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Motor cortex stimulation for neuropathic pain

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Summary

Since the initial publication of Tsubokawa in 1991, epidural motor cortex stimulation (MCS) is increasingly reported as an effective surgical option for the treatment of refractory neuropathic pain although its mechanism of action remains poorly understood. The authors review the extensive literature published over the last 15 years on central and neuropathic pain. Optimal patient selection remains difficult and the value of pharmacological tests or transcranial magnetic stimulation in predicting the efficacy of MCS has not been established. Pre-operative functional magnetic resonance imaging (fMRI), 3-dimensional volume MRI, neuronavigation and intra-operative neurophysiological monitoring have contributed to improvements in the technique for identifying the precise location of the targeted motor cortical area and the correct placement of the electrode array. MCS should be considered as the treatment of choice in post-stroke pain, thalamic pain or facial anesthesia dolorosa. In brachial plexus avulsion pain, it is preferable to propose initially dorsal root entry zone (DREZ)-tomy; MCS may be offered after DREZotomy has failed to control the pain. In our experience, the results of MCS on phantom limb pain are promising. In general, the efficacy of MCS depends on: a) the accurate placement of the stimulation electrode over the appropriate area of the motor cortex, and b) on sophisticated programming of the stimulation parameters. A better understanding of the MCS mechanism of action will probably make it possible to adjust better the stimulation parameters. The conclusions of multicentered randomised studies, now in progress, will be very useful and are likely to promote further research and clinical applications in this field.

Keywords: Neuromodulation; neuropathic pain; motor cortex stimulation; MCS; pain; post-stroke pain; facial anesthesia dolorosa; brachial plexus avulsion; phantom limb pain.

Introduction

Neuropathic types of pain (NP) are considered as difficult to treat, heterogeneous clinical syndromes that are secondary to a wide variety of peripheral and/or central nervous system injuries [2]. Currently, the pathophysiological mechanisms of neuropathic pain are much better understood [2, 16]; however, since the introduction of anticonvulsant and tricyclic antidepressant drugs in the management of NP, little progress has been made in the pharmacological treatment of this condition [44].

As early as late 1960s, the neuromodulation-based concept of the ''gate control theory'', was followed by the development of minimally invasive and reversible neurostimulation techniques; this represented a major step forward in the treatment of intractable neuropathic pain. Chronic spinal cord stimulation (SCS) is a minimally invasive percutaneous, epidural and increasingly adjustable technique because it is performed with multipolar and multichannel electrodes; however, it will control only pain secondary to incomplete peripheral nerve damage [20]. Deep brain stimulation (DBS) of the sensory thalamic nuclei has offered disappointing long-term results, especially in central pain [23]. This explains the interest aroused by motor cortex stimulation (MCS); this alternative treatment was proposed, in 1991, by Tsubokawa *et al.* [50] and was based on data derived from experiments in animal models of central sensory deafferentation pain. MCS inhibits the spontaneous thalamic neuronal hyperactivity induced by spinothalamic tractotomy [40]. The first clinical benefits were seen in cases of thalamic pain [51] or neuropathic facial pain [29].

The action mechanism of MCS remains poorly understood. It has been proposed that it may be related to the inhibition of nociceptive ascending pathways at the thalamic [3, 47, 48], or spinal level [43]. These scientific data have not been validated in humans. Furthermore, they do not explain the observed prolonged antinociceptive effects. Other proposed mechanisms involve supraspinal structures, namely the cingulate gyrus, orbitofrontal cortex, and brainstem [12, 35]. There are many unclear or unsettled issues that must be addressed. These include

the action mechanism, the best possible electrode structure, the optimum stimulation parameters, and the correct stimulation depth; the latter should be determined after taking into account the cortex layers and the orientation of the fibers in the motor cortex. Despite all these uncertainties, nearly 300 cases have been reported describing MCS applications to most types of intractable peripheral and central neuropathic pain [1, 3, 6, 47]. Many clinical studies have reported beneficial effects, but in several reports, the results were contradictory [18]. Similarly to all other neuromodulation techniques, the patients must be strictly selected; this is especially important in MCS because the optimum indications are not yet fully determined. Many studies [32, 33, 36, 45] have emphasized that the degree and duration of the analgesic effect depend on the accuracy of electrode placement on the motor cortical area that corresponds ideally to the somatic area of pain. This objective is difficult to achieve because: a) the patient does not feel any stimulation-induced paraesthesias, and b) the sensory deafferentation is often associated with cortical reorganization [11, 28, 37, 56].

Patient selection criteria

The diagnosis of neuropathic pain (NP) must be confirmed by a multidisciplinary evaluation. The pain should: a) be localized in an area of extensive sensory deafferentation (hypoaesthesia), b) be secondary to either a peripheral nerve damage or a central nervous system lesion (or malfunction) which can be demonstrated by neuroimaging, electrophysiology or surgical exposure, and c) be a symptom of a non-progressive condition. Furthermore, it should be possible for the pain to be classified definitively as NP according to the classification proposed by Rasmussen *et al.* [39]. NP should have an intense character and a chronic progression for over 6 months and should be intractable to pharmacological or physical treatments. It is important to investigate whether the patient has received any benefits from properly prescribed and observed anticonvulsant or antidepressant treatments. The development of new anticonvulsants has prolonged the period of medical treatment before NP is recognized as being refractory [2, 39, 44]. Some authors [8, 47, 58] have attributed predictive value to certain pharmacological tests such as the lack of response to morphine, the attenuation of pain by barbiturates and the response to transcranial magnetic stimulation (TMS) [7, 22, 30, 34]. The predictive value of these tests has not been established [42].

Targeting and surgical technique

The first objective of the procedure is to define accurately the motor cortex area that corresponds to the somatic area of pain and should be stimulated. Current neuroimaging techniques allow us to determine directly the anatomical position of the central sulcus (CS) and indirectly the somatotopic representation of the motor homunculus (Area 4) in the precentral gyrus. The theoretical cortical target to be identified and stimulated depends on the size of the somatic region of pain. The main body segments and their respective motor cortex areas to be stimulated are described below:

1) face: lower part of the central gyrus,
2) upper limb and hand: middle part of the central gyrus between the inferior frontal sulcus and the superior frontal sulcus, and
3) lower limb and trunk: upper part of the central gyrus between the superior frontal sulcus and the interhemispheric fissure.

The distal part of the lower limb lies on the inner surface of the hemisphere, and therefore, it cannot be directly stimulated epidurally; this limb representation, however, can be extended to the upper part of the motor gyrus [55]. With current neuronavigation methods, it is possible to reconstruct three-dimensionally the cortex from morphological MRI data and identify these anatomical structures precisely. These topographical data can be subjected to image fusion with functional MRI (fMRI) data obtained during an actual motor task [31, 36, 38, 45] or a virtual motor task [41, 45]; the latter should correspond to the pain territory in a painful phantom limb, or to the neighbouring territory in cases of complete motor deficits (upper limb following brachial plexus avulsion). This correlation is particularly useful because the deafferentation may have reorganized the motor cortex and therefore reduced or displaced the target area that should be stimulated. Some authors use TMS to identify the motor cortex and then combine TMS with neuronavigation [34] and PET data [35, 45].

Intraoperative techniques

Craniotomy

The initial procedure by Tsubokawa consisted of a simple burr hole under local anaesthesia. This has been replaced by a small craniotomy [10, 32–35], which offers the advantage of better intraoperative neurophysiological exploration and minimizes the risk of a post-operative

epidural haematoma. The location and borders of the craniotomy are defined by neuronavigation analysis of the preoperative targeting data. A 4–5-cm sized bone flap is sufficient; alternatively, a 5-cm-diameter trephine craniotomy may be done when the target lies on the outer surface of the hemisphere (face or upper limb).

Intraoperative neurophysiological exploration

The first stage consists of pinpointing the CS on the dural surface. In practice, neuronavigation is sufficient but, if there is doubt, target confirmation can be done by recording somatosensory evoked potentials (SEPs) after stimulation of the contralateral median nerve at the wrist [33, 55]. The SEPs are recorded using an electrode grid with multiple poles (20–40) or the 4-contact plate electrode with contacts 4 mm in diameter spaced 10 mm apart (Resume®, Medtronic Inc., Minneapolis, USA). Many studies have provided evidence of a relationship between the location of the CS and the location of the N20/P20 phase reversal [47, 53]. The N20 is elicited in the motor gyrus area that corresponds to the hand, i.e. in front of the CS. In several NP conditions that are accompanied by severe sensory deafferentation (e.g. brachial plexus avulsion), the intraoperative SEPs cannot be used. Furthermore, the intraoperative SEPs recorded after trigeminal or tibial nerve stimulation are often difficult to interpret. Therefore, it is useful to check the quality of SEPs intra-operatively.

The second stage is critical. It consists of localising accurately the targeted cortical area by MCS. It may be difficult to induce transdurally muscle contractions in the somatic area of pain because: 1) the dura-to-cortex distance is affected by the variable thickness of the subarachnoid space or the presence of cortical atrophy, 2) the stimulation delivered by the neurostimulators is not intense (10 mA max), and 3) the suppression of neuronal activity by general anaesthesia [33, 34]. In practice, it is possible to use the final quadripolar electrode (Resume®) to perform this motor stimulation test and to couple the electrical stimulation (pulse width: 1 msec, low frequency: 1–3 Hz, intensity: 5–10 mA, monophasic pulse) with electromyographic (EMG) recording of the activity of the appropriate muscles. Thus, it is possible to detect a subclinical response without necessarily inducing muscle contraction.

Placement of the electrode array

Based on the intraoperative electrophysiological data and the extent of the pain territory, one or two quadripolar plate electrodes (Resume®) are sutured to the dura either perpendicularly or parallel to the SC; the electrode orientation depends on surgeon's preference but it is important to have at least two poles over the targeted motor cortex. The electrode extensions are tunnelled and connected to an implantable pulse generator (IPG), (ITREL 3® or SYNERGY®, Medtronic Inc., Minneapolis, USA) which is inserted in the subclavicular or the lateral thoracic region. Experience has shown that it is not worthwhile to perform a prolonged percutaneous stimulation test intraoperatively; the identification of the optimal stimulation parameters may require multiple adjustments because the patient usually does not feel any MCS-induced paraesthesias or sensations. The parameters are selected empirically and usually are: amplitude: 2 V (1–4 V), frequency: 40 Hz (25–55 Hz), pulse width: 120 μsec (60–180 μsec).

It is important that the negative contact (cathode) is placed over the motor cortex area that corresponds ideally to the territory of somatic pain. Most surgeons prefer bipolar stimulation with the negative contact (cathode) over the motor area and the positive contact (anode) over the sensory area [47]. In bipolar stimulation, both cathode and anode electrode contacts are active and their position can be relevant to the clinical effects of MCS [26]. The response of any cortical fiber varies and depends on its orientation in the stimulation-induced field [15]. An interpolar distance of 20–30 mm is preferred in order to cover widely the motor cortex area. It is possible to apply bipolar stimulation using the ITREL 3® system. The time course of the analgesic effect is variable. Under optimal neuroanatomical conditions, Tsubokawa [47] reported that the pain begins to decrease 5 minutes after the start of MCS and disappears completely after 10–20 minutes; after stimulation is stopped, there is a 2- to 6-hour post-MCS effect. Based on these observations, he recommended intermittent stimulations with a rate of 5–7 per day. Conversely, Nguyen *et al.* [34] underlined the latency of the analgesic effect, which is rarely immediate but may last for several days. Very often, it is found that the intensity must be increased in order to keep the stimulation efficacious; this can be explained by an increase in the impedance of the ''electrode to dura'' contact.

Results

A literature review in the Pubmed beginning in 1991 identified 29 publications, describing over 251 patients [3, 6, 34, 47]. It is difficult to compare their results

because most studies are retrospective and use different assessment scales. No prospective studies have been published and the number of available controlled studies is limited. A randomized (on/off) multicentered study is currently being conducted in France.

Central pain

Thalamic pain syndromes are intractable, disabling, and particularly resistant to medical and conservative treatments. The long-term failure of DBS in this type of NP has been verified. Tsubokawa *et al.* [49] reported disappointing results following stimulation of the sensory nuclei of the thalamus; although the initial effect was satisfactory in certain patients, tolerance to stimulation developed in a few months and, after 2 years the stimulation was efficacious only in 38% of the cases. More recently, following a literature review of long-term results, Levy *et al.* [23] reported that, in 24 cases, the DBS improvement rate was only 24%; the complications were uncommon (5.3%) but serious (5 cerebral haemorrhages). The main indication of MCS is post-stroke pain [50, 51]. Nguyen *et al.* [34] estimated that our experience on the treatment of this condition by MCS is based on over 159 cases of central pain secondary to ischaemic or haemorrhagic stroke; the MCS success rate was 52% (83/159). Table 1 summarizes the results of the main published series on MCS. Several authors [18, 34] have underlined that the association of pain with a major motor deficit is a poor prognostic indicator. Nevertheless, the management of central pain by MCS should be considered as an alternative treatment of confirmed efficacy.

Trigeminal neuropathic pain

Trigeminal neuropathic pain is one of the most common indications of MCS. This type of NP is most often secondary to an iatrogenic injury to the roots of the trigeminal nerve (thermocoagulation or conventional surgery). MCS has replaced the chronic stimulation of the Gasserian ganglion in the treatment of trigeminopathic pain. In the latter procedure, it is possible to perform not only a prolonged percutaneous test-stimulation but also a long-term stimulation of the ganglion [19]; there is, however, a serious risk of late dislodgment of the percutaneously inserted electrode. The alternative method of electrode implantation through a temporal approach is a major surgical procedure. This technique has been abandoned gradually, although its results were satisfactory in facial neuropathic pain of central or peripheral origin [46]. The results of thalamic stimulation were disappointing [23]; in 12 cases of anaesthesia dolorosa, the long-term success rate was only 18%. With regard to MCS, 47 cases have been reported in the literature; the success rate was high with the average

Table 1. *Published series on the results of MCS on central neuropathic pain*

Authors (reference number)	Patients number/ age range (years)	Follow-up in months	Success rate at latest follow-up (≥50% analgesia)
Tsubokawa *et al.* [51]	11/52–72	≥24	45% (5/11)
Nguyen *et al.* [34]	18	46 (mean)	marked improvement (>60%): 7 satisfactory improvement (40–60%): 8 failure (<40%): 3
Meyerson *et al.* [29]	3	–	0%
Yamamoto *et al.* [57]	28/35–72	≥12	46%
Mertens *et al.* [27]	16/29–78	23 (mean)	67%
Saitoh *et al.* [42]	8	26 (mean)	25% (2/8)
Caroll *et al.* [9]	5		40% (2/5)

Table 2. *Published series on the results of MCS on trigeminal neuropathic pain*

Authors (reference number)	Patients number/ age range (years)	Follow-up in months	Success rate at latest follow-up (≥50% analgesia)
Meyerson *et al.* [29]	5/44–71	4–28	100% (5/5)
Herregodts *et al.* [14]	5/40–45	15 (mean)	88% (4/5)
Ebel *et al.* [10]	7/37–81	5–24	43% (3/7)
Nguyen *et al.* [32, 34]	22		marked improvement (>60%): 59% (13/22) satisfactory improvement (40–60%): 23% (5/22)
Brown and Barbaro [3]	8/37–73	10 (mean)	75%

Table 3. *Published series on the results of MCS in neuropathic limb pain*

Authors (reference number)	Indications	Patients number	Mean follow-up in months (range)	Success rate at latest follow-up (%)
Nguyen *et al.* [33]	brachial plexus avulsion	2		50%
Mertens *et al.* [27]	brachial plexus avulsion	4		50%
Saitoh *et al.* [42]	brachial plexus avulsion	4	19	25%
	phantom limb pain	2	20	50%
Sol *et al.* [45]	phantom limb pain	3	27.3	67%
Caroll *et al.* [9]	phantom pain	3	–	67%
Pirotte *et al.* [36]	plexus avulsion	3	–	33%
Lazorthes *et al.* [21]	phantom	7	42 (6–76)	85%
Katayama *et al.* [18]	phantom limb pain	5	>24	20%

long-lasting improvement being evaluated as greater to 50% in 73–75% of the cases (Table 2).

Neuropathic limb pain

In this group, MCS may be indicated only after SCS either has failed or is contraindicated. This category includes patients with NP secondary to complete sensory deafferentation after either brachial plexus avulsion or limb amputation (phantom limb pain). Table 3 summarizes the main published series. In brachial plexus injuries, the results are not satisfactory (average success rate 40%). In this condition, it is not feasible to identify the CS by intraoperative SEP monitoring. Therefore, it is preferable to perform a DREZotomy as the first procedure of choice. In phantom limb pain, the results are variable with an average success rate of 55% [9, 33, 34, 42]. We have reported comparable results [41, 45]. In a recent retrospective study [21], in 7 patients with a mean follow-up of 42 months (range: 6–76), the success rate was 85% (excellent: 3, significant: 3, failure: 1). Conversely, Katayama *et al.* [18] reported conflicting results; he achieved a lasting analgesic effect in 6 of 19 patients with painful phantom limbs after SCS. Of 10 patients who did not respond to SCS, he reported lasting improvement after thalamic DBS (nucleus ventralis caudalis) in 6 cases (60%), whereas only 1 out of 5 patients treated by MCS had a lasting improvement (success rate: 20%). In this article, there was little information on the pre- and intraoperative identification of the motor cortex target; in addition, 3 of the 5 patients who received MCS had brachial plexus avulsion without being clear whether this was associated with an amputated upper limb. MCS represents the preferred treatment in phantom limb pain which is otherwise considered intractable and irreversible. The historical failures of sensory cortex removals are well-known [24, 25, 52]. In a literature review, Levy *et al.* [23] reported 5 cases of periventricular gray matter (PVG) DBS who had an initial good response (4 of 5 improved) but a disappointing long-term response (only 1 of 5 improved); this was not confirmed by the recent study of Katayama *et al.* [18].

Table 4. *Published series on the results of MCS in post-spinal lesion pain*

Author (reference number)	Indication	Patients number	Success rate at latest follow-up (%)
Nguyen *et al.* [33]	post-trauma paraplegia	4	75
Mertens *et al.* [27]	post-trauma	3	100

Post-spinal lesion pain

This type of NP, particularly in the lower limbs, represents a very difficult problem because the pain is bilateral and the cortical target area is located near the midline. To overcome this difficulty, surgeons have implanted the electrodes interhemispherically [42]; this, however, induces an increased risk of complications. Paradoxically, Nguyen [33] has reported that unilateral cortical stimulation can have a bilateral effect (Table 4).

Side effects and complications

Complications are uncommon and of moderate severity. The most serious are epilepsy, and epidural or subdural haematomas; they occur approximately in 3% of the cases.

Stimulation-induced seizures

These have been seen mostly during the test-stimulation period [29]. Their incidence during chronic MCS is very low if the stimulation intensity remains below the motor threshold. The incidence can become higher after ''intense reprogramming'' [13, 34].

Epidural haematoma

Theoretically, if the dura is correctly secured around the edges of the craniotomy, the risk is negligible. However, several cases have been reported, especially during the early period of MCS, when the electrodes were inserted through a single burr hole [29, 51].

Skin ulceration and infection

This is a common risk which is associated with the implantation of any stimulation device. In the literature, the frequency is estimated between 0.7 and 2.2%. Any implantation should be postponed as long the patient has untreated urinary, pulmonary or other infections.

Loss of efficacy

After the initial benefit, which may last for several months, some authors have reported a tolerance-like phenomenon [10]. In such cases, the efficacy can be restored by replacing the electrode on a more optimal cortical target [33, 45, 51]. Sometimes, a simple increase in the electrode-dural impedance is required by either increasing the stimulation intensity or changing the bipolar configuration. A loss of efficacy secondary to neural plasticity and reorganization of the deafferentated cortical area is another possibility; this hypothesis led Henderson *et al.* to perform ''intensive reprogramming'' in order to restore the initial efficacy [13].

Conclusions

Neuropathic pain (NP) is considered as a difficult-to-treat clinical condition which is associated with various lesions in the peripheral or central nervous system. Antidepressant and anticonvulsant medications are considered as the primary treatment and offer satisfactory relief to most patients [2, 44]. Over the last few years, a new approach to the treatment of NP has developed; this is based on the current understanding of pain mechanisms and aims to target specifically these mechanisms [54]. This rational approach cannot yet be implemented widely because of difficulties in converting our understanding of the pathophysiological mechanisms, obtained from animal studies, to treatment protocols in patients [16]. Nevertheless, chronic motor cortex stimulation (MCS) is no more just a promising method; it has gained an established role in the treatment of chronic intractable pain secondary to sensory deafferentation. It provides a therapy to a category of pain which until now has been proved resistant to any other treatment. In certain types of central neuropathic pain, such as post-stroke pain, MCS constitutes the first-choice therapeutic alternative after the failure of medical and conservative treatments. The same applies to facial anaesthesia dolorosa. Conversely, in pain secondary to brachial plexus avulsion, it is preferable to propose first selective ablative surgery, such as DREZotomy. Other indications need to be confirmed, even if lasting efficacy has been reported by various authors in ''phantom limb pain'' or paraplegia-related pain.

The efficacy of MCS depends directly on the accurate placement of the stimulation electrode over the appropriate area of the motor cortex. The primary motor cortex that corresponds to the somatic area of pain may have been displaced because of either brain plasticity or cortical reorganization secondary to the sensory deafferentation or to the causal lesion in the nervous system. Brain mapping using fusion of three-dimensional volume MRI with fMRI in combination with intraoperative electrophysiology is a valid technique for identifying the precise location of the targeted motor cortex. There are still many unclear issues such as which neurons or axons should be stimulated, which cortical afferents or efferents are stimulated by MCS, and whether antidromic stimulation contributes to the clinical effects. Multicenter prospective studies are being conducted. They will describe larger clinical series with a ''study design'' of MCS that includes ''on/off'' sequences evaluated in a ''blind'' manner. Hence, the conclusions of these studies are expected to be of particular significance. A better understanding of MCS mechanisms of action will probably make it possible to program better the stimulation parameters; currently, the programming remains empirical and is based on practical clinical observations. Experimental studies predicting the bioelectrical effects of MCS by computer modelling [26] and more sophisticated neuronal fiber models are in the stage of development and are likely to promote further research and clinical applications in this field.

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