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Extradural cortical stimulation for movement disorders

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Summary

Extradural cortical stimulation is a recent addition to the armamentarium of operative neuromodulation. Motor cortex stimulation (MCS) is offered by positioning a stimulating plate extradurally on the primary motor cortex. It is a minimally invasive technique that was originally proposed for the control of central neuropathic pain. Currently, its use has been extended to patients with movement disorders. The need for minimally invasive therapies, with low morbidity-mortality which can be applied to patients who are excluded from deep brain stimulation (DBS), led to the first attempt of MCS in Parkinson's disease (PD). Following the demonstration that transcranial magnetic stimulation (TMS) is beneficial in PD, we attempted direct extradural MCS on patients with advanced PD not meeting the criteria for DBS. The mechanisms of action may include "hyperdirect" motor cortex-subthalamic nucleus (MI-STN) input, inhibition, resynchronisation, plasticity changes, interhemispheric transfer of inhibition/excitation and modulation of other cortical areas. In this article, we review the mechanism of action of MCS in movement disorders, the predictive factors of MCS efficacy in PD, the indications, particularly in the elderly who are not suitable for DBS, the adverse effects, and the technique for localization of the central sulcus and for performing the procedure. The future prospects and developments are also discussed.

Keywords: Neuromodulation; motor cortex stimulation (MCS); Parkinson's disease; movement disorders.

Introduction and historical note

Extradural cortical stimulation is a recent addition to the armamentarium of operative neuromodulation. Motor cortex stimulation (MCS) is offered by positioning a stimulating plate extradurally on the primary motor cortex (BA4, MI). It is a minimally invasive technique that was originally proposed for the control of central neuropathic pain [7]. Currently, its use has been extended to patients with movement disorders [4–6, 8–10, 23, 24, 30].

In the first half of the 20th century, Paul C. Bucy relieved extrapyramidal symptoms such as tremor by surgical ablation of cortical areas BA4 and 6; this was done at the expense of inducing motor deficits [3]. Other groups relieved Parkinsonian tremor by pyramidotomy [19, 32]. These pioneering works showed that the primary motor cortex plays a role in the pathophysiology of extrapyramidal disorders; however, at the time, there was no practical way to modulate its function and the cortex was later disregarded as an important location in the pathogenesis of extrapyramidal disorders. In the early 1970s, drawing from animal experiments, showing that pressure on or cooling of MI could stop surgically-induced Parkinson-like tremor in monkeys, Alberts [1] reported that stimulation at 60 Hz with a 7-contact Delgado plate electrode of an area near the rolandic fissure, between motor and sensory sites, could initiate or augment Parkinsonian tremor in patients. Post-central cortical stimuli had the same effect at, above or below the sensory threshold. A few years later, Woolsey *et al.* [37] temporarily alleviated Parkinsonian rigidity and tremor in two patients by direct acute intraoperative stimulation of MI. They wrote that: "*. . .marked tremor and strong rigidity. . .The results suggest the possibility that subthreshold electrical stimulation through implanted electrodes might be used to control these symptoms in Parkinsonian patients*."

In the 1980s, two major advances followed; in 1985, Barker introduced cortical transcranial magnetic stimulation (TMS), a technique allowing focal activation of cortical areas by means of an external magnetic coil and, in Japan, Tsubokawa's group exploited available technology to stimulate MI extradurally for the relief of central pain, with the first patient undergoing surgery in 1989 [7]. In 1993, Benabid's group showed that bilateral subthalamic nucleus stimulation (STNS) provided dramatic relief of advanced Parkinson's Disease (PD) and in 1994 Siegfried reported similar results with pallidal stimulation. Ever since, STNS has become the neurosurgical

intervention of choice for advanced drug-resistant PD. Yet, patients who score less than 30–40 in the off condition on Part III of the Unified Parkinson's Disease Rating Scale (UPDRS) or have an improvement of less than 40–50% when undergoing the levodopa challenge test are not suitable for STNS. Importantly, age 70 is an upper limit for surgery at several centers and patients with major cortical atrophy or focal lesions or patients showing severe psychiatric disturbances and cognitive decline in the off phase are generally excluded. All in all, rougly half the patients may be excluded from deep brain stimulation (DBS). Moreover, the risk of intracranial hemorrhage or cerebral abscess makes DBS not completely safe. This procedure can be complicated by hardware-related problems, persistent neurological deficits, infection, and perioperative mortality.

The need for minimally invasive therapies, with low morbidity-mortality which can be applied to cases that are excluded from DBS, led to the first attempt of MCS for PD. Following the demonstration that transcranial magnetic stimulation (TMS) was beneficial for PD (see review in [26]), we attempted direct extradural MCS for the first time in July 1998 on a patient with advanced PD not meeting the criteria for DBS [4–6, 8–10]. Further evidence that MCS could be effective for motor disorders was accumulated over the late 1990s–early 2000s. Katayama *et al.* and later other authors (see review in Refs. [9] and [23]) reported that MCS may be effective for hemichoreoathetosis, distal resting and/or action tremor, proximal postural tremor associated with brain and/or brainstem stroke, and focal post-stroke dystonia. Moreover, subjective improvement of motor performance was observed in patients in whom involuntary movements were associated with mild to moderate motor weakness [23].

Mechanisms of action

Several mechanisms of action are possible but they apply at variable degrees not only in PD, but also in dystonia and all relevant movement disorders described in this chapter.

Hyperdirect MI-STN input

In primates, MI has a direct, somatotopographically organized, input to the subthalamic nucleus-STN [20]; this corticosubthalamic pathway is in parallel with the corticostriatal path. A human study found electrophysiological evidence of such direct cortico-STN glutamatergic pathway [16]. The Oxford group [27], on the basis of human studies, proposed that the functional connection between the STN and arm muscles is mainly contralateral, but cross-talk may occur between the two subthalamic nuclei via a frequency-dependent pathway. This frequency-dependent pathway could contribute to the bilateral effects of unilateral high frequency STN DBS; the same may apply to MCS. In addition, MCS induces increases of rCBF in the thalamic motor nuclei ventral anterior, ventrolateral (VA-VL) [18] and these are the only thalamic nuclei directly connected to motor and premotor areas. It should be recalled how a modification of motor cortex metabolism contributes to the efficacy of several surgical procedures for Parkinson's disease [8, 9] and neurometabolic evidence from our studies suggests that MCS might be able to upregulate dopamine receptors in the striatum ([8] and unpublished observations). Strafella *et al.* using TMS during intraoperative single-unit recordings from STN in 6 patients with PD undergoing DBS, observed that the MI activation produced a long-term inhibition in the STN neuronal activity [34]. The importance of deep influences is highlighted by a clinical observation. In a central post-stroke pain patient with associated parkinsonian tremor, MCS (50–75 Hz, 120–210 msec) was analgesic, but neither relieved tremor nor improved the UPDRS score (Dario A, personal communication 2002); it is likely that the stroke had altered the motor loop upon which MCS acted. If STN is the primary target, this might explain the whole body effect from unilateral stimulation.

Inhibition

TMS studies suggest that cortical stimulation acts via an MI intracortical mechanism; cortical inhibitory neurons that surround pyramidal cells may be selectively activated by low intensity TMS [14] and a large coil activates all relevant surrounding interneurons. Also, pyramidal cells can be inhibited by TMS without previous excitation. Thus, MCS could reduce MI excitability, which is increased in several movement disorders including Parkinson disease (PD), as long trains of low frequency TMS do (see Refs. [8, 9]). MCS appears to activate axons in the cortex, which excite both corticospinal neurons and inhibitory neurons [21, 33]. In PD patients, TMS studies showed that there is excess excitability or reduced inhibition at MI levels [12]. During production of a voluntary output, motor cortex activation is defective or inadequately modulated, and this may be due to a dysfunction of GABAergic (both A and B) interneurons mediating the level of excitation within BA 4 [11].

GABA modulation is at the core of MCS effect on neurogenic pain [7]. Local cortical changes during MCS have been documented with neuroimaging [8].

Resynchronization

Disruption of oscillation and/or temporal synchronization is considered a fundamental mechanism of neurological diseases, including PD; just as cortical stimulation acts by resetting an out-of-balance thalamoparietal oscillatory loop in central pain [7], likewise MCS might actually act via an oscillatory repatterning of the corticoganglionar pathway; given that 15–30 Hz oscillations are observed during physiologic postural maintenance, it may be surmised that MCS marshals this frequency to reset the abnormal pattern [9].

Plasticity changes

These are suggested by findings in our first PD patient, in whom switching off the stimulator led to a slow, delayed decline of effect – unlike DBS-, and in central pain cases submitted to MCS [5, 7]; they may take place cortically and/or in the basal ganglia, at both synaptic or receptor levels [25].

Interhemispheric transfer of excitation/inhibition

Unilateral MCS improves Parkinsonian symptoms bilaterally, a consistent finding in all successfully operated cases. Several lines of evidence show that MI is involved in contra as well as ipsilateral hand movements, with greater involvement in more complex tasks and with the left hemisphere playing a greater role than the right; moreover, transmission of inhibitory and excitatory signals via the corpus callosum has been demonstrated [5, 15]. Transcallosal spread of electrically induced neuronal alterations by surface recordings from the opposite motor cortex has been observed in humans in a TMS study [13].

Modulation of other cortical areas

Neurometabolic studies have demonstrated hypofunction of the supplementary motor (SMA) and premotor areas (PMA) in the generation of rigidity and bradykinesia; it may be hypothesized that abnormal prolonged firing of preparatory movement-setting SMA and PMA cells cause disruption of the neuronal activity of MI. MCS may activate myelinated axons connecting SMA with MI both anti and orthodromically, thus rebalancing the disrupted SMA activity.

Functional considerations

The efficacy of MCS is strongly affected by the thickness of the cerebrospinal fluid (CSF) layer between the electrode and MI. When the CSF layer thickness is increased, both the current intensity in the cortex at a given voltage and the load impedance are reduced, thus increasing the energy needed for stimulation. In particular, when the CSF thickness is increased from 0 to 2.5 mm, the load impedance decreases by 28%, and the stimulation amplitude increases by 6.6 V for each millimetre of CSF [28]. On the other hand, variation of the width of MI and the central sulcus has a negligible effect on the current distribution in the cortex. During bipolar MCS, due to the rather large electrode distance (1 cm center-to-center), the cathodal and anodal fields in the cortex hardly interfere and have a shape similar to a monopolar field. Due to a different load impedance, however, the monopolar field has a larger extent than the bipolar one when the same voltage is applied [28] and monopolar MCS alleviates Parkinsonian symptoms in MPTP monkeys. Nerve fibers under the cathode and parallel to the electrode surface are depolarized and possibly excited, whereas fibers normal to its surface are hyperpolarized. Under the anode, the opposite effects are observed. Due to the curved shape of MI, the orientation of its afferent and efferent fibers varies, thereby changing their response to stimulation. Whereas efferents in MI are hyperpolarized by cathodal stimulation, they are depolarized in the walls of the (pre-) central sulcus. In addition, the magnitude of a fiber's response depends on its caliber and its distance from the electrode. Thus, hardly any difference will be present among the cathodal fields in mono- and bipolar stimulation, although monopolar stimulation is more energy efficient. To avoid potential anodal responses in a different motor cortex area interfering with cathodal responses in bipolar MCS, it is suggested that the anode should not be placed over MI [28]. Another study found that anodal stimulation over vertically oriented pyramidal cells induces depolarization at the initial segment. Since anodal stimulation activates corticospinal neurons mainly indirectly, it turns out to be less effective than cathodal stimulation; moreover, there is a lower threshold to cathodal than to anodal stimulation [21].

On subdural stimulation, although the muscles that are activated roughly correspond to the expected cortical representation, discrete somatotopic excitation of upper limb muscles does not exist [21]. Also, body areas represented only deep in a sulcus or fissure are unlikely to be stimulated by an electrode on the brain surface [28], but

this may not affect global efficacy. The combined worldwide experience up to now points to low frequency stimulation (below 80 Hz) as the standard of stimulation for movement disorders. This is an important distinguishing feature of MCS as compared to STN DBS, which is effective at the highest range (>100 Hz). Clearly, these two types of stimulation work differently.

Predictive factors for MCS effectiveness in PD

Dopa and apomorphine unresponsiveness are known poor predictors of STNS efficacy; hence, patients with levodopa-resistant Parkinsonism associated with ischemia-anoxia, multisystem atrophy or progressive supranuclear palsy are unlikely to draw a significant benefit from STNS. The same should apply to MCS: the benefit has been at best modest and/or transitory [9, 24], but optimization of the parameters (continuous versus cyclical stimulation, low versus high voltage, and low versus high frequency) might help a few patients. Propofol, a GABA-A agonist which is useful in selecting patients with central pain for MCS [7], appears not to renormalize dystonic symptoms [6]; therefore, it may be speculated that MCS acts differently on pain and dystonia, and other movement disturbances as well [7, 30]. Decreased striatal D2 receptor binding seems to be a predictor of nonresponse to STN surgery, but a patient of ours showing decreased IBZM binding had a successful response to implantation [9].

Adverse effects

MCS has proven to be a very safe neuromodulatory technique, with no reported mortality or long-term disabling morbidity [7]. In particular, the much-feared kindling of long-term epilepsy has never been substantiated at therapeutic stimulation parameters. On the other hand, PD patients submitted to MCS up to now tend to be older and often above the age of 70. Preliminary experience suggests that psychiatric and cognitive adverse effects may turn out to be more common in this age than in the younger patients submitted to DBS. Even if psychiatric symptoms and dementia frequently occur in PD patients as part of the natural history of the disease, caution must be exercised, particularly since the minimal invasiveness of the technique makes it potentially applicable to a much greater number of patients than DBS [8]. An evoked potentials study found a significant relationship of MCS efficacy with the patient's age; it showed a significant delay, during MCS, of the cognitive responses N2 (but not N1) and P3 (N200 and P300) in patients older than 50 years. This effect was rapidly reversible after MCS discontinuation. These results, together with experiments showing P300 alteration during rTMS, suggest that MCS may interfere with relatively simple cognitive processes such as those underlying target detection, and that the risk of abnormal cognitive effects related to cortical stimulation may increase with age, but also in the presence of pre-existent cerebral lesions [29].

Central sulcus localization and operative procedure

The target of MCS for PD is the hand area, on the side most affected. While in surgery for central pain somatotopography is important, even not as stringently as previously thought, in PD patients, hand area targeting is able to affect the whole body. The motor hand area in the axial plane on standard MRI, is a knob-like, broad-based, posterolaterally directed structure of the precentral gyrus. It usually has an inverted omega shape (90%) and sometimes a horizontal epsilon shape (10%), with a mean diameter of 1.4 cm. On average, it is located about 23 mm from the midline, just posterior to the junction of the superior frontal sulcus with the precentral sulcus and 19 mm from the lateral surface [39]. However, the motor hand area may extend to, or be located exclusively in SI, on functional magnetic resonance (fMRI) [38]. In particular, this area is most often located in the posterior bank of the precentral gyrus (80%), but it is seen additionally in the postcentral gyrus in 50% or exclusively in SI in 20% [31, 38], even during the simplest tasks. Other areas, e.g. the supplementary motor area, are also activated and, occasionally, bilateral activation of MI following unilateral hand activation is observed. It is well known how pyramidal cells are located in SI (particularly BA3a) and how direct electrical stimulation of all SI can also elicit motor responses in the contralateral skeletal muscles, as it was classically demonstrated by Penfield and replicated by others [35]. In these cases, SI stimulation may be as effective. A major issue should be taken into consideration. In a sizable minority of patients (20%) there are variations in the organization of MI, i.e. mosaicism (overlapping of functional areas), variability (inverted disposition of MI functional areas) or both [2]. These data challenge the orderly topography of MI and suggest that the motor homunculus may not always be considered a definite and absolute representation of MI. Also, BA44 (found 2 cm anterior to the

primary tongue motor area) has direct fast conducting corticospinal projections and has a role in voluntary hand movements [36]. Clearly, MCS is not a straightforward surgical procedure.

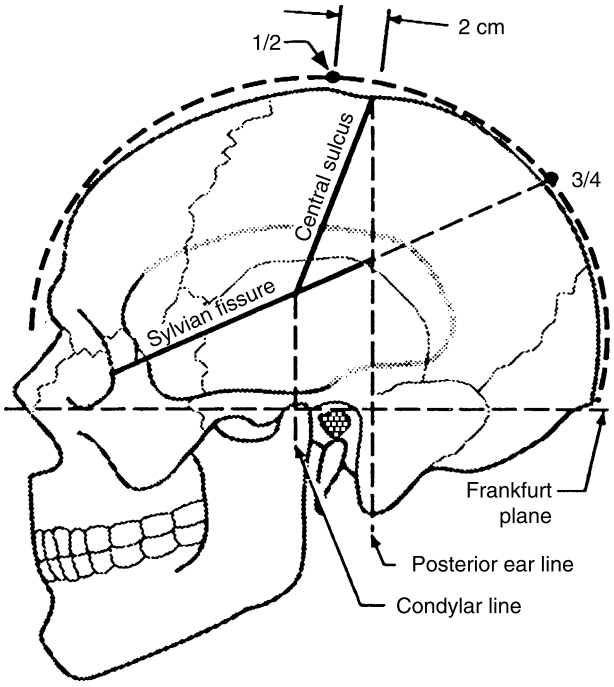


Fig. 1. Taylor-Haughton lines used for initial identification of the central sulcus

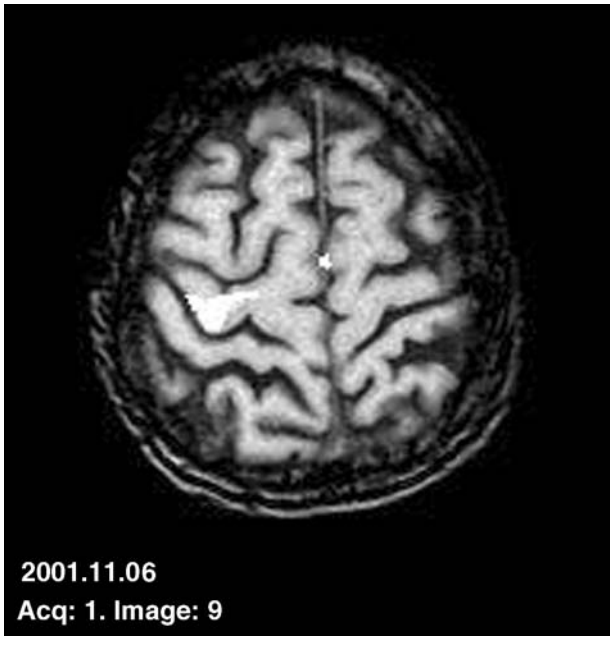
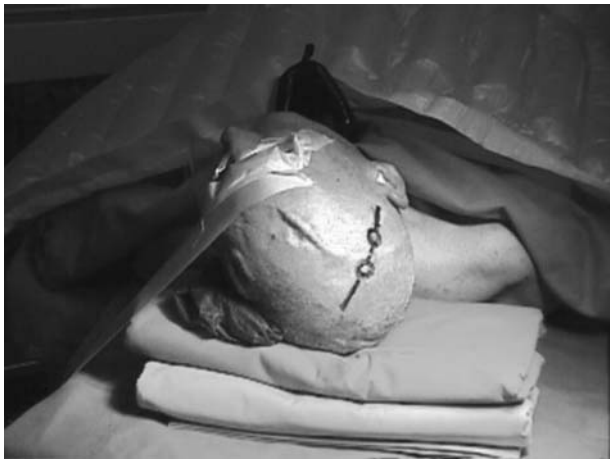
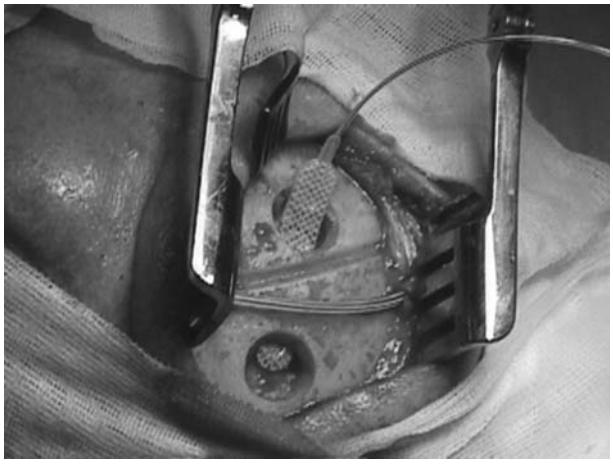


Fig. 2. Functional MR image showing the focus of motor hand activation in the appropriate area in BA4 (from Canavero *et al.*, 2002, with permission)

After shaving the patient's head, the approximate location of the central sulcus is marked on the skin along the Haughton-Taylor lines (Fig. 1). Motor area localization is confirmed by standard fMRI sequences while the patient makes repetitive self-paced opposition movements of the thumb to the rest of the fingers at an approximate rate of $1/\text{sec}$. The echoplanar multiphase acquisition in a 1-tesla MRI consists of a 3.31-minute sequence with 3×30 seconds of motor activation interleaved with 4×30 seconds of rest. A fiducial paramagnetic marker applied on the skin is adjusted under MR conditions until the skin marking and the actual target area match (Fig. 2). The operation is performed under local anesthesia, with mild i.v. sedation if required. We strongly discourage general anesthesia for electrode placement because of the added risks, particularly in elderly patients. After a linear incision along the projection of the central sulcus (arm area) is made (Fig. 3a),



a



b

Fig. 3(a, b). Patient in position for surgery (a) and implantation of the stimulating paddle through a pair of burr holes (b)

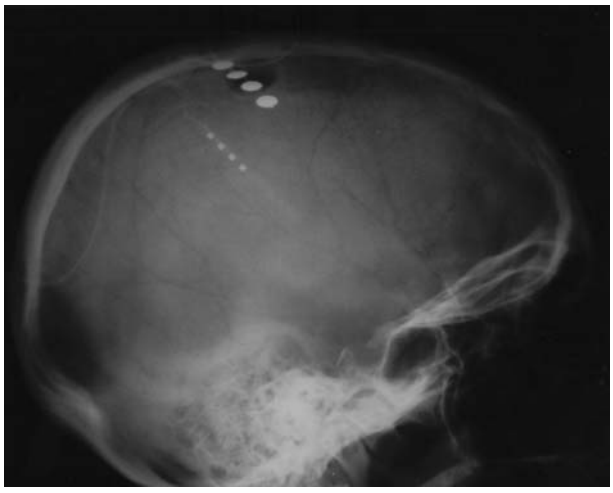


Fig. 4. Radiograph showing the MCS apparatus in place

two burr holes are drilled in front of the projection of the central sulcus to accomodate the length of the stimulation paddle. After dural hemostasis is achieved, the paddle is slid under the bone over the primary motor area (Fig. 3b). Intraoperative stimulation to elicit motor responses is the usual next step. Once the surgeon is satisfied with positioning, the electrode is externalized behind the ear. We usually drill a groove in the bone parallel to the paddle's long axis in order to accommodate the joint between the paddle and the electro-catheter. After a stimulation test period generally lasting a few weeks, during which the most beneficial parameters are sought, the pulse generator (IPG) is implanted in the subclavicular area under general anesthesia, or local anesthesia under mild sedation, and connected to the subcutaneous electrode (Fig. 4). Alternatively, both the paddle and the IPG can be implanted simultaneously during the same surgical session.

Indications

Parkinson disease and Parkinsonism

Worldwide, more than 50 patients have been implanted up to now (congress and privileged data). The first three patients have been implanted by the authors between 1998 and 2002 ([4, 5, 8–10]; Fig. 5). These were all patients above the age of 70 and excluded from DBS due to MR evidence of atrophy, ventricular enlargement, ischemic white matter disease, neuropsychiatric deficits or poor medical conditions. All the relevant observations regarding MCS for PD were obtained in these patients, notably bilateral effects from unilateral stimulation (e.g. the tapping test improved in both hands) with minimal asymmetry, efficacy of stimulation at low frequency (beneficial) versus high (>100 Hz) frequency (disruptive or not beneficial), and the effect on all three cardinal signs of PD, i.e. tremor, rigidity, bradykinesia. An interesting finding was that after a few weeks of continuous stimulation, the stimulator could be switched off at night without losing benefit (up to weeks), an observation which is relevant to energy sparing. Further experience shows that MCS also improves verbal understanding and fluidity, spatial orientation, dysphagia, void and fecal control. Dyskinesias are the one symptom which responds dramatically to stimulation. L-Dopa may be reduced in many patients. Currently, patients must meet the following criteria for implantation: UPDRS in OFF $\geq$40/180, Hoehn and Yahr (H/Y) $\geq$3, motor fluctuations plus disabling dyskinesias, UPDRS improvement to L-Dopa challenge test $\geq$30%. Although voltage should not exceed 3–3.5 V, some patients drew benefit at higher voltages. Pulse width varies from low (150 msec) to high (e.g. 400 msec); effective frequencies are usually in the low range (10–60 Hz). We, and others, have found that, with a few exceptions, the best electrode setting tends to encompass as much cortex as possible (0–3).

Slight adjustments of parameters may be necessary over time, although much less often than in pain patients.

In several cases improvement is around 30% on UPDRS, but can be lower or higher. However, due to the abolition of disabling dyskinesias and improvement of axial symptoms (standing, walking, falling, swallowing, facial hypomimia, swallowing), life quality and self-grooming are improved – sometimes dramatically – with lesser degrees of assistance, a fact often noted by family members. A few patients have benefited from MCS after ineffective DBS. Longest follow-up is now several years. Similarly to DBS, some symptoms remain relieved, while others tend to worsen with time. Although rigidity and, less so, tremor are abolished within several minutes of stimulation, the full effect on bradykinesia and gait grows with time (days, weeks, and even months). Thus, compared to DBS, additional time should be allowed for in searching for effective parameters. Failures have been noted, perhaps due to extensive atrophy (see *Functional considerations* above). While the experience with parkinsonism associated with multiple system atrophy has been disappointing up to now, vascular parkinsonism may respond.

Post-stroke movement disorders

Movement disorders are one of the most disabling sequelae of stroke. In the mid- and late-1990s, Katayama

a b

Fig. 5(a, b). Images of the first patient ever to receive MCS for Parkinson's disease at 1 year follow-up

et al. reported on the effects of MCS in patients with post-stroke involuntary movements (in most of whom MCS was performed for controlling central pain) [23]. MCS appreciably attenuated hemichoreathetosis associated with thalamic stroke and completely abolished distal resting and/or action tremor associated with multiple lacunar, striatal or thalamic infarcts, independent of analgesia. Proximal postural tremor was not well controlled by MCS and SI and supplementary motor area (SMA) stimulation had no effect on hemichorea and resting tremor. In patients with Wallenberg's syndrome, MCS was effective in improving pain, tremor, dysarthria and paresis. Postural tremor and frozen gait seemed resistant to stimulation. MCS effect, when present, began immediately after the start of stimulation; after its termination, the effect reappeared at stimulation intensity below the threshold for muscle contraction and a frequency of more than 15 Hz. Thus, post-stroke motor disorders seem to respond to higher frequencies (50–125 Hz) than pain (25–75 Hz) and at intensities below the threshold for muscle contraction. Subjective improvement of voluntary motor performance, which had been impaired in association with mild or moderate hemiparesis, was reported during MCS by approximately 20% of patients with post-stroke pain, independent of analgesia. Such an effect on voluntary motor performance appears to be caused by an inhibition of their rigidity. No improvement occurred in patients who demonstrated severe motor weakness and/or no muscle contraction in response to MCS at a higher intensity. MCS completely

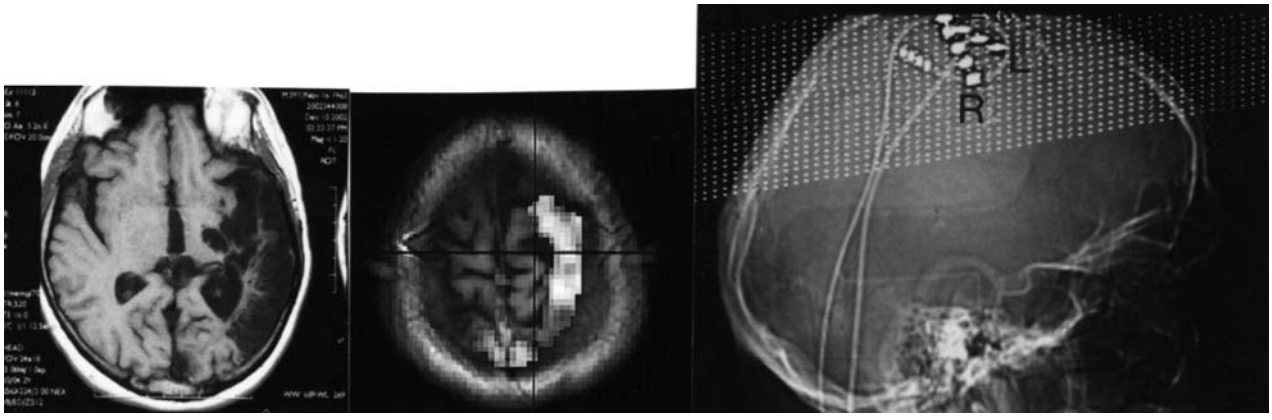


Fig. 6. MR image of a patient with stroke (a), fMR image following motor activation of the paretic arm (b) and double cortical stimulator ion motor areas (c) (Ref. [10b])

relieved both pain and tremor for at least 32 months in a patient with severe upper limb action tremor and facial pain following removal of an acoustic Schwannoma [30]. In this patient, tremor increased by decreasing the frequency below 50 Hz. In other series, a few patients experienced reversible improvements in facial sensory discrimination, motor strength and post-stroke dysarthria after successful stimulation for neuropathic pain.

Dystonias

We reported the effects of MCS on a female patient with spasmodic torticollis who later developed post-thalamotomy painful paroxysmal hemidystonia [9]; lesions of the thalamus, including surgical lesions of the posterior-posterolateral or paramedian thalamus, may originate dystonia, including paroxysmal dystonic attacks. During the trial period, stimulation at low frequency (10 Hz), at long impulse duration (450 msec) and low voltage (1 V) relieved the pain and dystonia almost completely, while the neck symptoms were not affected or slightly worsened. Duration of paroxysms and free intervals were not affected. Increasing the frequency to 60 Hz and even more to 130 Hz at short impulse duration (60 msec) worsened both pain and dystonia and increased the duration of her crises up to 40 min. In addition, previously never reported rebound crises lasting 5–10 min were triggered. A second plate positioned over the neck-head area at effective parameters as above worsened both pain and dystonia; the picture was even worse at 700 msec. Other experience suggests that MCS may affect post-stroke pain and dystonia (thalamic hand) variably, with dystonia responding to high frequency (130 Hz) [6], but also other dystonic syndromes.

Post-stroke motor rehabilitation

In 2002, we were the first to submit a plegic patient to bilateral cortical stimulation for post-stroke motor rehabilitation (Fig. 6) and found modest effects. Similarly to another recent controlled US study, it seems that cortical stimulation of areas undergoing plastic changes as evidenced on fMR may help rehabilitation of patients who have been left with disabling deficits after intensive physiotherapy [11].

Future prospects and developments

MCS holds great promise for the treatment of selected motor disorders, notably Parkinson's disease and several

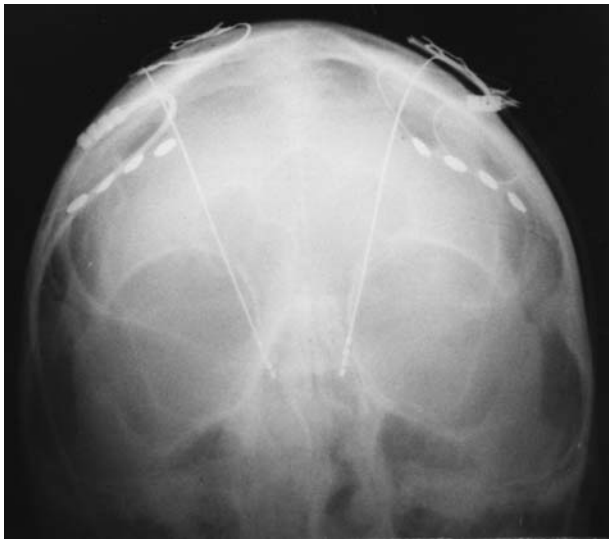


Fig. 7. Radiograph of a Parkinsonism case with a double STN and MCS stimulator (Ref. [9])

post-stroke disorders. Bilateral Parkinson's disease appears to be controlled by unilateral MCS, making it cost-effective compared to DBS. Although bilateral stimulation may be additive (Fig. 7), contralateral stimulation, on the least affected side, may be attempted in failures. SMA is not accessible to extradural MCS, but premotor areas could be targeted in future studies. Old data point to a motor suppressing area (BA4a) (see McCullock in [3]) and this region should be better explored. Finally, STN DBS does not prevent cell death and glutamate excitotoxicity [22] and it would be interesting to assess MCS for this effect. It seems every movement disorder that responds to TMS will also respond to MCS, including a wide range of dystonias, such as writer's cramp, tics (as in Tourette's syndrome), myoclonus (primary and secondary) and others. Lack of mortality and disabling surgical morbidity (due to lack of insertion of electrodes into the brain) plus cost-effectiveness (no need for stereotactic equipment) may contribute towards a massive resort to this technique, which is likely to spill over to psychiatric neuromodulation; epilepsy is now undergoing experimental treatment with closed-loop cortical stimulation [17]. Even if future head-to-head studies find DBS more effective, MCS will remain an option for all those patients who are not suitable for DBS, i.e. a huge population.

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