Improved Dexterity after Chronic Electrical Stimulation of the Motor Cortex for Central Pain: A Special Relevance for Thalamic Syndrome

Christophe Nuti^{a,d} François Vassal^{a,d} Patrick Mertens^{d,e}
Jean-Jacques Lemaire^f Michel Magnin^d Roland Peyron^{b–d}

Departments of ^aNeurosurgery and ^bNeurology, and ^cPain Center, CHU Saint-Etienne, and ^dINSERM, U879, UCB Lyon 1 and UJM, Saint-Etienne, ^eDepartment of Neurosurgery and Pain, Hospices Civils de Lyon, Lyon, and ^fDepartment of Neurosurgery, CHU Clermont-Ferrand, Clermont-Ferrand, France

Key Words

Dystonia · Motor cortex · Motor function ·
Neurostimulation

Abstract

Objectives: To demonstrate that motor cortex stimulation (MCS) could improve motor function in patients with neuropathic pain. **Methods:** In this prospective clinical study of 38 patients referred for MCS as treatment for their neuropathic pain, we collected any declaration of improvement in motor performance that could be attributed to MCS. **Results:** Ten patients (26%) declared a benefit in their motor function. Eight presented objective evidence of recovered dexterity for rapid alternating movements. A minor proportion had improvement in dystonic posture ($n = 2$), but none had detectable increased motor strength or tone changes. Overall, 73% of the patients with limb ataxia declared a benefit after MCS. In 6 out of 10 patients (60%), the anatomic lesion responsible for pain was restricted to the lateral aspect of the thalamus. All of them had either clinical or electrophysiological evidence of lemniscal dysfunction (proprioceptive ataxia). No correlation was found between the scores of pain re-

lief and the modification of motor status. The correlation between thalamic lesions and benefits in motor performance was significant (Fisher's exact test, two-tailed, $p = 0.0017$). **Conclusions:** Up to 26% of patients estimated that MCS improved their motor outcome through recovered dexterity and in cases of lateral thalamic lesions.

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Introduction

Since the first reports by Tsubokawa et al. [1, 2] electrical chronic stimulation of the motor cortex (MCS) has been widely used as a surgical technique that may alleviate medically refractory neuropathic pain, including poststroke, posttraumatic, or trigeminal neuropathic pain [3–7]. There are substantial arguments supporting the efficacy and long-term analgesic effects of MCS in patients with desperate and medically refractory cases of neuropathic pain [8, 9], and this effect is supported by the results of a recent randomized double-blind trial [10].

As ancillary results, several groups have stressed the observation that patients with MCS may also experience

a benefit in motor functions. Isolated case reports or anecdotal but convincing observations of patients have described improvement in motor performance [1, 2], or complete relief of tremors [11], or complete recovery of hand dystonia [12] after MCS. These observations have even prompted pilot studies investigating the effects of MCS in the treatment of movement disorders including poststroke involuntary movements [13], intentional myoclonus [14], or Parkinson's disease [15, 16]. Accordingly, as suggested by preclinical studies in rats and monkeys [17, 18], MCS was also recently proposed in human pilot studies as a possibly safe and promising therapy for stroke recovery [19, 20]. However, the nature of the benefit that can be expected from MCS, its incidence, and the categories of patients in whom this effect can be encountered are still three unresolved issues. Here we propose the intermediate results of a prospective clinical study including 38 consecutive patients undergoing MCS for refractory central neuropathic pain. This study shows that up to 26% of patients declared a benefit in motor performance, the reality of which can be confirmed by a double-blind trial and through observation of their movements on video recordings. These findings provide the opportunity to discuss the possible underlying mechanisms of action.

Materials and Methods

General Description of the Study

The present double-blind, randomized, prospective study was conducted in patients who underwent MCS for the treatment of medically refractory chronic central neuropathic pain in an attempt to objectively investigate whether or not MCS had an efficacy on pain intensity regardless of a placebo effect. Therefore, the main criteria of the study were dedicated to evaluation of pain and pain relief; those results will only be partly discussed here, but more information on the details of the study and long-term follow-up of these patients can be found in a previous paper [9]. Since improvement in motor performance had been previously reported (see above), information on an ancillary criterion defined as 'improvement in motor performance' was collected throughout the study, the results of which are shown here. The study was conducted in conformity with the Helsinki Declaration and was approved by the local ethics committee (Saint-Etienne University Hospital, France).

Evaluation of Improvement in Motor Performance

In the postoperative stage, evaluations were performed monthly for a 4- to 6-month period that included the double-blind randomized and placebo-controlled trial. Schematically, patients had the MCS turned on during the first 2–4 months postoperatively. Parameters of stimulation were progressively set and it was checked that every set-up was correct (progressive increase in

stimulation intensity, frequencies, checking of electrode polarities). In this period, only minor adaptations of stimulation parameters were performed in order to reach both standardized parameters for each subject and a stable period of reference after MCS implantation. In this postoperative stage, it was also checked that MCS did not induce any adverse effects.

Then, patients were randomized for an additional 2-month period (either on-off or off-on) during which the double-blind evaluation was conducted. The question of any 'motor effect' was systematically addressed to patients through a standardized 'yes/no' questionnaire. In cases of positive responses, they had to describe what they considered as a 'motor effect' and they had the possibility to describe a worsening. Then, a clinical description of the 'motor effect' was provided by the investigators by taking into account the patient's description, his clinical examination, and, if he was accompanied, an interview with the relatives. In case of a declared 'motor benefit', it was then classified as either a motor deficit per se, spasticity, dystonia, a motor consequence of somatosensory deafferentation/limb ataxia, extra-pyramidal syndrome, or combinations of these items. Finally, if the patients accepted such a recording, sequences of motor actions that the patients declared to be modified were performed in both off and on periods.

Patients

The study refers to 38 patients, 27 of whom had their pain outcome reported previously [9]. All of them had a lesion of the central nervous system responsible for contralateral neuropathic pain but also had various (and contingent) combinations of motor or proprioceptive sensory deficits that are known to interfere with the global motor performance. Since the intensity of motor deficit had been reported as a negative prognostic factor [3] for MCS analgesia, patients with monoplegia/hemiplegia/paraplegia were excluded from this study. Autonomy for walking alone was required, but walking with the assistance of a cane was tolerated. Therefore, only patients with a limited motor deficit could be included. Thus, according to the classification of Dejong [21], no patient in the present study was found to have grade 0–3 severe motor impairment and most of them had minor (grade 4: 19/38) or no (grade 5: 19/38) motor deficits. No patient was found to have extrapyramidal signs, 11/38 had spasticity, 2/38 had dystonia (dystonia being the only symptom in these 2 patients), and 11/38 had ataxic/proprioceptive symptoms in limbs.

Original lesions were hemorrhagic or ischemic stroke, ruptured vascular malformation, myelopathy complicating herniated discs, and brain trauma with intracranial hematomas.

Surgical Procedure and MCS Parameters

The surgical procedure has been described in previous works [4, 9]. Briefly, one or two quadripolar electrodes (Resume Medtronic®) were placed over the dura through a frontoparietal craniotomy (40 × 50 mm) made over the motor representation of the painful area, i.e. the suprasylvian region of the convexity was stimulated if the pain was located in the face and/or the upper limbs (electrode immediately anterior and parallel to the central sulcus), while the paramedian region was stimulated if the pain was in the lower limbs (parasagittal anteroposterior electrode). The motor area was localized with use of the somatosensory evoked potential (SEP) phase reversal technique [22] and an MRI 'neuronavigation' system (Stealth Station; Medtronic Sofamor

Table 1. Clinical data of patients with a declared benefit of MCS on motor function

Patient No.	Sex, age	Type	Anatomic localization	SEPs	%R	Preoperative impairment	Preoperative dystonia
1	F, 48	Isch	Th (VPL)	Abs	59	–	+ Blepharospasm
2	M, 71	Isch	Frontoparietal	Abs	41	Proprioceptive ataxia Spastic hemiparesis predominating in the lower limb (gr 4)	
3	F, 62	Hem	Lenticular Insula	Imp	52	–	+ Hand dystonia, blepharospasm
4	F, 72	Isch	Th (VPL)	Imp	30	Proprioceptive ataxia	
5 ^a	M, 59	Isch	Th (LP)	N	80	Proprioceptive ataxia predominating in the upper limb	
6	M, 71	Hem	Th (VPL)	Imp	43	Proprioceptive ataxia	
7	F, 58	Isch	Parietal SI SII Insula Anterior cingulate	Imp	73	Proprioceptive ataxia	
8	M, 53	Isch	Th (VPL)	Imp	30	Proprioceptive ataxia	
9	M, 54	Isch	Th (VPL)	Abs	40	Proprioceptive ataxia	
10	M, 62	Hem	Brainstem	Abs	40	Proprioceptive ataxia Spastic hemiparesis (gr 4)	

Ages are presented in years. %R = Percentage of postoperative pain relief; Isch = ischemic stroke; Hem = hemorrhagic stroke; Th = thalamus; Abs = absent; Imp = impaired (amplitude decrease and/or latency increase); N = normal; – = absence; + = presence; gr = motor score grade.

^a Two successive ischemic strokes (right thalamus and left brainstem) occurred in this patient, resulting in bilateral pain. A bilateral MCS was implanted in two stages. In this study, only the left side of the body was evaluated (online suppl. video), corresponding to the implantation over the right motor cortex.

Danek®). The electrode(s) were implanted extradurally and connected to a subcutaneously implanted stimulator (Xtrel, Matrix, Itrel II, or Synergy Medtronic®). The whole stimulation device including the pulse generator was implanted in a single session under general anesthesia.

After adaptation (2–4 postoperative months), standardized stimulation parameters of MCS (frequency = 35 Hz, intensity = 1.5 V, pulse width = 180 µs, cyclic mode = 30 min on/2 h off) were used for the double-blind evaluation (4–6 postoperative months). No subjective sensation was induced during the phases of stimulation. Then, patients were engaged in a long-term follow-up and open study.

Explaining Variables

The following variables were tested as possible explaining parameters of the declared ‘motor benefit’ as follows: (i) localization of the lesion, (ii) its origin (i.e. ischemia/hemorrhage/trauma), (iii) SEP abnormalities, and (iv) percentage of pain relief (PR).

Anatomical Thalamic Lesion

MRI (or CT scans, patient 9) of patients with a thalamic lesion were projected onto the appropriate planes of the stereotactic thalamus atlas of Morel et al. [23] in order to define the limits of the lesion with respect to thalamic nuclei.

Results

Overall Results

Ten (26%) out of 38 (for details, see table 1) patients gave a positive response to the question ‘do you have any motor effect?’. The description always consisted of an improvement in motor performance. Even though the patients had the possibility to describe a worsening, no such effect was observed in this study or in our previous expe-

Table 2. Positive motor effects of MCS

No.	Dystonia (preop/ postop)	Manual dexterity (preop/postop)	Bimanual movements (preop/postop)	Walk (preop/postop)	Muscle strength (preop/postop)	Subjective improvement (patient's or relatives' opinion)
1	+/-	N	N	N	N	P
2	-	def/def	def/def	def/ben	def/def	P
3	+/-	def/ben	N	def/ben	N	P
4	-	N	N	def/ben	N	P
5	-	def/ben	N	N	N	P
6	-	def/ben	N	def/ben	N	P
7	-	def/ben	def/ben	N	N	P
8	-	def/ben	N	def/ben	N	P
9	-	N	N	def/ben	N	P
10	-	def/ben	N	def/def	def/ben (upper limb) ^a	P

preop = Preoperative; postop = postoperative; + = presence; - = absence; def = deficit; ben = benefit; N = normal; P = positive.

^a Slight increase in muscle strength but without any change in the preoperative motor score (see Results).

rience. No patient declared serious adverse motor effects due to surgery or stimulation. This declaration was confirmed by interviews with relatives in all cases and can be seen in two representative cases (online suppl. video, www.karger.com/doi/10.1159/000338681). A summary of the observed effects is presented in table 2.

Clinical Symptoms

In a first group of two patients (1 and 3), complete resolution of poststroke focal dystonia was observed during MCS. Both patients had a blepharospasm while patient 3 had additional hand dystonia which impaired her manual dexterity in simple actions of daily life. These two patients had a motor dysfunction that was: (i) unexplained by elementary sensory and motor deficits and (ii) typically comprised of abnormal and focal contractions (spasms) in the orbicularis/hand muscles, with (iii) a consequent impairment of eye/hand opening, on the side contralateral to the lesion. These findings were typical of eye/hand dystonias, which are known to occur after deep brain strokes, particularly in the thalamus [24], as in these two patients with thalamic infarct and capsulo-thalamic hematoma, respectively. Recurrence of dystonias that preceded pain reappearance was observed in several occasions in the long-term follow-up of these patients. In all cases, this outcome was associated with spontaneous MCS dysfunction, the incidence of which could not be predicted or detected by patients who did not perceive the electrical stimulation. This outcome was always reversed

after MCS had been restored and, in patient 3, without any dissociation of the effect between eye and hand dystonias. These patients were the only two in the series with dystonias.

In a second group of 8 patients (2, 4, 5, 6, 7, 8, 9, and 10), the improvement in motor performance was attributed to enhanced dexterity and velocity for alternating movements. This outcome after MCS was not secondary to improved motor strength, as verified during clinical examination and since most of these patients had only minimal or no motor deficit. In only one patient (No. 10) with a slight spastic hemiparesis, the motor deficit (score 4 on the classification of Dejong [21]) was declared to improve in the upper limbs since the patient was able to handle a bottle when MCS was turned on but not when MCS was turned off. Thus, a slight increase in motor strength was possible even though motor function did not return to normal, did not change in the classification of Dejong [21], and was not associated with objective changes in clinical testing. Thus, MCS may have slightly decreased the motor deficit in only 1 of 19 patients (5%). Only 2 of these patients (2 and 10) had spasticity, and none of them had improved dexterity through changes in spasticity or tonus. Only one patient (No. 7) with a lesion on somatosensory cortices that also included the anterior cingulate cortex declared an improvement in bimanual activities that was dramatically verified during clinical examination. Conversely, all 8 patients had limb ataxia resulting in walking instability and/or functional dysfunctions for

grasping, eating, or writing. In all of these patients, a somatosensory deficit involving lemniscal pathways was clinically present and was confirmed by SEPs in all but one case (patient 5). In all of them, clinical examination was consistent with an improvement in ataxic symptoms and proprioceptive deficits after MCS. Considering the whole series ($n = 38$), 73% (8/11) of patients with limb ataxia were improved by MCS.

Anatomical Lesions

A unilateral lesion was found in the lateral thalamus (fig. 1), located within (or adjacent to) the ventral posterior lateral (VPL) nucleus in 5 patients (1, 4, 6, 8, and 9) and within the lateral posterior (LP) nucleus in 1 patient (No. 5). One patient (No. 10) only had a lesion below the thalamus. Two patients (2 and 7) had cortical lesions. Patient 2 had a parietal infarct involving the posterior parietal and SII cortices. Patient 7 had ischemic infarcts involving the SI, SII, and anterior cingulate cortices (previously described in detail) [25]. In the two latter patients,

sparing of a thin ribbon in SI and MI cortices made the MCS possible. In the last patient (No. 3), the hemorrhagic lesion was shown to induce a residual lesion in the white matter immediately below the insular cortex that spared the thalamus (fig. 2).

Correlations

The correlation between lateral thalamic lesions and benefits in motor performance was highly significant (Fisher's exact test, two-tailed, $p = 0.0017$; for details, see table 3), and the perception of motor benefit was true in 6 out of 8 patients. Conversely, only 2 out of 8 patients with thalamic lesions declared no improvement in motor performance after MCS regardless of their preoperative impairment. With a thalamic lesion, the odds ratio of having a motor improvement was 19.5 (3–132).

No correlation was observed between motor performance and the origin of the lesion (hemorrhagic/ischemic/trauma).

In all but one patient (No. 5) with improved motor performance, lemniscal abnormalities were present as demonstrated by SEPs. Regardless of the presence of lemniscal abnormalities, SEP data were not discriminant for the presence of motor benefit since SEP abnormalities were frequently observed in patients with neuropathic pain, including those without motor benefit (16 patients).

We did not find any correlation between the scores of pain relief and the presence (or lack thereof) of improvement in motor performance.

Discussion

Even though the study was designed to evaluate primarily the effects of MCS on neuropathic pain, the present report discloses additional benefits in motor performance. The observation of such effects in our patients treated with MCS is in agreement with the first case reports describing improvement in motor status after MCS in poststroke patients [1, 2] or reversal of poststroke hand dystonia [12]. Considering that MCS could positively influence motor performance, MCS has even been applied in the surgical treatment of movement disorders such as poststroke involuntary movements [13] and Parkinson's disease [15, 16]. Clinical trials investigating the usefulness of MCS for motor recovery after stroke have also been prompted [19, 20]. A recent study nevertheless demonstrated that MCS could improve motor performance, but only in specific indications like essential tremor, with no benefit in Parkinson's disease [26]

Fig. 1. Thalamic lesion localization after MRI or CT scan (case 9) projection onto appropriate planes of the stereotactic thalamus atlas of Morel et al. [23]. In all cases, the VPL was the main nucleus involved, excepted in patient 5, in whom the lesion was located in the lateral portion of the LP, extending to the posterodorsal part of R and possibly interrupting efferent VPL fibers to the somatosensory cortex. In other cases, thalamic nuclei adjacent to the VPL, such as the PuA, LP, and VPI (case 6), PuA, VPM, and CM (case 8), LP, VLp, and CL (case 9), and PuA and PuM (case 1), were more or less encroached by the lesion. In cases 4, 5, 6, and 8, axial and a coronal MR images representative of the maximal extent of the lesion are presented together with an enlarged area centered on the thalamus. In cases 1 and 9, only horizontal images were available. The white dash (black in case 1) in each enlarged thalamic view indicates the level of the horizontal (vertical in cases 1 and 9) plane passing through the posterior commissure. AV = Anteroventral nucleus; CeM = central medial nucleus; CL = central lateral nucleus; CM = center median nucleus; Hb = habenula; IC = internal capsule; LD = lateral dorsal nucleus; LGN = lateral geniculate nucleus; MD = mediodorsal nucleus (pl = paralamina, pc = parvocellular, mc = magnocellular divisions); Pf = parafascicular nucleus; Pu = pulvinar (A = anterior, L = lateral, M = medial divisions); R = reticular thalamic nucleus; RN = red nucleus; SN = substantia nigra; VA = ventral anterior nucleus; VLa = ventral lateral anterior nucleus; VLp = ventral lateral posterior nucleus; VPI = ventral posterior inferior nucleus; VPL (p = posterior, a = anterior divisions); VPM = ventral posterior medial nucleus (pc = parvocellular division). Scale bar = 5 mm.

Fig. 2. ‘Nonthalamic’ lesion localization on an MRI or CT scan (case 2) in patients with motor benefit after MCS. Case 2: parietal (SI), SII. Case 3: capsulo-lenticular. Case 7: parietal (SI), SII, insula, anterior cingulate cortex. Case 10: brainstem. SI = First somatosensory area; SII = second somatosensory area.

Table 3. Relationship between benefit in motor performance and presence/absence of lateral thalamic lesions in the whole series of patients (n = 38) with MCS for refractory neuropathic pain

	Motor performance improved	
	yes	no
Lateral thalamic lesion		
Yes	6	2
No	4	26

There is a strong correlation between lateral thalamic lesions and motor performance benefit (Fisher's exact test, two-tailed, $p = 0.0017$).

The present study describes, with the use of videos, the kind of effects that can be encountered in patients after MCS but also investigated the predictive factors that seem to be important for the occurrence of such motor benefits, including the localization of the original lesion. As shown in videos, the effect may be important enough to

lead to obvious improvements in motor performance in daily life.

The effect on motor performance that did not correlate with the amount of pain relief induced by MCS suggests a parallel mechanism that may involve outputs from the stimulated primary motor cortex. A first intuitive hypothesis would be that MCS could increase the excitability of pyramidal neurons at the origin of the corticospinal tract [27] and thus directly influence the patients' motor status [28]. These motor-like effects could also originate from the basal ganglia, as suggested by PET imaging data demonstrating: (i) a striatal dopamine release in the ipsilateral putamen after repetitive transcranial magnetic stimulation (rTMS) of the primary motor cortex [29] and (ii) increased CBF in basal ganglia, mainly in striatum ipsilateral to MCS [30]. Electrophysiological studies in primate models of Parkinson's disease [31] have also suggested further effects of MCS on thalamocortical balance and pyramidal cortical outputs [12, 14]. However, our data did not confirm such a hypothesis since no clinical improvement directly linked to the motor circuitry per se (pyramidal or extra-

pyramidal) was observed, except in one patient (No. 10) in whom a slight improvement in hemiparesis was described.

More than an effect on motor strength per se, our study therefore suggests that the benefit is mostly related to improved dexterity and velocity for alternating movements and subtle changes in motor coordination, including for walking or, in one patient (No. 7), for bi-manual activities. It seems likely that these conclusions may be explained in part by the localization of the lesions and our patients who, compared to patients in other studies on MCS, did not have a severe motor deficit. Conversely, this bias may also be considered a unique opportunity to exclude (from a pathophysiological point of view), the participation of the motor system in the benefit observed with MCS. In other words, despite the low incidence and the low severity of motor deficits in this series of patients, we observed improved motor performance, suggesting that it is not associated with improved motor strength. Accordingly, the majority of our patients with a benefit in motor performance have either a lesion in the lateral thalamus or evidence of lemniscal involvement. This may be due to the absence of improvement in a large number of patients with lesions located elsewhere in the brain, or even to the absence of motor deficits in patients with lesions located elsewhere. However, the proportion of patients with improvement and thalamic lesions is very high and suggests that such outcomes and thalamic lesions may be linked. The latter is verified either anatomically with a lesion involving the lemniscal pathways (all patients) or functionally with abnormal SEPs (all but one patient had abnormal SEPs). Conversely, only a few of them had extension of the lesion to motor systems, and only 2 patients out of 38 had a VPL lesion and did not present any benefit in motor performance. These results suggest that the declared improvement in motor performance may have something to do with improved somatosensory function and may be supported by experi-

mental data showing that an ischemic lesion located either in the lateral thalamus (VPL, LP nuclei) or in the first somatosensory area interferes with motor cortex excitability [32, 33]. The finding of improved proprioceptive ataxia (patients 2 and 4–10) is an additional argument in favor of this hypothesis, as is the finding that MCS may also dramatically improve poststroke dystonia (patients 1 and 3), a disease in which a primary dysfunction of lemniscal afferents to the somatosensory cortex has been proposed as a pathophysiological mechanism [34–39].

Finally, we did not find any evidence of a contribution of MCS to decreased spasticity. Eleven of 38 patients had spasticity but only 2 of them declared a motor benefit. In these 2 patients, clinical examination showed that the motor improvement was related to other effects. Further, this finding is an additional argument linking the effects of MCS with the somatosensory system rather than with the motor system.

Conclusion

It can be suggested that approximately 25% of patients with MCS, and among them a large proportion of patients with isolated lateral thalamic lesions and/or lemniscal dysfunction, can experience a marked improvement in their motor performance in daily life. The main benefit is neither a strict motor improvement nor improvement in spasticity or hypertonia but rather improvement in dexterity and velocity possibly through improvement in ataxia/proprioception and/or focal dystonia. These observations may prompt future, pilot, prospective trials of MCS in selected patients who may benefit from improved motor performance after a stroke. The present study may be helpful in determining the prognosis for this selection of patients.

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