Invasive brain stimulation for the treatment of neuropathic pain

Jean-Paul Nguyen, Julien Nizard, Yves Keravel and Jean-Pascal Lefaucheur

Abstract | Neurostimulation therapy is indicated for neuropathic pain that is refractory to medical treatment, and includes stimulation of the dorsal spinal cord, deep brain structures, and the precentral motor cortex. Spinal cord stimulation is validated in the treatment of selected types of chronic pain syndromes, such as failed back surgery syndrome. Deep brain stimulation (DBS) has shown promise as a treatment for peripheral neuropathic pain and phantom limb pain. Compared with DBS, motor cortex stimulation (MCS) is currently more frequently used, mainly because it is more easily performed, and has a wider range of indications (including central poststroke pain). Controlled trials have demonstrated the efficacy of MCS in the treatment of various types of neuropathic pain, although these trials included a limited number of patients and need to be confirmed by large, controlled, multicenter studies. Despite technical progress in neurosurgical navigation, results from studies of MCS are variable, and validated criteria for selecting good candidates for implantation are lacking. However, the evidence in favor of MCS is sufficient to include it in the range of therapeutic options for refractory neuropathic pain. In this Review, the respective efficacies and mechanisms of action of DBS and MCS are discussed.

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Introduction

Neuropathic pain has been defined by the International Association for the Study of Pain as "a pain initiated or caused by a primary lesion or dysfunction in the nervous system." [1]To establish a degree of certainty that pain has a neuropathic origin, the location of pain should correspond to a distinct neuroanatomical distribution, associated with evidence of a relevant lesion or disease of the somatosensory nervous system.[2] Thus, neuropathic pain is distinct from other types of pain, such as headache, nociceptive inflammatory pain, postoperative pain, or musculoskeletal pain. Chronic neuropathic pain has been estimated to affect up to 3% of the population.[3] The most frequent etiologies of neuropathic pain are: diffuse peripheral neuropathy or focal lesions of the nerve trunk, plexus or root, or spinal ganglion, including postherpetic neuralgia and trigeminal nerve lesions; phantom limb pain; spinal cord lesions, including traumatic injury to the spine and syringomyelia; and focal brain lesions, including multiple sclerosis and central poststroke pain.

Chronic neuropathic pain syndromes can be managed by primary care physicians and pain specialists, who are able to propose various pharmacological, physical and psychological therapies as the first lines of treatment. Drugs of various classes are effective in patients with neuropathic pain: antidepressants, including tricyclic agents and serotonin–norepinephrine reuptake inhibitors; anticonvulsants, including presynaptic voltage-gated calcium blockers, voltage-gated sodium blockers and γ-aminobutyric acid (GABA)-receptor agonists; topical lidocaine; and opioids. Use of these drugs is based on empirical evidence or the results of controlled clinical trials. Various guidelines, recommendations and evidence-based algorithms have been proposed for the pharmacological treatment of neuropathic pain.[4–7] Despite the value of these strategies and the development of new medications, patients with neuropathic pain do not always respond to treatment with these drugs. For the nonresponsive patients, therapeutic alternatives—including lesional surgery and neurostimulation techniques—are required.

Lesional surgery has been virtually abandoned as an approach for the treatment of neuropathic pain, with the exception of destruction of small-diameter nociceptive fibers in the dorsal root entry zone (DREZtomy), which can be used to treat the paroxysmal component of neuropathic pain secondary to brachial plexus avulsion.[8,9] By contrast, neurostimulation therapy is increasingly being used to treat chronic neuropathic pain that is refractory to drug treatment.[10] The neurostimulation techniques can be divided into noninvasive and invasive methods. Noninvasive methods include transcutaneous electrical nerve stimulation (TENS) and repetitive transcranial magnetic stimulation (rTMS) of the cortex. An analgesic effect was reported in patients with chronic neuropathic pain who received rTMS consisting of at least 1,000 pulses delivered at 5–20 Hz over the primary motor cortex (M1), contralateral to the pain territory.[11–13] If daily rTMS sessions are continued for about 2 weeks, they might have a therapeutic effect; however, the duration of this beneficial

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Key points

- Neurostimulation therapy is indicated for drug-resistant neuropathic pain
- Neurostimulation therapy for pain mainly includes spinal cord stimulation, deep brain stimulation, and motor cortex stimulation
- Motor cortex stimulation is more easily performed and has currently a wider range of indications than deep brain stimulation
- The efficacy of motor cortex stimulation has been demonstrated in the treatment of neuropathic pain by a small number of controlled trials
- The criteria for selecting good candidates for deep brain or motor cortex stimulation still remain to be clearly delineated

effect is rather short, and maintenance treatment (that is, further stimulation sessions performed at regular intervals) is often required to control chronic refractory neuropathic pain. The role of rTMS in the treatment of chronic pain syndrome is, therefore, limited; this technique is mainly used for preoperative assessment of patients who are eligible for implanted epidural MCS. In the future, TMS methods, including rTMS tests and cortical excitability studies, should be developed for use in the selection and evaluation of candidates for implanted MCS. Another promising noninvasive method of cortical stimulation is transcranial direct current stimulation (tDCS), which, from a technical point of view, is easier to perform than rTMS. However, tDCS has rarely been applied to treat neuropathic pain syndromes, and its mechanism of action (neuromodulation) differs from that of rTMS and implanted MCS (neurostimulation). Therefore, the role of tDCS in the treatment of chronic pain remains to be defined.

Invasive methods of neurostimulation involve surgical interventions to implant electrodes and a pulse generator, such as dorsal spinal cord stimulation (SCS), deep brain stimulation (DBS), and motor cortex stimulation (MCS). These techniques vary in their mechanisms of action, and in the types of neuropathic pain for which they are most suitable.[10] For instance, the efficacy of SCS was mainly demonstrated in patients with failed back surgery syndrome (FBSS) or complex regional pain syndrome type I—two conditions that are not definitely neuropathic.[10] SCS might be indicated in the treatment of pain syndromes that have a peripheral origin, especially when the pain is located in the lower limbs. For central pain of brain origin, such as poststroke pain, SCS is effective only in a small minority of patients;[14–17] for these individuals, a therapy that involves direct stimulation of the brain would be preferred.

Therapeutic brain stimulation is achieved by performing either DBS or MCS. In this article, we compare the mechanisms of action, clinical evidence and safety of these techniques and compare their potential as therapies for neuropathic pain.

Deep brain stimulation

Mechanisms of action

The first attempts to treat refractory pain using DBS[18] preceded both the discovery of the gate control theory of pain transmission[19] and the development of SCS.[20] Various deep brain structures, including the sensory thalamus (mainly the ventroposterolateral nucleus), the posterior limb of the internal capsule, and the periventricular and/or periaqueductal gray matter (PVG and PAG, respectively), have been targeted in the attempt to induce pain relief.[21–24] The exact mechanisms by which DBS relieves pain probably depend on the exact location of the stimulating electrode. For instance, the analgesic effect of PVG and/or PAG stimulation is thought to be mediated by an increase in the release of endogenous opioids, and this effect can be reversed by administration of the opioid antagonist naloxone.[23,25–27] However, an increase in opioid release was not confirmed in all patients who were treated with PVG and/or PAG stimulation, which suggested the existence of opioid-independent mechanisms of DBS-induced pain relief.[28–30]

An opioid-independent mechanism is also assumed to account for the analgesia induced by sensory thalamus stimulation.[31] The ventral posterolateral nucleus of the thalamus represents the second relay of sensory pathways and receives projections from all ascending tracts that carry sensory signals, including pain. The value of thalamic stimulation to induce pain relief is based on Head and Holmes's theory that the thalamus is the chief organ through which nociceptive information is integrated and pain is perceived.[32] In line with this theory, thalamic stimulation could act by modulating the integration of sensory information transmitted via lemniscal and extralemniscal systems, or by modulating the propagation of sensory information along the corresponding spinal tracts, leading to regulation of neuronal activities in the dorsal horns. However, the analgesic effects produced by sensory thalamus stimulation could also result from activation of long-loop polysynaptic pathways involving the sensorimotor cortex, basal ganglia and medial thalamus.[33] The influence of stimulation frequency on the clinical efficacy of DBS suggests that this technique acts by regulating some disease-related rhythmic or oscillatory activities within specific neural circuits.[34]

Clinical results

Thalamic stimulation was first performed by Mazars in 1961 to treat cases of neuropathic pain associated with sensory deafferentation.[35,36] Since then, more than 600 patients with chronic pain syndrome have been treated by DBS and, according to two meta-analyses, this technique has a mean long-term success rate of 46%.[10,37] These analyses also showed that sensory thalamus stimulation alone (58% efficacy) was less efficacious than PVG and/or PAG stimulation, either alone (79% efficacy) or in combination with sensory thalamus or internal capsule stimulation (87% efficacy).[37] Overall, DBS is a more effective treatment for nociceptive pain than for deafferentation pain, with long-term success rates of 63% versus 47%, respectively. Finally, it can be concluded that PVG and/or PAG stimulation is beneficial for the treatment of nociceptive pain, whereas sensory thalamus stimulation is indicated in the treatment of deafferentation pain.[38]

The most successful outcomes of DBS therapy are seen in patients with cancer-associated pain or FBSS (65–78% long-term success). This treatment is least successful in patients with poststroke pain or postherpetic neuralgia, who show only 31–36% long-term success;[10,37,39–41] however, the published data are conflicting, and some studies have shown good clinical outcomes after DBS treatment in patients with these conditions.[42,43] The therapeutic value of DBS as a treatment for phantom limb pain is also controversial, as some studies have demonstrated favorable results for this treatment,[37,44,45] whereas others have not.[39] Taking into account the results of all studies in patients with neuropathic pain, DBS seems to be more efficacious for peripheral pain than for central pain.[37,41] Although some patients with neuropathic pain of any origin can benefit from DBS, good results are most likely for patients with peripheral pain, facial pain, or phantom limb pain.[45] However, DBS efficacy is quite variable from one patient to another, and several studies have reported negative results (that is, the absence of significant pain relief).[46,47] One multicenter study—promoted by the FDA—also showed negative results of DBS therapy, and this finding has further hindered the use of DBS in clinical practice in the USA.[48] Finally, one study suggested that long-term pain relief might result from electrode implantation alone, without any requirement for switching on the stimulator.[48] These observations stress the need for randomized controlled trials (RCTs) that include an off-stimulation (placebo) group or period. The development of DBS has also been limited by the absence of any clear consensus regarding the choice of target for stimulation, leaving several unanswered questions about the optimal electrode locations in the PVG and/or PAG region and the sensory thalamus, and about the advantage from concomitant stimulation of the PVG and/or PAG region and the sensory thalamus rather than each separately. Finally, implantation of DBS electrodes can be complicated by a severe adverse event—intracranial hemorrhage. This complication is rare (occurring in 2–4% of procedures), but can cause a permanent neurological deficit, and even death.[46]

The risk-to-benefit ratio of DBS has clearly improved over time, partly as a result of the advances in imaging guidance for the stereotactic procedure of electrode placement. Currently, however, DBS can only be performed by experienced neurosurgeons trained in DBS techniques, and still requires clinical validation for its therapeutic use in various chronic pain syndromes.[10] If controlled clinical trials confirm the promising results that have been reported in the past 5 years,[41,43–45] a resurgence of interest in DBS might be possible. Nonetheless, in the past few years, DBS has been largely replaced by MCS, for several reasons that were cited above.[46] For example, one study showed the superior efficacy of MCS compared with DBS in patients with central poststroke pain.[14] DBS obviously suffers by comparison with alternative methods of neurostimulation that can be used for the same indications, such as SCS, MCS, or drug infusion pumps, which are safer and technically easier to implement.[46]

Motor cortex stimulation

Historical overview of target strategy

As SCS and DBS showed poor efficacy in the treatment of refractory poststroke pain, Tsubokawa and colleagues looked for alternative targets, particularly in the cortex, for the treatment of central neuropathic pain (especially pain related to a thalamic lesion).[49,50] These researchers developed a cat model of thalamic deafferentation, in which induction of a mesencephalic lesion resulted in thalamic hyperactivity that was considered to reflect the degree of deafferentation associated with the development of pain. Thalamic hyperactivity was reduced by MCS, whereas stimulation of the sensory cortex had no effect. Tsubokawa concluded that MCS could potentially be used to treat deafferentation pain, especially when secondary to a brain lesion. Although the choice of target seemed somewhat surprising, very encouraging short-term and intermediate-term results of MCS therapy for drug-resistant thalamic pain were reported by Tsubokawa's team,[50] and their findings were subsequently confirmed in studies on neuropathic pain syndromes of other origins. MCS was shown to improve neuropathic trigeminal pain,[51] and the beneficial effect of MCS was reported in published case reports or in various series of patients with all types of refractory neuropathic pain.[52–80] Currently, MCS is considered as a good alternative to DBS for the treatment of neuropathic pain.

Cortical targets other than the motor cortex—especially the somatosensory cortex—have been proposed in the treatment of neuropathic pain using MCS.[81] Some studies have shown pain relief from postrolandic cortical stimulation,[52,53] and some experimental data support the analgesic effect of primary or secondary somatosensory cortex stimulation.[82] However, in line with Tsubokawa's work, most research teams have found that stimulation using precentral contacts was more efficacious than stimulation using postcentral ones when the MCS lead was positioned perpendicular to the central sulcus. The results of a study that used navigated rTMS confirmed that stimulation of M1, but not of adjacent areas (such as the postcentral gyrus [S1] and the premotor or supplementary motor area), could provide statistically significant pain relief.[83] Stimulation over the anterior bank of the central sulcus, therefore, remains the preferred targeting strategy for analgesic cortical stimulation. Furthermore, these studies showed that targeting of the motor cortex alone was insufficient to achieve analgesia—positioning of the electrode over the area of somatotopic representation of the painful zone within the primary motor cortex was also required to obtain optimal benefit.

Targeting the motor cortex

In this section, the current mapping techniques for motor cortex somatotopy used in the practice of MCS therapy will be described. The motor cortex is located in Brodmann area 4, and M1 corresponds to the anterior wall of the central sulcus and the part of the precentral gyrus situated immediately anterior to this fissure.[84] Anatomically, the central sulcus has a very consistent

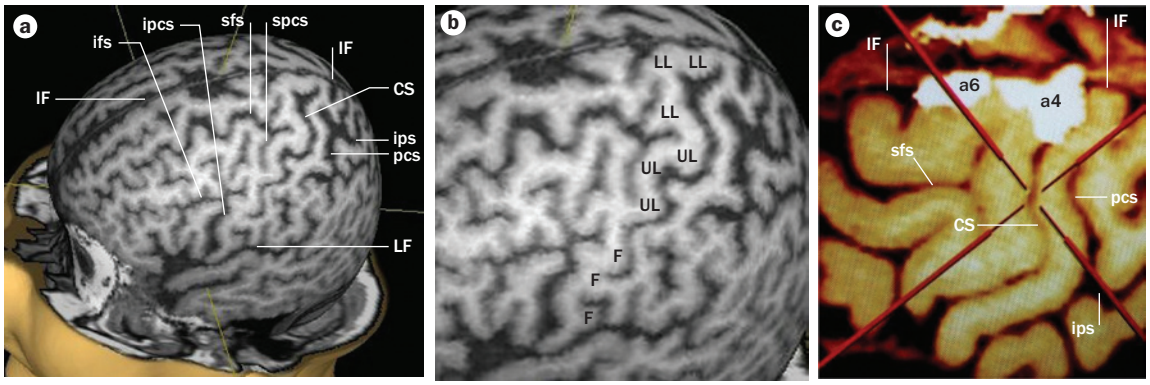

Figure 1 | Three-dimensional images of the brain reconstructed from MRI scans, depicted without the superficial layers of the cortex. **a** | Localization of brain regions and **b** | functional representation of body parts within the motor cortex. **c** | Activation (white areas) on functional MRI occurs when the patient is asked to imagine movements of both lower limbs. Activation is observed predominantly on one side and extending largely onto the medial surface of the hemisphere. Abbreviations: a4, superior part of the precentral area; a6, premotor area; CS, central sulcus; F, face. IF, interhemispheric fissure; ifs, inferior frontal sulcus; ipcs, inferior precentral sulcus; ips, intraparietal sulcus; LF, lateral fissure; LL, lower limb; sfs, superior frontal sulcus; spcs, superior precentral sulcus; pcs, postcentral sulcus; UL, upper limb.

morphology and is not connected to any other sulcus, facilitating its identification (and therefore that of M1) on neuroimaging scans. Anterior to the central sulcus is the precentral sulcus, which is usually divided into two sulci that are orthogonally connected to the superior and inferior frontal sulci, running parallel to the midline. Posterior to the central sulcus is the postcentral sulcus, which is connected to the intraparietal sulcus and can also be easily identified. Considerable progress has been made in neuroimaging, including the development of planar and three-dimensional reconstructions. Curved reconstructions are especially informative when the superficial layer of the cortex is not depicted. The sulci and fissures can be easily identified at about 5 mm below the brain surface, enabling the various structures of the central region (such as the central sulcus) to be targeted under neuroimaging guidance (Figure 1a).

The various anatomical regions of the body have distinct representations in M1 (Figure 1b), according to the classic work of Penfield.[85] In the usual somatotopic distribution, the face is represented in the inferior part of the motor cortex, generally between the lateral fissure and inferior frontal sulcus. The upper limb is represented in the part of M1 posterior to the middle frontal gyrus, between the inferior and superior frontal sulci. Specifically, hand representation corresponds to a zone in which the central sulcus presents a hook-shaped or omega-shaped appearance (the motor hand knob). The lower limbs are usually represented on the medial surface of the hemisphere, in a cortical zone corresponding to the anterior part of the paracentral lobule. However, direct cortical stimulation and functional MRI (fMRI) have shown that lower limb motor representation can extend laterally onto the superior part of the convexity of the precentral gyrus (Figure 1c),[86] and this area is, therefore, accessible for MCS therapy.

As previously mentioned, the efficacy of MCS depends on appropriate positioning of the electrode. This goal can be achieved through neuroimaging guidance and neurophysiological monitoring.[65,87] In particular, intraoperative neurophysiological mapping techniques enable anatomical and functional data to be integrated to determine the location of the zone to be stimulated.[88] Somatosensory evoked potentials (SEPs),[89,90] obtained by stimulation of the median nerve at the wrist, can be used to identify the position of the central sulcus and, therefore, to confirm data from neuroimaging. Motor evoked potentials (MEPs) are generated by anodal, rather than cathodal, stimulation of the motor cortex.[91] The optimal cortical representation of a given muscle territory is defined by the region where the motor threshold (that is, the intensity of stimulation required to produce MEPs) is the lowest. Alternatively, the optimal cortical representation can be defined by the region that shows the largest MEPs when stimulation is given at a constant intensity. In practice, repetitive stimulation of the motor cortex should be avoided because it increases the risk of seizure,[92] and MEPs can instead be recorded in response to a single electric shock of relatively high intensity (10–50 mA).[93] The most appropriate procedure for mapping the representation of the painful zone is to record MEPs to anodal cortical stimulation using each contact of the epidural MCS lead. From these recordings, the best anode placement—that is, the contact that induces MEPs of maximal amplitude in the target territory—can be determined. This location usually corresponds to the placement that provides optimal analgesic effects when the corresponding contact is selected as a cathode for chronic stimulation.[91] The data provided by intraoperative neurophysiological mapping, especially by MEPs, are very useful to optimize electrode placement and to guide the first tests of MCS programming.

Besides intraoperative electrophysiology, preoperative fMRI examination can be useful to identify the best site for performing MCS to relieve pain.[71,87] By asking a patient to make repeated alternating finger movements, separated by rest periods, the clinician can identify the area of the motor cortex that corresponds to the

representation of the hand. The region of cortical activation can then be compared to that defined anatomically on neuroimaging data. In the absence of motor deficit, the anatomical data are generally consistent with the functional data. Morphological MRI can, therefore, be sufficient to define the target location. In patients with a major or complete motor deficit in the painful territory, or in those who have undergone amputation, only fMRI data are reliable for cortical mapping. Activation of a designated motor region can be triggered using mental motor imagery;[86] that is, by asking the patient to think about performing a given movement involving muscles in the painful territory. The results of fMRI in patients with amputated limbs have shown that the motor cortex area corresponding to an amputated limb segment is generally smaller and laterally shifted compared with the normal cortical representation of the limb.[76,94]

Anatomical and functional mapping of the cortical representation of a painful territory is the key step to optimize both electrode placement and MCS efficacy. The surgical approach originally proposed by Tsubokawa *et al.* for MCS electrode implantation consisted of a simple burr hole made under local anesthesia. However, this approach increases the risk of epidural hematoma and reduces the accessibility of the cortical surface for reliable electrophysiological mapping. In our institution, cortical electrodes are placed after a small craniotomy, while the patient is under general anesthesia.[65]

Mechanisms of action

Tests of electrical stimulation of the cortex were initially applied directly to the cortical structure, either in experimental animal protocols[95] or during surgery in patients who were under local anesthesia.[85] Tests of cortical stimulation in humans have mostly been performed in the context of cortectomy for the treatment of severe epilepsy to determine whether or not a cortical area that was about to be resected had a functional role. In all cases, cortical stimulation activates axons rather than neuron cell bodies. However, studies using direct cortical stimulation have demonstrated that anodal stimulation (in which the positive electrode is applied to the cortex) preferentially activates fibers that are perpendicular to the cortical surface. These fibers correspond to pyramidal cell axons, so direct anodal stimulation of the pyramidal tract generates early direct waves (D-waves) descending down to the spinal cord. Conversely, cathodal stimulation of the motor cortex (in which the negative electrode is applied to the cortex) preferentially activates fibers of cortical interneurons that run parallel to the cortical surface. Therefore the pyramidal tract is indirectly stimulated by a cathode, producing indirect waves (I-waves) at the spinal cord level (Figure 2).[96–98]

Subsequent studies led by Holsheimer and colleagues demonstrated that a current delivered by MCS that reached the cortical layers was sufficient to generate neuronal activation, even when the electrodes were placed on the dura mater.[99,100] In our experience, the best results are obtained when MCS is performed with the cathode over the convexity of the precentral gyrus and the anode over the anterior edge of the central sulcus. According to the principles of electrical stimulation cited above, this combination of electrode placements should preferentially stimulate the fibers of cortical interneurons within M1.[99,100] This hypothesis has been confirmed by recording the descending waves that were elicited during chronic bipolar MCS. Maximal pain relief was associated with a configuration of electrodes that mostly generated late I-waves,[101] suggesting that MCS induces analgesia by activating top-down controls that originate from intracortical horizontal fibers of interneurons, rather than through direct stimulation of the pyramidal tract. In fact, the analgesic efficacy of MCS seems to be mostly related to cathodal stimulation of the precentral gyrus, which activates axons that run parallel to the surface of the cortex (Figure 2). Moreover, axons are preferentially activated where they end or bend.

The descending volleys elicited by bipolar MCS are similar to those elicited by rTMS for producing analgesic effects.[101] The nature of pyramidal tract activation depends on the orientation of the stimulating figure-of-eight-shaped coil used to perform rTMS (Figure 2). When the coil is placed perpendicular to the interhemispheric midline (lateromedial orientation), TMS generates D-waves, similarly to anodal electrical stimulation (Figure 2a). Conversely, when the coil is placed parallel to the midline (anteroposterior orientation), TMS generates I-waves, similarly to cathodal electrical stimulation (Figure 2b), and this orientation is the one associated with pain relief.[101,102]

MCS produces analgesia by activating interneuronal circuits within M1; however, some uncertainty remains regarding the nature and connections of the recruited neuronal circuits. Early studies showed that MCS acted through a reduction in pain-related thalamic hyperactivity,[49,50] which suggested that this technique involved antidromic modulation of the thalamocortical pathways. The connections between afferent fibers from thalamic nuclei and pyramidal cells are thought to have an important role in the control of nociception.[103] This hypothesis was later supported by PET studies,[56,104] which also showed that MCS could activate mesencephalic and cortical regions that were remote from the site of stimulation, such as the insular, cingulate and orbitofrontal cortices. These activated cortical areas are mostly involved in the affective, cognitive and emotional aspects of pain.

The findings of another PET study suggested that MCS could enhance the release of endogeneous opioids in various brain structures; this effect correlated with pain relief when such release was observed in the cingulate cortex and PAG.[105] Furthermore MCS could activate descending pathways, leading to reinforced or restored inhibitory control of nociceptive transmission in the dorsal horns of the spinal cord.[106] The mechanisms of action of MCS could also involve inhibitory intracortical and interneuronal circuits. These GABAergic circuits can be assessed by a paired-pulse TMS technique, which measures the percentage of intracortical inhibition of MEPs. Inhibition of MEPs is reduced in many patients

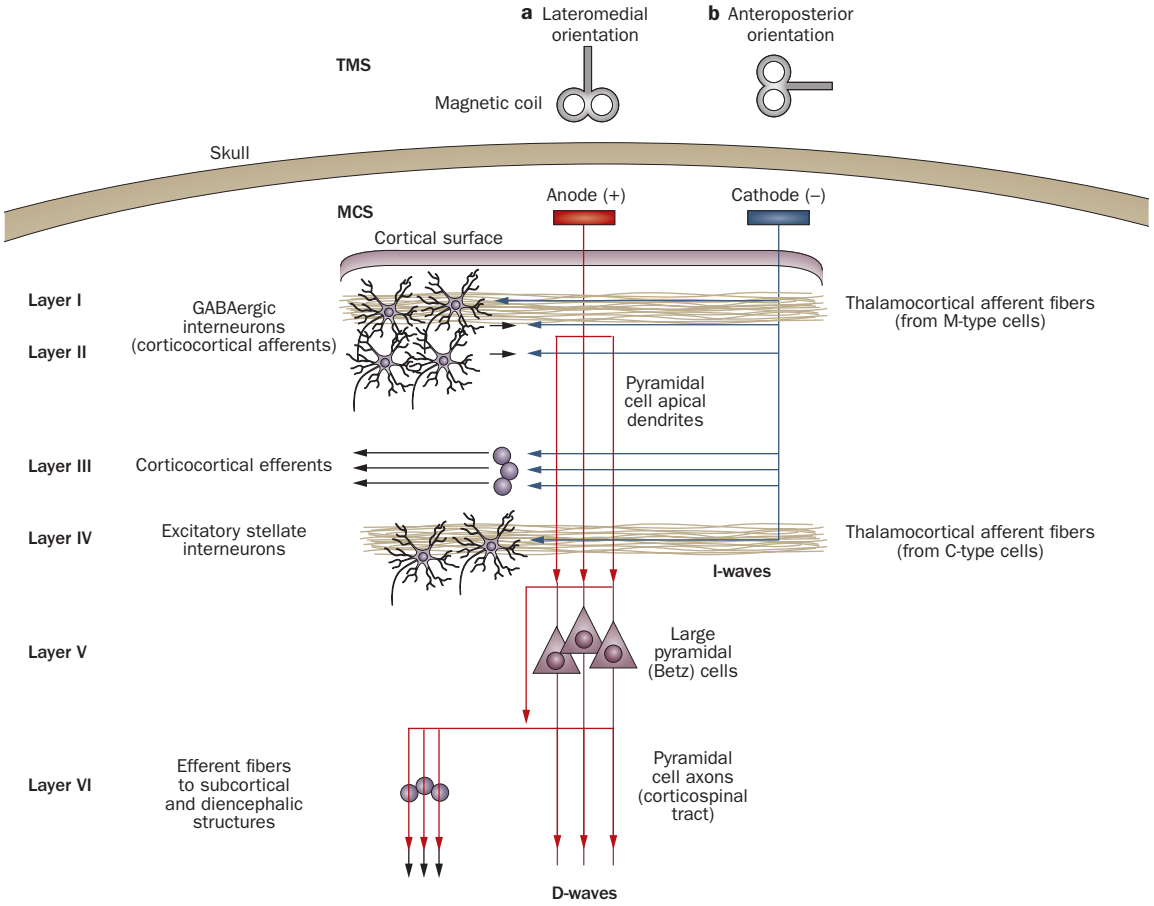

Figure 2 | Mechanism of action of epidural electrical stimulation or TMS of the cortex. **a** | Fibers perpendicular to the cortical surface are preferentially excited by anodal stimulation, or by focal TMS with lateromedial orientation of the coil. Both techniques result in direct (D-wave) stimulation of the corticospinal tract. **b** | Fibers that run parallel to the cortical surface are preferentially excited by cathodal stimulation, or by focal TMS with anteroposterior orientation of the coil. These techniques result in indirect (I-wave) activation of the corticospinal tract. Abbreviations: GABA, γ-aminobutyric acid; MCS, motor cortex stimulation; TMS, transcranial magnetic stimulation.

with neurological disease, including those with neuropathic pain in the hemisphere contralateral to the painful zone.[107,108] Interestingly, rTMS of the motor cortex restores intracortical inhibition in patients with neuropathic pain, and the restoration of inhibition correlates with the degree of pain relief (Figure 3).[107] This result suggests that MCS could also act through reinforcement of intracortical GABAergic inhibition.

The mechanisms of action of MCS probably involve various circuits that are activated in the response to the simultaneous activation of various fibers in the precentral gyrus, which run parallel to the cortical surface. Activation of these fibers could lead to orthodromic activation of corticofugal pathways, as well as antidromic activation of thalamocortical pathways. This capacity of MCS to act on various neural structures and pathways involved in pain modulation that are distant from the site of stimulation probably explains the remarkable analgesic effect of this technique. Similar patterns of fiber activation can be achieved by cathodal stimulation in the case of surgically implanted electrodes, and by TMS using a figure-of-eight coil with an anteroposterior orientation parallel to the interhemispheric midline.

Evidence for efficacy

Meta-analyses have confirmed that various types of refractory neuropathic pain syndromes can be improved by MCS.[109–111] However, most of the original studies included only a few patients (up to 32 participants) and were not controlled. In addition, results greatly varied between these studies, raising questions about the real efficacy of MCS. RCTs published in the past 5 years have helped to remove this doubt, as discussed below.[112–115]

We have reviewed the results obtained in 155 patients from nine studies that included at least 10 patients and had medium-term (6–12 months) to long-term (2–10 years) follow-up.[111] Treatment with MCS was considered to be effective when pain levels, scored on a visual analog scale (VAS), improved by over 40%. The treatment was effective in 65% of all patients; substantial pain relief was reported by 60% of patients with central poststroke pain, 75% of patients with trigeminal neuropathic pain, 53% of patients with phantom limb pain, 45% of patients with neuropathic pain secondary to brachial plexus lesion, and 60% of patients with pain related to spinal cord injury. All studies reported a delay of several days to several weeks between the onset of stimulation and

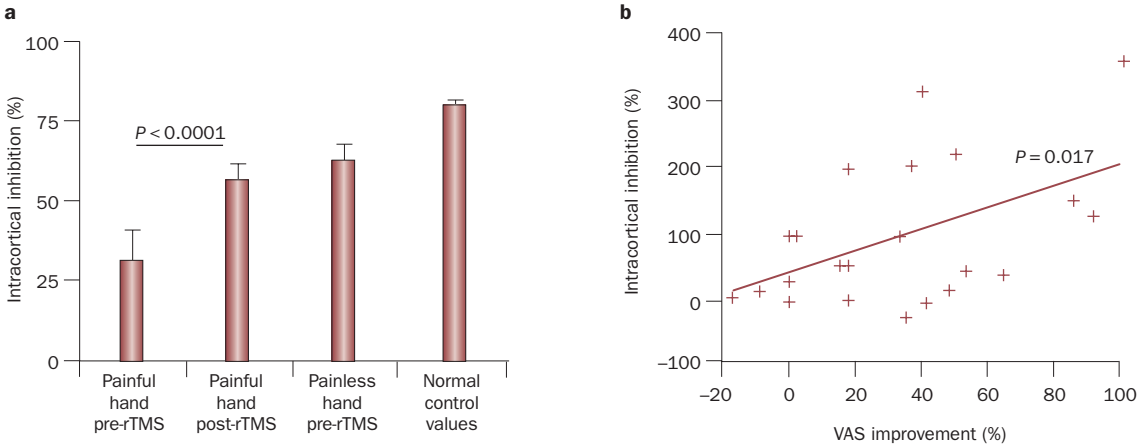

Figure 3 | Restoration of intracortical inhibition using rTMS of the motor cortex corresponding to a painful hand. **a** | Improvement in intracortical inhibition following rTMS therapy (mean and standard errors of the mean [bars] values from a series of 22 patients with unilateral neuropathic hand pain and 22 age-matched healthy controls). **b** | Intracortical inhibition positively correlates with pain relief, as measured by VAS scores. Abbreviations: rTMS; repetitive transcranial magnetic stimulation; VAS: visual analog scale. Permission obtained from Lefaucheur, J.-P. *et al.* Motor cortex rTMS restores defective intracortical inhibition in chronic neuropathic pain. *Neurology* **67**, 1568–1574 (2006) Wolters Kluwer Health.

clinical improvement. Adverse events associated with the procedure included 29 cases of seizures—which occurred during the immediate postoperative period—in programming trials (but never during chronic stimulation), nine cases of infection, and two cases of skin ulceration over the implanted material. Two cases of serious subdural hemorrhage have been reported after implantation of MCS electrodes into the subdural space, which led either to severe, persistent neurological deficits or to the patient's death.[74] Subdural implantation is also associated with an increased risk of seizures compared with epidural electrode implantation.[92] Finally, cortical stimulation induced phantom arm pain in one patient.[116]

Two other meta-analyses of MCS therapy for pain reported similar results. The first of these analyses included 327 patients from 22 studies, and showed that an average of 64% of treated patients responded to MCS treatment.[109] The second meta-analysis included 210 patients from 14 studies, and showed that 57% of patients responded to MCS treatment.[110]

We also reviewed the results obtained from 100 consecutive patients who underwent electrode implantation for MCS in our center between May 1993 and October 2004.[111] This series comprised 43 women and 57 men, aged 21–84 years, with a mean follow-up of 89 months. The patients' pain scores were assessed by a VAS and, in at least half of the cases, by the McGill Pain Questionnaire (MPQ),[117] Brief Pain Inventory (BPI) or Wisconsin Brief Pain Questionnaire,[118] and the Medication Quantification Score (MQS).[119] A good response was defined as an improvement of these scores by over 60%. An improvement of 40–60% was defined as a satisfactory response, and less than 40% improvement was defined as treatment failure. Overall, an average of 64% of patients responded to the treatment. A good or satisfactory result was found in 80% of patients with central post-stroke pain, 76% of patients with trigeminal neuropathic pain, 36% of patients with neuropathic pain secondary to brachial plexus lesion, and 56% of patients with pain related to spinal cord injury. Procedure-associated complications consisted of three cases of infection at the level of the pulse generator, one case of partial dehiscence of the skull scar, one case of postoperative ischemic stroke contralateral to the operated hemisphere, and one case of seizure during a programming trial that used high-intensity (8 V) stimulation.

In practice, MCS and DBS are associated with similarly low overall rates of adverse events. Complications of both techniques are mainly related to infections in the vicinity of the implanted generator; however, MCS is considered the safer of the two techniques, as intracranial hemorrhage does not occur.

A review of the literature has revealed that good clinical results for epidural MCS can be obtained using relatively low intensities of stimulation (around 2 mA, which corresponds to 2 V at an impedance of 1,000 Ω).[66] However, the intensity of stimulation should be adapted according to the thickness of the cerebrospinal fluid layer between the dura mater and the cortical surface. For instance, in a patient with severe cerebral atrophy, effective stimulation of the cortex might be impossible using epidural electrodes; in such individuals, electrodes should, therefore, be placed in the subdural space in contact with the cerebral cortex.[74]

No clear recommendations have been defined for pulse width and signal frequency. The only indications concerning pulse width are derived from the rare patients in whom MCS induced an almost immediate effect; in these individuals, stimulation with a pulse width of 60 μs seemed to be more effective than stimulation with longer pulse widths.[66] Relatively low values for stimulation frequency (less than 100 Hz) are generally used for MCS, perhaps by analogy to the frequencies used in SCS and DBS for pain relief.[66] In fact, we believe that a range of stimulation parameters can be used—amplitude 1–6 V, mean 2 V; pulse width 60–450 μs, mean 100 μs; and

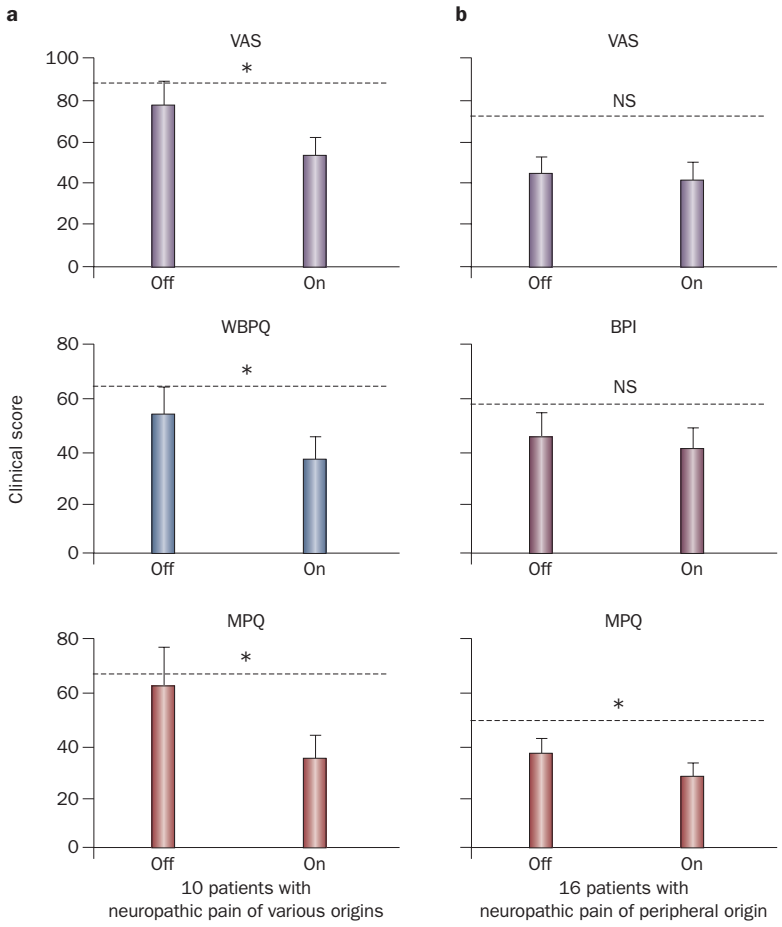

Figure 4 | Comparison of on-stimulation and off-stimulation outcomes in patients undergoing MCS. Mean clinical scores from double-blind MCS trials using implanted epidural electrodes during on-stimulation and off-stimulation conditions in **a** | patients with neuropathic pain of various origins, and **b** | patients with neuropathic pain of peripheral origin. The dotted horizontal line corresponds to the mean preoperative baseline value for each score; bars indicate standard errors of the mean. Significant differences (P <0.05) between on-treatment and off-treatment scores are indicated by asterisks. Abbreviations: BPI, Brief Pain Inventory; MPQ, McGill Pain Questionnaire (pain rating index); MCS, motor cortex stimulation; ns, not significant; VAS, visual analog scale; WBPQ, Wisconsin Brief Pain Questionnaire. Figures for part a reprinted from *Brain Stimulation* **1**, Nguyen, J.-P. *et al.* Treatment of chronic neuropathic pain by motor cortex stimulation: results of a bicentric controlled crossover trial. 89–96 © (2008) with permission from Elsevier, and for part b reprinted from Lefaucheur, J.-P. *et al.* Motor cortex stimulation for the treatment of refractory peripheral neuropathic pain. *Brain* **132**, 1463–1471 (2009) by permission of Oxford University Press.

frequency 20–65 Hz, mean 40 Hz—without losing the optimal analgesic effect of the stimulation. However, there is no clear evidence to suggest that analgesic efficacy can be enhanced by enlarging the ranges of each of these values, and especially not by increasing amplitude.

Several research groups have reported that the benefits of MCS could be lost over time.[57,59,67,120] One study demonstrated that recovery of pain control could be obtained following an intensive reprogramming of the parameters of stimulation in patients who had lost the analgesic effects seen after initial therapy with MCS.[121] At our center, long-term loss of treatment efficacy rarely occurred. In fact, a meta-analysis of 152 patients with chronic pain who were treated with MCS for more than 1 year showed that 57% of patients initially responded to the treatment, and that 45% of the 152 patients still had significant pain relief in the long term (more than 1 year postoperation).[110] The reasons for the loss of efficacy of MCS in a small minority of patients are unknown, as is the respective importance of this phenomenon in MCS compared with DBS.

A few double-blind RCTs have compared on-stimulation and off-stimulation conditions in patients treated with MCS. This investigation is possible because, unlike individuals treated with SCS and sensory thalamus stimulation, patients treated with MCS are unable to distinguish between on-stimulation or off-stimulation conditions as they have no motor or sensory effects (except for paresthesia in some cases) during active stimulation. Results from the first of these RCTs were published in 2006;[112] this study investigated the immediate postoperative period, during which patients were tested via an external stimulator connected to the epidural lead for 6 days before chronic implantation. However, clear conclusions are difficult to draw from this study, as patients who were considered to be nonresponders to the trial of external stimulation did not undergo implantation. Furthermore, owing the delayed onset of clinical efficacy noted above, a period of a few days of stimulation is probably too short to assess whether or not a patient would respond to MCS. Subsequent studies provided more-conclusive results,[113,114] as randomization started 2 months after implantation, leaving sufficient time to optimize stimulation settings, and the on-stimulation and off-stimulation periods lasted 2 weeks each. The optimal stimulation parameters for individual patients are difficult to determine, because subjective changes in pain relief may have a delayed onset or persist beyond the duration of changes to programming, which further complicates parameter selection.

In the Nguyen *et al.* study, significant differences in VAS, BPI and MPQ scores were observed between on-stimulation and off-stimulation periods,[113] reflecting the efficacy of MCS (Figure 4a). However, this study included a heterogeneous group of 10 patients with various types of neuropathic pain secondary to central and peripheral lesions. A further RCT, published in 2009, overcame this limitation, as the participants were 16 patients who all had neuropathic pain related to peripheral lesions, and the study design involved long on-stimulation and off-stimulation periods of 1 month each.[115] Patients were followed-up for 12 months and evaluated by VAS, BPI, MPQ and Sickness Impact Profile scores.[122] VAS and Sickness Impact Profile scores were significantly improved at 1 year postimplantation, but only the MPQ results differed between on-stimulation and off-stimulation conditions (Figure 4b).[115] Although the results of the crossover phase of this trial were not fully positive, the observations made during the nonblinded phase support the efficacy of MCS in patients with peripheral neuropathic pain. Further trials to replicate these findings, or multicenter, double-blind studies that include large series of patients, are still needed to definitively confirm the value of MCS

as a treatment for refractory neuropathic pain. Even if the balance of evidence supports the analgesic efficacy of MCS in groups of patients with chronic neuropathic pain, some individuals clearly do not benefit from this procedure. Unfortunately, predictive factors to select good candidates or specific indications for MCS electrode implantation are lacking.

Unlike DBS, MCS seems to be similarly effective in patients with central or peripheral neuropathic pain, even though these two types of pain have different intrinsic mechanisms. Pain secondary to thalamic stroke, and facial pain related to a trigeminal nerve lesion are generally considered the best indications for treatment with MCS, probably because most patients who received MCS in the early days of its development had these presentations. In fact, MCS can relieve various neuropathic pain conditions, irrespective of their etiology.[67] The location of pain symptoms and the duration of pain syndrome also do not seem to be valuable criteria to select candidates for implantation. Preserved motor strength[56] and sensory discrimination of innocuous stimuli[123] in the painful territory have been proposed as predictors of a good outcome of MCS therapy; however, these criteria were unreliable predictors of efficacy in a large series of MCS-treated patients.[67] In fact, only the clinical response to preoperative rTMS tests showed correlations with a good response to MCS-induced analgesia.[58,124,125]

Conclusions

Epidural MCS is now widely used for various chronic neuropathic pain syndromes that are refractory to medical treatment, or even after a failure of SCS therapy. The mechanism of action of MCS is now understood to involve excitation of fibers running parallel to the cortical surface in the precentral gyrus, and modulation of various neural structures distant from the site of stimulation, such as the sensory thalamus or limbic nervous system. Restoration of defective intracortical GABAergic inhibition could be also involved in the therapeutic effects of MCS. The efficacy of MCS in the treatment of neuropathic pain has been proved by a number of RCTs; however, the clinical results of this technique are variable, and validated predictors of treatment efficacy are lacking. Multicenter RCTs based on large series of patients are, therefore, needed to clearly define the role of this procedure in the treatment of various neuropathic pain conditions, according to pain location and origin.

The role of DBS as a therapy for neuropathic pain also remains to be established. DBS rather than MCS is indicated for patients with nociceptive pain, whereas MCS is favored over DBS for patients with central deafferentation pain. The relative benefits of DBS and MCS for the treatment of peripheral neuropathic pain of the face and limbs, or for the treatment of phantom limb pain, are still unclear. However, MCS seems to be technically easier and safer to perform than DBS, which is an important reason for the current emphasis on development of MCS over DBS in the surgical treatment of refractory pain.

Review criteria

In addition to our personal collections of references, we searched for original articles or reviews focusing on neurostimulation therapy for pain in MEDLINE and PubMed, published between 1970 and 2011. The search terms we used were “spinal cord”, “deep brain”, “thalamus”, “thalamic”, “gray matter”, “cortex” or “cortical” in combination with “stimulation”, “pain” and “treatment”. All papers identified were English-language full-text papers. We also searched the reference lists of identified articles for further relevant papers.

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J.-P. Nguyen, J. Nizard and J.-P. Lefaucheur researched the data for the article. Y. Keravel provided a substantial contribution to discussions of the content. J.-P. Nguyen, J. Nizard and J.-P. Lefaucheur contributed equally to writing the first draft of the article. J.-P. Lefaucheur reviewed and edited the final version of the manuscript.