BRAIN
CLINICAL TRIAL

Motor cortex stimulation for chronic neuropathic pain: results of a double-blind randomized study

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Motor cortex stimulation via surgically implanted electrodes has been used as an off-label treatment for chronic neuropathic pain, but its efficacy has not been fully established. We aimed to objectively study the efficacy of motor cortex stimulation and characterize potential predictors of response.

In this randomized, double-blind, sham-controlled, single centre trial, we recruited 18 patients with chronic neuropathic pain who did not adequately respond to conventional treatment and had a numerical pain rating scale (NRS) score ⩾6. Patients were initially assigned to receive 3 months of active ('on') or sham ('off') stimulation in a double-blind cross-over phase. This was followed by a 3-month single-blind phase, and 6 months of open-label follow-up. A meaningful response in our trial was defined as a ⩾30% or 2-point reduction in NRS scores during active stimulation.

Using Bayesian statistics, we found a 41.4% probability of response towards on versus off motor cortex stimulation. The probability of improvement during active stimulation (double-blind, single-blind and open-label phases) compared to baseline was 47.2–68.5%. Thirty nine per cent of the patients were considered long-term responders, 71.4% of whom had facial pain, phantom limb pain or complex regional pain syndrome. In contrast, 72.7% of non-responders had either post-stroke pain or pain associated with brachial plexus avulsion. Thirty-nine per cent of patients had a substantial postoperative analgesic effect after electrode insertion in the absence of stimulation. Individuals with diagnoses associated with a good postoperative outcome or those who developed an insertional effect had a near 100% probability of response to motor cortex stimulation.

In summary, we found that ∼40% of patients responded to motor cortex stimulation, particularly those who developed an insertional effect or had specific clinical conditions that seemed to predict an appropriate postoperative response.

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Abbreviations: CRPS = complex regional pain syndrome; DBS = deep brain stimulation; MCS = motor cortex stimulation; NRS = numerical pain rating scale; TMS = transcranial magnetic stimulation

Introduction

Motor cortex stimulation (MCS) is an invasive neuromodulation technique that has been offered in many centres as a therapeutic alternative to patients with medically refractory chronic neuropathic pain. Despite being used for almost three decades, the effectiveness of MCS remains unclear.[1] A recent review investigating the outcome of MCS for chronic neuropathic pain reported that ~60% of patients had a good postoperative response.[2] To date, only a few clinical trials including double-blind assessments have been published.[3–5] Studies comparing numerical pain rating scale (NRS) scores during active versus sham treatment[3] or high versus low stimulation (longer 'on' versus 'off' stimulation cycling)[4] found no differences in clinical response. In contrast, a significant analgesic effect of MCS has been reported when stimulation was activated at different intervals.[5]

A major problem in the field of brain neuromodulation for pain is the lack of predictors of a positive outcome. Previously hypothesized factors include an early analgesic effect, clinical diagnosis, the development of an analgesic effect after the insertion of electrodes and electrophysiological responses.[6–9]

We aimed to objectively study the efficacy of MCS and characterize potential predictors of response in a prospective, double-blind, randomized, cross-over trial.

Materials and methods

This single centre trial was approved by the Research Ethics Board of the Hospital das Clínicas, University of São Paulo, Brazil and registered in clinicaltrials.gov (NCT01554332). Written informed consent was obtained from all patients. Enrolment occurred between January 2012 and December 2014. Patients with chronic neuropathic pain were referred by neurologists, neurosurgeons, physiatrists and anaesthetists of the Pain Centre of the Hospital das Clínicas, University of São Paulo.

Inclusion and exclusion criteria

Inclusion criteria were as follows: (i) males and females aged 21–70 years; (ii) able to provide informed consent; (iii) diagnosis of chronic neuropathic pain according to the current International Association for the Study of Pain (IASP) criteria and a positive Douleur Neuropathique 4 (DN4) scale score $\geqslant 4$[10]; (iv) documented pain for at least 12 months; (v) previous or current treatment with neuropathic pain medications from at least two of the following groups at adequate doses: antidepressants, anticonvulsants and/or gabapentinoids; (vii) NRS score $\geqslant 6$ at baseline; (vii) clinical diagnosis of neuropathic pain associated with one of the following conditions: facial pain, post-stroke pain, brachial plexus avulsion, complex regional pain syndrome (CRPS) or phantom limb pain of the upper extremities; (viii) in the group with post-stroke pain, only patients with predominant face and upper extremity symptoms were included ($\geqslant$30% or $\geqslant$2 NRS points between these regions and the lower extremity); (ix) no change in the current neuropathic pain medication regimen for at least 4 weeks before study enrolment; (x) able to comply with all testing and follow-up requirements; and (xi) determined medically stable to undergo the surgical procedure.

Exclusion criteria were as follows: (i) alcohol, medication or illegal substance dependence or abuse within last 12 months; (ii) trigeminal neuralgia; (iii) post-stroke pain predominantly in the lower extremity; (iv) clinical conditions that could render anaesthesia and surgery unsafe; (v) clinically relevant abnormality (e.g. tumour) on brain imaging, previous intracranial surgery; (vi) cardiac pacemaker/defibrillator or other implanted stimulators; (vii) conditions requiring repetitive MRI body scans, chemotherapy, immunosuppressive, steroid therapy or fibromyalgia; (viii) unable to comply with the study visit schedule and timeline; (ix) a female lactating or of child bearing potential with a positive pregnancy test or not using adequate contraception; (x) history of seizures or epilepsy; (xi) chronic infection; (xii) plans to use diathermy; and (xiii) currently participating in another investigational device, drug or surgical trial.

Baseline evaluations and surgical procedure

Forty-seven patents were screened. Nine did not fulfil inclusion criteria while 20 did not agree to participate in the trial. Eighteen patients were included (Supplementary Fig. 1). After signing the consent form, NRS, Neuropathic Pain Symptom Inventory (NPSI) and Brief Pain Inventory index (BPIi) scores were collected, followed by brain MRI. Within 2 weeks, patients underwent a trial of repetitive transcranial magnetic stimulation (TMS) to test whether this therapy could predict MCS response. TMS was delivered with a MagPROX100 device (Magventure Tonika Elektronic) using a figure-of-eight coil (10 Hz, 90% of rest motor threshold, postero-anterior direction, 3000 pulses) targeting the M1 region contralateral to the pain. The trial consisted of one active and one sham TMS session delivered in a double-blind fashion 15 days apart. NRS scores were recorded 1 day following each session. Surgery was conducted ~4 weeks later. Before the procedure, pre-MCS NRS scores were registered and considered as the trial baseline. These values (8.3 ± 0.3; average $\pm$ standard error) were similar to those recorded during initial screening (8.7 ± 0.3; t-test $P = 0.40$).

Surgery

Two paddle leads (Abbott; St Jude Medical model 3240) were implanted in the epidural space perpendicular to the motor strip, as previously described.[11] The centre of the craniotomy was placed

in the motor hand region, defined by MRI (omega sign) and TMS. During the operative procedure, stimulation was conducted while motor evoked potentials (MEPs) were recorded. Stimulation amplitude was defined at 80% of the MEP. The most frequently selected pulse width was 90 μs. A fixed 50 Hz frequency was chosen, as this is the most commonly reported value in the literature.[2] Contact(s) that induced MEPs at the lowest threshold were used as cathodes. Contacts closer to the postcentral gyrus in the implanted electrode arrays were used as anodes. After the procedure, electrodes were externalized for testing and a computed tomography was obtained to confirm electrode placement. At this point, a brief stimulation session was conducted to confirm that the selected stimulation amplitude was not associated with adverse events. The implantable pulse generator (IPG; Abbott; St Jude Medical Genesis model 3608) was implanted 3–5 days later in the infraclavicular region. Patients returned to the clinic ~2 weeks after surgery for the evaluation of pain scores. The MEP threshold to define the stimulation amplitude was reconfirmed. During pre-randomization testing, one patient developed a tonic-clonic seizure and required a decrease in amplitude. At the selected thresholds, no patient could identify whether stimulation was on or off. Testing to define stimulation thresholds was conducted before each stimulation phase of the trial (double-blind; single-blind; open label).

Randomization and study design

Randomization was conducted in the postoperative period, either when patients reached a pain threshold ⩾80% of baseline or after 1 month. Two individuals with the same diagnosis (e.g. post-stroke pain, facial pain, phantom limb, plexus avulsion, CRPS) were recruited together and randomized in pairs to avoid the overrepresentation of a single condition in groups initially receiving active or sham stimulation. When an odd number of individuals was recruited per condition, the last patient was paired with that of a condition also presenting an odd number of patients. For allocation concealment, sealed envelopes containing the order of the double-blind segments (active/placebo or placebo/active) were randomly assigned for each patient in the pair. These were opened immediately before the initiation of the blind phase by a third party not involved in patient care, who was the only party responsible for adjusting the stimulation settings. Neither investigators nor patients were aware of the order of the blind segments.

The study consisted of blind and open-label phases (Fig. 1). The blind phase comprised three segments. In the first two segments (double-blind cross-over) patients were assigned to receive active (on) or sham (off) stimulation for 3 months. Thereafter, they underwent a 4-week washout, followed by the inverse treatment for an additional 3 months. The last segment of the blind assessments comprised a 3-month single-blind phase in which all patients received MCS without awareness. By comparing the obtained values with those recorded during the open-label phase, we expected to characterize whether knowledge that the systems were on could influence surgical outcome. During the consent process, we told patients 2-fold: (i) that they could receive either active or sham stimulation during any of the three blind segments; and (ii) that they would receive stimulation during at least one of the segments. After all blind assessments, patients were followed for another 6 months during an open-label phase. Patients were evaluated with NRS, NPSI and BPIi scales at the end of each segment. Medications were not changed during the blind phase. If/when necessary, tramadol was used as rescue for no longer than 1 week. During the open-label phase, medication changes were authorized. As patients had previously tried several regimens without success, those who did not respond to MCS opted to explore changes in stimulation settings and additional physiotherapy.

Statistical analyses

We initially designed a trial to detect significant NRS score changes between on/off blind cross-over assessments. Based on literature data, we estimated that 40 patients would have been required to detect a ⩾30% or 2-point reduction during active stimulation with an 80% power. However, a pre-planned interim analysis performed after the inclusion of approximately half of the target sample showed that over 350 participants would have been necessary to reach this end point. Bayesian multilevel models were used to assess the probability of an MCS effect (⩾30% or 2-point reduction). We have selected this approach as it would be suited for the number of patients enrolled, while accounting for the longitudinal follow-up, the interventions and blinding associated with each of the trial phases. This is because, in contrast to single-level regression, Bayesian models allow the evaluation of expected correlations among measurements of the same individual and individuals in the same group and still account for the dependency of observations.[12] In addition, Bayesian multilevel modelling is particularly well suited to handle multiple comparisons.[13] Using weakly informative priors, we set all models *a priori* and based them on clinical assumptions.[13] In our study, Bayesian estimates were implemented using the R statistical language with the rstanarm package- stan package.[14] Our modelling strategy used the Markov chain Monte Carlo repeated four times (i.e. four chains) with 1000 warm-up iterations followed by 3000 posterior sampling iterations per chain.

We interpreted model results as a point estimate representing the magnitude of each treatment effect (i.e. regression coefficient) and an interval estimate for precision. The point estimate was a median of the posterior distribution for each treatment effect. We used 95% credible intervals (CrI) to represent the posterior distribution of each treatment effect. Each interval estimate consists of the range of the most credible values for the magnitude of the treatment effect considering our data, model, the amount of variability in the random effect, and the sampling error. The spread of the posterior distribution indicated the uncertainty of the estimate.

Considering that our study included a cross-over phase, we also evaluated carry-over and period effects. The former was calculated as the sum of outcome values after treatment in period one and period two (periods one plus two). The period effect attempts to identify whether there is a change over time for any reason besides treatment. It was calculated as the difference between the outcome values after treatment in periods two and one (period two minus period one). We evaluated cross-over and period effects through the Bayes factor computed via a Gaussian quadrature. Results when NRS was taken into account suggest that the probability of no carry-over was more than twice as high as that of a carry-over effect (1.35; 95% CrI –3.17 to 643; Bayes factor 0.49). Similarly, the probability of no period effect was more than two times higher than that of a period effect (–0.262; 95% CrI –2.6, 1.76; Bayes factor 0.43). Based on these data, we have grouped on and off MCS data irrespective of randomization sequence.

Finally, we performed subgroup analyses by testing the same association between our intervention and outcomes within specific subgroups of our sample. These subgroups consisted of patients who presented an insertional effect and those who had diagnoses associated with a 'good' (facial pain, CRPS, phantom limb) or 'poor' clinical response (post-stroke, brachial plexus avulsion). We used the same methods previously applied to the whole population to evaluate pain outcomes within each subgroup.

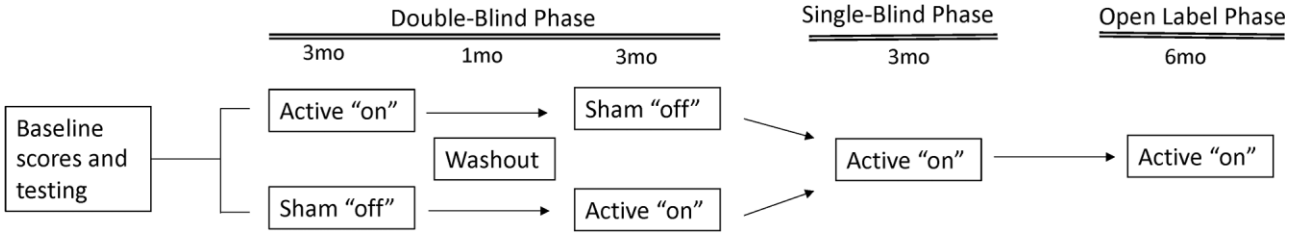

Figure 1 Study timeline. After preoperative evaluations, patients were implanted with MCS systems and randomized to initially receive active or sham stimulation. The blinded phase of the trial was composed of three segments. In the first two segments (double-blind cross-over) patients were assigned to receive active (MCS 'on') or sham (MCS 'off') treatment for 3 months. This was followed by a 4-week washout phase and the inverse treatment for an additional 3 months. Thereafter, patients underwent a 3-month single-blind phase, followed by 6 months of open-label follow-up.

In addition to Bayesian models, comparison of percentages was done using Fisher's exact test. Association between variables was measured with the Pearson correlation coefficient. Unless otherwise specified, data in the text and tables are presented as mean ± standard error. Percentage improvement compared to baseline was calculated as (1 – scores/baseline scores) × 100. Long-term responders were patients who had ⩾30% or 2-point reduction in NRS scores in all active phases of the trial compared to baseline.

Data availability

The data that support the findings of this study may be available at the discretion of the corresponding author, on reasonable request.

Results

Demographics may be found in Table 1. Stimulation settings during the different phases of the trial are provided in Supplementary Table 1. The average amplitude was 7.9 ± 0.6 mA in the on stimulation phase, 8.6 ± 0.7 mA in the single-blind phase and 9.3 ± 0.7 mA in the open-label phase.

Numerical pain rating scale

Using Bayesian statistics, we found a 41.4% probability of active MCS reducing NRS scores by ⩾2 points compared to sham stimulation (–1.7; 95% CrI –4.5 to 1.23). The probability of active MCS reducing NRS scores by >0 points compared to sham stimulation was 88.6% (–1.7; 95% CrI –4.5, to 1.23) (Fig. 2).

The reduction in NRS scores compared to baseline when all patients were considered was 17.2% for the sham stimulation phase, 27.8% for the active double-blind phase, 29.8% for the single-blind phase and 31.8% for the open-label phase (Fig. 3A). The probability of NRS scores being 2 points lower than baseline was found to be of 47.2% for the active double-blind phase (–2.0; 95% CrI –3.8 to –0.3), 57.6% for the single-blind phase (–2.1; 95% CI –3.7 to –0.4) and 68.5% for the open-label phase (–2.4; 95% CrI –3.9 to –1.0). In contrast, the probability of NRS scores being 2 points lower than baseline in the sham double-blind phase was only 12.3% (–1.1; 95% CrI –2.5 to 0.1) (Fig. 3B).

Responders versus non-responders

In our trial, seven patients (39%) were considered to be long-term responders. In these patients, the reduction in NRS scores compared to baseline was 40.7% during sham stimulation, 57.6% in the active double-blind phase, 67.8% in the single-blind phase and 64.4% in the open-label phase (Fig. 3C). Eleven patients were deemed to be non-responders (61%). In this subpopulation, NRS reduction when these same phases were compared to baseline was 2.2%, 8.7%, 5.4% and 10.9%, respectively (Fig. 3D). Non-responders did not deteriorate after the procedure.

Neuropathic Pain Symptom Inventory and Brief Pain Inventory index

Reduction in NPSI scores compared to baseline when all patients were considered was 28.4% during sham stimulation, 43.9% in the active double-blind phase, 31.6% in the single-blind phase and 40.5% in the open-label phase (Supplementary Fig. 2A). The probability of MCS reducing NPSI scores by ⩾10 points lower than baseline was found to be 68.8% during sham stimulation (–13.7; 95% CrI –30.1 to 2.21), 93.4% in the active double-blind phase (–23; 95% CrI –40.6 to –5.7), 74.4% in the single-blind phase (–15.8; 95% CrI –32 to 0.64) and 91.5% in the open-label phase (–21.4; 95% CrI –38.3 to –4.56) (Supplementary Fig. 2B).

Reduction in BPIi scores compared to baseline when all patients were considered was 12.9% for the sham phase, 23.6% for the active double-blind phase, 30.0% for the single-blind phase and 27.9% for the open-label phase (Supplementary Fig. 2C). The probability of MCS reducing BPIi scores by ⩾2 points compared to baseline was found to be of only 12.1% during sham stimulation (–1.15; 95% CrI –2.48 to 0.23), 46.8% in the active double-blind phase (–1.94; 95% CrI –3.65 to –0.33), 56.9% in the single-blind phase (–2.13; 95% CrI –3.37 to –0.58) and 68.7% in the open-label phase (–2.35; 95% CrI –3.84 to –0.87) (Supplementary Fig. 2D).

Prognostic factors

With 18 patients included in the trial, we chose to study three factors deemed to be important for the analgesic effects of MCS rather than to conduct a multifactorial analysis. These were (i) clinical diagnosis; (ii) the effect of electrode insertion; and (iii) the preoperative use of TMS. Diagnoses associated with a good postoperative outcome in previous trials were facial pain, CRPS and phantom limb pain.[2,7] Forecasting a poor prognosis were pain due to brachial plexus avulsion and stroke.[2,7]

Response according to clinical diagnosis

Of the seven responders, five (71.4%) had diagnoses associated with a good clinical response (two facial pain, two CRPS, one phantom limb). Two patients (28.6%) had post-stroke or brachial plexus pain (Fig. 4). In contrast, 8 of 11 non-responders (72.7%) had conditions associated with a poor outcome (three post-stroke pain and five with brachial plexus injury pain). Three patients (27.3%) had facial pain ($n = 1$) or phantom limb pain ($n = 2$). Despite these striking differences, results were not found to be significant ($P = 0.15$). The two CRPS patients included in our trial were type II. Of the three facial pain patients, responders had atypical facial pain

Table 1 Demographics

Patient	Sex	Diagnosis	Age (years)	Pain duration (months)	Pain intensity (NRS)	Pain location	Medications	Additional treatments
1	Male	Post-stroke	61	118	7	UE/Face	AD, AC, GP	Phys, ACP
2	Male	Post-stroke	61	71	7	UE/Face	AD, AC, GP	ACP
3	Male	Post-stroke	71	215	6	UE	AD, AC, GP	ACP
4	Female	Post-stroke	49	71	8	UE	AD, AC, GP	Phys, ACP
5	Male	Facial pain	55	31	10	Face	AD, AC, GP	–
6	Male	Facial pain	37	22	9	Face	AD, AC, GP	Phys
7	Male	Br plexus	33	27	9	Hand	AD, AC, GP	ACP, Surg
8	Male	Br plexus	25	21	8	Hand	AD, AC, GP	Phys, Surg
9	Male	Pht limb	57	109	9	Hand	AD, AC, GP	ACP
10	Female	Pht limb	40	52	8	Hand	AD, AC, GP	Phys, ACP
11	Male	Br plexus	51	17	9	Hand	AD, AC, GP	Phys
12	Male	Br plexus	47	161	7	UE	AD, AC, GP	Phys, Surg
13	Male	Br plexus	60	200	10	Hand	AD, AC, GP	Phys
14	Male	Br plexus	37	36	10	UE	AD, AC, GP	Phys, ACP
15	Male	CRPS	47	41	8	UE	AD, AC, GP	Phys, ACP
16	Female	CRPS	38	42	10	UE	AD, AC, GP	Phys, ACP
17	Female	Facial pain	65	128	9	Face	AD, AC, GP	Phys, ACP
18	Male	Pht limb	58	72	7	UE	AD, AC	Phys

AC = anti-convulsants; ACP = acupuncture; AD = antidepressants; Br plexus = brachial plexus; CRPS = complex regional pain syndrome; GP = gabapentinoids; Pht limb = phantom limb; Phys = physiotherapy; Surg = surgery (neurolysis); UE = upper extremity

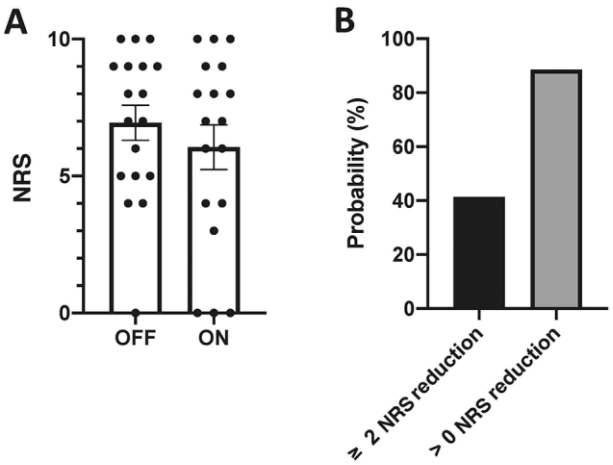

Figure 2 Active versus sham double-blind stimulation. (**A**) Average NRS scores, standard errors and individualized patient data (dots) during active versus sham double-blind evaluations. (**B**) Bayesian statistics revealed a 41.4% probability of active stimulation reducing NRS scores by ⩾2 points compared to sham treatment. The probability of active stimulation reducing NRS scores by >0 points compared to sham treatment was 88.6%.

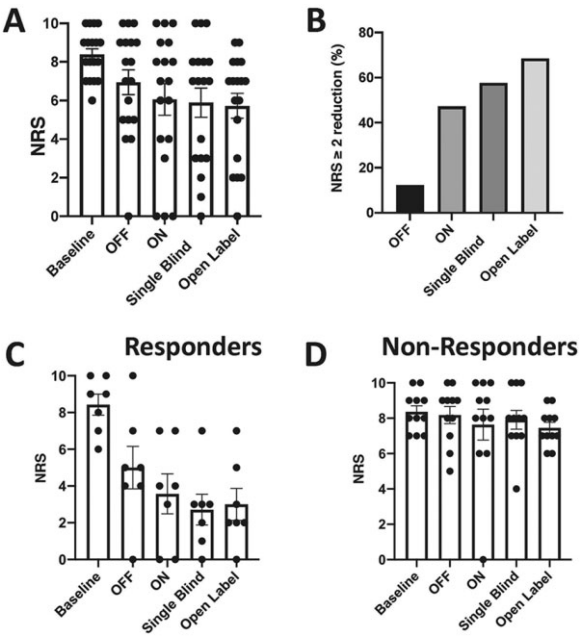

Figure 3 NRS scores during all phases of the trial in treatment responders and non-responders. (**A**) Average NRS, standard errors and individualized patient data (dots) during the double-blind, single-blind and open-label phases of the trial. (**B**) Bayesian statistics revealed that the probability of NRS scores being ⩾2 points lower than baseline was substantially higher during active stimulation (on' double-blind, single-blind and open label) compared to sham treatment. (**C**) Long-term responders in our trial were 39%. NRS scores in these patients were substantially lower than baseline values in all phases of the trial (40.7–67.8%). (**D**) In contrast, the per cent reduction in NRS scores in patients that did not respond to motor cortex stimulation was 2.2–10.9%.

($n = 1$) and trigeminal neuropathy ($n = 1$). The non-responder had trigeminal neuropathy.

Diagnoses associated with a good clinical response

In the eight patients with facial pain, CRPS or phantom limb pain, the reduction in NRS scores compared to baseline was 34.3% during sham stimulation, 51.4% in the active double-blind phase, 54.3% in the single-blind phase and 50% in the open-label phase (Fig. 4A). In these patients, the probability of NRS scores being ⩾2 points lower than baseline was found to be of almost 100% in all phases of the trial (sham stimulation 96.2%; –2.22; 95% CrI –4.57 to 0.45; active double-blind 98.8%; –3.57; 95% CrI –6.89 to –0.51; single-blind 99.8%; –4.11; 95% CrI –6.81 to –1.31; open label 99.7%; –3.72; 95% CrI –6.24 to –1.1) (Fig. 4D).

Diagnoses associated with a poor clinical response

In the 10 patients with post-stroke or brachial plexus injury pain, the reduction in NRS scores compared to baseline was 2.5% during

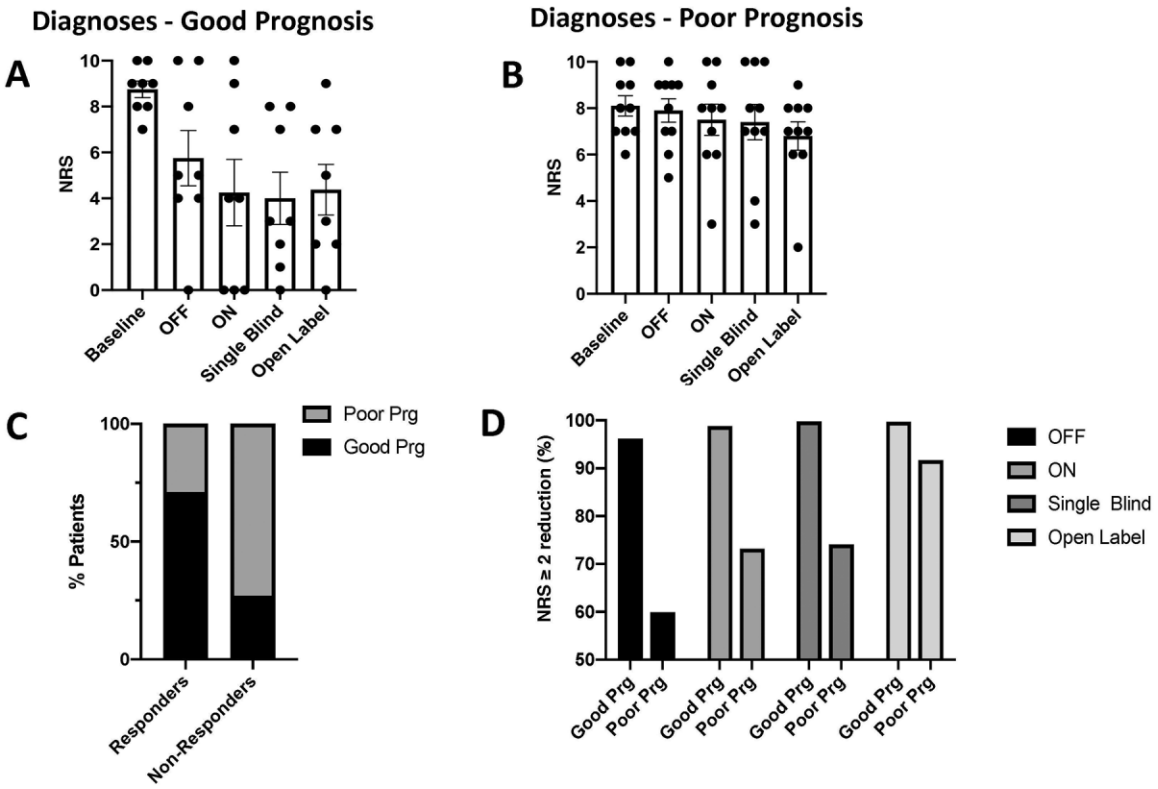

Figure 4 NRS scores according to diagnosis. Average NRS, standard errors, and individualized patient data (dots) in patients presenting clinical diagnoses associated with a (**A**) good (facial pain, complex regional pain syndrome, phantom limb) or (**B**) poor postoperative response (post-stroke, brachial plexus avulsion). (**C**) Percentage of responders and non-responders with conditions associated with a good or poor prognosis (Prg). (**D**) Bayesian statistics revealed that the probability of NRS scores being ⩾2 points lower than at baseline in patients with conditions associated with a good prognosis was near 100%. The probability of improvement in conditions forecasting a poor prognosis was found to be substantially lower.

sham stimulation, 7.4% in the active double-blind phase, 8.6% in the single-blind phase and 16.0% in the open-label phase (Fig. 4B). In these patients, the probability of NRS scores being ⩾2 points lower than baseline was found to be of a much smaller magnitude than values recorded in good prognostic conditions (sham stimulation 59.9%; –0.13; 95% CrI –1.25 to 1.09; active double-blind 73.9%; –0.39; 95% CrI –1.77 to 0.95; single-blind 74.1%; –0.46; 95% CrI –2.08 to 0.98; open label 91.7%; –0.91; 95% CrI –2.31 to 0.48) (Fig. 4D).

Insertional effect

Improvements in pain scores after the insertion of electrodes have been described with the use of multiple therapeutic approaches.[3,6] In our series, we found that 1 week after surgery a reduction in NRS scores >50% was noted in seven patients (39%). This was still observed 1 month after the procedure (i.e. when randomization took place) in four patients (22%). Interestingly, six of seven long-term responders (86%) but only 1 of 11 non-responders (9%) presented an insertional effect. One responder (14%) and 10 non-responders (91%) did not develop such a response ($P = 0.0025$; Fig. 5).

In the seven patients who had an insertional effect, reduction in NRS scores compared to baseline was 42.1% during sham stimulation, 68.4% in the active double-blind phase, 66.7% in the single-blind phase and 63.1% in the open-label phase (Fig. 5A). In these patients, the probability of NRS scores being ⩾2 points lower than at baseline was almost 100% in all phases of the trial (sham stimulation 97.3%; –2.58; 95% CrI –5.03 to 0.21; active double-blind 99.9%; –5.01; 95% CrI –7.54 to –1.76; single-blind 100%; –4.67; 95% CrI –7.07 to –2.14; open label 99.9%; –4.99; 95% CrI –7.37 to –2.5) (Fig. 5D).

In the 11 patients who did not have an insertional effect, reduction in NRS scores compared to baseline was only 2.1% during sham stimulation, 3.2% in the active double-blind phase, 7.4% in the single-blind phase and 12.8% in the open-label phase (Fig. 5B). In these patients, the probability of NRS scores being ⩾2 points lower than at baseline was 60.4% during the sham double-blind phase (–0.12; 95% CrI –1.01 to 0.88), 65.2% in the active double-blind phase (–0.18; 95% CrI –1.29 to 0.737), 79.1% in the single-blind phase (–0.43; 95% CrI –1.56 to 0.70) and 96.2% in the open-label phase (–0.83; 95% CrI –1.73 to 0.13) (Fig. 5D).

When the percentage of improvement after the insertion of electrodes was correlated with the percentage of improvement during the various phases of the trial, the following results were noted (Fig. 6A–D): Significant correlations between insertion and clinical improvement in the open-label phase ($r = 0.69$; $P = 0.002$), the single-blind phase ($r = 0.49$; $P = 0.04$) and a trend towards improvement in the active double-blind phase ($r = 0.41$; $P = 0.09$). In contrast, no correlation was found between electrode insertion and sham stimulation improvement ($r = –0.02$; $P = 0.92$).

Transcranial magnetic stimulation

No analgesic effects were found when NRS scores before and after active or sham TMS were compared (Supplementary Fig. 3). Moreover, not a single patient was found to respond to TMS (30% or ⩾2 points reduction in NRS scores when active versus sham TMS were compared). Post-TMS scores in patients who later responded or did not respond to TMS were found to be of the exact same magnitude, suggesting that a single preoperative TMS session does not predict MCS outcome.

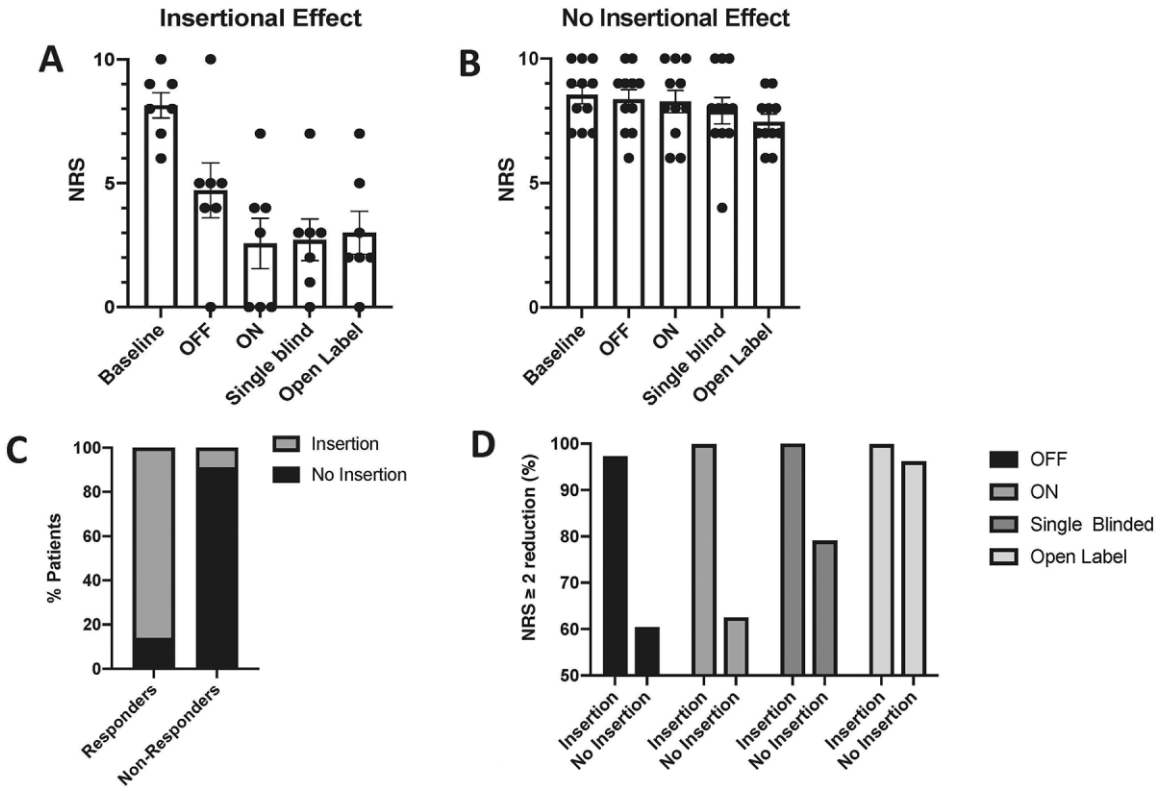

Figure 5 NRS scores following an insertional effect. Average NRS scores, standard errors and individualized patient data (dots) in patients who did (**A**) and did not (**B**) develop an insertional effect following electrode implantation. In the former group, a substantial 42.1–68.4% reduction in NRS scores was observed in all phases of the trial. In patients who did not develop an insertional effect, NRS decrease compared to baseline was in the order of 2.1–12.8%. (**C**) In patients who developed an insertional effect, 86% were treatment responders. This is in contrast to the 14% of responders observed in the group of patients who did not have an insertional effect. (**D**) Bayesian statistics revealed that the probability of NRS scores being $\geqslant 2$ points lower than baseline in patients that developed an insertional effect was near 100%. The probability of improvement in patients that did not have an insertional effect was found to be substantially lower.

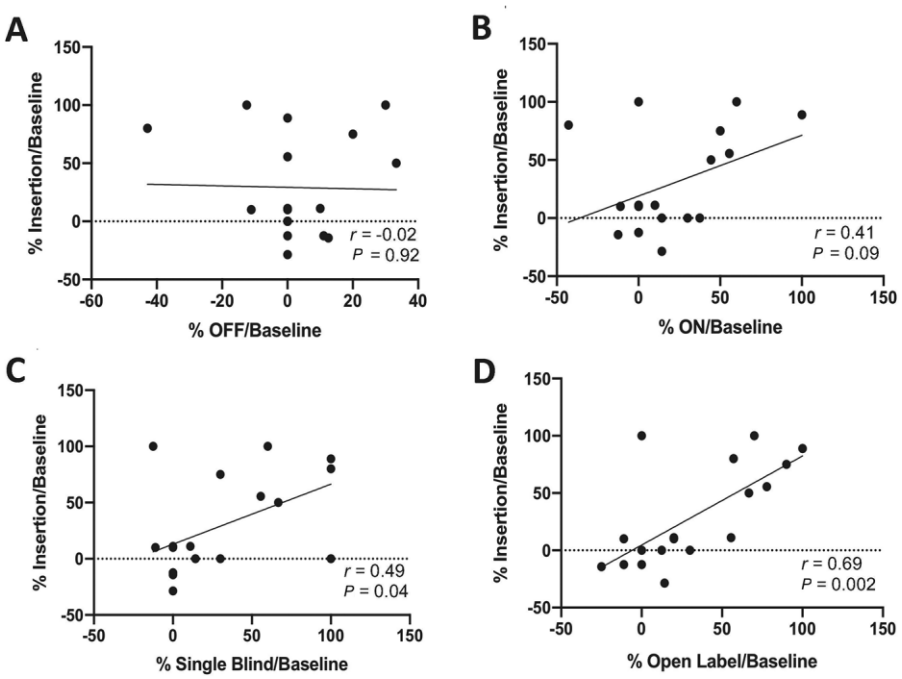

Figure 6 Correlation between insertional effect and clinical outcome. The following results were found when the percentage of improvement observed after electrode insertion was correlated with the percentage of improvement during the various phases of the trial relative to baseline: (**A**) no significant correlation with off stimulation scores; (**B**) a trend towards significant results with the on stimulation phase; and a significant correlation with (**C**) the single-blind, and (**D**) open-label phases.

Table 2 Side effects

Side effects	Phase of the trial	Number of patients
Infection requiring removal of the system	Open label	1
Pseudo-seizures	Open label	1
Isolated seizure during programming	Pre-randomization	1
Discomfort neck	Single-blind	6
Tethered extension	Open label	1
Incision hyperaemia	First segment of the double-blind phase ($n = 2$ on and $n = 1$ off stimulation)	3

Adverse effects

A summary of the adverse effects and phase of occurrence during the trial may be found in Table 2. As previously described, one patient experienced an isolated tonic-clonic seizure during the initial programming sessions. Another patient developed complex partial events characterized as pseudo-seizures with video-electroencephalography. One patient developed an infection during the open-label phase and required removal of the pulse generator along with antibiotics for 6 weeks. As no signs of infection were noticed at that point, the system was reimplanted. The patient resumed the trial from the phase it was stopped. Three patients presented hyperaemia in the infraclavicular incision and were treated conservatively with anti-inflammatories (1 week). Six patients complained of neck discomfort, being successfully treated with analgesics. One patient presented tethered extension cables during the open-label phase of the trial and needed to be revised.

Discussion

Although open-label studies have routinely reported on the analgesic effects of MCS,[1,2] results of blinded trials are far more difficult to interpret.[3–5] Comparisons between on versus off stimulation[3] or high versus low-settings[4] have been largely negative, whereas a delayed activation of MCS systems has shown positive therapeutic effects.[5] Confounders in some of those studies were the fact that patients initiated the trial right after surgical implantation, a lack of standardization of stimulation parameters and the exclusive inclusion of patients who responded to test stimulation. In the current trial, we addressed some of these issues by including all surgical candidates, extending the blinded arms to 3 months each, adding a washout phase in between arms, standardizing the frequency and pulse width according to settings commonly used in the literature, and delivering current at 80% of the motor threshold. In addition, as certain clinical diagnoses are known to forecast a poor surgical response,[1,2,7] patients were randomized in pairs so that one would be assigned to receive active and the other sham stimulation first. This would avoid the bias of having multiple patients with poor or good diagnoses randomized to the same arm in the beginning of the trial.

Because our study had multiple phases and included 18 patients, we have decided to use Bayesian rather than frequentist statistics. This was informative, as it provided the probability of observing a specific outcome for each group and phase of the trial. We found that the probability of MCS reducing NRS scores by $\geqslant 2$ points or by any amount compared to sham stimulation was 41.4 and 88.6%, respectively. When pain intensity scores recorded during active stimulation were compared to baseline, the probability of a meaningful improvement was in the order of 50–70%. This provides more informative values to clinicians that may quote these probabilities to patients who decide to undergo MCS. Also important in our study was the fact that a clinically relevant analgesic effect was observed in ~40% of the patients. This shows that only a subpopulation of chronic neuropathic pain patients responds to MCS and raise the important question of potential treatment biomarkers.

The first predictor of response investigated in our trial was the clinical diagnosis associated with the development of pain. Based on previous reports,[1,2,7] we have subdivided patients into those presenting clinical conditions associated with a good (facial pain, CRPS, phantom limb) or poor prognosis (post-stroke and brachial plexus pain). In addition to an ~50% analgesic effect, patients with favourable clinical diagnoses had a near 100% probability of a good therapeutic response following MCS. This is in contrast to the 7–16% reduction in NRS scores observed in patients with post-stroke and brachial plexus pain. Most trials so far have combined data from patients with multiple diagnoses. Based on our findings, novel studies may take this variable into account and consider recruiting only patients with clinical conditions associated with a good postoperative response. That said, we note that some of our post-stroke and brachial plexus patients did improve following MCS. Moreover, previous trials have shown a good postoperative outcome in patients with the former condition.[15–17]

The second predictor of response in our trial was the development of an insertional effect, which has been characterized as an improvement in clinical symptoms after electrode implantation in the absence of stimulation. This response has also been called microlesion effect following deep brain stimulation (DBS) electrode implantation in the field of movement disorders.[18] Although its relevance and mechanisms are still disputed, the insertion of brain electrodes in rodents induces an initial inflammatory response along with the focal release of glutamate and adenosine.[19–22] At long-term, electrode insertion in preclinical models has been shown to induce volumetric changes, hippocampal neurogenesis, alter circuit connectivity, metabolic activity and increase the diameter of vessels.[20,23–25] In addition to these neurochemical and plastic phenomena, rodents with implanted brain electrodes develop changes in memory performance, anxiety- and depressive-type responses.[22,26–29] In humans, the amelioration of clinical symptoms after electrode insertion has been clearly documented in patients with movement disorders,[18] epilepsy,[30] and depression.[31] In patients with chronic pain, electrode insertion has been suggested to predict the analgesic effects of DBS.[6] Although no study has formally reported an insertional effect after MCS for pain, NRS scores in a few clinical trials were substantially lower immediately after the procedure compared to those recorded at baseline.[3] In contrast to DBS, no anti-nociceptive effects have been documented following MCS electrode implantation in rodents.[32] Alternative mechanisms to explain the acute analgesic effects observed in our trial include the stimulation delivered during surgical mapping and early programming sessions. We find this to be unlikely, however, as brief stimulation pulses lasted for seconds/minutes whereas the reported clinical results of electrode insertion in our trial continued for several weeks. In our study, patients who developed an insertional effect had a 60–70% reduction in NRS scores during active stimulation, as well as a near 100% probability of a good therapeutic response. In addition, we found significant correlations between the improvement observed following electrode insertion and the analgesic effects of MCS during active, but not sham stimulation. Despite these intriguing results, the development of an insertional effect would be unsuited as a preoperative biomarker, since it is only documented after electrode placement. From a practical perspective, however, one could stage the

procedures and only implant pulse generators in patients who develop an insertional effect. Although the cranial step is the riskier part of the MCS operation, patients undergoing invasive neuromodulation may develop side effects related to extension cables (e.g. tethering, wire fractures) and pulse generators (e.g. infection). Not only these could be avoided, but the cost of the procedure would be decreased, since the generator is the priciest component of the system.

Although well documented in the DBS field, the concept of an insertional effect is sometimes questioned. An alternative explanation for this effect would be that of a placebo response. In patients with pain syndromes, placebo has been extensively documented after pharmacological, surgical and neuromodulation treatments.[1,33–36] Moreover, the magnitude of placebo responses increases with the invasiveness of the procedure.[37] In contrast to paraesthesia-generating neuromodulation therapies (e.g. DBS, some forms of spinal cord stimulation), MCS is not perceived by the patients, making it suitable to be investigated in on versus off blind stimulation trials. Based on our previous DBS study showing that the insertional effect predicted treatment response, we have decided to design an MCS trial with two blind comparisons. The first comprised a typical on/off MCS cross-over design in which patients received either active or sham stimulation followed by the inverse treatment. The second consisted of a single-blinded assessment during which patients received active stimulation without being aware. Patients were told before the study that they would be given either active or sham treatment during any of the three segments of the blind assessments (i.e. double- and single-blind arms). Our rationale was that, even in the presence of an insertional effect, we would be able to detect a placebo response. For example, in the absence of placebo one would expect the analgesic effects of both on double-blind and single-blind results to be similar and more striking than those recorded in the off stimulation phase. In addition, as awareness that the activation of the systems was the only difference between the open-label and single-blind assessments, a placebo response should have yielded a better outcome in the former. In our study, we found that (i) on double-blind and single-blind scores were equally lower than those observed when no stimulation was delivered; and (ii) NRS scores recorded in the single-blind and open-label phases were fairly similar. These results obviously do not rule out a placebo response but suggest that results obtained in our trial cannot be simply explained by this factor. In pharmacological trials, placebo responders have been shown to actively improve following therapeutic interventions. In fact, treatment effect in these patients is often lower than the combination of active and placebo responses.[38] In our trial, two methodological aspects helped to mitigate the influence of placebo responders. First, our cross-over design allowed the comparison of NRS scores in the same individuals during different phases of the study. Second, placebo responses occur less frequently in treatment-refractory patients, as demonstrated in pharmacological and non-pharmacological reports.[39]

Another aspect that deserves to be discussed is whether the insertional effect observed in our study can be solely attributed to placebo. In other words, patients who showed an insertional effect would be more prone to develop a placebo response. Following the rationale described above, we find this to be unlikely. In patients who developed an insertional effect, NRS scores during off stimulation were twice as high as those recorded during blind on and single-blinded stimulation. In addition, these patients presented no differences in NRS scores recorded in the single-blind and open-label phases of the trial. We acknowledge that our results cannot fully rule out the possibility of a placebo response partially driving the postoperative improvement observed in some patients. However, the occurrence of an insertional effect in multiple DBS applications, the fact that it seems to predict the analgesic effects of DBS in patients with chronic pain, and the reported neurochemical and behavioural effects of electrode insertion in several animal models highlight the biological nature of this event. Rather than fully dismissing this as a potential biomarker of treatment response, our results indicate that the effects of electrode insertion should be taken into account and studied in greater detail in future work.

As a final predictor in our study, we tested whether the delivery of TMS could indicate potential MCS responders. TMS protocols for the treatment of pain often consist of 1- or 2-week treatments.[40,41] As we did not want to extend our trial even further, we opted for two single sessions of active versus sham stimulation. This was based on work suggesting that single TMS sessions are associated with some degree of analgesia.[40] Our prediction was that active MCS would reduce, at least to some extent, NRS scores and this would correlate with MCS outcome. We found that single TMS session neither induced analgesia nor predicted MCS response. These data, however, do not rule out the potential predictive value of repeated TMS delivered in multiple sessions.

Our study contained a few caveats and design particularities that need to be discussed in detail. Although 18 patients were included, this is one of the largest blinded series published in the literature. With the NRS scores recorded during active versus sham double-blind stimulation, hundreds of patients would have been necessary for a significant difference to be detected. This suggests that standard on/off comparisons may not be suited for the study of the analgesic effects of MCS. As almost 40% of patients were found to be treatment responders, different study designs need to be sought (e.g. the sole inclusion of patients with positive predictive factors). One possibility would be the use of alternative strategies, as recently proposed for DBS. In depression, for example, blinded studies comparing the effects of active versus sham stimulation were largely negative.[42,43] In patients receiving DBS at long-term, however, blinded treatment discontinuation was associated with a significant clinical deterioration only in responders.[44]

From a technical perspective, patients in our trial had the leads externalized before the implantation of pulse generators. While this is common practice for selecting stimulation settings and deciding whether patients will receive an IPG in many centres, we note that when all patients are to be implanted with the full system, surgery may be conducted in a single procedure. As electrodes in our trial were manipulated and largely tested during the first procedure and all patients had a similar interval between electrode and IPG implants, we find it unlikely that staging the procedure might have been associated with the development of either an insertional effect or a placebo response.

As a final remark, our trial focused mainly on outcome measures of pain. In a previous study,[7] we have shown that MCS significantly improved quality of life, with no correlation being observed between such measures and the recorded reductions in NRS scores. Further studies are necessary to better characterize MCS-induced improvements in quality of life and whether this is related to its analgesic effects.

In summary, MCS is an invasive neuromodulation technique and, as such, is associated with adverse events. We showed that ~40% of patients with chronic neuropathic pain have a clinically relevant improvement following the procedure. Our study also confirmed previous open-label data suggesting that patients with facial pain, CRPS and phantom limb pain may have a better response to MCS than those with pain associated with stroke and brachial plexus avulsion. Finally, we found that almost 40% of patients undergoing MCS had a substantial pain reduction for at least a few weeks after surgery in the absence of stimulation. While mechanisms for this effect remain elusive, patients who

developed an insertional effect had an almost 100% probability of responding to MCS. In light of the previously mentioned findings, our study, although not definitive, provides novel insight that may increase the likelihood of a successful outcome in future clinical trials.

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Competing interests

The authors report no competing interests.

Supplementary material

Supplementary material is available at *Brain* online.

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