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Supraspinal stimulation for treatment of refractory pain

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ABSTRACT

Refractory pain syndromes often have far reaching effects and are quite a challenge for primary care providers and specialists alike to treat. With the help of site-specific neuromodulation and appropriate patient selection these difficult to treat pain syndromes may be managed. In this article, we focus on supraspinal stimulation (SSS) for treatment of intractable pain and discuss off-label uses of deep brain stimulation (DBS) and motor cortex stimulation (MCS) in context to emerging indications in neuromodulation. Consideration for neuromodulatory treatment begins with rigorous patient selection based on exhaustive conservative management, elimination of secondary gains, and a proper psychology evaluation. Trial stimulation prior to DBS is nearly always performed while trial stimulation prior to MCS surgery is symptom dependent. Overall, a review of the literature demonstrates that DBS should be considered for refractory conditions including nociceptive/neuropathic pain, phantom limb pain, and chronic cluster headache (CCH). MCS should be considered primarily for trigeminal neuropathic pain (TNP) and central pain. DBS outcome studies for post-stroke pain as well as MCS studies for complex regional pain syndrome (CRPS) show more modest results and are also discussed in detail.

Contents

1. Introduction

In the not so distant past, neurosurgical management of pain was limited to lesioning and ablative procedures treating only the most severely impaired patients with time limited effects. Today,

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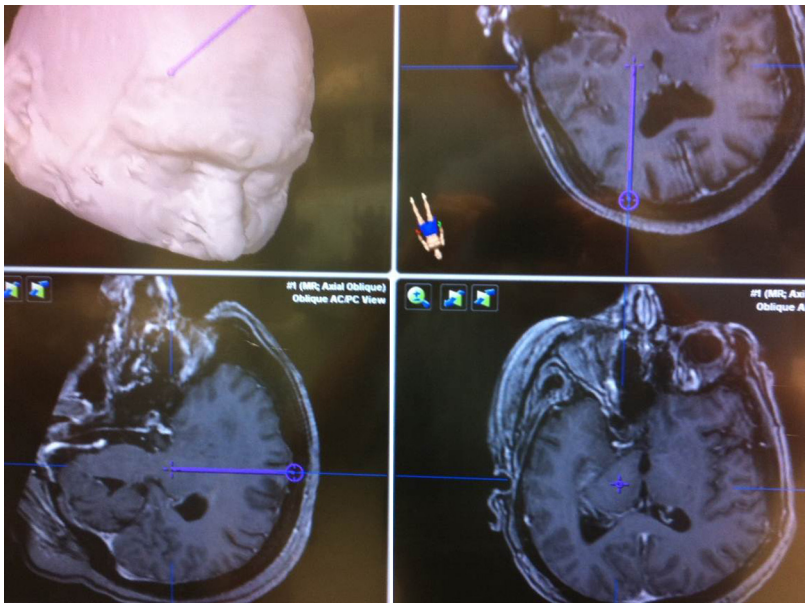

Fig. 1. MR guided planning in deep brain stimulation. Snapshot from planning station demonstrating target, entry, and trajectory for a DBS insertion on T1 weighted MR with gadolinium.

however, the neurosurgical treatment of pain has far transcended lesion-inducing procedures and also incorporates site-specific neuromodulation. Neurostimulators may be placed at virtually any site in the nervous system from the cerebral cortex, deep nuclei of the brain, spinal cord, and/or cranial/peripheral nerves. Despite the fact that neurostimulatory devices have been used for 50 years, our understanding of how stimulation works is still in its infancy. Melzack and Wall's gate theory of pain is most commonly referenced, typically for spinal cord stimulation [1].

Stimulatory devices can be placed at a variety of levels in the nervous system and proper location is essential to achieving adequate pain relief. In the majority of cases, the electrode should be placed "above" the level of pain involvement. For example, if patients suffer a nerve root injury after back surgery, a spinal cord stimulator (SCS) is generally the first neuromodulatory strategy attempted for refractory pain. Placing the device above allows the descending pathways to be targeted rather than the interneurons and cells at the level of injury, i.e. the very same pain transmission cells one is trying to inhibit [1]. An antidromic as well as an orthodromic activation of the dorsal column fibers may also play a role. In this article, we intend to better elucidate outcomes based on disease process by focusing on supraspinal stimulation (SSS) for treatment of pain and discussing off-label uses of deep brain stimulation (DBS) and motor cortex stimulation (MCS) for specific pain conditions to that avail. It is our hope, that stratifying outcomes by disease process will better guide future clinical-neuroscientific decisions.

2. Deep brain stimulation

DBS is the most invasive form of neuromodulation. Specifically, it involves targeting a deep structure in the brain. In order to do this effectively, thin cut T1 with gadolinium and T2 weighted MRIs must be obtained (Fig. 1). Stereotaxy must be used, which involves putting the location in the MRI into vector space. This entails obtaining imaging in a stereotactic frame. The MRI may either be obtained in advance and a CT done the day of surgery with the frame in place or the MRI may be done the day of surgery with the frame in place. After planning the target and entry site to avoid blood vessels and critical structures, a burr hole is made and DBS lead is placed into the target region (Fig. 2). Microelectrode recording and macrostimulation is often performed intra-operatively to ensure that no adverse effects are seen at parameters commonly used in the clinic.

DBS has been used in a selection of pain syndromes (Table 1). Overall, percent success is 61% for nociceptive pain, 54% for neuropathic pain, 71% for phantom limb, 36% for central pain, and 71% for chronic cluster headache. Certain pain etiologies seem to have better treatment outcomes than others for DBS; speculation as to why this occurs may arise from maladaptive plasticity development in central based etiologies. DBS targets CNS

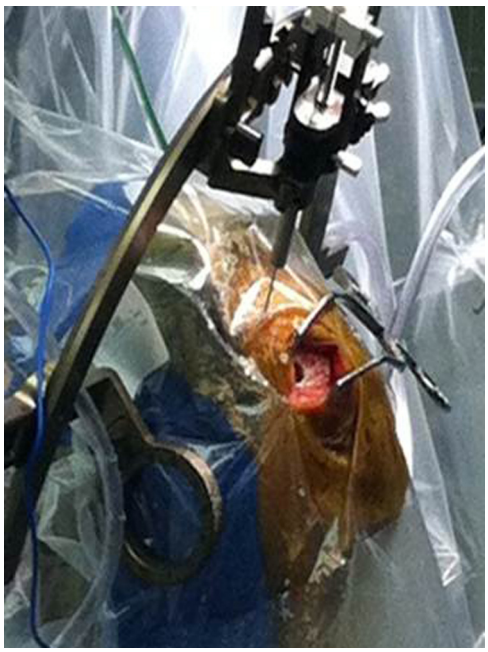

Fig. 2. Intra-operative photograph of DBS surgery. Demonstration of burrhole based on entry point chosen on MRI. The photograph shows the stereotactic frame that allows for determination of vector coordinates and the microdrive which allows for electrode implantation.

Table 1
DBS for select studies. Data represents implanted patients and success in the last decade based on mixture of objective outcomes as well as pain relief greater than 40% at most recent follow-up.

Study	Patients	Deep brain stimulation		Percentage success (%)
		Type of pain	Pain relief success	
Tsubokama et al. [48]	11	Central	8	72
Nguyen et al. [52]	10	Central	5	50
Nguyen et al. [53]	13	Central	10	77
Tanei et al. [58]	1	Central	0	0
Saitoh et al. [59]	4	Central	2	50
Rasche et al. [75]	7	Central	1	14
Katayama et al. [77]	31	Central	15	48
Mertens et al. [84]	20	Central	12	60
Tirakotai et al. [83]	5	Central	5	100
Katayama et al. [85]	3	Central	2	66
TOTAL	105		60	57%
Previnaire et al. [18]	7	Central (SCI)	4	57
Nguyen et al. [52]	2	Central (SCI)	1	50
Tanei et al. [58]	2	Central (SCI)	2	100
TOTAL	11		7	64%
Meyerson et al. [51]	7	Central (PSP)	3	43
Tanei et al. [58]	8	Central (PSP)	6	75
Carroll et al. [72]	5	Central (PSP)	2	40
Drouot et al. [86]	13	Central (PSP)	9	69
Fukaya et al. [87]	31	Central (PSP)	29	94
Garcia Larrea et al. [88]	7	Central (PSP)	4	57
TOTAL	71		53	75%
Meyerson et al [51]	2	Peripheral	1	50
Nguyen et al. [52]	1	Peripheral	1	100
Saitoh et al. [59]	4	Peripheral	4	100
Drouot et al. [86]	18	Peripheral	12	67
TOTAL	25		18	72%
Son et al. [61]	1	CRPS II	1	100
Velasco et al. [62]	4	CRPS I/II	4	100
Fonoff et al. [63]	2	CRPS I	2	100
TOTAL	7		7	100%
Brown and Pilitsis [49]	8	TNP	6	75
Ebel et al. [50]	6	TNP	3	50
Meyerson et al. [51]	5	TNP	5	100
Nguyen et al. [52]	7	TNP	7	100
Nguyen et al. [53]	12	TNP	10	83
Tanei et al. [55]	1	TNP	1	100
Nguyen et al. [57]	4	TNP	3	75
Rasche et al. [75]	10	TNP	3	30
TOTAL	53		38	72%

structures; if such structures are injured/maladaptive, suboptimal inhibition may be evident. On the other hand, in peripheral lesions, the target areas for DBS are generally intact. Pain is regardless an off label use for DBS jointly due to insufficient prospective analysis and efficacy. Two multicenter trials of DBS for pain were conducted for FDA approval and yielded unsatisfactory results [2]. However, success has been reported with refractory pain. A meta-analysis of DBS for pain relief by Bittar et al. demonstrates that DBS for nociceptive pain resulted in pain relief in 63% of patients; whereas, pain relief for deafferentation pain was obtainable in 47% of patients [3]. 61% of nociceptive pain patients and 42% of neuropathic pain patients experienced long term pain relief [4]. Nociceptive pain is typically targeted with periaqueductal gray (PAG)/periventricular gray (PVG) stimulation. The physiology of PAG/PVG stimulation is based upon naloxone reversible endorphin release and connections with descending pathways for inhibitory actions against pain transmission cells [5–7]. Recent studies also suggest ascending projections from PAG/PVG to the thalamus and frontal lobes as well [8]. Accumulated studies indicated that when the PVG was stimulated 59% of nociceptive pain patients achieved long term success, but when the Ventroposterolateral nucleus (VPL) of the thalamus was stimulated 0% of 51 nociceptive pain patients achieved long term success [4]. Thus, the PAG/PVG targeting plays a greater role in treating nociceptive pain.

2.1. Neuropathic pain

Though clinical trials failed to show efficacy by population, pain relief with DBS in approximately 40% of individuals with neuropathic pain has been reported [9]. Therefore, this modality

is still a viable option in patients refractory to all other modalities of pain management. Success with DBS for neuropathic pain has been shown for poly- and mono-neuropathies, phantom limb syndrome, and complex regional pain syndrome type 1 (CRPS1) [7,10–13]. Boccard et al. recently published a prospective, 12 year study on DBS outcomes for several neuropathic pain syndromes [14]. Of 197 patients referred, 85 patients received DBS implantation, making this study one of the larger studies of DBS for pain. In an overall outcome analysis for neuropathic pain within 1 year, VAS, SF-36, MPQ,EQ-5D, and health state improved by 48%, 27%, 24%, 20%, and 76%, respectively. Even at the 4 year follow-up clinical scores still demonstrated improvement compared to preoperative scores. In terms of anatomical targets, the meta-analysis by Levy et al. demonstrated that with VPL stimulation 56% of neuropathic pain patients achieved long term pain relief; on the other hand, with PVG stimulation only 23% had adequate long term pain relief [4]. Thus, VPL stimulation was best associated with treatment for neuropathic pain. However, because there is often overlap in terms of nociceptive and neuropathic symptomatology, optimizing treatment necessitates simultaneous PAG/PVG and VPL implantation trials. Boccard et al. in fact, advocate for starting with PVG stimulation first, observe for intraoperative pain relief, and if inadequate proceed to the VPL site [14]. For facial pain, VPM was targeted first.

2.2. Phantom limb syndrome

DBS for phantom limb pain has been investigated. Bittar et al. showed that 3 patients at a mean follow-up of 13.3 months reported 55–70% pain relief [3]. Another group, Katayama et al. had 19 cases of phantom limb pain treated with initial spinal cord stimulation (SCS) with the addition of, MCS and/or DBS, if the pain persisted despite SCS [15]. The group reported that 6 out of 10 (60%) of the SCS-refractory phantom limb pain had satisfactory long term pain control with DBS. Only 20% with MCS had satisfactory results. Four patients had both DBS to the nucleus ventralis caudalis (Vc) of the thalamus as well as MCS. Two reported superior pain control with DBS, whereas one patient noted better results with MCS. Additionally, the recent prospective 12 year study of DBS for neuropathic pain by Boccard et al. included 7 patients with phantom limb syndrome and long term outcomes [14]. At 1 year follow-up, mean pain relief was 39% for 7 of 9 phantom limb syndrome patients. Pereira et al. also recently published 5 patients with implanted DBS for neuropathic pain following amputation. Based on post-op VAS, 3 patients reported successful (>40% pain relief) outcomes [16].

2.3. Post-stroke pain

Outcomes with specifically post-stroke pain (PSP), a condition of neuropathic pain, are also important to become aware of if considering DBS treatment. Bittar et al. reported 50% (24/45) of post stroke patients had a successful trial; of those, only 58% (14/24) of them were able to sustain ongoing pain relief [7,8,11,12]. Essentially, 29% of all post-stroke patients will have continuing pain relief with DBS trial and implantation [3]. Based on a study of 47 patients with various etiologies of pain, patients with neuropathic post-stroke pain trialed successfully 33% of the time [17]. Again, the 12 year prospective study by Boccard et al. reported long term outcomes for 13 of 23 post-stroke pain patients. At 1 year follow-up, mean pain relief based on VAS was 44% [14]. DBS still remains a consideration for refractory post-stroke pain, although the percentage of patients with successful trials and long term success is lower than that for other indications. For other central pain syndromes, such as spinal cord injury (SCI) and thalamic pain syndrome, results with DBS have been more modest. 16% of 19 SCI patients had long term efficacy with DBS; Boccard et al. reported 63% mean pain relief based on VAS for 3 patients with spinal insult at 1 year follow up [14,18]. Similarly, only 1 of 5 thalamic pain syndrome patients had sufficient pain relief to even undergo implantation [18]. Additionally, Hosobuchi et al. also reports only 1 of 3 thalamic pain syndrome patients having successful, ongoing pain relief [11]. It is important to recognize that in thalamic pain syndrome, though often etiologically post-infarction, treatment success may be related to the extent of encephalomalacia. If significant thalamic matter is damaged, targeting of the thalamus by DBS is thought to be futile [10,11]. Internal capsule targeting has shown to be ineffective as well [10]. It is generally believed central pain syndromes are not an indication for DBS implantation.

2.4. Chronic cluster headache

DBS has more recently been used to treat refractory, chronic cluster headache (CCH), targeting the posterior hypothalamus. Approximately 10–20% of CCH are resilient to medical treatment [19]. A randomized controlled double blinded trial with active and sham stimulation for 1 month was performed on 11 patients with CCH [20]. At 1 month, there was no significant difference in frequency of headaches between groups. However, after 1 year, 3 of 11 patients were entirely pain free, and a 6 of 11 had a decrease in frequency by 50% or more [20]. Others have shown similar results. In Broggi's cohort, 10 of 16 patients were pain free at 18 months, and at the 5 year follow up the percentage of pain free days jumped from 2% to 71% in the remainder of patients [21]. Similarly, 13 of 16 of Leone's patients at 23 months were either “pain-free” or “almost pain-free” [22]. Data using a slightly modified target, i.e. the posterolateral hypothalamus, appears similar with 2/5 patients pain free at 33 months, another 2/5 patients having greater than 90% decrease in attacks, and 1/5 having attacks reduced by half [23]. Failures have also been reported [24,25]. Overall, the general consensus is that the percentage of CCH patients with positive response to DBS is about 50% to 60% and that this procedure has the potential to provide complete long term pain resolution or no pain resolution whatsoever [26,27].

2.5. Affective component of pain

Conventionally, the target locations for neurostimulatory treatment of pain include areas involving sensory-discrimination, i.e. VPL thalamus and PAG/PVG. However, newer studies and reviews shift toward targeting the affective connections to the pain matrix [28,29]. Surgical cingulotomies have first demonstrated decreased affective response to pain and continue to be used for cancer pain among refractory psychiatric disorders [30–32]. Since then, a case report by Boccard et al. describes implanting bilateral DBS electrodes into the anterior cingulate cortex (ACC) and stimulation provided >50% pain relief even at 2 years out [33]. An ongoing randomized, double-blinded trial of DBS for 10 thalamic pain syndrome patients attempts to characterize the efficacy of targeting the affective ventral striatum/anterior limb of internal capsule [34].

2.6. Complications

Finally, it is important to note potential complications of DBS. Intracranial hemorrhage (ICH) is certainly the most feared complication and has a reported incidence from 1.9% to 4.1% [4]. Generally, ICH occurs at cortical entry site and most are asymptomatic. In the event that symptoms result, i.e. a seizure and/or new neurological deficit, generally evacuation or device revision is not required. In fact, patients typically improve with supportive therapy alone. The more common complication is

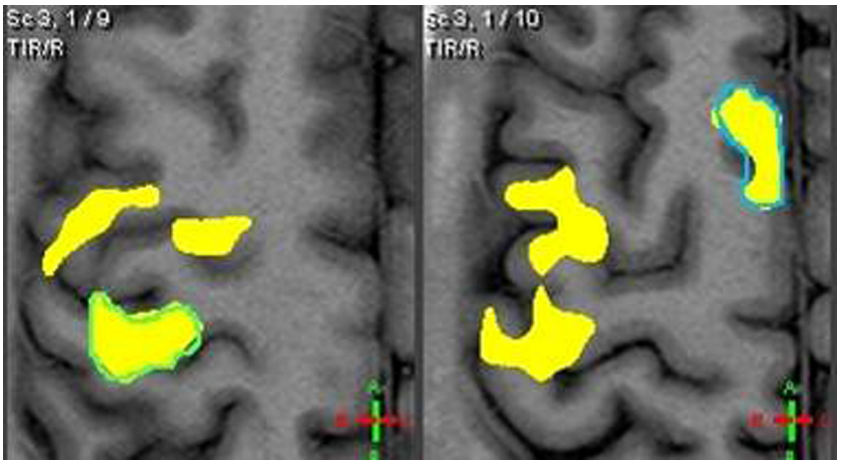

Fig. 3. Functional MRI Preoperative to MCS implantation. Preoperative fMRI is often used to localize the motor cortex (MC). (A) Pain originating from the left hand as shown in green outline is localized to the lateral aspect of MC. (B) Pain originating from the left leg as shown in blue outline is localized to the medial aspect of MC. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

infection (2.4%) which tends to be hardware related rather than intracranial [35]. Occasionally, these infections may be treated with antibiotics alone; however often devices must be removed. They may be reimplanted once the infection clears, but is no doubt a major setback for the patient. Hardware complications (7%) may also occur over the lifespan of the device and include lead fracture, internal pulse generator (IPG) failure, migration, device infections, or erosions [36]. Less common complications include ischemic events, cerebral edema, and venous air embolism [37–40]. Peri-operative seizures are rare [41]. Nausea (10.6%) and various transient vision changes have occurred with PAG/PVG stimulation implantation [4].

3. Motor cortex stimulation

Motor cortex stimulation (MCS) is another neuromodulatory modality used to treat refractory pain. The surgical approach in MCS involves stereotactic navigation, craniotomy, and intra-operative physiologic localization of the precentral gyrus and central sulcus. Specifically, patients commonly undergo thin slice MRI as well as functional MRI to identify the area of the motor strip that correlates with their painful area (Fig. 3). Surgery requires a frameless neuronavigation system and physiological monitoring of phase reversal. Once the motor cortex is located intraoperatively, epidural electrodes are placed and sutured to the dura (Fig. 4). Trials of MCS device are often debatable. Because effective pain relief for MCS is often delayed, trials often have to be prolonged, which on the other hand increases infectious risk. Thus, trials are dependent on the surgeon's discretion. Others however have suggested that most patients who forego trial fail therapy within 6 months [42]. Based on their results, 62.5% of patients that passed trials of MCS would achieve adequate pain relief for an average of 33 months with complete implantation [42].

The physiologic basis for MCS is based upon both increased neuronal activity via increasing blood flow to the thalamus and brainstem and stimulating endogenous opioid production in the PAG region [43,44]. Originally, it was speculated that motor cortex electrical stimulation linked to neurons of the primary somato-sensory cortex and provided descending pain relief from there. However, recent studies with fMRI clearly identify thalamus induced circuits rather than short-loop circuits with the post-central gyrus, or primary somatosensory cortex, as sites of greater activity [43–47]. On the other hand, particularly in thalamic pain patients, Tsubokawa et al. emphasize MCS ability to reduce thalamic hyperactivity via stimulation of inhibitory areas of sensory cortex [41,48]. In patients with thalamic injury, thalamic circuits may no longer be dominant. As such, MCS effect on the post-central gyrus may be more pronounced. When broken down by etiology, we have learned that percent success of MCS appears to be 57% for general central pain, 64% for SCI, 75% for PSP, 100% for CRPS I/II, and 72% for trigeminal neuropathic pain (TNP) (Table 2).

3.1. Facial pain

Numerous studies have explored the use of MCS for various pain syndromes. Most MCS reports focus on TNP, including anesthesia dolorosa and postherpetic neuralgia. Compiled results from all studies of MCS for trigeminal neuropathic pain showed 76% of 38 reported patients obtaining substantial ($\geq$50%) pain relief [49–54]. Brown and Pilitsis report 8 patients with TNP from postherpetic neuralgia, deafferentation following surgery, and post-stroke pain [49]. Medication dosage was reduced by greater than 50% because of the substantial pain reduction. Tanei et al. describes a case of multiple sclerosis-related facial pain that was resistant to carbamazepine, gabapentin, morphine, amitriptyline, diazepam, and ketamine drip infusions [55]. After MCS, patient had >60% pain relief, was taken off of twice-monthly ketamine drip, and had marked reduction in other

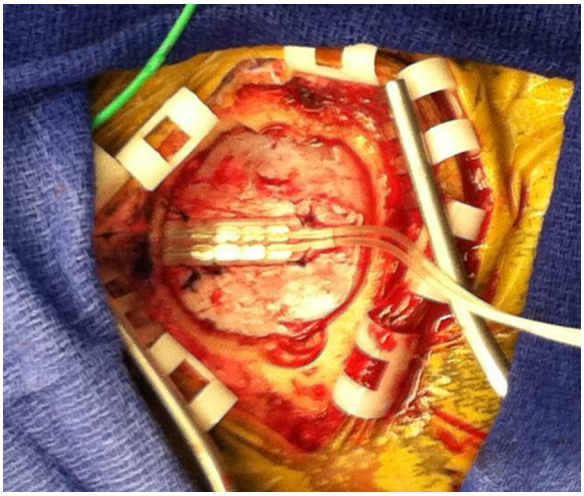

Fig. 4. Intraoperative photograph from MCS procedure. Demonstration of placement of Epidural electrode placement during MCS. The paddle lead location was finalized based on neuronavigation and electrophysiological determination of the motor cortex.

Table 2
MCS for select studies. Data represents implanted patients and success in the last decade based on mixture of objective outcomes as well as pain relief greater than 40% at most recent follow-up reported.

Study	Patients	Motor cortex stimulation		Percentage success (%)
		Type of pain	Pain relief success	
Bittar et al. [3] (meta-analysis)	204	Nociceptive	129	63
Levy et al. [4] (systemic review)	291	Nociceptive	172	59
TOTAL	495		301	61%
Bittar et al. [3] (meta-analysis)	220	Neuropathic	103	47
Levy et al. [4] (systemic review)	409	Neuropathic	228	56
Boccard et al. [14] (case series)	59	Neuropathic	39	66
Hamani et al. [89]	13	Neuropathic	5	38
TOTAL	701		375	54%
Bittar et al. [3]	3	Phantom limb	3	100
Boccard et al. [14]	9	Phantom limb	8	89
Katayama et al. [15]	10	Phantom limb	6	60
Pereira et al. [16]	5	Phantom limb	3	60
Rasche et al. [90]	4	Phantom limb	2	25
TOTAL	31		22	71%
Richardson et al. [7]	5	Central (PSP)	2	40
Kumar et al. [10]	5	Central (PSP)	1	20
Kumar et al. [10]	3	Central (SCI)	0	33
Hosobuchi et al. [11]	8	Central (PSP)	6	75
Hosobuchi et al. [11]	3	Central (TPS)	1	33
Boccard et al. [14]	23	Central (PSP)	13	57
Boccard et al. [14]	3	Central (SCI)	3	100
Previnaire et al. [18]	19	Central (SCI)	3	16
Rasche et al. [90]	12	Central (SCI)	2	17
Rasche et al. [90]	11	Central (PSP)	2	18
TOTAL	92		33	36%
Fontaine et al. [20]	11	CCH	6	55
Broggi et al. [21]	16	CCH	10	63
Leone et al. [22]	16	CCH	13	81
Seijo et al. [23]	5	CCH	5	100
TOTAL	48		34	71%

pain medications. Successes with MCS have also been seen in cases trigeminal deafferentation pain following trigeminal neuralgia surgery and meningioma resection [56].

A double blinded crossover trial of MCS in ten patients with trigeminal neuropathic and hemifacial pain, also demonstrated encouraging results [57]. Various pain scales and quality of life measurements initially indicated reduced pain for "ON" stimulation than "OFF" stimulation. Ebel et al. report 7 cases of dysaesthesia, anaesthesia dolorosa and postherpetic neuralgia [50]. Long lasting pain relief was demonstrated in 50% of patients, while the other half had reduction in efficacy over time. Small sample sizes limit true conclusions to be drawn [49,50,56]. Largely based on the evidence of double blinded cross over cohort studies and retrospective individual case reports, MCS improved pain outcomes and decreased pain medication dosages in trigeminal facial pain. Results, however, seem to vary dramatically in clinical practice.

3.2. Central and peripheral etiologies

MCS has also shown some success in other pathologies. A retrospective study of 11 patients with intractable central neuropathic pain included 8 patients with post-stroke thalamic pain, 2 with spinal cord injury (SCI), and 1 with a multiple sclerosis brainstem plaque [58]. Notably, 6 of 8 (75%) thalamic pain patients and the entire spinal cord/brainstem lesion group experienced effective pain relief as measured by the VAS. Additionally, Nguyen et al. describes 77% of 13 central pain patients experiencing $\geq$75% pain relief [53]. Previnaire et al. identifies that for spinal cord injury, 57% of 7 patients had long term efficacy with MCS [18].

Saitoh et al. reported a comparison study of 8 patients that underwent MCS for either central pain (4 patients) or peripheral pain (4 patients), specifically phantom limb syndrome and brachial plexus injury [59]. One hundred percent of peripheral pain patients rated pain reduction from fair to excellent anywhere from 6 months to 19 months. When comparing central versus peripheral etiologies of pain in select studies, MCS stimulation demonstrates successful outcomes in 57% of central etiology patients and in 72% of peripheral etiology patients as demonstrated on Table 2.

3.3. Complex regional pain syndrome

Although TNP and central pain syndromes are the classic MCS indications, CRPS patients have also been treated. A case report demonstrated MCS being effective for a patient with CRPS type II with hemibody allodynia [61]. Another larger study of 5 patients with CRPS1 and CRPS2 reported 4 patients with successful trials [62]. In follow-up ranging from 3 to 6 years, the VAS and McGill pain scores decreased significantly and allodynia and hyperalgesia were essentially no longer present. Intriguingly, sympathetic signs also dissipated. At 27 months and 36 months postoperatively, another group reported a continued reduction of 60–70% in VAS

scores of 2 CRPS type 1 patients [63]. The group also notes improved motor function, i.e. increased range of motion of affected limbs, after MCS. However, whether the analgesic effect itself allowed for greater motor involvement or whether MCS directly improved motor function is difficult to discriminate between. MCS may be a potential treatment option for drug resistant, SCS resistant CRPS.

3.4. Ancillary tools

In the last decades, novel neurostimulatory devices, techniques and thought processes have revolutionized supraspinal stimulation's potential in pain modulation. Neuromodulation of pain will continue to expand as our knowledge of the pathophysiology grows. To that avail, functional imaging and electrophysiological data will provide correlates. Specifically, diffusion tensor imaging (DTI), bold activation MRI and FDG-PET may also aid by determining which conditions may be altered by MCS and to optimize the placement of the implanted electrodes. An electrophysiological tool that may be employed is repetitive transcranial magnetic stimulation (rTMS).

rTMS involves a magnetic induction subthreshold to motor evoked potentials in site specific neurons. In one study, 16 patients underwent rTMS prior to MCS [64]. Eight patients had TNP and 8 were hemi-body neuropathic pain patients; 10 of 16 patients showed a positive response to rTMS. Of the positive rTMS responders, 3 patients were found to have very good response (greater than 75% pain reduction) to MCS. In the rTMS non-responders, no patients had a greater than 75% pain reduction. However, all patients treated with rTMS, both responders and nonresponders, achieved at least >50% pain reduction to treatment with MCS.

However, the largest study to date elaborating on rTMS and its ability to assess substantial pain relief with MCS is by Lefaucheur et al. [65]. 79% of 33 patients who responded to active rTMS responded to MCS; 100% of 21 patients who responded to sham rTMS responded to MCS. Other studies also confirm that positive response to rTMS can be used to assess responsiveness to surgical interventions, i.e. MCS [68–71]. However, the converse may not necessarily be accurate; failed response to rTMS may not indicate failed response to MCS [64,65].

3.5. Complications

The most common complication of MCS is seizures (12%, range 0–41%) based on a pool of 157 patients with MCS [46,48,49,51,53,59,72–76]. This can occur during implantation, reprogramming of the stimulator settings, or after long term MCS [46,50,59,74,77–80]. In our experience, this most often occurs during programming and may be an expected complication. In the vast majority of cases, the seizures resolve with a decrease in stimulation. It should be noted that epidural MCS has never been described at the origin of chronic epilepsy. Transient neurological changes have also been seen due to settings. Esfahani et al. reports a patient with facial droop and speech complications that resolved quickly after decreasing the stimulation settings [56]. Another potential complication of MCS is ICH (2.5%). Other complications include infections (5.7%) and hardware difficulties (5.1%) [73]. As with any neuromodulation technique, MCS efficacy may decrease over time and patients should be warned of that possibility.

4. Conclusion

Pain is one of the most common complaints that brings patients to the attention of primary care providers and specialists. Fortunately most pain is transient and responsive to medical therapy. For the subset of patients with refractory chronic pain, the suffering, disability, and socioeconomic effects are far reaching.

With the help of neurostimulator devices, advances in medical therapies, and a multidisciplinary approach, our hope is that refractory chronic pain complaints can be managed more effectively. We have learned that DBS, based on efficacy, currently should be considered for refractory conditions including: nociceptive pain (61%), phantom limb pain (71%), and CCH (71%). MCS should be considered for central based pain (57–75%) as well as TNP (72%). Thus, the decision making process for MCS versus DBS we believe should be focused on pain etiology. It is also our hope that by stratifying patient outcomes by disease process and neurostimulatory treatment, clinical practitioners can now have a stronger grasp of the efficacy of such practices and use this information to both reform future clinical decisions and relate treatment success to pathophysiology as a neuroscientific tool. The next pressing steps for DBS/MCS for refractory pain treatment must without a doubt include large, randomized trials in the hopes of gaining general acceptance, paving the way to FDA approval. Taken together, however, it is clear that the practice of neurostimulation has fruitfully transcended above the level of the spine. We will no doubt continue to use functional imaging, electrophysiological correlates with TMS, pre-clinical research and clinical experiences to expand the field.

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