula as demonstrated by PET studies [8, 20, 23]. Biochemical processes such as action on the endorphin sites in the brainstem or control on the GABAergic interneurons at cortical level, may also be implicated, in the mechanisms of MCS.

Future prospects

In our opinion, it is time for a prospective multicenter randomized double blind study. Electrode placement should be precisely documented (both topographically and neurophysiologically), different stimulation parameters should be tested, pain relief assessment should follow the existing guidelines, and the predictive value of rTMS should be studied. Technical advances such as new electrode designs, covering a larger area of the motor cortex may be helpful in improving the clinical results. The new generation of neurostimulators may reduce the need for time consuming multiple programming visits.

References

1. Brown JA (2001) Motor cortex stimulation. Neurosurg Focus 11: E5
2. Brown JA, Barbaro NM (2003) Motor cortex stimulation for central and neuropathic pain: current status. Pain 104: 431–435
3. Brown JA, Pilitis JG (2005) Motor cortex stimulation for central and neuropathic facial pain: a prospective study of 10 patients and observation of enhanced sensory and motor function during stimulation. Neurosurg 56: 290–297
4. Carroll D, Joint C, Martens N, Shlugman D, Stein J, Aziz TZ (2000) Motor cortex stimulation for chronic neuropathic pain: a preliminary study of 10 patients. Pain 84: 431–437
5. Cruccu G, Anand P, Attal N, Garcia-Larrea L, Hanpaa M, Jorum E, Serra J, Jensen TS (2004) EFNS guidelines on neuropathic pain assessment. Eur J Neurol 11: 153–162
6. Drouot X, Nguyen JP, Pescanski M, Lefaucheur JP (2002) The antalgic efficacy of chronic motor cortex stimulation is related to sensory changes in the painful zone. Brain 125: 1660–1664
7. Ebel H, Rust D, Tronnier V, Boker D, Kunze S (1996) Chronic pre central stimulation in trigeminal neuropathic pain. Acta Neurochir (Wien) 138: 1300–1306
8. Garcia-Larrea L, Pyron R, Mertens P, Gregoire MC, Lavenne F, Le Bars D, Convers P, Mauguiere F, Sindou M, Laurent B (1999) Electrical stimulation of the motor cortex for pain control: a combined PET-scan and electrophysiological study. Pain 83: 259–277
9. Katayama Y, Fukaya C, Yamamoto T (1998) Poststroke pain control by motor cortex stimulation: neurological characteristics predicting a favourable response. J Neurosurg 89: 585–591
10. Katayama Y, Tsubokawa T, Yamamoto T (1994) Chronic motor cortex stimulation for central deafferentation pain: experience with bulbar pain secondary to Wallenberg syndrome. Stereotact Funct Neurosurg 62: 295–299
11. Khedr EM, Kotb H, Kamel NF, Ahmed MA, Sadek R, Rothwell JC (2005) Long lasting antalgic effects of daily sessions of repetitive transcranial magnetic stimulation in central and peripheral neuropathic pain. J Neurol Neurosurg Psychiatry 76: 833–838
12. Lefaucheur JP, Drouot X, Menard-Lefaucheur I, Zerah F, Bendib D, Cesaro P, Keravel Y, Nguyen JP (2005) Neurogenic pain relief by repetitive transcranial magnetic cortical stimulation depends on the origin and the site of pain. J Neurol Neurosurg Psychiatry 75: 612–616
13. Manola L, Roelofsen BH, Holsheimer J, Marani E, Geelen J (2005) Modelling motor cortex stimulation for chronic pain control: electrical potential field, activating functions and responses of simple nerve fibre models. Med Biol Eng Comput 43: 335–343
14. Meglio M, Cioni B, Montano N (2005) Motor cortex stimulation for pain control In: Meglio M (ed) Proceedings of the 14th Meeting of the World Society for Stereotactic and Functional Neurosurgery. Medimond, Bologna, pp 175–181
15. Meyerson B (2005) Motor cortex stimulation-effective for neuropathic pain but the mode of action remains illusive. Pain 118: 6–7
16. Meyerson B, Lindblom U, Linderoth B, Lind G, Herregodts P (1993) Motor cortex stimulation as treatment of trigeminal neuropathic pain. Acta Neurochir Suppl 58: 150–153
17. Nguyen JP, Lefaucheur JP, Decq P, Uchiyama T, Carpentier A, Fontaine D, Brugières P, Pollin B, Fève A, Rostaing S, Cesaro P, Keravel Y (1999) Chronic motor cortex stimulation in the treatment of central and neuropathic pain. Correlation between clinical, electrophysiological and anatomical data. Pain 82: 245–251
18. Nguyen JP, Lefaucheur JP, Le Guerinel C, Eizenbaum JF, Nakano N, Carpentier A, Brugières P, Pollin B, Rostaign S, Keravel Y (2000) Motor cortex stimulation in the treatment of central and neuropathic pain. Arch Med Res 31: 263–265
19. Nuti C, Peyron R, Garcia-Larrea L, Brunon J, Laurent B, Sindou M, Mertens P (2005) Motor cortex stimulation for refractory neuropathic pain: four year outcome and predictors of efficacy. Pain 118: 43–52
20. Peyron R, Garcia-Larrea L, Deiber MP, Cinotti L, Convers P, Sindou M, Mauguière F, Laurent B (1995) Electrical stimulation of the precentral cortical area in the treatment of central pain: electrophysiological and PET study. Pain 62: 275–286
21. Pirotte B, Voordecker P, Neugroschi C, Baleriaux D, Wikler D, Metens T, Denolin V, Joffroy A, Masseger R, Brotchi J, Levivier R (2005) Combination of functional magnetic resonance imaging-guided neuronavigation and intraoperative cortical brain mapping improves targeting of motor cortex stimulation in neuropathic pain. Neurosurg 56: ONS344–ONS359
22. Rainov NG, Fels C, Heidecke V, Burkert W (1997) Epidural electrical stimulation of the motor cortex in patients with facial neuralgia. Clin Neurol Neurosurg 99: 205–209
23. Saitoh Y, Osaki Y, Nishimura H, Hirano S, Kato A, Hashikawa K, Hatazawa J, Yoshimine T (2004) Increased regional cerebral blood flow in the controlateral thalamus after successful motor cortex stimulation in a patient with post-stroke pain. J Neurosurg 100: 935–939
24. Saitoh Y, Shibata M, Hirano S, Hirata M, Mashimo T, Yoshimine T (2000) Motor cortex stimulation for central and peripheral deafferentation pain. J Neurosurg 92: 150–155
25. Senapati AK, Huntington PJ, Peng YB (2005) Spinal dorsal horn neurone response to mechanical stimuli is decreased by electrical stimulation of the primary motor cortex. Brain Res 1036: 173–179
26. Son BC, Kim MC, Moon DE, Kang JK (2003) Motor cortex stimulation in a patient with intractable complex regional pain syndrome type II with hemibody involvement. J Neurosurg 98: 175–179
27. Tsubokawa T, Katayama Y, Yamamoto T, Hirayama T, Koyama S (1991) Chronic motor cortex stimulation for the treatment of central pain. Acta Neurochir Suppl 52: 137–139
28. Tsubokawa T, Katayama Y, Yamamoto T, Hirayama T, Koyama S (1993) Chronic motor cortex stimulation in patients with thalamic pain. J Neurosurg 78: 393–401
29. Yamamoto T, Katayama Y, Hirayama T, Tsubokawa T (1997) Pharmacological classification of central post-stroke pain: comparison with the results of chronic motor cortex stimulation therapy. Pain 72: 5–12

Correspondence: Beatrice Cioni, Neurochirurgia Funzionale e Spinale, Università Cattolica, Lg A. Gemelli 8, 00168 Roma, Italy. e-mail: bcioni@rm.unicatt.it