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Motor cortex stimulation for facial chronic neuropathic pain: A review of the literature

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Abstract

Background: Facial chronic neuropathic pain (FCNP) is a disabling clinical entity, its incidence is increasing within the chronic pain population. There is indication for neuromodulation when conservative treatment fails. Motor cortex stimulation (MCS) has emerged as an alternative in the advanced management of these patients. The aim of this work is to review the worldwide literature on MCS for FCNP.

Methods: A PubMed search from 1990 to 2012 was conducted using established MeSH words. A total of 126 relevant articles on MCS focused on chronic pain were selected and analysed. Series of cases were divided in (1) series focused on MCS for FCNP, and (2) MCS series of FCNP mixed with other chronic pain entities.

Results: A total of 118 patients have been trialed for MCS for FCNP, 100 (84.7%) pursued permanent implantation of the system, and 84% of them had good pain control at the end of the study. Male: female ratio was about 1:2 in the whole group of studies; mean age was 58 years (range, 28–83), and mean pain duration was 7 years (range, 0.6–25). Four randomized controlled studies have been reported, all of them not focused on MCS for FCNP. The most common complication was seizure followed by wound infection. Preoperative evaluation, surgical techniques, and final settings varied among the series.

Conclusion: MCS for FNCP is a safe and efficacious treatment option when previous managements have failed; however, there is still lack of strong evidence (larger randomized controlled multicentre studies) that MCS can be offered in a regular basis to FNCP patients.

Key Words: Facial neuropathic pain, facial pain, motor cortex stimulation, neuropathic pain, trigeminal deafferentation pain, trigeminal neuropathic pain

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INTRODUCTION

Facial chronic neuropathic pain (FCNP) is a disabling, and devastating condition if left untreated.[40] It is characterized by stabbing, burning, and dysesthetic sensation resistant to treatment, and diminishes quality of life.[24] Pain could be located in any of the branches of the trigeminal nerve (V1, V2, or V3), in any combined area of these branches or in a nondermatomeric area of the face. Under the term of FCNP falls the following

terms: trigeminal neuralgia, trigeminal neuropathic pain (TNP), trigeminal deafferentation pain (TDP), symptomatic trigeminal neuralgia (STN), postherpetic neuralgia (PHN), and atypical facial pain (AFP).[6,30]

When the pharmacological[8,23,126] and rehabilitation treatment fail, surgery should be considered in an escalating rationale of pain treatment.[20] It should begin with less invasive and the most proven options, evolving to the less proven and finally to more aggressive surgical options.[5,15,47,92,110]

Since the early reports of Tsubokawa *et al*., electrical stimulation of the motor cortex (Motor Cortex Stimulation (MCS)) has been an option to treat patients with chronic neuropathic drug-resistant pain.[118-120] In the worldwide literature, there is a growing interest on stimulation of the motor cortex for treatment of FCNP [Figure 1].[96] Initially tried for thalamic pain, it has been tried for many treatment-resistant pain syndromes[54] such as phantom limb pain,[95,101,106] postherpetic neuralgia, brachial plexus avulsion,[57] poststroke pain,[32,46,48,50,51,76,106,111] Wallenberg syndrome,[33,49] complex regional pain syndrome,[27,70,108] pain secondary to multiple sclerosis,[112] spinal cord injury pain,[88,113] and posttraumatic brain injury pain.[107] Recently, MCS has also been tried in other nonpainful conditions.[14]

Meyerson *et al*. in 1993 reported the first MCS placement aiming facial pain with good pain relief.[72] MCS has become one of the last options to treat this painful condition, before considering deep brain stimulation (DBS) of the sensory thalamus or periventricular gray (PVG) matter, even though DBS outcomes have been controversial. [5,31,65,75,92,109,115] Chronic pain management surgical teams are becoming familiar with MCS, and this therapy is appearing in worldwide reports in the current literature.[12,13,19,25,29,63,73,80,84,90,91,94,105,107,119,122] The author presents an updated literature review on the treatment of FCNP with MCS.

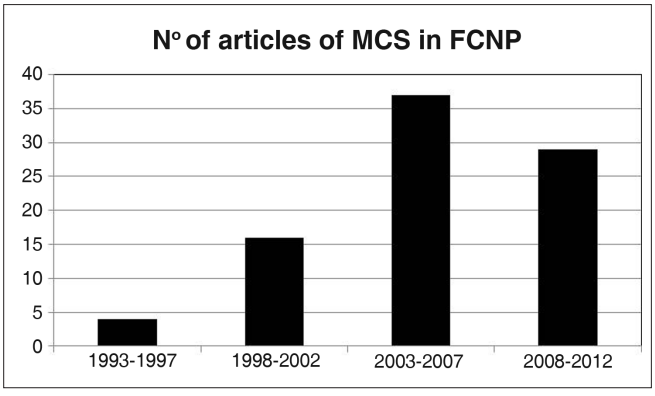

Figure 1: Number of articles published since 1993 on motor cortex stimulation as a treatment of facial chronic neuropathic pain

MATERIALS AND METHODS

A PubMed search from 1990 to 2012 was conducted, only articles in humans, and in English language were selected for analysis, there was no age limit for the search. The strategy of search was "Motor Cortex Stimulation" used in different combinations search with "neuropathic pain", "facial pain", "chronic neuropathic pain", "chronic neuropathic facial pain", "atypical facial pain", "trigeminal neuralgia", "trigeminal neuropathic pain", "trigeminal deafferentation pain". The search yielded 126 relevant selected articles. Editorials, animal studies, repeated reports of series of patients, and comments were considered in some cases for the discussion of this review, as well as articles reporting any form of motor cortex stimulation other than implantable and surgical technique, such as repetitive transcranial motor cortex stimulation (rTMS), direct current motor cortex stimulation, and reports on MCS aimed for other chronic pain condition out of FCNP.

Some of the series included patients who had been reported previously by teams of the same surgical centers. For this reason, selection criteria were: (1) reports of series with two or more cases of FCNT treated with MCS; and (2) nonduplicated series of cases if information was available.

RESULTS

Table 1 provides a summary of the reported series of cases focused in MCS for FCNP, and Table 2 shows the MCS series of FNCP mixed with other chronic pains (only the FCNP cases are reported) with a relevant number of cases of FCNP (≥2 patients) in those series; details of the demographics, diagnoses, previous pain treatment, surgery, stimulation parameters, and outcomes are also shown. There was a lack of consistency across studies regarding methods used to report and evaluate the outcome. Some authors do not report pain scores as a point in the Visual Analog Scale (VAS), report the pain score in a range of improvement, such as "excellent", "good", "fair", "poor", or "failure". In some cases, however, the definitions of these groups were different across studies. For example, 40% pain relief was considered a good outcome to some authors, while others required a >50% improvement to include patients in this category.[29,94]

Taking this fact into account, outcomes in this review have to be taken with critical judgment. Thus far there are 118 patients treated with MCS for FCNP reported in the worldwide literature [Tables 1 and 2], plus other few single-case reports (referenced in this review but not included in the tables). Male:female ratio was about 1:2 in the whole group of studies; mean age of the patients was 58 years (range, 28–83), and mean pain duration at time of implantation was 7 years (range, 0.6–25). Four randomized controlled studies have been reported,[57,80,104,121] all of them not focused on MCS for FCNP; the others are series of cases, within them

three are prospective series. One hundred of 118 (84.7%) patients were permanently implanted, and among those 84 (84%) had good pain control at the end of the study. Mean follow-up was 30.7 months (range, 3–120). Only one study reported the number of average programmings per year,[94] and only one a neuropsychological evaluation of the patients with Minnesota Multiphasic Personality Inventory (MMPI).[5] The most common complication was seizure followed by wound infection in the whole reviewed group. Seventeen studies report the placement of a 4 contact paddle lead, 1 report used a 5-6-5 paddle lead, 1 study placed an 8 contact paddle lead, and another one placed either a 4 contact or an 8 contact paddle lead, the rest of the studies did not report characteristics of the implanted lead. Seventeen studies placed the lead in the epidural space, and 3 reported placement in the subdural space (including within the central sulcus). Most of the reports used only 1 lead for final placement.

Anesthesia technique varied from local to general and in some cases sedation. Most of the studies used a preoperative imaging technique such as magnetic resonance imaging (MRI) scan, computed tomography (CT) scan, functional magnetic resonance imaging (fMRI) or even stereotactic angiography. Three studies used burr hole approach, 12 craniotomy, and 5 a mixed technique. There was an important concordance in most of the studies to use neurophysiology (somatosensory evoked potentials (SSEPs), and intraoperative cortical monitoring (iCM)) for motor cortex localization. Six studied located the lead perpendicular to the central sulcus, five parallel, one mixed, and one studied oblique.

Initial electrical parameters of stimulation were reported in ranges of amplitude: 1–7.6 volts, pulse width: 45–450 μs, frequency: 30–130 Hz; and final parameters were in amplitude: 1.3–9.5 volts, pulse width: 60–450 μs, frequency: 25–130 Hz. There was higher parameters in the final settings compared with those used at initial programming. Most of the studies set the pain improvement cut-off at ≥50% during the trial period to proceed with permanent implantation of the system, but there were an important number of studies that did not clearly report this value. The pain was evaluated in the majority of studies through the VAS, and a minority of reports also used McGill Pain Questionnaire (MPQ), Verbal Scale (VS), Wisconsin Brief Pain Questionnaire (WBPQ), Brief Pain Inventory (BPI), and others. Finally eight reports used cycling stimulation, while the others did not, or did not report if cyclic or continuous.

Motor cortex stimulation series focused in facial chronic neuropathic pain

Since the first report of MCS to treat FCNP, five more series were reported focusing on this therapy for FCNP. Meyerson *et al*. pioneered the use of MCS for FCNP, reported 10 patients in which 3 of them had central pain as sequelae of cerebrovascular disease (none responded to stimulation), 2 patients had pain from peripheral nerve injuries, 1 of them did not respond, but the other obtained about 50% pain relief, and the remaining 5 patients with Trigeminal Neuropatic Pain (TNP) experienced pain relief from 60% to 90%, thus reporting 6 permanent implantations of the MCS systems.[72] Ebel *et al*. in 1996 reported seven cases of TNP treated with MCS, of these seven cases, six cases were permanently implanted due to good to excellent pain control during the trial period and the other with pain relief at the follow-up.[22]

Rainov *et al*. reported two TNP cases with final implantation and success in the pain relief.[91] Brown *et al*. and Raslan *et al*. reported the largest series of final implanted cases, eight case series each, Brown's series is the only one that is prospective and report a neuropsychological evaluation of the patients.[5,94]

Of these series of reports focused on MCS for FCNP, 50% of them reported use of cycling stimulation while the rest do not. Esfahani *et al*. reported as complication brain swelling and tonic-clonic seizure in a case during intraoperative neurophysiological testing and electrode grid implantation, this was treated with mannitol and levetiracetam[24] Anderson *et al*. reported a case of a complex chronic pain in trigeminal and glossopharyngeal territory associated with dysphagia successfully treated with MCS, with significant pain control at 2-years follow-up.[2] Recently, Delavallée *et al*. reported the first pediatric patient (3 years old) treated with MCS for FCNP secondary to a malignant glioma in the cerebellopontine angle; the patient had pain control at the 12-months follow-up.[19]

Motor cortex stimulation series of facial chronic neuropathic pain mixed with other chronic pain entities

Fifteen series of cases are reported thus far, with four controlled randomized studies. Nguyen *et al*. reported the first mixed series of cases of FCNP with other causes of chronic facial pain, found a 75–100% improvement in the pain in the FCNP group with MCS, they use the neuronavigation technique for lead localization, which led to improved the outcomes.[78] Carroll *et al*. reported that in none of the two patients with FCNP did the MCS trial work, thus none of the patients had permanent implantation of the system; interestingly, this was the series of cases with older patients.[12] Smith *et al*. showed that in only one case, out of three, there was long-term pain relief.[104]

Henderson *et al*. treating two cases of FCNP with loss of pain relief over time showed that with "intense programming" they were able to recapture the benefit, widening the range of initial parameters.[41] Fagundes-Pereyra *et al*. reported 6 cases of a total of 27 patients with different types of pain, found that in the whole group of patients, 15 (57.7%) the pain was relieved in

Table 1: Description of the series of cases focused in motor cortex stimulation for facial chronic neuropathic pain

Author(s)	No. of patients	Type of report	Permanent implantation	Surgery from (year) to (year)	Male: Female ratio	Age at implantation (mean, range) (years)	Previous pain medications and treatment	Neuro-psychological evaluation	Etiology of the pain	Mean pain duration (range) (years)	Fails after permanent implantation	Report of final success	Mean follow-up – months (range)	Average programming sessions/year
Meyerson *et al*.[72]	10	Series of cases	6	NM	3:7	51.2 (44–71)	Gasserian ganglion stimulation, DBS, spinal cord stimulation	NM	3 sequelae of stroke, 2 peripheral nerve injury, 5 trigeminal neuralgia	6.3 (2–14)	None	6	12.6 (4–28)	NR
Ebel *et al*.[22]	7	Series of cases	6	1993–1995	1:6	55.4 (37–81)	Buprenorphine, baclofen, carbamazepine, tilidine, tramadol, metamizol, amitryptiline, local anesthetics, maprotilin, morphine, high cervical cordotomy, parapontine trigeminal rhizotomy, microvascular, decompression, retrogasserian injection of glycerol, thermal rhizotomy, stimulation of the ganglion of Gasser, local anesthetics blocks, decompression of the maxillary nerve	NM	4 anesthesia dolorosa, 1 postherpetic neuralgia, 2 dysesthesia dolorosa	8 (1–21)	None	6	05 to 24	NR
Rainov *et al*.[91]	2	Series of cases	2	NM	0:2	51.2 (43–60)	Carbamazepine, microvascular decompression, thermal lesion of the gasserian ganglion, TENS, phenytoin, phenobarbital	NM	2 TNP	NM	None	2	71 (69–72)	NR

(Contd...)

Table 1: Contd…

Author(s)	No. of patients	Type of report	Permanent implantation	Surgery from (year) to (year)	Male: Female ratio	Age at implantation (mean, range) (years)	Previous pain medications and treatment	Neuro-psychological evaluation	Etiology of the pain	Mean pain duration (range) (years)	Fails after permanent implantation	Report of final success	Mean follow-up – months (range)	Average programming sessions/year
Brown and Pilitisis (2005).[5]	10	Prospective, series of cases	8	1999–2002	6:4	55 (37–73)	Carbamazepine, gabapentin, antidepressants	MMPI	9 patients: TNP from postherpetic neuralgia, surgical injury, or unknown cause, 1 pain of central origin	6 (1–12)	None	8	10 (3–24)	NR
Esfahani *et al*.[24]	3	Retrospective, case series	3	2003–2009	2:1	61.3 (41–83)	Baclofen, carbamazepine, clonazepam, duloxetine, gabapentin, pregabalin, tramadol, fentanyl, hydromorphone, hydrocodone/ acetaminophen	NM	1 postherpetic neuralgia, 2 TDP	9.3 (8–10)	None	3	NM	NR
Raslan *et al*.[94]	11	Retrospective, case series	8	2008–2011	3:8	47.3 (31–76)	NM	NM	**TNP:** 3 dental procedure, 1 facial trauma, 1 surgical trauma of the trigeminal nerve, 1 Wallwnberg syndrome, 1 sinus surgery, 1 idiopathic trigeminal neuropathy **TNP:** 2 had MVD, 1 had anesthesia dolorosa	4.5 (1–12)	3 at 6 months of follow-up	5	33 (6–72)	2.2

(Contd…)

Table 1: Contd…

Complications	Surgical lead	Location	No. of leads implanted per patient	Anesthesia during electrode placement	Preoperative imaging	Approach technique	Intraoperative neurophysiology	Neuronavigation	Lead orientation	Initial stimulation parameters (after implantation)	Pain reduction cutoff during trial	Pain evaluating scales	Final stimulation parameters	Seizures	Stimulation cycling
Seizures, skin erosion (2 patients)	4-CPL	ED	1	L	NR	BH/CrT	SSEPs, iCM	No	Not clearly mentioned	Amp: 70–80% to produce muscle twitching, PW: 300 μs, Freq: 50 Hz	50%	VAS	NR	Yes	Yes
Seizure	4-CPL	ED	1	L	NR	CrT/BH (in the neuronavigation case)	SSEPs	Yes, only in one case	NR	NR	50%	VAS	Amp: 3.5–8.5 V, PW: 180–350 μs, Freq: 60–130 Hz, bipolar	Yes (1 case)	Yes
Seizure	4-CPL	ED	1	L	MRI and CT	CrT	SSEPs	No	NR	NR	50%	VAS	In one case: Amp: 5–6 V, PW: 400 μs, Freq: 100 Hz	Yes	Yes
1 wound infection at 6 months postoperative	4-CPL	ED	1	G	Stereotactic RMN	CrT	SSEPs, iCM, EMG	Yes	Parallel	Amp: 1–3 V, PW: 90 μs, Freq: 40 Hz	50%	VAS, MPQ, IDC	Amp: 2–8 V, PW: 90–240 ms, Freq: 40 Hz	No	No
Brain swelling, seizure	5-6-5 PL	SD	1	G	3T fMRI	CrT	iCM	Yes	Not explicitly mentioned	NR	50%	VAS	Amp: 1.6 $\pm$ 1.4 V, PW: 93.3 $\pm$ 5.8 ms, Freq: 43.3 $\pm$ 5.8 Hz	Yes	No
None	4-CPL or 8-CPL	ED	1	G	Stereotactic RMN	CrT	SSEPs, iCM	Yes	Parallel	Amp: 2–5 V, PW: 120–450 μs, Freq: 30–50Hz	50%	VAS	NR	No	No

TNP: Trigeminal neuropathic pain, TDP: Trigeminal deafferentation pain, Amp: Amplitude, PW: Pulse width, Freq: Frequency, V: Volts, ms: miliseconds, Hz: Hertz, VAS: Visual analog scale, MPQ: McGill pain questionnaire, IDC: Inventory of drug consumption, MMPI: Minnesota Multiphasic Personality Index, MQS: Medication quantification Scale, BPI: Brief Pain Inventory, SIP: Sickness Impact Profile, NM: Not mentioned, NR: Not reported, iCM: Intraoperative Cortical Monitoring, 4-CPL: 4 contact paddle lead, 8-CPL: 8 contact paddle lead, 5-6-5 PL: 5-6-5 paddle lead, BH: Burr Hole, CrT: Craniotomy, ED: Epidural, SD: Subdural, L: Local, G: General

Table 2: Description of the motor cortex stimulation series of facial chronic neuropathic pain mixed with other chronic pains

Author(s)	No. of patients	Type of report	Permanent implantation	Surgery from (year) to (year)	Male: Female Ratio	Age at implantation (mean, range) (years)	Previous pain medications and treatments	Neuro-psychological evaluation	Etiology of the pain	Mean pain duration (range) (years)	Fails after permanent implantation	Report of final success	Mean follow-up – months (range)	Average programming sessions/ year
Nguyen *et al*.[77]	7	Series of cases	7	1993–1995	2:5	62.3 (43–77)	Deep brain stimulation of the talamus in one case	NM	3 anesthesia dolorosa, 2 sinus surgery, 1 skull base trauma, 1 surgical trigeminal nerve trauma	8.4 (5–15)	None	7	28.3 (17–39)	NR
Nguyen *et al*.[78]	12	Series of cases	12	1993–1997	Not stated in the facial pain group, general group (18:14)	Not stated in the facial pain group, general group (mean: 54, range: 21–77)	NM	NM	7 from thermal rhizotomy, 3 from ENT operation, 1 from brainstem lesion, 1 from skull base trauma	Not stated in the facial pain group, general group 7.8 (4–14)	None	9	Not stated in the facial pain group, general group: 27.3 (3–50)	NR
Carroll *et al*.[12]	2	Prospective, series of cases	0	1996–1998	1:1	80	NM	NM	1 Poststroke (thalamic infarct) with previous stereotactic mesencephalotomy and cingulotomy, 1 with poststroke and trigeminal neuralgia	8.5 (6–11)	N/A	0	N/A	N/A
Smith *et al*.[104]	3	Prospective, randomized, double-blind, within-patient repeated cross-over study	3	1996–1998	1:2	71.3 (54–80)	NM	NM	1 posttraumatic neuralgia, 2 poststroke pain	Not stated in the facial pain group	2	1	36	NR
Henderson *et al*.[41]	2	Series of cases	2	NM	0:2	66 (55–77)	Stellate block, morphine pump, neurectomy of the trigeminal nerve	NM	1 atypical facial pain, 1 postherpetic facial pain	4	N/A	2	N/A	NR

(Contd...)

Table 2: Contd…

Author(s)	No. of patients	Type of report	Permanent implantation	Surgery from (year) to (year)	Male: Female Ratio	Age at implantation (mean, range) (years)	Previous pain medications and treatments	Neuro-psychological evaluation	Etiology of the pain	Mean pain duration (range) (years)	Fails after permanent implantation	Report of final success	Mean follow-up – months (range)	Average programming sessions/ year
Pirotte *et al*.[86]	6	Prospective, series of cases	6	Since 1998	2:4	60.8 (38–70)	NSAID, thermocoagulation, balloon compression, microvascular decompression, carbamazepine, radiation therapy, tricyclic antidepressants, benzodiazepines, deep brain stimulation	NM	4 trigeminal neuropathy, 1 dental avulsion, 1 multiple sclerosis, 1 subcortical stroke	Not stated in the facial pain group	None	6	26.2 (4–60)	NR
Gharabaghi *et al*.[38]	2	Series of cases	2	NM	2:0	65 (61–69)	NM	NM	1 trigeminal anesthesia dolorosa, 1 trigeminal pain	Not stated in the facial pain group	None	2	27 (14–40)	NR
Rasche *et al*.[93]	10	Retrospective, case series	5	1994–2006	0:10	64.1 (44–82)	Ibuprofen, tramadol, gabapentin, amitriptylin, promethazin, paracetamol, phenytoin, buprenorphin	NM	3 dental surgery, 4 trigeminal neuralgia, 3 nerve injury	6.3 (2–12)	None	5	50.4 (12–120)	NR
Cioni *et al*.[13]	8	Series of cases	8	NM	Not stated in the facial pain group	NM	NM	NM	4 posttraumatic, 2 postherpetic, 1 posttrigeminal surgical lesion, 1 multiple sclerosis	NM	7	1	NM	NR
Hosomi *et al*.[45]	2	Retrospective, case series	2	NM	1:1	52 (28–76)	Pharmacologic therapy, Transcranial magnetic stimulation, nerve blocks	NM	1 pontine infarction, 1 trigeminal pain	1.95 (1.8–2.1)	None	2	31.5 (5–58)	NR

(Contd...)

Table 2: Contd…

Author(s)	No. of patients	Type of report	Permanent implantation	Surgery from (year) to (year)	Male: Female Ratio	Age at implantation (mean, range) (years)	Previous pain medications and treatments	Neuro-psychological evaluation	Etiology of the pain	Mean pain duration (range) (years)	Fails after permanent implantation	Report of final success	Mean follow-up – months (range)	Average programming sessions/ year
Velasco *et al*.[121]	2	Prospective, randomized double-blind trial	2	NM	1:1	37.5 (43–52)	"All patients were treated with multiple analgesics drugs, nerve and sympathetic blocks"	NM	1 Thalamic infarct with pain in V2-V3, 1 postherpetic neuralgia with pain in V1	3.8 (0.6–7)	None	2	12	NR
Nguyen *et al*.[80]	3	Prospective, double-blinded crossover trial	3	NM	1:2	54.3 (31–75)	NM	NM	3 trigeminal neuropathy	4.6 (3–6)	1	2	Not clearly stated for the facial pain group	NR
Delavallée *et al*.[18]	3	Series of cases	3	2000–2005	2:1	62.3 (54–71)	Thermocoagulation, MVD, medical treatment	NM	3 TNP	18 (9–25)	None	3	NM	NR
Lefaucheur *et al*.[57]	7	Prospective, randomized controlled trial	6	NM	1:6	58.8 (30–80)	Alprazolam, clomipramine, clonazepam, clorazepam, fentanyl, morphine sulfate, sertraline, tramadol, gabapentin, buprenorphine, levomepromazine, amitriptyline, carbamzepine, venlafaxine, codeine, oxcarbazepine, paracetamol	NM	1 neurofibraomatosis type 1, 4 trigeminal neuralgia, 1 herpes zoster ophthalmicus, 1 atypical orofacial pain	10 (4–20)	None	6	Not clearly state for the facial pain group	NR
Fagundes-Pereyra *et al*.[25]	6	Series of cases	6	1994–2002 (not specifically stated for the facial pain group)	5:1	49.5 (35–67)	anticonvulsants, antidepressants, antiinflammatory agents, opioid grugs	NM	2 strokes, 2 brain injury, 1 TNP, 1 multiple sclerosis	5.6 (2–10)	None	6	Not clearly stated for the facial pain group	NR

(Contd...)

Table 2: Contd…

Complications	Surgical lead	Location	No. of leads implanted per patient	Anesthesia during electrode placement	Preoperative imaging	Approach technique	Intraoperative neurophysiology	Neuronavigation	Lead orientation	Initial stimulation parameters (after implantation)	Pain reduction cutoff during trial	Pain evaluating scales	Final stimulation parameters	Seizures	Stimulation cycling
Epidural hematoma, transient aphasia and dysesthesia	4-CPL	ED	1	L	fMRI	BH/CrT	SSEPs, iCM	Stereotactic frame	Not clearly mentioned	NR	NR	VAS	Amp:2.4 V (1.3-4 V), PW: 90 μs (60-180 μs), Freq: 40.8 Hz (25–55 Hz)	No	Yes
1 infection report in the facial pain group	4-CPL	ED	1	L/G	Stereotactic CT scan	BH/CrT	SSEPs	Yes in some cases, not clearly stated in the facial pain group	Perpendicular	NR	NR	VAS, MQS	Amp: 2.1 (1.3–4) V, PW: 82.5 (60–180) ms, Freq: 40 (25–55) Hz in the general group	No	Yes
N/A	4-CPL	ED	1	G	NR	CrT	iCM	NM	NM	N/A	N/A	Percentage of pain relief, 4-point verbal rating scale, 5-point scale, changes in analgesic consumption	N/A	N/A	N/A
Wound infection	4-CPL	ED	1	L /sedation	MRI	CrT	iCM	No	Parallel	NR	50%	VAS, MPQ	Amp: 2.1 V, PW: 450 μs, Freq: 20 Hz	Not in the facial pain group	NR

(Contd...)

Table 2: Contd…

Compli-cations	Surgical lead	Location	No. of leads implanted per patient	Anesthesia during electrode placement	Preoperative imaging	Approach technique	Intraoperative neuro-physiology	Neuro-navigation	Lead orientation	Initial stimulation parameters (after implantation)	Pain reduction cutoff during trial	Pain evaluating scales	Final stimulation parameters	Seizures	Stimulation cycling
Seizures.	4-CPL	NM	2	N/A	N/A	N/A	N/A	N/A	Parallel	Amp: 5.5–7.6 V, PW: 450 μs, Freq: 110–130 Hz	50%	VAS	Amp: 1.7–9.5 V, PW: 240–390 μs, Freq: 55–110 Hz	Yes	Yes
Infection, seizure	4-CPL	ED	1	G	1.5 T fMRI	CrT	SSEPs, iCM	Yes	Perpendicular	Monophasic square wave pulses, Freq: 40 Hz, PW: 100 μs, Amp: 1–5 V	NR	VAS	NR	Yes	Yes
NR	4-CPL	ED	1	L	1.5 T MRI, 3 T fMRI	BH	iCM	Yes	Not explicitly mentioned	NR	Not clearly stated	VAS	NR	No	NR
Seizure, wound infection	4-CPL	ED	1	L /sedation	MRI /fMRI	BH	SSEPs , iCM	Yes	Perpendicular	NR	50%	VAS	Amp: 3.5–4.5 V, PW: 210–360 μs, Freq: 50–85 Hz	Yes	Yes
NR	Not clearly stated	ED	1 to 2	NM	NR	BH/CrT	NM	NM	NM	NR	NR	NR	NR	NR	NR
Not reported in the facial pain group	4-CPL	SD, and within the central sulcus	1 to 2	G	MRI	CrT	SSEPs	None	Parallel	NR	Not clearly stated	VAS, SF-MPQ	NR	Not in the facial pain group	NR

(Contd...)

Table 2: Contd…

Complications	Surgical lead	Location	No. of leads implanted per patient	Anesthesia during electrode placement	Preoperative imaging	Approach technique	Intraoperative neurophysiology	Neuronavigation	Lead orientation	Initial stimulation parameters (after implantation)	Pain reduction cutoff during trial	Pain evaluating scales	Final stimulation parameters	Seizures	Stimulation cycling
None	4-CPL	ED	1	G	MRI	CrT	SSEPs, iCM	None	Parallel	Amp: 2–3.5 V, PW: 90 μs, Freq: 40 Hz	Not clearly stated	VAS, MPQ, Bourhis scale	Amp: 2–6.5 V, PW: 90 μs, Freq: 40 Hz	No	Yes
None	4-CPL	ED	1	L/G	MRI	CrT	SSEPs, iCM	Yes	Perpendicular	Amp: 2 V, PW: 60 μs, Freq: 40 Hz	NR	VAS, VS, WBPQ, MPQ, MQS	Amp: 1.4–2.1 V, PW: 60 μs, Freq: 35 Hz	No	NR
Wound infection, seizures, arachnoiditis	8-CPL	SD	1	G	NR	CrT	SSEPs, iCM	Yes	Oblique	NR	>40%	VAS	Amp: 1.5–4 V, P W: 210μs, Freq: 45–80 Hz	Yes	Yes
NR	4-CPL	ED	1	G	Yes, but not clearly stated	CrT	SSEPs, iCM	Yes	Perpendicular	NR	Not clearly stated	VAS, BPI, MPQ, SIP, MQS	Amp: 2–3 V, PW: 60 μs, Freq: 40–50 Hz	No	Yes
Seizures, scar dehiscence, wound infection	4-CPL	ED	1	L/G	Stereotactic angiography	BH/CrT	SSEPs, iCM	Stereotactic frame	Perpendicular	Amp: 2–4 V, PW: 45–60 μs, Freq: 45–60 Hz	NR	VAS, MPQ	Amp: 2–5.3 V, PW: 60–210 μs, Freq: 45–130 Hz	Yes, not clearly stated in the facial pain group	NR

TNP: Trigeminal neuropathic pain, TDP: Trigeminal deafferentation pain, Amp: Amplitude, PW: Pulse width, Freq: Frequency, V: Volts, ms: miliseconds, Hz: Hertz, VAS: Visual analog scale, VS: Verbal Scale, MPQ: McGill pain questionnaire, SF-MPQ: Short Form of McGill Pain Questionnaire, IDC: Inventory of drug consumption, MMPI: Minnesota Multiphasic Personality Index, MQS: Medication quantification Scale, BPI: Brief Pain Inventory, SIP: Sickness Impact Profile, NM: Not mentioned, NR: Not reported, N/A: Not available, 4-CPL: 4 contact paddle lead, 8-CPL: 8 contact paddle lead, BH: Burr hole, CrT: Craniotomy, ED: Epidural, SD: Subdural, L: local, G: General

50% or more, and no differences were found in relation to pain location (P=0.81).[25]

Lefaucheur *et al*. reported on a randomized controlled trial using MCS for refractory peripheral pain (FCNP and others) in 2008. Sixteen patients were enrolled. It included a cross-over trial in which the stimulator was switched "on" or "off" for 1 month in random order with double-blind evaluation of the effects. This period was followed by an open phase during which the stimulator was switched "on" in all patients. The mean rate of pain relief on VAS scores of 48% (range, 0–95%).[57]

Lefaucheur *et al*. reported a design of a new octopolar lead aimed to be used in MCS therapy, the authors implanted this new lead in the epidural space in 6 patients with poststroke pain. One patient had FCNP, this patient had good pain relief at the follow-up.[63]

DISCUSSION

The term "facial pain" encompasses a variety of clinical conditions and their presentations could overlap, and the treatment approaches differ based on nature and severity of pain, as well as its distribution, neurological and psychological variables, and medical comorbidities. FCNP is a syndrome of severe, constant facial pain related to disease or injury to the trigeminal nerve or ganglion. Causes of this type of pain can include injury from sinus or dental surgery, skull and/or facial trauma, or intentional destruction for therapeutic reasons (deafferentation) as well as intrinsic pathological conditions in any part of the trigeminal system.[42]

MCS has become one of the last resorts to treat refractory FCNP and has even been considered as part of a facial pain algorithm of treatment after some other invasive procedures.[103] Considering that in chronic pain management a good result means a decrease of at least 50% of the pain in the VAS, the pain relief for FCNP treated with MCS reported in the literature ranges from 45% to 84% including the present review.[12,22,72,78,79,118] Brown *et al*. hypothesized that a possible explanation for these particularly excellent results of MCS in FCNP is that the facial somatotopic representation on the motor cortex is large compared with that of other body regions.[4]

When doing a review of a very variable topic, and varied type of reports and measuring scales in terms of outcome, and specifically reviewing MCS for FCNP, only a limited of focused reports are found, the majority of the reports are mixed series of chronic pain patient, where few patients have FCNP. Reports published vary considerably in terms of surgical techniques, origin of the pain syndromes, and the methods to assess clinical outcome, and the lack of large, multicenter, controlled studies focused on MCS for FCNP, make it difficult to compare the results between the studies and to compare MCS with other pain therapies.

The evidence shows that a positive response is achieved in 44–100% of MCS-treated patients and long-term benefits have been achieved in 0–100% of those patients who responded to initial trials of stimulation, and there is evidence that response to stimulation decreases over time in some patients and "intensive programming" is necessary in those cases to recapture the pain relief of the therapy.[41,104]

Fontaine *et al*. in a critical review of the literature of MCS for chronic neuropathic pain reported that a good response to MCS (pain relief ≥40–50%) was observed in ~55% of patients who underwent surgery and in 45% in patients with follow-up ≥1 year. VAS scores revealed a 57% of pain improvement. A good response was achieved in 68% of the patients with TNP, higher than 54% of the patients with central pain. At follow-up >1 year this percentage was 50% of the patients improved with TNP treated with MCS. Complications were seizures in 12% in the early postoperative period, infection rate was found in 5.7%, hardware related problems in 5.1%.[29]

DaSilva *et al*. in a structural and functional MRI study of patients with TNP, found changes in cortical thickness of TNP patients were frequently colocalized and correlated with functional allodynic activations, and include both cortical thickening and thinning in sensorimotor regions, and predominantly thinning in emotional regions of the brain. Overall, such patterns of cortical thickness suggest a dynamic functionally driven plasticity of the brain. These structural changes, which correlated with the pain duration, age-at-onset, pain intensity and cortical activity, may be specific targets for evaluating therapeutic interventions.[17]

Lima *et al*. in a 22-studies meta-analysis showed a weighted responder rate of 72.6% (95% CI, 67.7–77.4) for MCS for chronic pain in comparison of 45.3% (95% CI, 39.2–51.4) of noninvasive motor cortex stimulation studies.[66] According the European Federation of Neurological Societies (EFNS) guidelines on neurostimulation therapy for neuropathic pain there is level C evidence that MCS is useful in 50–60% of patients with central or peripheral facial neuropathic pain.[16] Considering the words of the pioneer of the MCS therapy for FCNP, "it must be remembered that the forms of pain for which MCS can be effective, in at least half of patients, are those for which there is no, or very few other treatment".[71] Recently, Lefaucheur *et al*. published the first randomized controlled trial of MCS for treatment of intractable peripheral neuropathic pain, reporting a similar response rate, with 60% of cases showing good or excellent improvement.[57]

A gradual decrease in efficacy with long-term stimulation is not uncommon in neuromodulation procedures for

chronic pain. Some authors have reported a loss of efficacy over time and indicated that intensive reprogramming may help recapture benefits. In average, patients had lost benefits from stimulation 7 months after implantation. Use of two quadripolar electrode arrays instead of one improved the physician's ability to recapture beneficial stimulation.[68] Henderson *et al*. reported recovery of pain control after intensive reprogramming after loss of benefit from MCS for neuropathic pain in six patients.[41] However, with this intense reprogramming the chance to have a seizure increases.[54]

Saitoh *et al*. points out those patients with good preoperative response to ketamine seem to be good candidates for MCS;[97,99] however, this topic is controversial and deserves further study, as methods to predict a successful outcome from this relatively invasive procedure would be of great clinical significance.[4,123]

Nuti *et al*. reported in a non-FCNP series of patients that the intake in analgesic medications in these patients was decreased in 52% of patients and unchanged in 45% of them, complete withdrawal of analgesic medication was obtained in 36% of patients. Neither preoperative motor status, pain characteristics, type or localization of lesions, quantitative sensory testing, somatosensory evoked potential, nor the interval between pain and surgery were found to predict the efficacy of MCS. The level of pain relief, as evaluated in the first month following implantation was a strong predictor of long-term relief (regression analysis, $R = 0.744$; $P < 0.0001$).[81]

Postoperative outcomes are better when patients present with only mild to absent motor weakness in the region of pain and when there is pain in the trigeminal region. When motor weakness was present and was moderate to severe, there was therapeutic benefit in only 15% of the patients, and when motor contractions could not be induced, pain relief was achieved in only 9% of patients.[3,48]

A number of factors have been proposed to account for failures, including poor case selection, flaws in the electrode implantation technique, inadequate neurostimulator programming, loss of efficacy due to plastic changes in the motor cortex organization, excessive deafferentation of the painful territory, among others. However, despite the fact that these factors have been well recognized and described, the manner in which patients continue to be selected and surgically treated, their devices programmed, their outcomes evaluated and reported, and follow-up conducted is extremely heterogeneous.[121]

Velasco *et al*. emphasized that the most important factor for success of MCS for chronic pain is the correct electrode placement in the cortical representation of pain territory over the motor cortex, and this is better achieved by combining several imaging and electrophysiological techniques. Cycling modes and stimulation parameters are not as critical as electrode correct placement. Patients with severe or complete deafferentation of the painful territory frequently exhibit poor analgesic response and no modification of allodynia and hyperalgesia by MCS. These patients are probably not good candidates for MCS, and a subacute therapeutic trial aids in identifying these individuals.[121]

Mechanism of action

While MCS provides a significant treatment effect to many patients with FCNP, the mechanism underlying its efficacy remains largely unknown. A central analgesic mechanism has been proposed on the basis of comparative positron emission tomography (PET) studies performed before and after MCS. Neuronal activation (hypermetabolism) of cortical and thalamic areas related with sensory input (sensory thalamus), orbitofrontal cortex, mesencephalon/periaqueductal gray (PAG) and pons, posterior insula, areas of emotional interpretation of pain (cingulated cortex, Brodmann area 24, 32, and 10) was induced by MCS and remained after the stimulator was turned off,[33-36,53,82,83] interestingly, a similar posttherapy effect was also seen with the use of rTMS of the motor cortex.[52] It is hypothesized that the extent of pain alleviation from MCS also correlates with the increase of blood flow in the cingulate gyrus. This suggests that stimulation reduces the suffering experienced by a patient with chronic pain.[3,37] Ito *et al*. showed that successful MCS in poststroke pain patients significantly improves glucose use in the thalamus ipsilateral to MCS.[46]

Fonoff *et al*. reported in two patients with CRPS when studied with fluorodeoxyglucose (FDG) PET scan, an increased activity during MCS in the cingulate cortex, precentral gyri, posterior insula, inferior medial temporal cortex, nuclei acumbens and the mesencephalic region (periaqueductal gray), and a decreased activity in the thalamus bilaterally.[27] These findings suggest that MCS was able to modulate distant brain regions involved in the circuitry of pain. There is also evidence in animals as well as in humans that the MCS elicits a substantial and selective antinociceptive effect mediated through the endogenous opioid system.[26,67] Pain has an inhibitory influence over the motor cortex, which can interfere with motor learning capacities. Evidence suggests a relationship between chronic pain and motor-cortex reorganization, but it is still unclear whether one causes the other, and also that interventions aimed at normalizing motor-cortex organization can lead to pain relief.[70] Raij *et al*. showed suppression in the contralateral motor cortex oscillations (~20 Hz) after painful Aδ- and C-fiber stimuli in healthy subjects, supporting the close relationship between the motor cortex and pain control via both fast- and slow-conducting nociceptive pathways.[89]

Drouot *et al*. showed that patients with MCS with normal or quite normal nociceptive thermal thresholds

within the painful area, or the sensory thresholds improved when the MCS switched "on", were "good responders" to MCS.[21] Fontaine *et al*. reported a case with neuropathic facial pain due to peripheral nerve injury and after MCS, the tactile and thermal sensory loss improved, although the mechanisms leading to this effect remain unclear, and this observation enhanced the hypothesis that MCS acts through modulation of the sensory processing.[28]

The thickness of the cerebrospinal fluid (CSF) layer between the dura mater and the cortex below the cathode affects the threshold amplitude for motor responses and the therapeutic stimulation amplitude in MCS.[69] Holsheimer *et al*. reported based in a mathematical model of MCS, that bifocal (bipolar) stimulation gives the largest motor response in the pain region, and the anode of the bipole is the best electrode for pain management.[44] Sharan *et al*. in an electric field modeling with an extradural 4 contact paddle electrode and showed that the CSF has a large shunting effect on the effectiveness of the stimulus current. The effective stimulus amplitude depends strongly on the thickness of the CSF layer between the dura and cortex, and essentially, the activating function at the depth of the sulci is minimal.[102]

Canavero *et al*. found in two patients with central pain syndromes, a decrease in blood flow in the parietal lobe, further decreasing after stimulation by nonpainful maneuvers, suggesting a very important role of the sensory cortex in the generation of anomalous pain states,[11] and based on this results the same group placed an epidural parietal (sensory) cortex stimulating electrode for pain with good pain control[7] but this observation needs further study.

Lefaucheur *et al*. demonstrated in two patients with extradural MCS (EMCS) and implanted epidural cervical electrodes of spinal cord stimulation (SCS) for pain control, that direct and indirect volleys (D- and I-waves) were produced depending on electrode polarity and montage and stimulus intensity. At low-intensity, anodal monopolar EMCS generated D-waves, suggesting direct activation of corticospinal fibers, whereas cathodal EMCS generated I2-waves, suggesting transsynaptic activation of corticospinal tract. The bipolar electrode configuration used in chronic EMCS to produce maximal pain relief generated mostly I3-waves. This result suggests that EMCS induces analgesia by activating top-down controls originating from intracortical horizontal fibers or interneurons but not by stimulating directly the pyramidal tract. The descending volleys elicited by bipolar EMCS are close to those elicited by transcranial magnetic stimulation (TMS) using a coil with posteroanterior orientation. Different pathways are activated by EMCS according to stimulus intensity and electrode montage and polarity, which should be taken into account when programming EMCS for pain treatment.[62]

Preoperative investigations

Most of the studies on MCS for chronic pain reported the characterization of the pain with the VAS and MPQ, and few studies included Verbal Rating Scale (VRS), BPI, Sickness Impact Profile (SIP), and Medication Quantification Scale (MQS), WBPQ [Tables 1 and 2].[5,25,57,63,78,80,104] These scales are applied in the preoperative, during the trial, as well as in the postoperative period and follow-ups. In some studies the pain outcome was also reported according to a pain relief scale, similar to this one, but there is some variation between the reports in the ranges of percentages:[77,111]

- Excellent (pain reduction from 80% to 100%)
- Good (pain reduction from 60% to 79%)
- Fair (pain reduction from 40% to 59%)
- Poor (pain reduction less than 40%)

Predicting which patients will likely benefit from stimulation is a major clinical problem. Barbiturate sensitivity and opioid insensitivity have been suggested as possible predictors of response.[7,120,123] TMS may be another useful predictor of response.[55,58-61,64,87] Results of such preoperative testing, however, are no guarantee of a successful outcome, as not all patients who respond to propofol respond to MCS and, equally, morphine-insensitive patients have been shown to respond to stimulation.[7,104]

Appropriate pain psychological evaluation and realistic expectations of pain reduction are important preoperative considerations as well. Standardized questionnaires that have been validated for patients with chronic pain may contribute to outcomes measurement. All patients should be evaluated by a pain psychologist before surgery, given the significant psychological burden of pain and the possible contribution of psychological comorbidities to suffering. Screening that reveals significant psychological/psychiatric comorbidities does not preclude intervention, but must be weighted by the relevant health care teams. Patients must be appropriately educated about the procedure, and realistic expectations should be verified.[109]

In patients with epilepsy that have undergone an anterior temporal lobectomy, a number of postoperative complications have been identified in several domains: psychological, behavioral, affective, and social. This postoperative psychological adjustment was first described as the "Burden of Normality" (BoN), and then described as a syndrome.[39] The BoN syndrome is a described phenomenon of postoperative adjustment, and could be applied to chronic pain patient who undergo neuromodulation surgery (for instance, MCS) and who have difficulty coping with the expectations associated with becoming "normal". The pain psychological team

should be managing and assessing all these situations from the preoperative period to the surgical follow-up. It should be emphasized that psychological and psychiatric evaluations are not routinely reported in the literature review of MCS for FCNP.

Montes *et al*. demonstrated that MCS may interfere with relatively simple cognitive processes such as that underlying target detection, and that the risk of abnormal cognitive effects related to cortical stimulation may increase with age. MCS surgery appears on the whole remarkably safe, complementary neuropsychological studies in this category of patients are advised, as well as caution to possible adverse cognitive effects when using MCS in the elderly, notably in the presence of preexistent cerebral lesions.[74]

Surgical technique

Surgical techniques vary considerably among centers, there is no consensus in many of the issues related to surgery; for instance, the need to trial the MCS, burr hole vs craniotomy, epidural vs subdural electrode placement, time and place (regular floor, outpatient clinic, epilepsy monitoring unit[41,102]) of the initial programming,[104] there is also questioning about the optimal target area of the stimulation, most of the authors aim the motor cortex, some others place the electrodes in the motor and sensory strips, and there is one report aiming specifically the sensory strip for pain control with good results. [7] Hosomi *et al*. studied the central sulcus electrode placement and found that during the trial this location was more effective than that of the precentral gyrus, but in the long-term did not significantly improve the outcome.[45] Following the author presents the most usual way to perform MCS.

Stage I procedure

In this description, stage I refers to the electrode placement over the motor cortex. There are several proper ways to perform this surgical stage. Antibiotics are administered 30 minutes before incision. Under general anesthesia without muscle relaxant the patient is pinned in the 3-fixation point head holder and after proper cushioning of the bonny parts, the head is rotated to the contrary side of the craniotomy. External landmarks are taken to identify the central sulcus, and also with the aid of fMRI and neuronavigation confirmation, the face and hand area in the precentral gyrus is identified. A small round craniotomy is done (5 × 5 cm) over the target area and the dura carefully coagulated. Epidural neurophysiological testing and confirmation (SSEPs, motor evoked potentials (MEPs), and/or Electromyography (EMG)) of the painful area is performed, central sulcus is localized, two 4 contact paddle lead are perpendicularly placed over the motor and sensory cortex of the painful area, and stitched to the dura mater in several anchoring points. There is also a thought to cover with the stimulation the neighboring area of the pain, for a better pain control and to optimize the programming of the stimulator. The bone flap is relocated and closure is performed.

Saitoh *et al*. reported a case in which a 4 contact paddle electrode was placed within the central sulcus for pain control, this patient had a pain secondary to spinal cord injury and had an excellent outcome.[97,98] Insertion of the electrode arrays was originally proposed through burr holes, a trend exists toward performing craniotomies over the sensory cortex. This allows for better electrophysiological (SSEPs and electrical cortical mapping (ECM)) assessment of the motor cortex, which can be performed using electrode grids instead of the electrode itself.[100] The grids cover a greater cortical surface and help refine the location and orientation of the central sulcus, and the generous exposure is also advantageous for securely anchoring the electrode array(s) in position by anchoring sutures. Although some patients could complain of a more painful wound due to the extension of the surgical approach.[68]

Delavallée *et al*. studied eight patients with chronic neuropathic pain, and subdural plate electrode placement, found that all of the patients with trigeminal neuropathy had excellent and satisfactory outcome at the last follow-up, of the whole group three patients had seizures related to an abrupt increase in stimulation intensity, and two patients had hardware infections that required system replacement.[18]

Intraoperative monitoring

SSEPs are used intraoperative for localization of the central sulcus and precentral cortex. The N20-P20 phase reversal is used to identify the central sulcus and to guide the implantation of the permanent electrodes. A grid of electrodes allows for localization of the central sulcus at more than one point, determining its course within the craniotomy.[68] iCM is routinely used intraoperative and can be accomplished with the implantable electrodes or a monitoring grid. The electrode contact that produces motor contraction at the lower thresholds in the topography of pain should be identified. The surgical and anesthesia teams should be watching carefully for the occurrence of contractions and be prepared to manage intraoperative seizures. In patients without corticospinal injuries, iCM is thought to be the "gold standard" for localization, and even if cortical reorganization occurred as consequence of neuronal plasticity.[68]

Yamamoto *et al*. described in two patients the D-wave of the MEP as an intraoperative indicator for the placement of stimulating electrodes over the motor cortex for pain relief, the percentage VAS reduction was significantly correlated with the D-wave amplitude, indicating that D-wave recording provides and intraoperative guide

for placing the stimulating electrode at the optimum position on the motor cortex.[124]

Holsheimer *et al*. reported that monopolar stimulation should be applied in intraoperative neurophysiological testing because, contrary to bipolar stimulation, the corresponding MEPs are unambiguously related to a single stimulating electrode and their amplitude is not affected by the anode–cathode distance. The anode providing the largest MEPs intraoperatively should be selected as the chronic stimulation.[43]

Therefore, direct cortical stimulation (DCS) is the gold-standard technique for motor mapping during craniotomy, preoperative noninvasive motor mapping is becoming increasingly accurate. Two such noninvasive modalities are navigated TMS and magnetoencephalography (MEG) imaging. Tarapore *et al*. found that maps of the motor system generated with TMS correlate well with those generated by both MEG imaging and DCS. Negative TMS mapping also correlates with negative DCS mapping; hence navigated TMS is an accurate modality for noninvasive generating preoperative motor maps[114] and this can be a technique to explore for MCS surgery.

Velasco *et al*. reported that electrophysiological confirmation of the limits between motor and sensory cortices by studying phase-reversal polarity of N20 and P20 components is not always possible, and a more reliable method to determine the transition between somatosensory cortex and motor cortex seems to be corticocortical potential induced by stimulation of different pairs of grid contacts.[121]

Lefaucheur *et al*. reviewed the literature on intraoperative neurophysiologic mapping of the central cortical region for epidural electrode placement in the treatment of neuropathic pain by MCS, and found 41 reports addressing this theme, with different author's preference and methods. Lefaucheur *et al*. recommend based the localization of the electrode(s) based on MEP recordings in response to monopolar (anodal) stimulation of the cortical region corresponding to the painful area, and MEP mapping cannot be used in patients with total or severe motor deficit, and recommend in this case using fMRI-guided navigation for electrode placement. fMRI has good concordance between contours with SEPs and MEPs.[56]

Functional MRI scan and neuronavigation

A critical step in MCS treatment for FCNP is the localization of the somatotopic face region on the precentral gyrus. Recent imaging methods have introduced three-dimensional (3-D) MRI scan reconstruction that uses blood oxygen level-dependent (BOLD) contrast can also be helpful in determining the orientation of the precentral gyrus along the surface of the cortical convexity, specifically the face and hand area.[68]

In a series of reports with increasing number of patients, Pirotte *et al*. reported 21 patients with different types of neuropathic pain who underwent frameless neuronavigation MCS, all patients had a preoperative fMRI and had iCM with SSEP and motor cortex stimulodetection. Concordance between contours of fMRI activation area and iCM in precentral gyrus (mean distance, 3.8 mm) was found in 95% of the patients. The authors recommend combining both techniques in functional neurosurgical procedures because it can improve the quality of the operative targeting of selective motor cortex areas.[84-86] Gharabaghi *et al*. operated six patients with the combination of 3-D functional neuronavigation, intraoperative electrical stimulation, and continuous motor output in awake patients and reported that this combined imaging and stimulation approach for electrode positioning offers a safe and minimal invasive strategy for the treatment of chronic pain.[38]

There is also a very useful tool for MCS surgery such as the neuronavigation based on CT or MRI scan. This planning technique was pioneered by Nguyen *et al*. and the anatomical reference points can clearly be seen on oblique curved scans reconstructions. On these reconstructions, central, lateral, the interhemispheric, superior, and inferior frontal sulci can be clearly identified. The face area in the motor cortex is found 3 cm above the lateral sulcus (Sylvian) and does not exceed the inferior frontal sulcus. The target can thus be easily located and verified in real time on the CT or MRI images by using the pointer or the laser beam of the navigation system.[9,79] Tirakotai *et al*. reported 5 patients with central pain operated with a minimally invasive technique with the aid frameless neuronavigation and vacuum headrest. All patients obtained postoperative pain relief, no surgical complication occurred, and the postoperative course was uneventful in all patients.[116] Mogilner *et al*. in a study of 5 patients with chronic pain conditions, and reported that integration of functional and anatomical imaging data allows for precise and efficient surgical planning and may reduce the time necessary for intraoperative physiological verification.[73] In clinical settings where technology is not available, is expensive, or is not affordable, Velasco *et al*. recommends a good MRI imaging technique and a reliable iCM.[121]

Trial period

This trial period is necessary to assess the effects of the MCS therapy in terms of pain control and side effects; however, there is still a chance to have a placebo effect. Typically the trial lasts 7 days (range, 5–10 days) and in some countries by law the trialing period has to last 30 days.[18] The longer the trial period the higher risk of infection. Others authors do not perform a trial, directly implant the permanent system since the permanent electrode placement.[12] In author's experience in neuromodulation for chronic pain, during the trial patient should fill in a pain record (time of the day, stimulator

on or off, settings (stimulation group or program), and day activity, VAS and patient's comments) to objectivize the pain control with the MCS therapy and support the permanent implantation of the system.

Stage II procedure

This stage refers to the implantable pulse generator (IPG) placement. Stage II surgery is always performed under general anesthesia, with a shoulder roll elevating the shoulders and the head slightly rotated to the contrary side of the IPG implantation. Antibiotics are administered 30 minutes before incision. Typically for MCS therapy, the IPG is implanted in the subclavian region; therefore, a subcutaneous pocket is done, the implantation depth depends on the type of generator (nonrechargeable vs rechargeable), and the amount of fat tissue in the patient chest region. For a nonrechargeable IPG or a lean patient, the IPG can be located in the pectoral subfascial layer, and if it is a rechargeable IPG this should be located in a more superficial layer. It is also advisable to follow the recommendations of the manufacturer.

Surgery closure

The craniotomy flap site is usually fixed with titanium miniplates to the skull, and the test cable is exteriorized through the scalp in a different wound (counter-opening). After generous saline irrigation, scalp wound is closed in multiple layers, antibacterial absorbable suture 1 or 0 for the galea and deep subcutaneous tissue, antibacterial absorbable suture 3-0 for superficial subcutaneous tissue and subcuticular, and scalp with staples or antibacterial absorbable monofilament 3-0 for intradermal closure, and at the end skin sealant. The external cable is fixed to the scalp with monofilament nonabsorbable suture 2-0.

As the closing of the scalp, chest pocket is closed in multiple layers, taking care of not puncturing the hardware extensions with the needles. Author preference is to close the skin with antibacterial absorbable monofilament suture 3-0, and to apply skin sealant. This manner to close the skin avoids a likely painful stitch removal and diminishes the risk of wound infection.

Complications

Although in many studies no adverse events with MCS have been reported,[38,106,108,113] complications of MCS therapy are around 20% of patients experiencing one or more complications, in general of benign nature, but are reported such as battery failure, seizures (in the early or late postoperative period[93]), wound infections (2.2%), wound dehiscence, pain induced by stimulation, epidural or subdural hematoma, gradual diminution of pain relief benefit over a period of time,[3] hardware malfunction.[16] Seizures occasionally occurred during the motor mapping, but chronic seizures have been rarely reported at optimum electrical settings [Table 3].[13,104] Death is an extremely rare complication in MCS therapy.[1,42] Patients and their families should be clearly informed of the potential complications, and the need to look for prompt medical assistance if one or more complications present.

Table 3: Reported side effects and complications with MCS therapy

Procedure-related complication
Bleeding
• Epidural hematoma[77,79]
• Subdural hematoma[104]
• Large cerebral hematomas[72,97,99]
Infection[5,12,18,25,45,79,81,86,93,99,104]
Postinfection arachnoiditis[18]
Wound dehiscence[25,79]
Transient neurological deficits[45,81,93]
Breakage and/or malfunction of the hardware [12,104]
Epidural fibrosis[122]
Stimulation-related complication
Seizures[22,41,48,72,81,86,90,93,97,100,102,104]
Painful stimulation of the dura mater[49,72,79]
Dysesthesias[32,48,77]
Dysarthria[12,77,104]
Dysphasia[104]
Fatigue[12,104]
Unusual events
Impairment in a motor imagery task[117]
Development of a painful supernumerary phantom arm[10]
Cognitive function alteration[74]
Unpleasant pain in the same area of the original pain[9]
Analgesia via ipsilateral MCS[9]
Bilateral analgesia (or sensory effects) from unilateral MCS[9]

Velasco *et al.* reported a case of development of epidural fibrosis that interfered with the MCS, which was suspected by means of the increase in electrodes impedance (>2000 Ω) and the loss of effect to evoke cortico-cortical potentials by setting the IPG stimulation at 6–10 Hz, 450 μs, and up to 10.5 V, and this required a surgical removal or the fibrosis. In addition, the same group also reports a migration of the distal part of the electrode outside the area it was originally placed, this was corrected with another surgery.[122]

There are some unusual and very interesting effects related to the MCS, Tomasino *et al.* reported that the task involving motor imagery were slowed down by cortical stimulation, whereas those involving visual imagery were not. When the patient performed the motor-imagery task, the interference effect on response times disappeared if the stimulator was switched off, hence suggesting that the motor cortex is also involved in higher cognitive functions.[117] Canavero *et al.* reported a painful supernumerary arm following MCS for central poststroke pain [Table 2],[10] as well as other bizarre phenomena such as: a very unpleasant pain in the

same area of the original pain, analgesia via ipsilateral stimulation, and bilateral analgesia (or sensory effects) from unilateral MCS.[9]

Permanent stimulation parameters

Stimulation parameters used for MCS varied considerably not only across studies, but also among patients treated in the same center. The most commonly used settings were 2–3 V (range 0.5–9.5 V), 25–50 Hz (range 15–130 Hz), and 200 μs (range 60–450 μs). It was not possible to established a correlation between stimulation parameters and outcome because individual stings were not reported in several of the articles, stimulation parameters were not systematically studied in all studies, and stimulation settings in nonresponders were rarely reported.[29] For electrodes placed in the subdural space the stimulation parameters are usually less in amplitude, but similar in the pulse width and frequency.[18] Because many investigators have noted that MCS frequently produces a period of poststimulus pain relief that ranges from minutes to hours, many neurosurgeons try a cycling mode of MCS, with 10 minutes to 3 hours on stimulation followed by 15 minutes to 6 hours off stimulation.[42] Once the pain is relieved in the painful region, with no side effects related to the stimulation, electrode polarity and other parameters are adjusted. The optimal stimulation parameters vary widely from patient to patient, and testing requires time and effort to find the settings that provide the most pain relief with the minimum energy use.[3,102] Chronic stimulation was usually conducted in a bipolar configuration.[5,12,72,78,81,86,93,118]

Cost-effectiveness of motor cortex stimulation

MCS has crossed 21 years now in the chronic pain management armamentarium, and there is only one report addressing the cost-effectiveness of the therapy. Zaghi *et al*. studied the cost-effectiveness of the MCS and showed that comparing MCS vs rTMS, and found that at 1 year, rTMS was the most cost-effective approach, but MCS was the most cost-effective modality for neuromodulation of chronic pain at 5-year treatment consideration.[125]

Key questions and topics

The functional neurosurgeon facing the patient with FCNP, and considering MCS for treatment should respond these questions before considering and offering MCS as a treatment option:

- Have all the conventional treatments been tried in this case?
- Do I know perfectly this patient and his/her family situation?
- Is there something else that I could offer to this patient before neuromodulation?

There are a number of very interesting points that thus far have not been resolved, or more work needs to be done on them:

- More models of electrodes specifically thought for MCS are needed, besides of the new lead design reported and studied by Lefaucheur *et al*.[63]
- What is the best electrode placement, epidural or subdural?
- Does the surgeon need to take into account the distance between the dura and the cortex surface, to make a decision on whether place the electrode epidural or subdural?.
- What is the best number of electrodes to treat the patients with FCNP?
- Should we change the name of motor cortex stimulation, for sensory cortex stimulation, or sensorimotor cortex stimulation, or simply cortex stimulation?
- What is the best electrode orientation to the central sulcus, parallel or transversal?
- Does the neurosurgeon need to stimulate also the neighbor area to assure a better pain control?
- Is there a pharmacological trial useful before indicating MCS for FCNP?
- Does the rTMS have a role in the preoperative assessment of the patients who undergo MCS for FCNP?

CONCLUSION

MCS is a useful and important tool for treating FCNP patients, is a nondestructive, adjustable, and reversible therapeutic technique that is efficient for treating patients presenting FCNP, which are refractory to other types of treatment, even though its mechanisms of action are still not well established.[25] To the light of the current knowledge and the evidence in favor, MCS is a safe and efficacious therapy to include in the range of therapeutic options and to consider in patients with FCNP; however, large prospective randomized, multicenter clinical trials focusing on MCS for FCNP, and with longer follow-ups are needed.

In order to make more comparable the reported studies, more data are necessary to be taken into account (a clear mention of type of study, if patients had psychiatric, psychological and/or neuropsychological evaluations, initial parameters of stimulation, cycling of the stimulation, and other information). There are still some unresolved controversies on the topic, such as electrode placement (epidural vs subdural, perpendicular vs parallel to the central sulcus), number of electrodes, and number of contacts in the electrode, what is the best number of days to trial these patients and several other issues that need to be properly addressed in the next MCS reports.

Moreover, it is therefore important to mention that this procedure be performed by an experienced surgical team (including a functional neurosurgeon with experience in the field of pain), in institutions with the proper technology and expertise in order to minimize surgical risks and deal with complications in a prompt manner.

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