

# Motor cortex stimulation for the treatment of refractory peripheral neuropathic pain

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**Epidural motor cortex stimulation (MCS) has been proposed as a treatment for chronic, drug-resistant neuropathic pain of various origins. Regarding pain syndromes due to peripheral nerve lesion, only case series have previously been reported. We present the results of the first randomized controlled trial using chronic MCS in this indication. Sixteen patients were included with pain origin as follows: trigeminal neuralgia ( $n=4$ ), brachial plexus lesion ( $n=4$ ), neurofibromatosis type-1 ( $n=3$ ), upper limb amputation ( $n=2$ ), herpes zoster ophthalmicus ( $n=1$ ), atypical orofacial pain secondary to dental extraction ( $n=1$ ) and traumatic nerve trunk transection in a lower limb ( $n=1$ ). A quadripolar lead was implanted, under radiological and electrophysiological guidance, for epidural cortical stimulation. A randomized crossover trial was performed between 1 and 3 months postoperative, during which the stimulator was alternatively switched 'on' and 'off' for 1 month, followed by an open phase during which the stimulator was switched 'on' in all patients. Clinical assessment was performed up to 1 year after implantation and was based on the following evaluations: visual analogue scale (VAS), brief pain inventory, McGill Pain questionnaire, sickness impact profile and medication quantification scale. The crossover trial included 13 patients and showed a reduction of the McGill Pain questionnaire-pain rating index ( $P=0.0166$ , Wilcoxon test) and McGill Pain questionnaire sensory subscore ( $P=0.01$ ) when the stimulator was switched 'on' compared to the 'off-stimulation' condition. However, these differences did not persist after adjustment for multiple comparisons. In the 12 patients who completed the open study, the VAS and sickness impact profile scores varied significantly in the follow-up and were reduced at 9–12 months postoperative, compared to the preoperative baseline. At final examination, the mean rate of pain relief on VAS scores was 48% (individual results ranging from 0% to 95%) and MCS efficacy was considered as good or satisfactory in 60% of the patients. Pain relief after 1 year tended to correlate with pain scores at 1 month postoperative, but not with age, pain duration or location, preoperative pain scores or sensory-motor status. Although the results of the crossover trial were slightly negative, which may have been due to carry-over effects from the operative and immediate postoperative phases, observations made during the open trial were in favour of a real efficacy of MCS in peripheral neuropathic pain. Analgesic effects were obtained on the sensory-discriminative rather than on the affective aspect of pain. These results suggest that the indication of MCS might be extended to various types of refractory, chronic peripheral pain beyond trigeminal neuropathic pain.**

**Keywords:** cortical stimulation; crossover trial; motor cortex; neuropathic pain; pain questionnaire; peripheral pain

**Abbreviations:** BPI = brief pain inventory; MCS = motor cortex stimulation; MPQ = McGill Pain Questionnaire; MQS = Medication Quantification Scale; PRI = pain rating index; SIP = Sickness Impact Profile

## Introduction

Implanted motor cortex stimulation (MCS) was first proposed by Tsubokawa *et al.* (1991) as a treatment for chronic, drug-resistant neuropathic pain. Initial positive results have been obtained in patients with central pain secondary to thalamic stroke and later confirmed in various other types of neuropathic pain. In the literature, peripheral pain was the indication for MCS therapy in about 45–60 patients with trigeminal neuropathic pain and 13–25 patients with neuropathic pain secondary to plexus or nerve trunk lesion (review in Nguyen *et al.*, 2003; Cruccu *et al.*, 2007; Lazorthes *et al.*, 2007; Saitoh and Yoshimine, 2007). All these cases have been reported in open studies. Although MCS has a unique possibility for sham stimulation because there is no percept from active stimulation, only three randomized controlled trials have been published so far in which MCS efficacy was assessed with a crossover design (Rasche *et al.*, 2006; Nguyen *et al.*, 2008; Velasco *et al.*, 2008). In the first of these studies, a test trial of about 1 week was conducted in the immediate postoperative period. In the two other studies, stimulation was randomized between 'on' and 'off' condition at 2 or 3 months postoperative for 2 weeks or 1 month. All these studies showed significant analgesic effects when MCS was switched 'on' compared to 'off-stimulation' condition. However, these studies enrolled a limited number of patients with neuropathic pain of various origins and were, therefore, not conclusive regarding MCS efficacy in a specific indication, such as peripheral neuropathic pain.

The present study is the first randomized controlled trial in which MCS efficacy—to treat peripheral neuropathic pain—is assessed. Sixteen patients with drug-resistant pain secondary to peripheral nerve lesion were enrolled. The study included a crossover trial in which the stimulator was switched 'on' or 'off' for 1 month in random order with double-blind evaluation of the resulting effects, followed by an open phase, during which the stimulator was switched 'on' in all patients.

## Patients and Methods

### Patient selection and demographics

Patients were selected according to the following criteria: (i) age between 18 and 80; (ii) presence of unilateral or lateralized neuropathic pain due to peripheral nervous system lesion; (iii) chronic pain resistance for more than a year to at least three different types of analgesic medical treatments, including antiepileptics and antidepressants; (iv) average pain score  $\geq 50$  on a 0–100 visual analogue scale (VAS) over 7 days of self-assessment; and (v) informed consent signed before implant of the cortical stimulation lead.

Patients presenting any of the following conditions were excluded: (i) pregnancy; (ii) malignant disease; (iii) history of epileptic seizures;

(iv) thrombocytopaenia ( $<50\,000$  platelets/mm<sup>3</sup>) or leukopaenia ( $<2000$  WBCs/mm<sup>3</sup>); (v) heart, renal or hepatic failure; (vi) psychotic disorder; or (vii) patient unable and/or unwilling to cooperate with study procedures or to comply with the required follow-up visits.

Sixteen patients were enrolled in the study, which was approved by the local ethics committee. All patients signed an informed consent form after reading a document that provided detailed information about the protocol. Patient demographics are presented in Table 1. Briefly, mean age was 49.3 years (ranging from 21 to 80), mean pain duration before surgery was 9.3 years (2–20) and mean pain score on VAS was 73.7 at preoperative baseline (51–100). Pain origin was as follows: trigeminal neuralgia ( $n=4$ ), brachial plexus lesion ( $n=4$ ), nerve trunk lesion as a complication of neurofibromatosis-1 ( $n=3$ ), upper limb amputation ( $n=2$ ), herpes zoster ophthalmicus ( $n=1$ ), atypical orofacial pain secondary to dental extraction ( $n=1$ ) and traumatic nerve trunk transection in a lower limb ( $n=1$ ). Trigeminal neuralgia were diagnosed as essential typical forms in three cases and occurred with a history of benign cavernous sinus tumour in one case. These cases were resistant to both medical and surgical treatments. Previous surgical interventions included microvascular decompression and thermal rhizotomy in cases of essential typical trigeminal neuralgia and tumour resection and gamma knife radiosurgery for the case of cavernous sinus tumour. Brachial plexus lesion was incomplete and of traumatic origin in all cases. In the two cases of upper limb amputation (secondary to electrocution burn injury of distal upper limb and to brachial plexus lesion due to car accident), pain syndrome concerned the stump and not a phantom limb. Pain was located at the face ( $n=7$ ), neck ( $n=1$ ), upper limb ( $n=6$ ) or lower limb ( $n=2$ ). In the painful territory, sensory deficit was complete or severe in five patients and moderate in two patients. There was no sensory deficit in nine patients (Table 1). Although it was thought unlikely that neuropathic pain was associated with the absence of sensory loss in the pain region (Rasmussen *et al.*, 2004), all these patients had neuroanatomically plausible distribution of pain. In addition, they had a history suggestive of a relevant lesion, irritation or disease affecting the peripheral somatosensory system (trigeminal neuralgia, neurofibromatosis-1, stump neuroma, postherpetic neuralgia and orofacial pain secondary to dental extraction). Therefore, they fulfilled the diagnostic criteria of neuropathic pain condition according to its classical definition: 'pain initiated or caused by a primary lesion or dysfunction in the nervous system' (Merskey and Bogduk, 1994) or to the recently proposed definition: 'pain arising as a direct consequence of a lesion or disease affecting the somatosensory system' (Treede *et al.*, 2008). Regarding motor evaluation, weakness was noticeable in four patients and complete in one (Table 1).

### Surgical procedure, study design and stimulation parameters

Surgery was performed as previously described (Nguyen *et al.*, 1999). First, a craniotomy was centred on the motor cortical representation of the painful zone, according to magnetic resonance imaging- or computed tomographic-guided neuronavigation. Then, a quadripolar lead (Resume<sup>®</sup>, Medtronic, Minneapolis, USA) was placed over this theoretical target. Intra-operative neurophysiological mapping, based on

**Table 1** Demographic data of the patients

Patient number	Sex	Age (years)	Pain origin	Pain location	Pain side	Pain duration (years)	Baseline pain level (per 100)	Sensory deficit in the painful zone	Motor deficit in the painful zone	Treatment at baseline
1	F	21	Neurofibromatosis 1	Neck	R	2	79	None	None	Amitriptyline, clonazepam, hydroxyzine, tramadol
2	F	51	Neurofibromatosis 1	Face	L	5.5	65	None	None	Alprazolam, clomipramine, clonazepam, clorazepam, fentanyl, morphine sulfate, sertraline, tramadol
3	F	71	Trigeminal neuralgia (essential typical)	Face	R	19	58	None	None	Clonazepam, gabapentine
4	M	29	Brachial plexus trauma (incomplete)	Upper limb	R	3	67	Moderate	Moderate	Carbamazepine, clomipramine, dextropropoxyphene
5	F	57	Trigeminal neuralgia (essential typical)	Face	R	20	51	None	None	Buprenorphine, clomipramine, clonazepam, gabapentine, levomepromazine
6	F	28	Neurofibromatosis 1	Lower limb	R	5.5	68	None	None	Amitriptyline, clonazepam, dextropropoxyphene, gabapentine, tramadol
7	F	63	Limb nerve trunk trauma (sutured nerve transection)	Lower limb	L	7	79	Severe	None	Bromazepam, morphine sulfate, paracetamol
8	F	69	Amputation secondary to electrical shock	Upper limb	L	16	92	None	None	Clonazepam, gabapentine
9	F	80	Herpes zoster ophthalmicus	Face	L	4	90	None	None	Amitriptyline, clonazepam
10	M	42	Brachial plexus trauma (incomplete)	Upper limb	R	2	55	Severe	Moderate	Amitriptyline, clonazepam, gabapentine
11	M	70	Trigeminal neuralgia (essential typical)	Face	R	10	77	None	None	Clonazepam, tramadol
12	M	47	Brachial plexus trauma (incomplete)	Upper limb	L	20	74	Moderate	Moderate	Bromazepam, fentanyl
13	M	38	Brachial plexus trauma (complete, arm amputation)	Upper limb	L	18	69	Complete	Complete	Amitriptyline, clonazepam, gabapentine, morphine sulfate, paracetamol
14	F	30	Trigeminal neuralgia (cavernous sinus tumour)	Face	R	4	100	Severe	None	Alprazolam, carbamazepine, clonazepam, morphine sulfate, venlafaxine
15	F	53	Atypical orofacial pain (dental extraction)	Face	L	7.5	77	None	None	Codeine, gabapentine, oxcarbazepine, paracetamol
16	M	41	Brachial plexus trauma (incomplete)	Upper limb	L	4.5	78	Severe	Moderate	Codeine, paracetamol

the recording of somatosensory and motor-evoked potentials, was performed with a Keypoint machine (Alpine-Biomed, Skovlunde, Denmark). Cortical somatosensory evoked potentials to median nerve stimulation were recorded by using each contact of the quadripolar lead as an active electrode with an extra-cephalic reference placed at the shoulder. Somatosensory evoked potentials were used to determine the location of the central sulcus with respect to N20/P20 phase reversal. The various contacts of the epidural lead were also tested for their ability to produce motor-evoked potentials in the targeted painful zone using bipolar combinations. After neurophysiological confirmation of the accuracy of electrode placement, the lead was sutured onto the dura mater and connected, via an extension, to an implanted pulse generator (Itrel II<sup>®</sup>, Medtronic). The implanted pulse generator was placed subcutaneously in the subclavicular (pectoral) region.

After implantation, the patients stayed in hospital for 1 week to ensure proper healing of the incision. During this time, several stimulation parameters were tested. At hospital discharge, the stimulator was turned 'off' for about 3 weeks. At 1 month postoperative, the stimulator was switched 'on' or remained 'off'. At 2 months postoperative, the 'on/off' condition of the stimulator was reversed.

Half of the patients were randomly assigned to start with the 'on' phase and the other half with the 'off' phase to avoid order effect. Double-blind examinations were performed at the end of each month (M2, M3) of the crossover trial. Neither the patient nor the clinical investigator could be aware of stimulator condition during this period, especially because no sensory percept or motor effect was resulting from active MCS. The stimulator was then switched 'on' in all cases and open examinations were performed at 6, 9 and 12 months postoperative.

In summary, the investigation included a preoperative period (one evaluation per month for 3 months), an immediate postoperative period (1 month during which the stimulator was not permanently activated), a randomized crossover trial (2 months during which the stimulator was switched 'on' or 'off' alternatively for 1 month) and a long-term postoperative period (9 months during which the stimulator remained switched 'on'). The sequence of study events is illustrated in Fig. 1.

In most cases, a bipolar montage was used for chronic stimulation. The contact optimally placed over the motor cortical representation of the pain region (according to intraoperative image-guided navigation and neurophysiological mapping) was selected as the cathode; the

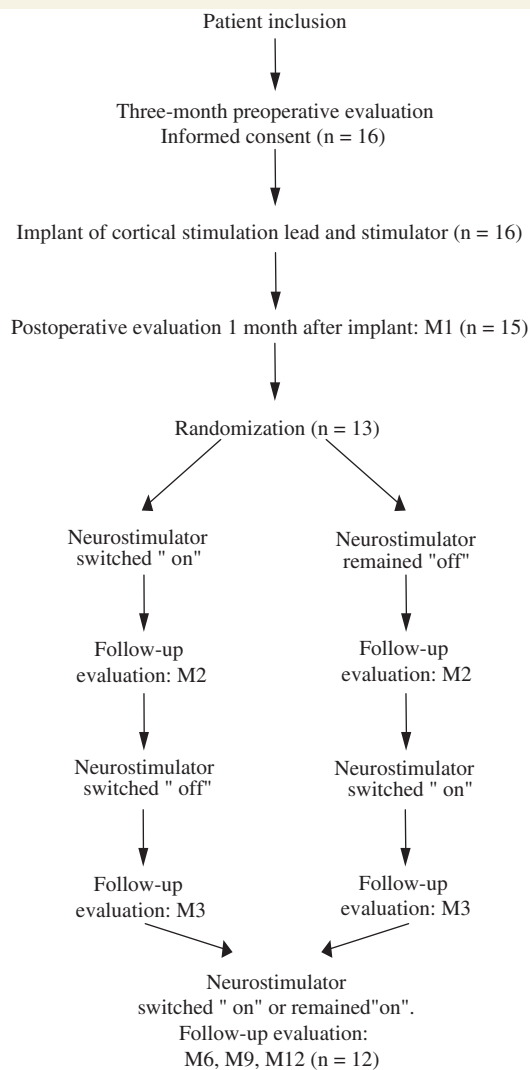


Figure 1 Sequence of study events.

contact situated immediately behind (over the central sulcus or post-central area) was selected as the anode (Nguyen *et al.*, 1999, 2003, 2008). In two patients, monopolar cathodal stimulation was performed, selecting the implanted pulse generator case as the anode. Initial stimulation settings were as follows: amplitude 2 V, pulse width 60  $\mu$ s, rate 40 Hz, continuous mode. These parameters were those classically used in chronic MCS therapy for neuropathic pain (Nguyen *et al.*, 1999, 2003, 2008). These parameters were readjusted during the study, with respect to clinical efficacy observed within the week after the time of programming. Stimulation settings at final examination are presented in Table 2.

## Clinical assessment

The patients were given a pain diary and asked to self-rate every day the mean pain intensity that they experienced on a 0–100 VAS (from 0 = no pain to 100 = highest imaginable pain). For analyses, the seven daily pain ratings preceding each visit were averaged.

Pain assessment was also carried out using the short form of the brief pain inventory (BPI), a tool initially designed for cancer patients (Cleeland and Ryan, 1994) and then validated for use in noncancer

pain (Keller *et al.*, 2004). The BPI provides information on the degree to which pain interferes with seven different functions (general activity, mood, walking ability, normal work, relations with other people, sleep and enjoyment of life). Interference was rated for each item on a 0–100 scale (0 = pain does not interfere to 100 = pain completely interferes), and the average value was taken for analysis.

Finally, pain was assessed by the McGill Pain Questionnaire (MPQ) (Melzack, 1975) in its validated translation into the French language. The MPQ consists of 20 descriptors that fall into four major groups: sensory (descriptors 1–10), affective (11–15), evaluative (16) and miscellaneous (17–20). The rank value for each descriptor is based on its position in the word set. The sum of the rank values is called the pain rating index (MPQ-PRI). A ratio (MPQ-ratio) was also calculated by dividing the affective subscore by the sensory subscore. This ratio was previously used to appraise the respective impact of MCS on affective and sensori-discriminative aspects of pain (Nguyen *et al.*, 2008).

General health disturbance related to sickness was quantified with the Sickness Impact Profile (SIP) (Bergner *et al.*, 1981). This questionnaire consists of 136 items of 12 domains of daily functioning: ambulation, mobility, body care and movement, social interaction, alertness behaviour, emotional behaviour, communication, sleep and rest, eating, work, home management and recreation and pastimes. Only the total SIP score was taken into account.

Analgesic drug consumption was quantified using the Medication Quantification Scale (MQS) (Masters-Steedman *et al.*, 1992). The MQS was developed as a tool for patients with chronic non-malignant pain. An MQS score was calculated for each medication by taking a consensus-based detriment weight for a given pharmacologic class and multiplying it by a score for dosage. The calculated values for each medication are then summed for a total MQS score.

Regarding individual results at final examination, analgesic effects of MCS were classified into three categories (Nguyen *et al.*, 1999): good (VAS score reduction by 70–100%), satisfactory (reduction by 40–69%) and poor (reduction by <40%).

## Statistical analyses

Nonparametric tests were used since not all data passed the normality test as assessed by the Kolmogorov–Smirnov method. First, the evolution of the clinical scores (VAS, BPI, MPQ-PRI, MPQ-ratio, SIP and MQS) in the open phase was assessed using nonparametric repeated measures ANOVA (Friedman Test). One of the three preoperative evaluations was missing in 4 of the 12 patients who completed the study, and M9 evaluation was missing in two of these patients. Therefore, we averaged all available data collected during the preoperative period on one hand and at 9 and 12 months postoperative on the other hand. Repeated measures ANOVA were based on four time-points: preoperative, M1, M6 and M9–12. When a significant effect was found ( $P < 0.05$ ), Dunn's multiple comparison *post hoc* tests were used to compare all pairs of columns.

In the 13 patients who completed the crossover trial, clinical scores (VAS, BPI, MPQ-PRI, MPQ-ratio, MPQ affective and sensory subscores, SIP, MQS) were compared between 'on-stimulation' and 'off-stimulation' conditions using the Wilcoxon matched-pairs signed-ranks test. The level of significance was set at  $P < 0.05$ , but a stricter threshold of 0.0062 was considered, resulting from Bonferroni correction for multiple testing.

From the whole series of 15 stimulated patients, the percentage of pain relief on VAS score between preoperative baseline and final examination was compared in subgroups, according to pain location [face ( $n = 6$ ) versus upper limb ( $n = 6$ )] or sensori-motor deficit [present ( $n = 7$ ) versus absent ( $n = 8$ )], using the Mann–Whitney U-test.

**Table 2** Results of intra-operative electrophysiological tests (somatosensory and motor evoked potentials, SSEPs and MEPs). Stimulation settings at final examination. Pain score reduction on VAS at final examination (9–12 months postoperative)

Patient number	Phase reversal of intra-operative SSEPs	Intra-operative MEPs in the painful zone	Active electrodes	Voltage (V)	Pulse width ( $\mu$ s)	Frequency (Hz)	VAS score reduction (%)
1	Obtained	Obtained	1–2+	2	60	40	91
2	Obtained	Obtained	1–2+	2.1	60	50	5
3	Obtained	Obtained	0–3+	2	60	45	66
4	Obtained	Obtained	0–3+	2	60	45	3
5	Obtained	Obtained	1–2+	2	60	40	11
6	Obtained	Not obtained	1–Case+	2	60	40	93
7	Obtained	Obtained	1–Case+	2.5	60	35	31
8	Not obtained	Obtained	0–3+	2.5	60	45	63
9	Obtained	Obtained	Not stimulated				
10	Not obtained	Obtained	1–2+	1.6	60	40	58
11	Obtained	Obtained	1–2+	3	60	40	86
12	Obtained	Obtained	1–3+	5	60	45	1
13	Not obtained	Not obtained	2–3+	1.5	60	40	95
14	Obtained	Obtained	1–2+	2	60	40	0
15	Obtained	Obtained	2–3+	2.5	60	45	45
16	Not obtained	Obtained	2–3+	1.5	60	40	72

Correlation between pain relief at final examination on VAS score and age, pain duration or pain level at baseline or at 1 month postoperative was studied using the Spearman test. The significance level was set at  $P < 0.05$ , but Bonferroni correction for multiple testing led to a stricter threshold of 0.0125. Similar comparison and correlation studies were performed with the percentage of MPQ-PRI changes between 'off-stimulation' and 'on-stimulation' conditions during the crossover period in place of the percentage of pain relief at final examination.

## Results

### Outcome of the surgical procedure and adverse events

The quadripolar leads and implanted pulse generators were implanted under general anaesthesia in a single procedure in all patients. Intra-operative somatosensory evoked potentials showed N20/P20 phase reversal in 12 patients and were absent in four patients (Table 2). Motor-evoked potentials were successfully recorded in the painful territory in 14 patients and were absent at the painful thigh in 1 patient and at the painful stump in another patient (Table 2).

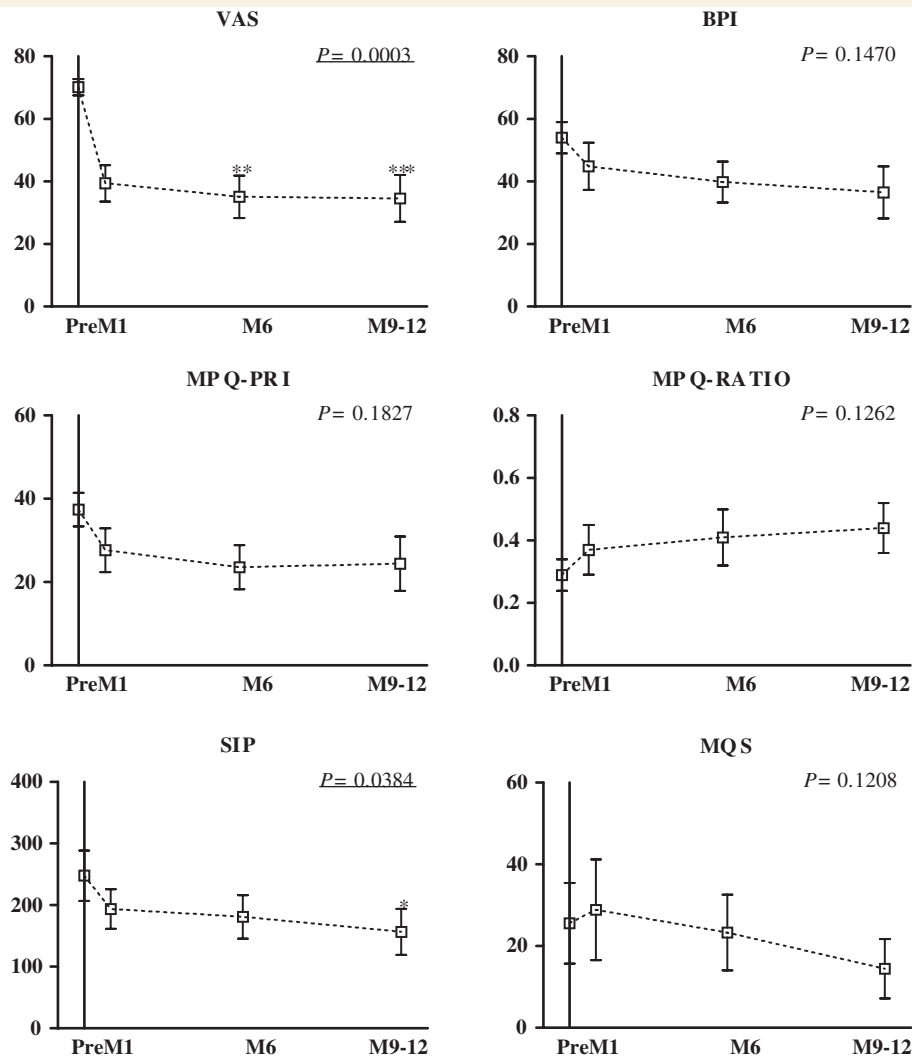
Only 12 patients completed the study. Two patients (Patients 8 and 10) greatly improved after implantation and refused to accept the crossover trial and further evaluations. The stimulator was switched 'on' at M1. For both of them, we obtained the 7-day VAS pain ratings at 12 months postoperative: Patient 8 experienced 63% pain relief (mean VAS score decrease from 92 to 34); Patient 10 experienced 58% pain relief (mean VAS score decrease from 55 to 23). One patient (Patient 14) completed the crossover trial but refused to perform further evaluations due to the lack of efficacy of the procedure. She was still presenting maximal pain (VAS score of 100) 1 year after implantation.

Finally, MCS was not activated in one patient (Patient 9). This patient accidentally fell in her hospital room the day after MCS electrode implantation. She broke one right rib, leading to the rupture of an emphysematous bulla that caused pneumothorax. She developed acute respiratory distress requiring drainage by a chest tube inserted into the pleural cavity and ventilation. After 1.5 months stay in intensive care unit, she was transferred to a rehabilitation unit and progressively improved, leading to almost complete clinical recovery. Five months after her accident, she was able to return home with only minor fluctuating dyspnoea. However, taking into account this complication, the spontaneous reduction in pain level during this episode and the age of the patient (80 years old), it was decided not to use the stimulator. This was the only serious adverse event. No haemorrhage, infection or neurological complications occurred in this series of patients.

### Group and individual results

The evolution of the mean clinical scores (VAS, BPI, MPQ-PRI, MPQ-ratio, SIP and MQS) in the 12 patients who completed the open study is presented in Fig. 2. Only the VAS and SIP scores varied significantly in the follow up. Dunn's multiple comparison *post hoc* tests showed that the VAS and SIP scores were reduced at 6 or 9–12 months postoperative compared to the pre-operative baseline. In contrast, the various MPQ subscores did not vary over time.

Regarding the randomized crossover trial, only MPQ-PRI differed between the two conditions of stimulation (27.4 'on-stimulation' versus 33.6 'off-stimulation',  $P = 0.0166$ , Wilcoxon test) (Fig. 3). However, this difference did not persist after adjustment for multiple comparisons. Although the MPQ-ratio did not vary with the condition, the MPQ sensory subscore tended to decrease when MCS was switched 'on' (14.3 'on-stimulation'



**Figure 2** Evolution of the clinical scores (mean, SEM) from preoperative baseline to 1, 6 and 9–12 months postoperative. The first slope represents evolution in the first month postoperative. VAS=visual analogue scale; BPI=brief pain inventory; MPQ-PRI, MPQ-ratio=McGill pain questionnaire—pain rating index, ratio between affective and sensory subscores; SIP=sickness impact profile; MQS=medication quantification scale. *P* significance of the repeated measures ANOVA is presented in the upper right corner. Significance of Dunn's post-tests are presented for VAS and SIP scores, compared to baseline values (\**P*<0.05; \*\**P*<0.01; \*\*\**P*<0.001).

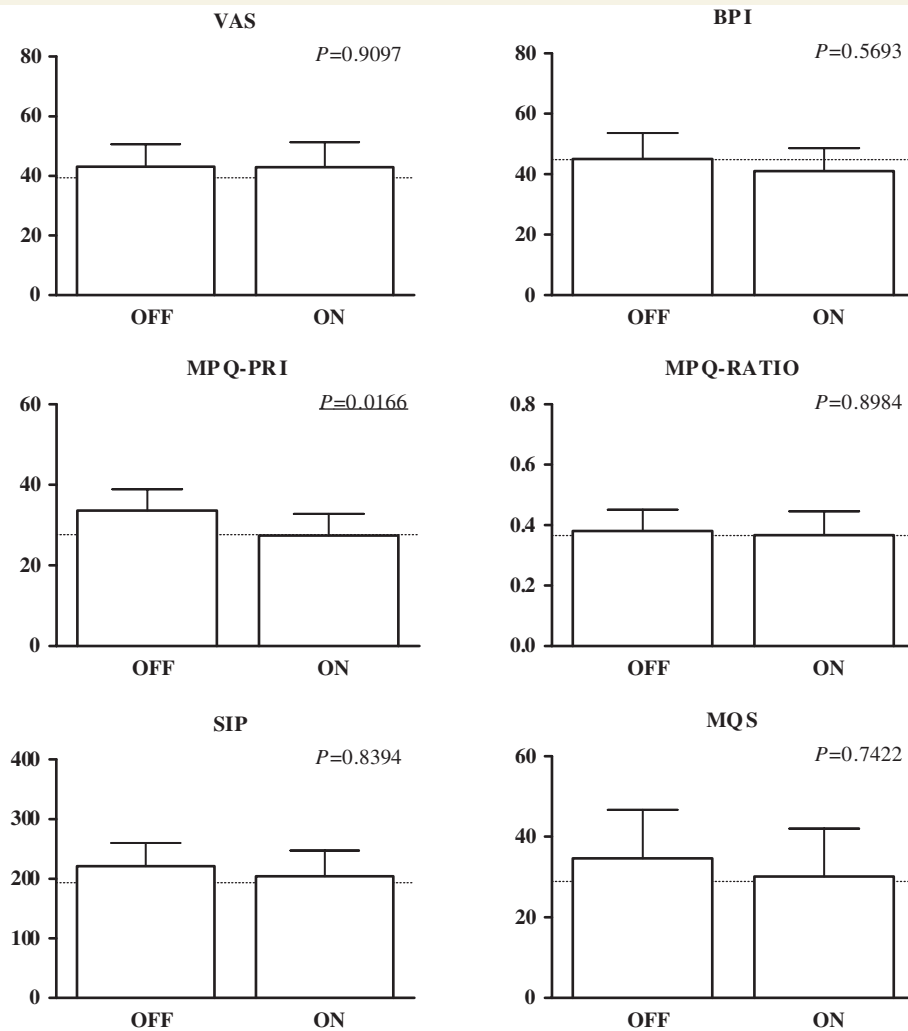
versus 17.8 'off-stimulation', *P*=0.01), whereas the MPQ affective subscore did not change (*P*=0.30) (Fig. 4).

At final examination, including the 12 patients who completed the study and the three stimulated patients in whom we obtained VAS scores at 12 months postoperative, the mean rate of pain relief on VAS scores was 48% (individual results ranging from 0 to 95%). Analgesic efficacy was considered good in five patients (33%), satisfactory in four patients (27%) and poor in six patients (40%). Good or satisfactory outcome was found in three of six patients with trigeminal pain (50%) and in five of seven patients with limb pain (71%). For patients with good results, the stimulator was switched 'on' at M1 in three patients and at M2 in two patients.

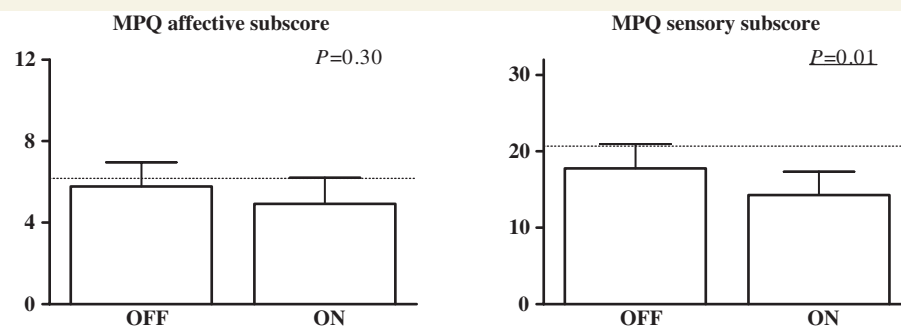
During the crossover trial, the mean MPQ-PRI decrease was 29% (individual results ranging from +60% to –100%). Seven

of the 13 patients who completed the crossover trial showed MPQ-PRI reduction greater than 30% between 'on-stimulation' and 'off-stimulation' conditions. The stimulator was switched 'on' at M1 in three of these patients and at M2 in four. Pain was located at the face (*n*=3), neck (*n*=1), upper limb (*n*=1) or lower limb (*n*=2). Among these seven patients, five showed good or satisfactory MCS efficacy at final examination compared to the preoperative baseline. Two patients who responded to MCS during the crossover trial remained poorly relieved at M12 (VAS score decreased by 10% and 31%). Conversely, two patients who did not respond to MCS during the crossover trial (MPQ-PRI reduced by 5% and 19%) were found to be greatly relieved at M12.

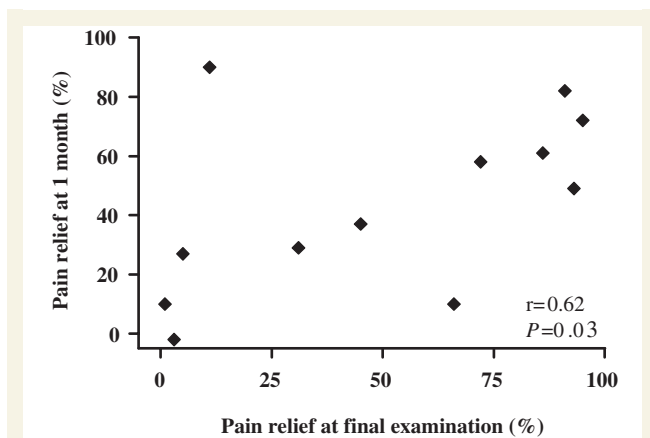
The reduction of VAS score between preoperative baseline and final examination did not vary with pain location (35% facial pain



**Figure 3** Clinical scores (mean, SEM) in 'on-stimulation' and 'off-stimulation' conditions during the crossover trial performed between 1 and 3 months postoperative. The dotted horizontal line corresponds to the mean value at 1 month postoperative before the crossover trial. *P* significance of the Wilcoxon matched-pairs signed-ranks test is presented in the upper right corner. VAS = visual analogue scale; BPI = brief pain inventory; MPQ-PRI, MPQ-ratio = McGill pain questionnaire—pain rating index, ratio between affective and sensory subscores; SIP = sickness impact profile; MQS = medication quantification scale.



**Figure 4** Affective and sensory subscores (mean, SEM) of the McGill pain questionnaire (MPQ) in 'on-stimulation' and 'off-stimulation' conditions during the crossover trial performed between 1 and 3 months postoperative. The dotted horizontal line corresponds to the mean value at 1 month postoperative before the crossover trial. *P* significance of the Wilcoxon matched-pairs signed-ranks test is presented in the upper right corner.



**Figure 5** Correlation between pain relief on the VAS at final examination and at 1 month postoperative (Spearman test).

versus 49% upper limb pain,  $P=0.70$ , Mann–Whitney test) or the presence of sensori-motor deficit (37% sensori-motor deficit versus 57% no deficit,  $P=0.28$ ). Similarly, MPQ-PRI reduction in 'on-stimulation' compared with 'off-stimulation' condition during the crossover period did not vary with pain location (29% facial pain versus 10% upper limb pain,  $P=0.91$ ) or the presence of sensori-motor deficit (14% sensori-motor deficit versus 43% no deficit,  $P=0.45$ ).

Pain relief at final examination did not correlate with age, pain duration before surgery or preoperative baseline pain level ( $P=0.75$ , 0.98, 0.93, Spearman test), but with pain level at 1 month postoperative ( $P=0.03$ ) (Fig. 5). However, this correlation did not persist after adjustment for multiple testing. The reduction of MPQ-PRI in 'on-stimulation' condition during the crossover period did not correlate with age, pain duration before surgery, preoperative baseline or 1 month postoperative pain level ( $P=0.48$ , 0.68, 0.65 and 0.17).

## Discussion

In the literature, MCS efficacy in peripheral neuropathic pain was only appraised in case reports and a few patients included in open studies. The design of the present study was complex, part of it was a randomized crossover trial and part was an open study.

In the crossover trial, a significant difference between 'on-stimulation' and 'off-stimulation' conditions was only found for the MPQ-PRI before correction for multiple testing, and not for the VAS score, which was the main outcome. The results of the crossover phase appeared to be negative, and the main reason might be a mixture of carry-over and ceiling effects. The crossover trial took place 1 month after implantation, while there was already an improvement in pain (see VAS score evolution in Fig. 2), although this was not significant in *post hoc* tests. It is likely that such improvement resulted from the cumulative after-effects of the surgical intervention (general anaesthesia and intra-operative cortical stimulations) and of the MCS tests performed during the first week after surgery. Although the stimulator was turned 'off' for about 3 weeks before the crossover period,

carry-over effects could be expected because MCS applied for even a couple of days could induce long-lasting effects up to several weeks. Given the carry-over effect, a ceiling effect might have occurred, therefore preventing further improvement in this population and thus explaining the lack of difference between the conditions in most of the clinical scores. This is an important limitation of this controlled study.

In the open evaluation in the long term (1 year after implantation), MCS was found to produce good or satisfactory pain relief in 60% of implanted patients. This rate of MCS responders is in the average of previous reports when neuropathic pain syndromes of various origins are pooled: a recent meta-analysis showed that the mean responder rate was 64% (95% CI, 58.7–69.2) (Lima and Fregni, 2008). Regarding patients with peripheral neuropathic pain, MCS responder rate was 73–77% in cases of trigeminal pain and 52% in cases of limb pain (Lazorthes *et al.*, 2007; Saitoh and Yoshimine, 2007). Conversely, we found 50% of responders in patients with trigeminal pain and 71% of responders in patients with limb pain. Because these results were obtained in an open design, we could not rule out a placebo response. However, only two patients who benefited from MCS in the long term did not show more than 30% reduction of MPQ-PRI in the 'on-stimulation' phase of the crossover trial. In addition, we did not notice any loss of benefits over time, but rather a progressive improvement in terms of pain level and functional capacities. The reduction in VAS score was more marked at 9–12 months than at 6 months postoperative, while the decrease in SIP score only became significant at final examination. These observations were in favour of a real analgesic effect and not a placebo effect of MCS in peripheral neuropathic pain.

The concomitant VAS and SIP score reduction showed that MCS was able to reduce both the intensity of chronic pain and its impact on everyday activities. Most of previous MCS studies assessed outcome only in terms of pain intensity changes. Changes in VAS scores are useful to monitor the effectiveness of therapy but insufficient for determining its benefit with regard to functional capacity or quality of life. We attempted to address this issue by including SIP as functional assessment scale.

Another important issue was to determine what aspects of pain MCS exerted its action on. Imaging studies showed that MCS could activate neural structures involved in either the emotional appraisal of pain (perigenual cingulate and orbitofrontal cortical areas) or the discriminative perception of pain intensity (brainstem or spinal relays) (review in Garcia-Larrea and Peyron, 2007). In the present study, the MPQ-ratio (between affective and sensory subscores) tended to increase over time with MCS therapy, but not at a significant level. In addition, the MPQ sensory subscore tended to decrease when MCS was switched 'on' during the crossover trial. From these observations, a preferential action of MCS on the sensory-discriminative aspect of pain could be hypothesized. This was in line with previous studies showing that MCS was able to reduce first-perception sensory thresholds, allowing patients with sensory deficit to regain discriminative sensation in the painful zone (Drouot *et al.*, 2002; Brown and Pilitsis, 2005). Conversely, we found a reduction of the MPQ-ratio induced by MCS in two series of patients: the first one including neuropathic pain syndromes of various origins (Nguyen *et al.*, 2008) and the other



one only including patients with post-stroke pain (unpublished data). Such a result suggested preferential effect on the affective-emotional component of pain in post-stroke pain. Nevertheless, it is too early to conclude that the mechanisms of action of MCS may vary with the origin of pain.

Finally, we wondered whether some factors could be associated with MCS outcome. As previously observed (Nuti *et al.*, 2005), we found that the level of pain relief at the end of the first month following implantation tended to correlate with the efficacy of MCS at 1 year postoperative. The fact that pain scores were reduced 1 month after implantation, while the stimulator was not yet permanently switched 'on', may be surprising. As previously mentioned, pain relief at M1 postoperative could be explained by the combination of prolonged after-effects produced by the anaesthetic drugs used during the surgical procedure, by the numerous stimulations delivered to the motor cortex to perform intra-operative MEP mapping and by the MCS trials performed during the first week postoperative to determine the optimal parameters for chronic stimulation.

We did not find other factors associated with clinical outcome, including the interval between pain onset and surgery, the age of the patients, the preoperative pain scores or the presence or absence of sensori-motor deficit in the painful area. However, considering the small number of patients, correlation analyses were underpowered, and no firm conclusions could be drawn from the present results regarding predictive factors of MCS efficacy.

It was proposed that MCS could be effective in a variety of intractable pain conditions (Nguyen *et al.*, 2003; Lazorthes *et al.*, 2007; Saitoh and Yoshimine, 2007). This study confirmed that MCS could be effective in chronic, refractory peripheral neuropathic pain, including trigeminal neuropathic pain, which was already known to be one of the best indications for MCS therapy (Meyerson *et al.*, 1993; Cruccu *et al.*, 2007). In fact, the reduction of VAS score at final examination was not greater in patients with facial than upper limb pain. This suggests that MCS indication could be extended to a variety of neuropathic pain syndromes related to peripheral nervous system lesion. However, these results remain to be reproduced in larger series, comparing the rate of MCS efficacy on various scales in patients with either peripheral or central neuropathic pain syndromes.

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