

# Motor Cortex Stimulation for Neuropathic Pain: A Randomized Cross-over Trial

Julia A.E. Radic, Ian Beauprie, Paula Chiasson, Zelma H.T. Kiss,  
Robert M. Brownstone

**ABSTRACT: Background:** Chronic motor cortex stimulation (MCS) has been used to treat medically refractory neuropathic pain over the past 20 years. We investigated this procedure using a prospective multicentre randomized blinded crossover trial. **Methods:** Twelve subjects with three different neuropathic pain syndromes had placement of MCS systems after which they were randomized to receive low (“subtherapeutic”) or high (“therapeutic”) stimulation for 12 weeks, followed by a crossover to the other treatment group for 12 weeks. The primary outcome measure was the pain visual analogue scale (VAS). Secondary outcome measures included McGill Pain Questionnaire (MPQ), Beck Depression Inventory-II, medication log, work status, global impression of change, and SF-36 quality of life scale. **Results:** The trial was halted early due to lack of efficacy. One subject withdrew early due to protocol violation and five subjects withdrew early due to transient adverse events. Six subjects with upper extremity pain completed the study. There was no significant change in VAS with low or high stimulation and no significant improvement in any of the outcome measures from low to high stimulation. SF-36 role physical and mental health scores were worse with high compared to low stimulation ( $p = 0.024$ ,  $p = 0.005$ ). **Conclusions:** We failed to show that MCS is an effective treatment for refractory upper extremity neuropathic pain and suggest that previous studies may have been skewed by placebo effects, or ours by nocebo. We suggest that a healthy degree of skepticism is warranted when considering this invasive therapy for upper extremity pain syndromes.

**RÉSUMÉ: Stimulation du cortex moteur pour traiter la douleur neuropathique: une étude randomisée avec permutation. Contexte:** La stimulation chronique du cortex moteur (SCM) a été utilisée pour traiter la douleur neuropathique réfractaire au traitement médical au cours des 20 dernières années. Nous avons étudié cette technique au moyen d'un essai prospectif multicentrique randomisé à double insu avec permutation. **Méthode:** Un système de SCM a été mis en place chez douze sujets atteints de trois syndromes différents de douleur neuropathique. Ils ont été assignés au hasard au groupe recevant une stimulation faible (« sous-thérapeutique ») ou élevée (« thérapeutique ») pendant 12 semaines avec permutation des groupes et traitement pendant 12 semaines additionnelles. Le critère d'évaluation primaire était le résultat obtenu à l'échelle visuelle analogue (EVA). Les critères d'évaluation secondaires comprenaient le questionnaire McGill sur la douleur, l'Inventaire de dépression de Beck II, un journal de la médication, la situation d'emploi, l'impression globale de changement et l'échelle SF-36 de qualité de vie. **Résultats:** L'étude a été interrompue précocement en raison du manque d'efficacité. Un sujet a été exclu tôt pour cause de non-respect du protocole et 5 sujets se sont retirés peu de temps après le début du traitement en raison d'effets indésirables passagers. Six sujets présentant de la douleur au niveau des membres supérieurs ont complété l'étude. Nous n'avons pas observé de changement significatif à l'EVA sous stimulation faible ou élevée et aucune amélioration significative dans les mesures de résultats de la stimulation, qu'elle soit faible ou élevée. Les scores pour les composantes de santé physique et mentale à l'échelle SF-36 étaient pires sous stimulation élevée que sous stimulation faible ( $p = 0,024$ ;  $p = 0,005$ ). **Conclusions:** Nous n'avons pas mis en évidence d'efficacité de la SCM comme traitement de la douleur neuropathique du membre supérieur réfractaire au traitement. Nous considérons que les études antérieures pourraient avoir été biaisées par des effets placebo ou que la nôtre l'a été par un effet nocebo. Nous suggérons qu'il convient de faire preuve de scepticisme à l'égard de ce traitement invasif des syndromes douloureux des membres supérieurs.

**Keywords:** Motor cortex stimulation, neuropathic pain

doi:10.1017/cjn.2015.292

Can J Neurol Sci. 2015; 42: 401-409

Although there are various neurosurgical treatments for pain<sup>1</sup>, few are effective for neuropathic pain syndromes affecting the face or upper extremity. The available treatments have proven generally unsatisfactory for central deafferentation pain including brachial plexus avulsion, phantom limb, or trigeminal neuropathic pain. Deep brain stimulation of the sensory thalamus or midbrain periaqueductal or periventricular gray<sup>2,3</sup>, peripheral nerve stimulation<sup>4,5</sup>, and spinal cord stimulation<sup>6</sup> have all been used, but long term success rates are poor<sup>7-9</sup>.

A possible role for the motor cortex in pain emanated from the work of Penfield and Jasper<sup>10</sup>, who found a lack of pain reduction

from primary sensory cortical resection, but relief following subsequent primary motor cortex resection<sup>11</sup>. Given that motor

From the Department of Surgery (Neurosurgery) (JR, PC, RB), Department of Anaesthesia (IB), Department of Medical Neuroscience (RB), Dalhousie University, Halifax, Nova Scotia, Sobell Department of Motor Neuroscience & Movement Disorders (RB), UCL Institute of Neurology, London, UK, Department of Clinical Neurosciences and Hotchkiss Brain Institute (ZK), University of Calgary, Calgary, Alberta, Canada.

RECEIVED JULY 23, 2014. FINAL REVISIONS SUBMITTED APRIL 27, 2015.

Correspondence to: Robert M. Brownstone, Sobell Department of Motor Neuroscience & Movement Disorders, UCL Institute of Neurology, Queen Square, London WC1N 3BG. Email: R.Brownstone@ucl.ac.uk

cortex resection is fraught with problems, little work proceeded in this area until the development of implantable brain stimulation technology. In the first report of the use of motor cortex stimulation (MCS) to treat central pain syndromes<sup>12</sup>, seven patients with thalamic pain syndrome were treated with MCS and all reported 'excellent' or 'good' early results and no adverse effects, with an 80% improvement in pain relief maintained for two years<sup>13</sup>. Thus the possibility that MCS could be useful for the treatment of neuropathic pain syndromes was born.

Several studies (mostly retrospective or open label prospective) have been published since, supporting MCS as an effective surgical intervention for central and neuropathic syndromes for which no other intervention has proven effective<sup>14-17</sup>. A review of the literature<sup>18</sup> showed that a good response to MCS (pain relief of >40-50%) was achieved for greater than one year in 9/18 patients with trigeminal neuropathic pain, and 12/23 patients with brachial plexus avulsion or phantom limb pain. However, studies examining MCS for pain control are limited by large variability in patient selection criteria, surgical protocols, stimulation parameters used, and a lack of blinding and controls<sup>19</sup>.

MCS is ideally suited for sham stimulation because patients are unable to perceive the stimulation. There are four previously published randomized crossover trials studying either continuous<sup>21,23</sup> or cycling<sup>20,22</sup> MCS. There were significant analgesic effects when MCS was switched 'on' compared to the 'off-stimulation' condition in three of these studies,<sup>20-22</sup> supporting MCS as a viable treatment. However, these studies included patients with diverse pain etiologies who first underwent a trial period of stimulation. This raises the possibility that there was either a carry-over effect of stimulation, or patients had learned to perceive – consciously or sub-consciously – when the stimulation was on, thus leading to a placebo effect. In the fourth trial, no differences in pain control were found during the crossover period, despite a reported mean rate of pain relief on pain visual analogue scale (VAS) scores of 48% and good or satisfactory results in 60% of the patients<sup>23</sup>. This again suggests that there was either a carry-over effect from an initial open label period, or a prominent placebo effect.

In order to mitigate the limitations of retrospective or open label series, we aimed to examine the effectiveness of cycling MCS in treating three groups of patients with refractory neuropathic pain using a prospective, randomized, blinded, crossover design. In order to eliminate possible carry-over effects, an open trial period was not used. We were unable to find benefit of MCS.

## METHODS

The study was approved by the Capital Health Research Ethics Board in Halifax, and by the University of Calgary Conjoint Health Research Ethics Board in Calgary, and was registered at [clinicaltrials.gov](http://clinicaltrials.gov) (NCT00462566).

All subjects who were referred for neurosurgical intervention to treat neuropathic pain at the Queen Elizabeth II Health Sciences Centre and at the Foothills Hospital from April, 2005 to September, 2010, were screened for admission into this study. Patients who continued their therapy have been followed since.

Inclusion criteria included: (1) a diagnosis in one of the following three categories: a) unilateral upper extremity neuropathic pain secondary to phantom limb pain, stump pain or brachial plexus avulsion, b) neuropathic deafferentation facial pain, or c) upper extremity complex regional pain syndrome

(CRPS); (2) pain refractory to conservative treatment (e.g. medications, regional blocks) as reviewed by a chronic pain physician and/or a multidisciplinary pain centre; (3) the patient was medically fit for neurosurgery; and (4) the patient was willing to provide informed consent.

Exclusion criteria included: (1) the patient was not medically fit for surgery; (2) the patient had not exhausted conservative methods of pain control prior to considering motor cortex stimulation; (3) the patient was not able to provide informed consent; and (4) the patient was unable to undergo magnetic resonance imaging (MRI).

## Surgical Procedure

Surgical approaches were slightly different at each site. In Halifax, a magnetic resonance image was obtained using one mm cuts, and a three-dimensional reconstruction of the brain was obtained using an image guidance system (Stealth Station – TREON 2001, Surgical Navigation Technologies, Medtronic). In Calgary the same MR imaging was obtained after placement of a stereotactic frame (Leksell, Elekta). The location of the hand representation in the contralateral motor cortex was determined and the target mapped onto the scalp.

A burr hole was made, and a four-contact electrode (Resume II lead, Medtronic) was placed in the epidural space, aligned parallel (in Halifax) or perpendicular (in Calgary) to the central sulcus. This electrode type is the same as those used in previous studies<sup>20,21,23</sup>. Intraoperative electrical stimulation was used to ensure that we were over the intended region. In patients who did not have a functional limb, such as those with brachial plexus avulsion, motor threshold was determined in a similar way but the threshold was determined to be the voltage at which the patient repeatedly and consistently reported the sensations of twitch (at low frequencies) or tetany (at high frequencies) in the appropriate somatotopic location or real motor twitching in the intact proximal limb, face, or shoulder girdle. At the Calgary site, somatosensory evoked potentials were also obtained in the subjects with brachial plexus avulsion to confirm motor hand territory using phase reversal<sup>24</sup>. Once satisfied with placement, the electrode was secured using a burr hole cover (in Halifax) or sutured to the calvarium and cemented in place (in Calgary), the patient was placed under general anaesthesia, and an extension (Medtronic 7426A) and infra-clavicular pulse generator (Medtronic Itriel 3) were inserted.

## Randomisation and programming

All subjects except one were randomized within two weeks of surgery to one of two groups ("high" and "low") and remained blinded to their group assignment. One (Subject 4) was randomized two months post-operatively when she felt that her pain returned to baseline. We selected a high/low stimulation protocol in order to reduce potential placebo effects from subconscious perception of stimulation. The use of a control arm of 'low stimulation' was similar to the original trials with vagus nerve stimulation for epilepsy<sup>25</sup> and the low setting was much lower than any previously published MCS cases. Stimulation was applied in the cycling mode in all cases: for "high" stimulation the device was 'on' for ten minutes and 'off' for two hours<sup>26</sup>; for "low" stimulation, 'on' was set for one minute and 'off' for six hours. The primary investigator (the neurosurgeon) remained unblinded and randomized

**Table 1: Outline of the schedule of study visits**

Visit	Study Week			
	0 <sup>a</sup>	1 <sup>b</sup>	12 <sup>c</sup>	24 <sup>d</sup>
Clinic Visit	X		X	X
Consent	X			
Surgery		X		
Program MCS		X	X	X
VAS	X		X	X
SF-36	X		X	X
Medications Log	X		X	X
Employment Status	X		X	X
McGill Pain	X		X	X
Beck Depression II	X		X	X
Global impression of change			X	X

MCS = motor cortex stimulation; VAS = visual analogue scale; SF-36 = Short form 36 quality of life scale.

<sup>a</sup>Screening visit in consideration of MCS.

<sup>b</sup>Post-operative visit (within 2 weeks of surgery), randomization to high or low settings.

<sup>c</sup>12 week crossover point.

<sup>d</sup>Final study visit, MCS programmed at 'best' settings.

study patients with the flip of a coin. 'Heads' indicated randomization to the group that began with "high" stimulation, while 'tails' entered the "low" stimulation group. The patient and all other study investigators remained blinded to group assignment. The other investigators completed all data collection and were not involved in programming the device.

Motor thresholds, having been determined initially in the operating room, were re-determined at the time of randomization and the parameter settings for all subjects were set to 50 Hz, with amplitude and pulse width (210-450  $\mu$ s) set to 70% motor threshold<sup>26</sup>. At 12 weeks, patients were evaluated and then crossed over to the other treatment group. At the conclusion of the 24-week study period, the evaluations were administered to patients and they were then programmed for best symptomatic control.

The primary outcome measure was the VAS. Pain reduction on the VAS was scored as follows: 80 to 100% excellent reduction; 60 to 79% good pain reduction; 40 to 59% fair pain reduction and less than 40% poor pain reduction<sup>15</sup>. The secondary outcome measures were the McGill Pain Questionnaire (MPQ), Short Form 36 quality of life scale (SF-36), Beck Depression Inventory-II, patient global impression of change (PGIC), medications log, and return to work. The measures were completed pre-operatively (during the screening visit), at 12 weeks (cross-over time point) and at 24 weeks post-operatively (study completion) for a total of three test points (Table 1).

### Sample size and analysis

Our goal was to enroll six subjects in each arm, given the assumption that the expected difference in VAS from 12 weeks to 24 weeks was a reduction of 50% for the low/high group and an

increase of 100% for the high/low group with a standard deviation of 10%. This expected clinical response was estimated based on prior literature<sup>27</sup> and because it was felt that it was necessary to have a good clinical response to justify the procedure and its risks, given its invasive nature.

Participation in the study was halted if patients were dissatisfied or wished for any reason to withdraw, if the neurosurgeon felt it was indicated, or if a serious adverse event occurred (defined as any event occurring after treatment assignment that was considered to cause temporary or permanent harm to the subject, as determined by the neurosurgeon looking after the subject). In the case of a serious adverse event, subjects would be withdrawn and would receive appropriate medical intervention.

Continuous measures (i.e. means of scores on McGill Pain Inventory, SF-36, and Beck Depression Inventory) were analyzed with paired t-tests comparing scores in each of the treatment conditions with the pre-intervention scores and comparing the scores between the treatment conditions. Categorical variables were analyzed with Chi Square and Fisher's Exact Test. Analyses were done using SPSS v.14. Results are presented with standard deviations, and were considered significant when  $p < 0.05$ . Data are expressed as mean  $\pm$  standard deviation unless otherwise stated.

## RESULTS

A total of 12 patients met inclusion criteria during the study period and had insertion of a MCS for refractory neuropathic pain (Table 2). The mean duration of neuropathic pain before MCS insertion was 78 months (range 20–183 months). Of these, eight patients were treated in Halifax, four in Calgary. Six patients withdrew from the study (three in Halifax, three in Calgary), all prior to the three-month crossover point. One patient was withdrawn because their stimulator turned off unexpectedly (breach of study protocol), one patient for panic attacks later shown to be unrelated to stimulation (adverse event), one patient for post operative infection (adverse event), two patients for focal motor seizures (adverse events), and one patient for anxiety related to a focal motor seizure experienced during threshold testing (adverse event). Thus, six patients completed the study and were included in the analysis. (When data from a seventh subject (Subject 11) was included in analysis – the only one of the six who withdrew after some data were collected – the results were unchanged.) The study was stopped before the target of 12 subjects because of a clear lack of patient satisfaction that suggested that the therapy was not effective.

### Motor cortex stimulation did not change primary outcome

Visual analogue scale pain scores at rest, during activities, least pain, and most pain were compared between baseline and at the end of low stimulation periods, between baseline and end of high stimulation periods, and between low and high stimulation periods (Fig. 1). There were no significant differences found for any of these comparisons.

### Motor cortex stimulation did not improve secondary outcomes

#### McGill Pain Questionnaire

The MPQ total, sensory, affective, evaluative, miscellaneous scales, and present pain intensity were compared between pre-

**Table 2: Subject Details.**

Subject	Age	Sex	Center	Finished or Withdrawn	High or Low Stimulation First	Motor Threshold	Final Setting	Pain Duration Prior to MCS Implantation (months)	Neuropathic Pain Etiology
1	54	M	Hal	Finished	L	3	Amp 2.1 PW 210 Freq 50	122	Left brachial plexus avulsion
2	26	F	Hal	Finished	L	3.5	Amp 2.5 PW 210 Freq 50	47	Right brachial plexus avulsion
3	43	M	Hal	Finished	H	3.9	Amp 2.7 PW 450 Freq 50	69	Left 2 <sup>nd</sup> finger phantom limb
4	47	F	Hal	Finished	H	9	Amp 6.0 PW 210 Freq 50	108	Right upper extremity CRPS type 2
5	28	M	Hal	Finished	H	7	Amp 5.0 PW 210 Freq 50	20	Right brachial plexus avulsion
6	30	M	Cal	Finished	L	8.5	Amp 4.5 (turned down from 5.5 initially) PW 450 Freq 50	85	Left brachial plexus avulsion
7	30	M	Hal	Withdrawn – Stimulator turned off unexpectedly	L	4	Amp 2.8 PW 210 Freq 50	48	Right second finger phantom limb
8	41	M	Hal	Withdrawn – Panic attacks	H	4	Amp 2.8 PW 210 Freq 50	84	Left upper extremity CRPS
9*	40	F	Cal	Withdrawn – Infection	H	6.1	Amp 3.5 PW 450 Freq 70	54	Left CRPS hand
10	29	M	Cal	Withdrawn – Focal motor seizure	H	6.5	Amp 3.5 (dropped from 4 and PW 360) PW 210 Freq 50	183	Left brachial plexus avulsion (and complete T5 spinal cord injury)
11	48	M	Cal	Withdrawn – Focal motor Seizure	L	9	Amp 6.8 PW 450 Freq 50	63	Left deafferentation facial pain (post-herpetic neuralgia)
12	23	M	Hal	Withdrawn – anxiety following an early seizure during threshold testing.	L	3.3	Amp 2.5 PW 210 Freq 50	57	Right brachial plexus avulsion

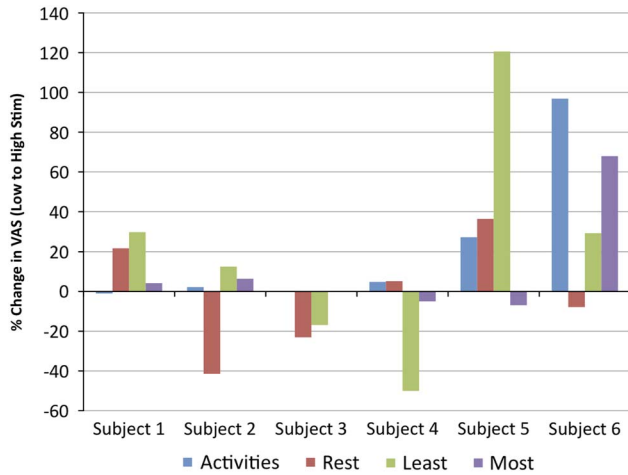
M = male; F = female, Hal = Halifax patient; Cal = Calgary patient; MCS = motor cortex stimulation; H = high stimulation first; L = low stimulation first; Amp = stimulation amplitude (V); PW = pulse width ( $\mu$ s); Freq = frequency (Hz); CRPS = upper extremity complex regional pain syndrome.

\*Note that subject 9 mistakenly received 70 Hz stimulation, however as infection appeared within one month of implantation the entire system was explanted without significant change in patient reported pain.

operative and low stimulation settings, pre-operative and high stimulation settings, and low and high stimulation settings (Fig. 2). There was a statistically significant worsening of the six subjects' MPQ miscellaneous pain scores when moving from baseline to low stimulation (increase of  $3.3 \pm 2.9$  points,

$p = 0.039$ ). There was also a statistically significant worsening of the six subjects' MPQ total pain scores when moving from pre-operative to high stimulation state (increase of  $4.5 \pm 4.1$  points,  $p = 0.045$ ). There were no other statistically significant differences.





**Figure 1:** Percent change in VAS pain scores from low intensity to high intensity stimulation conditions. Negative values indicate a reduction in pain. Categories of VAS pain scores illustrated in the graph include: VAS pain scores during activities and at rest, as well as VAS scores given for the least and the most pain experienced.

**Short Form-36 Quality of Life Questionnaire**

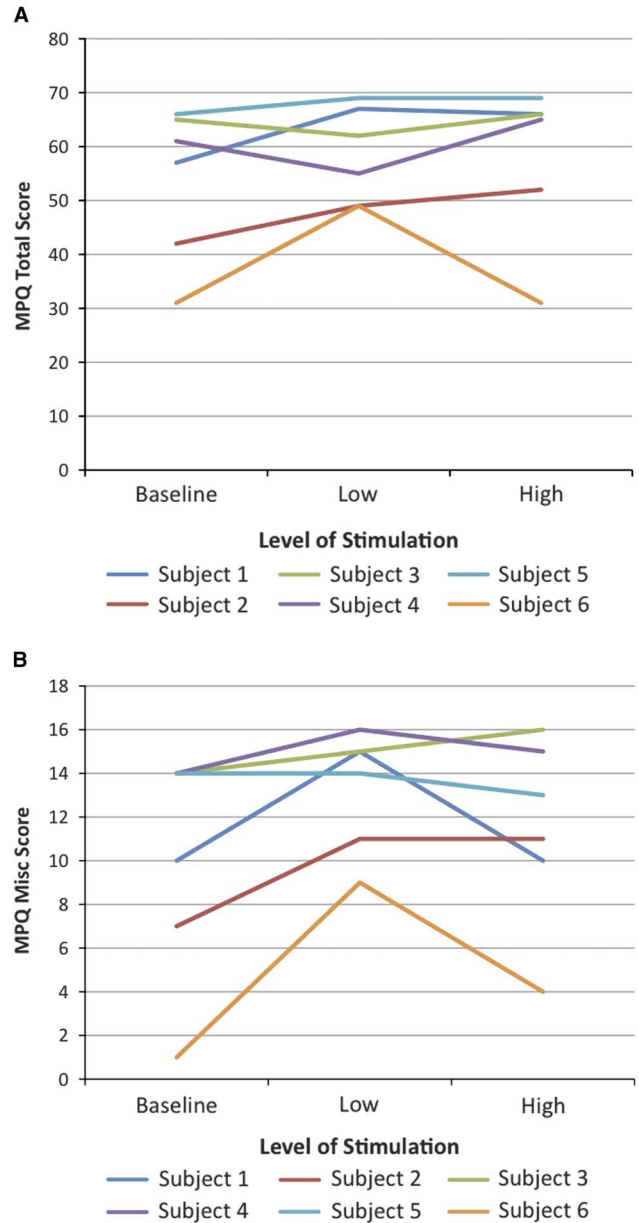
Short form-36 subsection scores were compared between pre-operative and low stimulation, pre-operative and high stimulation, and low and high stimulation states (Fig. 3). Complete data were only available for five of six patients who completed the trial. SF-36 subsections included bodily pain, general health, vitality, social functioning, emotional well-being, role limitations-emotional, physical functioning, role limitations-physical, as well as physical component and mental component summaries. The SF-36 role physical scores in the high stimulation condition were significantly lower (decrease of  $5.9 \pm 3.7$  points,  $p=0.024$ ) than in the low intensity condition, indicating a worsening of role physical scores when patients moved from low to high stimulation (Fig. 3B). The SF-36 bodily pain scores in the low stimulation condition were significantly higher than in the pre-operative condition (increase of  $4.5 \pm 3.2$  points,  $p=0.034$ ), indicating an improvement in bodily pain scores when patients moved from baseline to low stimulation. The SF-36 mental health scores in the high stimulation condition were significantly lower than in the low intensity condition (decrease of  $3.9 \pm 1.5$  points,  $p=0.005$ ), indicating a worsening of mental health scores when patients moved from low to high stimulation. There were no other statistically significant differences.

**Beck Depression Inventory II**

Beck Depression Inventory II scores from all six subjects were compared between baseline and low stimulation, baseline and high stimulation, and low and high stimulation using Chi square analysis. There were no differences in any of the conditions (Fig. 4).

**Standard 7-Point Patient Global Impression Of Change (PGIC)**

The Standard 7-Point PGIC scores were compared between low and high stimulation (Fig. 5). The PGIC is scored from 1-7, with 1 signifying no change, and 7 signifying a great deal better. A clinically significant improvement corresponds to a score of 5-7. The mean PGIC score after 12 weeks of high stimulation was

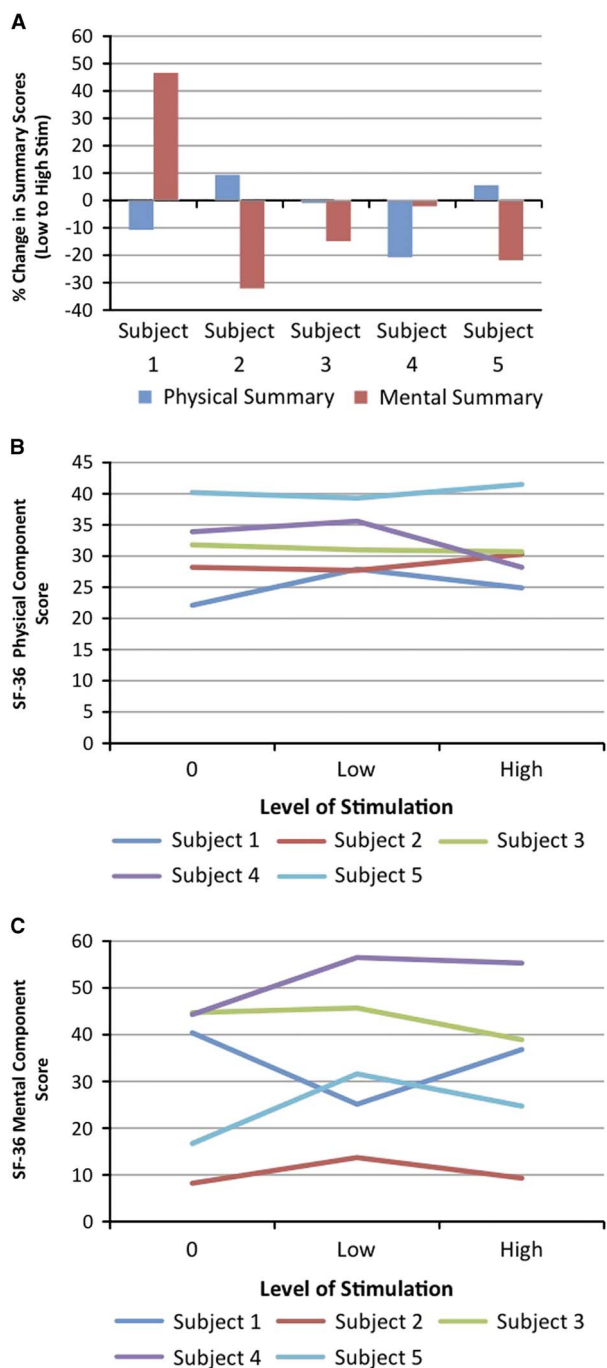


**Figure 2:** Absolute changes in each subject's McGill Pain Questionnaire scores between baseline, low and high levels of stimulation, including the (A) total score, and (B) miscellaneous scale. Higher scores correspond to worse pain.

$4.3 \pm 0.8$  compared to  $4.0 \pm 0.9$  after 12 weeks of low stimulation. This difference was not significant ( $p=0.465$ ).

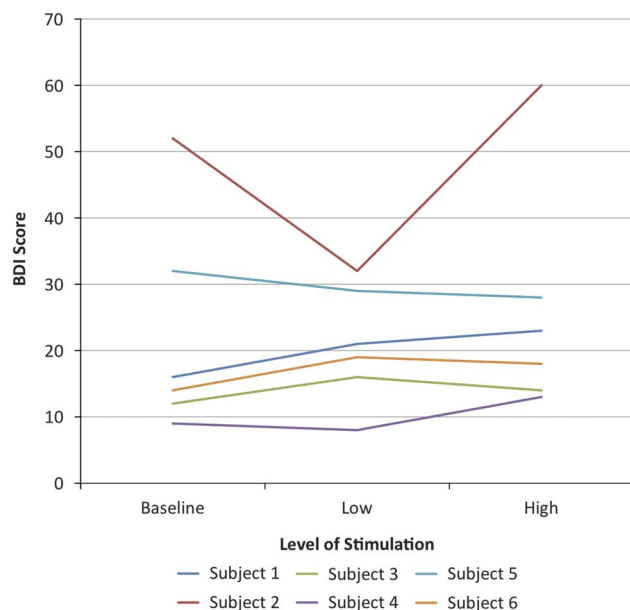
**Medication Logs**

The medication logs from baseline, low stimulation, and high stimulation settings were collected at each clinic visit. Three subjects, Subject 2, Subject 3, and Subject 4, had no change in dose or types of pain medications they were taking over the study period. Subject 5 had an overall increase in pain medications when moving from pre-operative to high stimulation states and a further increase when moving from high stimulation to low stimulation. Subject 1 had an overall decrease in pain medications when moving from

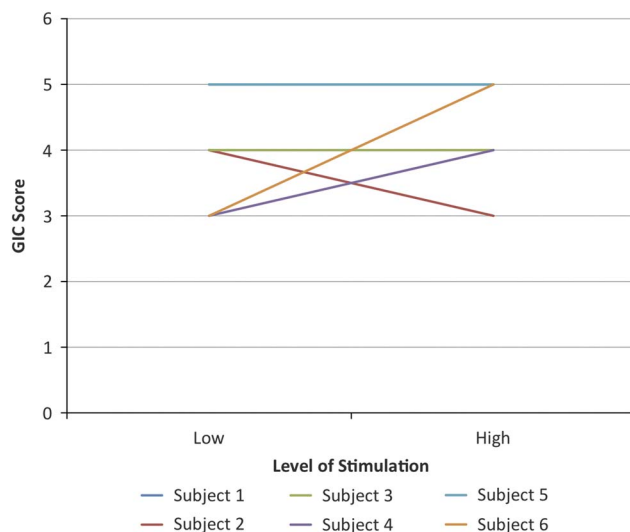


**Figure 3:** Changes in SF-36 during stimulation. (A) Percentage change in each subject's SF-36 physical and mental summary scores between low and high intensity stimulation conditions. (B) Absolute physical component summary scores, and (C) absolute mental component summary scores, comparing baseline to low to high stimulation. Note that some key SF-36 data was missing for Subject 6 and so this subject was not included in this analysis. Higher SF-36 scores correspond to better quality of life; a positive percentage change signals improvement.

pre-operative to low stimulation states and then an increase in pain medications when moving from low to high stimulation. Subject 6 had an overall decrease in pain medications when moving from pre-operative to low stimulation and a further decrease when moving from low to high stimulation. On average, therefore, there



**Figure 4:** Absolute changes in each subject's Beck Depression Index II scores between baseline, low and high levels of stimulation. Higher scores correspond to worse depression.

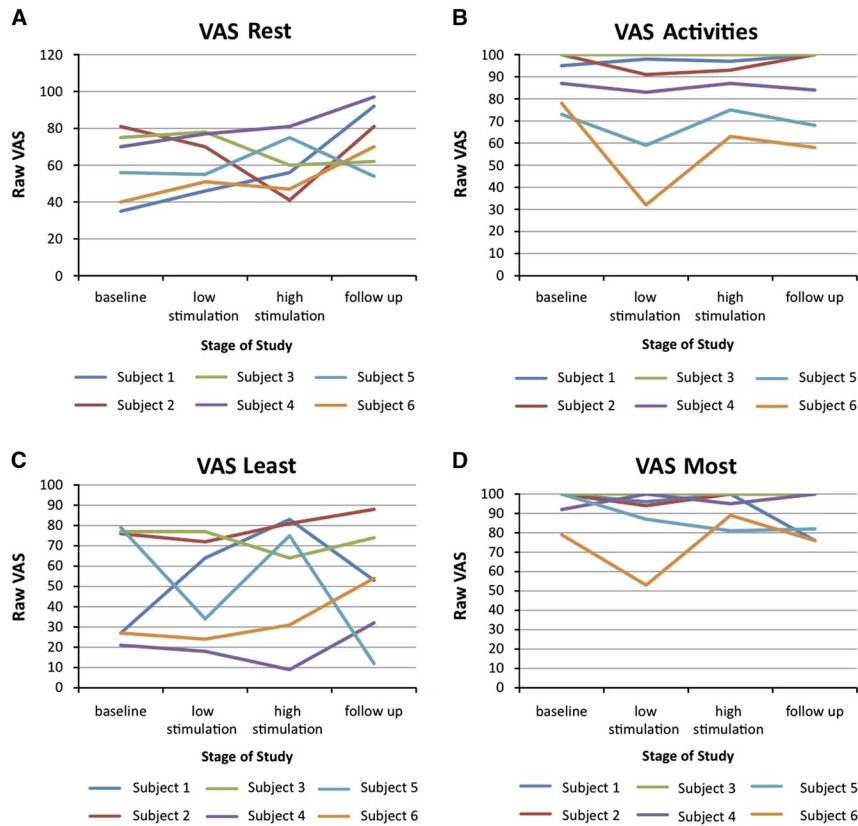


**Figure 5:** Changes in each subject's Patient Global Impression of Change scores between low and high levels of stimulation. Note that the GIC scores were the same for subjects 1 and 5. A score of 1 signifies no subjective favorable change, and higher scores correspond to greater perceived favorable change. A score of 1-4 means no significant change, 5-7 means a significant favorable change, and a 2 point change from the last reported score is significant.

was no significant decrease in pain medication usage during the high stimulation period compared with the pre-operative or low-stimulation period.

**Work Status Questionnaire**

The pre-operative, 12 week post-randomization and 24 week post-randomization work status of all six subjects were analyzed.



**Figure 6:** Absolute changes in each subject's VAS scores [A) at rest, B) with activities, C) least pain experienced, D) most pain experienced] between baseline, low levels of stimulation, high levels of stimulation and final follow-up. Higher scores correspond to worse pain. There was no statistically significant change in pain scores over the study period or over the open-label follow-up period.

**Table 3: Results of long term follow up.**

Subject	Number of Months of Follow-up	Using Stimulator at Time of Last Follow-up [Yes/No]	Subjective Long Term Outcome	Working at Baseline [Yes/No]	Working at End of Study Period [No/Full Time/Part Time]	Working at Last Follow Up [No/Full Time/Part Time]
1	51	No	Felt pain had worsened overall by 4 years post implantation, so turned off stimulator; has been off since with ongoing poor pain control	No	No	No
2	71	Yes	Reasonable multimodal pain control. IPG replaced 70 months post-operatively.	Full Time	Full Time	Full Time
3	33	No	No benefit from MCS and tension on extension so stimulator explanted	No	No	No
4	84	Yes	No benefit from MCS. Despite this, IPG replaced 83 months post-operatively.	Part Time	Part Time	Part Time
5	30	Yes	No benefit from MCS during study period; slightly better pain control during open label period	No	No	Part Time
6	53	No	No benefit from MCS so stimulator explanted	No	Full Time	Full Time

MCS = motor cortex stimulation; IPG = implantable pulse generator.

Four subjects were not working pre-operatively, one was working full time, and one was working flexible hours in a family business. Only one subject, Subject 6, changed employment status over the study period: from unemployed preoperatively, to

partially employed on low stimulation, to fully employed on high stimulation, but failed to have significant pain relief over the long term and ultimately requested explantation of their device.

### *Lack of Improvement at Follow-up*

For the six subjects who completed the study, the mean length of follow up after MCS implantation was 54 months (30 to 84 months). Pain visual analogue scores did not significantly change over this open-label follow-up period (Fig. 6). Two of the six subjects felt that MCS offered subjective pain relief. One (Subject 5) began part time work. Interestingly, despite no changes in VAS scores, two people (Subjects 2 and 4) requested replacement of their implantable pulse generators after noting an increase in pain after battery depletion (at 70 and 83 months respectively), suggesting either a subconscious awareness of stimulation or some modulation of their pain or suffering. The remaining subjects felt that MCS added no benefit to their pain management. One (Subject 1) felt that their pain had worsened and permanently turned off their MCS, and one of the six subjects requested explantation of their device (Table 3).

Overall, these results indicate a lack of benefit of cycling MCS in this study population.

### DISCUSSION

In this randomized, blinded, cross-over study, MCS did not improve neuropathic pain of the upper extremity, as measured by any of our outcome measures. In fact, there was a statistically significant worsening of the MPQ miscellaneous pain scores when moving from baseline to low stimulation and MPQ total scores when comparing pre-operative to high stimulation states. Also, SF-36 mental health scores in the high stimulation condition were significantly worse than in the low stimulation condition ( $p=0.015$ ). Despite the fact that one subject had an overall reduction in pain medications from pre-op/low stimulation to high stimulation and returned to work during the high stimulation period, this subject failed to have significant pain relief over the long term and had their system explanted.

This failure to demonstrate efficacy from MCS therapy was generally surprising, given most previously published findings in the literature. Despite one recently published retrospective review of 14 consecutive patients receiving MCS for neuropathic pain that failed to show an acceptable benefit<sup>28</sup> a literature review revealed that a good response to MCS was achieved for greater than one year in 50% of patients: 9/18 patients with trigeminal neuropathic pain, and 12/23 patients with brachial plexus avulsion or phantom limb pain<sup>18</sup>. Our own unblinded experience prior to this randomized trial demonstrated similar benefits (unpublished data). In fact, we and others (A. Parrent, personal communication) have had patients who noted significant pain worsening when their battery depleted and who requested battery replacement. It is interesting to consider, therefore, why our study failed to show efficacy of this therapy.

Blinded studies take into account placebo effects. Surgical procedures in general are very effective in inducing placebo effects<sup>29</sup> Four previous double blind, randomized prospective controlled trials found that MCS offered significant pain relief to many patients<sup>20-23</sup>. Three of these studies were conducted following an initial open label period<sup>21-23</sup> and one was only randomized during a blinded externalized trial period<sup>20</sup>. Therefore a possible reason for the discrepancy between our results and these previous studies are that the open label period may be confounding, patients may experience a subconscious “perception” of

stimulation, and/or the selection of “responders” – which may have been those most influenced by placebo<sup>29</sup>. For these reasons, our randomized trial was in stimulation-naïve patients: we did not begin with an open label time period, so subjects may not have “learned” to discern when the stimulator was on.

Another possibility to consider is whether our trial suffered from a nocebo effect<sup>30</sup>. As part of a clinical trial, our patients were told from the outset that the purpose of the trial was to determine whether or not this procedure works and that there were, in fact, risks. That is, an optimistic picture was not painted. Consent forms themselves can induce nocebo responses<sup>31</sup>. For example, one study found that 19% of subjects signing a consent form citing gastrointestinal (GI) symptoms as a potential adverse effect dropped out of the study because of GI symptoms, compared to 3% who received a form that did not cite GI symptoms as a potential adverse effect<sup>32</sup>. In other words, simply going through the consent process for participating in our study could have led to adverse events or elimination of a placebo response necessary for efficacy.

It is possible that the therapy is effective but we failed to demonstrate this, because of patient selection. Only six subjects completed the protocol to be included in analysis; therefore, it is possible that by chance, patients who were not predisposed to respond to MCS may have been selected. In addition, the subjects included in our final analysis had upper extremity pain, so we cannot make meaningful conclusions on the effect of MCS in the treatment of neuropathic facial pain, or other neuropathic pain syndromes. Although there were some technical differences between the two study sites, stimulation sites and parameters were the same so it is doubtful that these differences would have affected the results. Finally, our stimulation parameters may not have been optimal. While many groups used cycling stimulation for MCS<sup>20,22</sup>, two previous trials used continuous stimulation<sup>21,23</sup>.

It is possible that we committed a Type II error by not rejecting the null hypothesis that MCS did not confer benefit to people with specific neuropathic pain syndromes but we would suggest that this is unlikely to be the case. That is, there was no trend to suggest that we should reject the null hypothesis. Furthermore, to determine whether we committed a Type II error, additional people would need to be implanted. Given that there is not even a trend to suggest improvement, the ethics of doing so could be legitimately questioned. Finally, the consequence of a Type I error would be serious, whereas the consequence of a Type II error is not – this would simply put the onus on the community to find a convincing treatment.

In conclusion, we failed to find a meaningful therapeutic effect of MCS therapy in patients with refractory neuropathic upper extremity pain.

### ACKNOWLEDGEMENTS

RMB is a Canada Research Chair in Spinal Cord Circuits and receives funding from the Canadian Institutes of Health Research (CIHR), Canada Foundation for Innovation (CFI), and the Nova Scotia Research and Innovation Trust. ZHTK is an Alberta Heritage Foundation for Medical Research (AHFMR) Clinical Scholar, receives grant funding from AHFMR and CIHR, and has received fellowship funding from Medtronic and St. Jude Medical. IB has received speaker fees and meeting travel support



over three years ago from Medtronic, Boston Scientific, Purdue, Pfizer, Biovail, CDHA, Royal College of Physicians & Surgeons Canada, and Dalhousie University.

We would like to thank Dr. Colleen O'Connell from the Perinatal Epidemiology Research Unit at Dalhousie University, Halifax, NS, Canada, for her invaluable assistance with the statistical analyses required for this study.

#### DISCLOSURES

Julia Radic, Ian Beauprie, and Paula Chiasson do not have anything to disclose. Zelma Kiss has the following disclosures: AHFMR, Researcher, Salary grant; AIHS, Researcher, Salary grant. Robert Brownstone has the following disclosures: CIHR, Researcher, Research support; CFI, Researcher, Research support; CRC, Researcher, Research support; NSRIT, Researcher, Research support.

#### REFERENCES

- Stojanovic MP. Stimulation methods for neuropathic pain control. *Curr Pain Headache Rep.* 2001;5:130-7.
- Tasker RR, Vilela Filho O. Deep brain stimulation for neuropathic pain. *Stereotact Funct Neurosurg.* 1995;65:122-4.
- Brown J, Barbaro N. Motor cortex stimulation for central and neuropathic pain: current status. *Pain.* 2003;104:431-5.
- Campbell JN, Long DM. Peripheral nerve stimulation in the treatment of intractable pain. *J Neurosurg.* 1976;45:692-9.
- Long DM. The current status of electrical stimulation of the nervous system for the relief of chronic pain. *Surg Neurol.* 1998;49:142-4.
- Kumar K, Nath R, Wyant GM. Treatment of chronic pain by epidural spinal cord stimulation: a 10-year experience. *J Neurosurg.* 1991;75:402-7.
- Levy RM, Lamb S, Adams JE. Treatment of chronic pain by deep brain stimulation: Long term follow-up and review of the literature. *Neurosurgery.* 1987;21:885-93.
- Hosobuchi Y, Adams JE, Rutkin B. Chronic thalamic stimulation for the control of facial anaesthesia dolorosa. *Arch Neurol.* 1973;29:158-61.
- Tsubokawa T, Katayama Y, Yamamoto T, Hirayama T. Deafferentation pain and stimulation of thalamic sensory relay nucleus: clinical and experimental study. *Appl Neurophysiol.* 1985;48:166-71.
- Penfield W, Jasper H. *Epilepsy and the Functional Anatomy of the Human Brain*, 1st ed. Boston: Little, Brown, and Co; 1954.
- Lende R, Kirsch W, Druckman R. Relief of facial pain after combined removal of precentral and postcentral cortex. *J Neurosurg.* 1971;34:537-43.
- Tsubokawa T, Katayama Y, Yamamoto T, Hirayama T, Koyama S. Treatment of thalamic pain by chronic motor cortex stimulation. *Pacing Clin Electrophysiol.* 1991;14:131-4.
- Tsubokawa T, Katayama Y, Yamamoto T, Hirayama T, Koyama S. Chronic motor cortex stimulation for the treatment of central pain. *Acta Neurochir Suppl.* 1991a;52:137-9.
- Meyerson B, Lindblom U, Linderöth B, Lind G, Herregodts P. Motor cortex stimulation as treatment of trigeminal neuropathic pain. *Acta Neurochir Suppl.* 1993;58:150-3.
- Saitoh Y, Shibata M, Hirano S, Hirata M, Mashimo T, Yoshimine T. Motor cortex stimulation for central and peripheral deafferentation pain. *J Neurosurg.* 2000;92(1):150-5.
- Katayama Y, Fukaya C, Yamamoto T. Poststroke pain control by chronic motor stimulation: Neurological characteristics predicting a favorable response. *J Neurosurg.* 1998;89:585-91.
- Garcia-Larrea L, Peyron R, Mertens P, et al. Positron emission tomography during motor cortex stimulation for pain control. *Stereotact Funct Neurosurg.* 1997;68:141-8.
- Fontaine D, Hamani C, Lozano A. Efficacy and safety of motor cortex stimulation for chronic neuropathic pain: critical review of the literature. *J Neurosurg.* 2009;110:251-6.
- Coffey R. Deep Brain Stimulation for Chronic Pain: Results of Two Multicenter Trials and a Structured Review. *Pain Medicine.* 2001;3:183-92.
- Rasche D, Ruppolt M, Stippich C, Unterberg A, Tronnier VM. Motor cortex stimulation for long-term relief of chronic neuropathic pain: a 10 year experience. *Pain.* 2006;121:43-52.
- Nguyen JP, Velasco F, Brugieres P, et al. Treatment of chronic neuropathic pain by motor cortex stimulation: results of a bicentric controlled crossover trial. *Brain Stim.* 2008;1:89-96.
- Velasco F, Arguelles C, Carrillo-Ruiz JD, et al. Efficacy of motor cortex stimulation in the treatment of neuropathic pain: a randomised double-blind trial. *J Neurosurg.* 2008;108:698-706.
- Lefaucheur JP, Drouot X, Cunin P, et al. Motor cortex stimulation for the treatment of refractory peripheral neuropathic pain. *Brain.* 2009;132:1463-71.
- Lefaucheur JP, de Andrade DC. Intraoperative neurophysiologic mapping of the central cortical region for epidural electrode placement in the treatment of neuropathic pain by motor cortex stimulation. *Brain Stimul.* 2009;2:128-48.
- Ben-Menachem E, Mañon-Españallat R, Ristanovic R, et al. Vagus nerve stimulation for treatment of partial seizures: 1. A controlled study of effect on seizures. First International Vagus Nerve Stimulation Study Group. *Epilepsia.* 1994;35:616-26.
- Tsubokawa T, Katayama Y, Yamamoto T, Hirayama T, Koyama S. Chronic motor cortex stimulation in patients with thalamic pain. *J Neurosurg.* 1993;78:393-401.
- Forouzanfar T, Weber WE, Kemler M, van Kleef M. What is a meaningful pain reduction in patients with complex regional pain syndrome type 1? *Clin J Pain.* 2003;19:281-5.
- Sachs AJ, Babu H, Su YF, Miller KJ, Henderson JM. Lack of efficacy of motor cortex stimulation for the treatment of neuropathic pain in 14 patients. *Neuromodulation.* 2014;17:303-11.
- Price DD, Finniss DG, Benedetti F. A comprehensive review of the placebo effect: recent advances and current thought. *Annu Rev Psychol.* 2008;59:565-90.
- Benedetti F, Lanotte M, Lopiano L, Colloca L. When words are painful: unraveling the mechanisms of the nocebo effect. *Neuroscience.* 2007;147:260-71.
- Wells RE, Kaptchuk TJ. To tell the truth, the whole truth, may do patients harm: the problem of the nocebo effect for informed consent. *Am J Bioeth.* 2012;12:22-9.
- Myers MG, Cairns JA, Singer J. The consent form as a possible cause of side effects. *Clin Pharmacol Ther.* 1987;42:250-3.