Current Pain and Headache Reports (2018) 22: 45
https://doi.org/10.1007/s11916-018-0697-1

NEUROMODULATION (M GOFELD, SECTION EDITOR)

Motor Cortex Stimulation for Deafferentation Pain

Ahmed E. Hussein[1] · Darian R. Esfahani[1] · Galina I. Moisak[2] · Jamil A. Rzaev[2] · Konstantin V. Slavin[1]

Published online: 23 May 2018

Abstract

Purpose of Review Since the early 1990s, motor cortex stimulation (MCS) has been a unique treatment modality for patients with drug-resistant deafferentation pain. While underpowered studies and case reports have limited definitive, data-driven analysis of MCS in the past, recent research has brought new clarity to the MCS literature and has helped identify appropriate indications for MCS and its long-term efficacy.

Recent Findings In this review, new research in MCS, repetitive transcranial magnetic stimulation (rTMS), and transcranial direct current stimulation (tDCS) are analyzed and compared with historical landmark papers. Currently, MCS is effective in providing relief to 40–64% of patients, with decreasing analgesic effect over time addressed by altering stimulation settings. rTMS and tDCS, two historic, non-invasive stimulation techniques, are providing new alternatives for the treatment of deafferentation pain, with rTMS finding utility in identifying MCS responders. Future advances in electrode arrays, neuro-navigation, and high-definition tDCS hold promise in providing pain relief to growing numbers of patients.

Summary Deafferentation pain is severe, disabling, and remains a challenge for patients and providers alike. Over the last several years, the MCS literature has been revitalized with studies and meta-analyses demonstrating MCS effectiveness and providing guidance in identifying responders. At the same time, rTMS and tDCS, two time-honored non-invasive stimulation techniques, are finding new utility in managing deafferentation pain and identifying good MCS candidates. As the number of potential therapies grow, the clinician's role is shifting to personalizing treatment to the unique pain of each patient. With new treatment modalities, this form of personalized medicine is more possible than ever before.

Keywords Motor cortex stimulation · Neuromodulation · Neuropathic pain · Repetitive transcranial magnetic stimulation · Transcranial direct current stimulation · Trigeminal neuralgia

Deafferentation pain is a severe chronic pain secondary to an injury of the neural pathways and is characterized by a stabbing, burning sensation that ultimately negatively affects all aspects of personal life. Deafferentation pain can arise from a number of sources, ranging from central origin, such as an ischemic infarct, to a peripheral source, including trigeminal nerve injury, herpetic infection, or limb amputation [1]. Patients with deafferentation pain typically present with varying degree of sensory loss, as well as disturbance in pain and temperature sensation. In addition to sensory loss, many patients also experience abnormal sensory phenomena such as dysesthesias, hyperalgesia, and allodynia [2].

Recent literature has helped elucidate the mechanisms of deafferentation pain, allowing for more focused therapies. Deafferentation pain typically presents in a delayed fashion after neurologic injury and is associated with "maladaptive plasticity" that manifests as cortical and subcortical changes secondary to abnormal nociceptive input [1] and may be reversed with adequate pain treatment [3].

Motor cortex stimulation (MCS) is a unique neuromodulation intervention that has been used for patients with refractory pain and found to be effective for many sources of deafferentation pain. Over the last several years, MCS has been featured prominently in the pain literature, with studies illustrating various surgical techniques, exploring neuroanatomic mechanisms, and demonstrating the efficacy of the technique. In this review, we explore and evaluate some of these recent studies.

This article is part of the Topical Collection on *Neuromodulation*

✉ Konstantin V. Slavin
kslavin@uic.edu

[1] Department of Neurosurgery, University of Illinois at Chicago, 912 South Wood Street, 451-N NPI, (MC 799), Chicago, IL 60612, USA

[2] Federal Neurosurgical Center of Novosibirsk, Novosibirsk, Russian Federation

The Mechanism of Pain

Pain from noxious stimuli serves as an invaluable protective mechanism. To adapt to particularly intense pain stimuli, the nervous system is capable of sensitization, in which the nociceptive system lowers its threshold and increases the amplitude of the pain reflex to avoid further exposure to potentially dangerous stimuli. While usually adaptive, in certain conditions, pain can arise spontaneously by harmless stimuli (allodynia), elicit an exaggerated response (hyperalgesia), or spread away from the original site of injury (secondary hyperalgesia).

In deafferentation syndromes, persistent activity of the nociceptive pathways can result in dysfunctional, maladaptive plasticity. While plasticity is usually considered a positive, adaptive change of the brain, in maladaptive plasticity, rearrangement of pain structures, or central sensitization, results in significant allodynia and hyperalgesia [4]. Maladaptive plasticity can manifest as increased spontaneous activity of neurons, decreased threshold for activation from peripheral stimuli, and enlarged receptive fields [4, 5].

Motor Cortex Stimulation

First proposed by Tsubokawa and colleagues in 1991 [6], MCS was found to be effective in providing relief in patients with pain refractory to medical therapy. Since its discovery, MCS has been found to be effective for a number of pain syndromes, including post-stroke pain [7], post-herpetic neuralgia [8, 9], nerve injury [8, 9], and phantom limb syndrome [10], and other refractory to other methods conditions.

Stimulation of the motor cortex can be achieved through invasive techniques, such as implanted epidural or subdural electrodes, or non-invasive means, such as transcranial magnetic stimulation and transcranial direct current stimulation [11]. While non-invasive techniques carry fewer risks, implantation of epidural or subdural electrodes has been shown to achieve better outcomes [11].

Neuroanatomic Mechanisms of MCS

Although the ability of MCS to provide significant relief to many patients with intractable pain is well established, the mechanism underlying its efficacy remains largely unknown. Indeed, one of the great mysteries of functional neurosurgery is the seemingly disparate relationship between activation of a motor region, the precentral gyrus, and improvement of pain, the non-motor phenomenon. Most contemporary hypotheses are based on functional imaging studies.

To support the proposal of the initial research that analgesia from MCS was through modulation of thalamocortical pathways [6], more recent studies have confirmed that integrity of the thalamocortical tracts is essential in facilitating analgesia from stimulation of the primary motor cortex, either through direct electrical stimulation (i.e., MCS) or by repetitive transcranial magnetic stimulation (rTMS) [12, 13]. Electrical stimulation of the motor cortex has been demonstrated to reinforce thalamocortical inhibitory control over nociceptive signals in both animals [14, 15] and humans [16, 17].

The anti-nociceptive effect of MCS can be delayed, however, taking a few days to weeks [18], suggesting that pain relief may be mediated through pain network modulation involving several other structures, rather than providing a simple, inhibitory signal from the primary motor cortex. Other structures implicated include the periaqueductal grey [19–21], as well as the anterior cingulate gyrus [22], contralateral thalamus [23], somatosensory cortex, and prefrontal cortex [24], each of which demonstrate increased cerebral blood flow during MCS. The activation of these areas, associated with the subjective interpretation of pain, suggest that MCS may function as a "top-down" inhibitory signal providing long-lasting clinical effects that persist beyond the stimulation period.

Relief of facial pain has been associated with not only the contralateral but also the ipsilateral trigreminothalamic pathway, with transmission of information between dorsal parts of the principal sensory nucleus and cerebral cortex [25]. In studies of oral pain, fMRI studies have noted bilateral activation of the primary and secondary somatosensory cortex, mediodorsal thalamus, insular cortices, anterior cingulate cortex, and primary motor cortex after painful stimulation [26, 27].

Building on recent functional imaging studies, the role of the insular cortex has been subject to new investigation. In a recent paper by Jung et al., neuropathic pain was induced in rat models, and lesions were performed in the rostral anterior insular cortex (RAIC). Pain tolerance was noted to be significantly higher in the RAIC lesion group, and, when MCS was added, pain tolerance increased even further versus the unlesioned group with MCS alone. These results suggest that RAIC has an independent effect on pain modulation and is influenced by MCS [28].

The effect of MCS has been further connected to the opioid-related mechanisms. First described by Maarrawi et al., MCS was found to enhance the release of endogenous opioids in various brain areas [21]. Studies using naloxone, an opioid antagonist, revealed that naloxone administration reduced the analgesic effect of high-frequency primary motor cortex rTMS in healthy volunteers and also decreased rTMS activation of the dorsolateral prefrontal cortex (DLPC), a structure implicated in top-down pain inhibition [29].

Surgical Technique

Conventional MCS involves a frontal craniotomy (less often, a burrhole) for placement of an electrode grid or paddle over the precentral gyrus either epidurally or subdurally. For facial pain treatment, the electrodes are placed in the region corresponding to the facial area, which is traditionally identified

through intraoperative cortical mapping [30]. Preoperative anatomic (standard) or functional MRI studies paired with image guidance may be added to improve localization [8, 31] . Electrodes are then connected to a pulse generator, typically placed in the infraclavicular area, either immediately or after a trial period of stimulation (Figs. 1 and 2).

Despite the seemingly straightforward nature of MCS surgery, there is no standard approach to the procedure, and debate remains open over various aspects of the technique. The benefit of a stimulation trial or immediate pulse generator placement remains unclear [32•]. According to some authors, proper trial planning of MCS in patients with chronic post-stroke pain is necessary to account for altered neuronal excitability which may influence outcomes [33]. Conversely, other studies have illustrated no difference in outcome based on either baseline patient characteristics (stroke location, stroke type) or specific location of electrode placement [32•].

Debate persists between epidural and subdural electrode placement, with no standard electrode placement technique [34, 35]. While some authors have advocated for epidural placement to avoid the risks of subdural effusion and subdural electrode shift [32•], others have noted the greater precision of subdural electrode placement.

With all this, surgical techniques in MCS carry several limitations. Localization of the motor cortex can be challenging, and incorrect electrode positioning may negatively impact analgesic efficacy, emphasizing the importance of properly localizing the corresponding body area and securing accurate electrode position [36, 37]. Optimal stimulation settings and programming can be challenging as well, with analgesic effects sometimes not reached until stimulation settings are appropriately modified.

MCS Efficacy

MCS provides moderate analgesia for refractory pain patients, with variability in response from one patient to another. There is a difference in opinions on what constitutes a "good" response; most authors accept "good" as 30 to 50% improvement in pain intensity [38]. Over the last 25 years, multiple studies have been conducted and several meta-analyses were put together [38–40] to define the efficacy of MCS.

In a recent meta-analysis summarizing experience with different pain causes, MCS has been found to be effective in providing 40% or better relief in 55% of a population of 210 patients, with 45% maintaining pain relief at 1 year [38]. A second meta-analysis reported slightly better outcomes, with a 64% response rate to MCS in a population of 327 patients [39].

Initial pain relief effectiveness in the first month of MCS has been described to be an important predictor of long-term analgesia [41], although MCS efficacy has been reported to

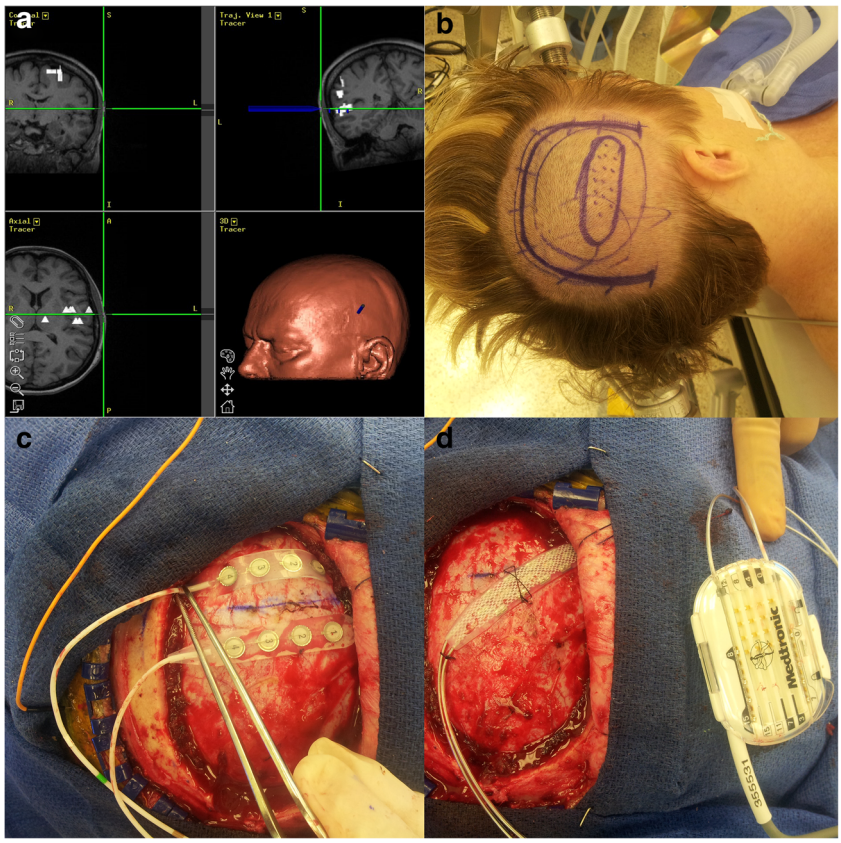

Fig. 1 **a** Intraoperative image-guidance system allows the surgeon to co-register anatomical and physiological data based on structural and functional magnetic resonance imaging. **b** The intraoperative photograph of the surgical field with an outline of planned craniotomy incision and location of the MCS electrode. **c** Intraoperative mapping involves recording using epidural grid to determine the location of the central sulcus. **d** The MCS electrode may be secured to the dura with sutures to minimize the risk of migration

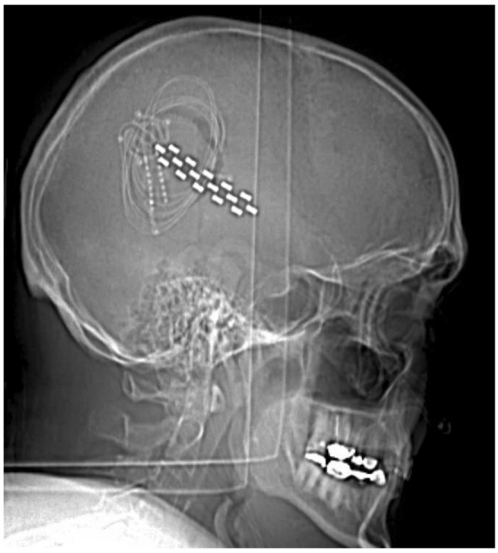

Fig. 2 Scout view of post-operative CT scan indicating position of 16-contact MCS electrode in a patient with deafferentation facial pain

decrease over time. While 80% of the patients who responded initially to the MCS continue to experience the analgesic effect for more than 1 year [42, 43], the proportion of patients who respond gradually decreases afterwards.

Decreased MCS analgesic effect may be caused by battery depletion, migration of the electrode, or change in dura mater reactivity. In a case by Velasco et al., a patient with decreasing MCS efficacy was found to have prominent epidural fibrosis with a significant increase in electrode impedance [35]. Loss of efficacy over time may also be attributable to development of electrophysiologic "tolerance" to MCS at a particular set of stimulation parameters [42], which may be improved by altering stimulation settings until analgesia is restored [8, 44, 45].

Identifying good candidates for MCS remains a challenge. Clinical response to high-frequency rTMS has been found to correlate with favorable responses to MCS [46–49], with poorer rTMS responses correlating with unfavorable long-term MCS outcomes [6]. To date, pain location, duration, sensory discrimination, and motor strength have not been found to predictive of MCS success [41, 49].

Repetitive Transcranial Magnetic Stimulation

Repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS) are two established non-invasive stimulation techniques now subject to new investigation for their utility in managing chronic pain. Potentially similar mechanisms between rTMS, tDCS, and MCS have also been subject to recent research.

rTMS for pain functions by administering a high-frequency transient magnetic field over the primary motor cortex, above the scalp, inducing an electrical current within the cortex in the perpendicular direction. tDCS, conversely, uses constant, low-intensity direct currents by means of electrodes on the scalp, increasing neuronal activity in the underlying region [50].

Clinical application of rTMS to provide analgesia in patients has been dependent on the stimulation frequency, with repetitive excitatory high-frequency (5–20 Hz) rTMS over the primary motor cortex producing good outcomes [51, 52•] while low-frequency rTMS has resulted in only limited analgesia [47, 53]. While a short-term analgesic effect can be achieved by a single session of rTMS, daily sessions of rTMS for 1–2 weeks are required for analgesia to have a lasting effect [42], and to control pain for months, a maintenance protocol is needed [54•].

The duration of each rTMS session for pain has been subject of research, with most sessions lasting about 20 min with an average of 2000 pulses. In a recent study, 73% of patients under this stimulation protocol reported decreased pain levels (defined as a pain score decrease of ≥ 30%), although this dropped to 40% at 6 months [54•]. In a separate arm of the study, analgesia decreased significantly when the session duration was shortened to 10 min, even when the total number of pulses was kept constant [54•].

The optimal frequency of rTMS sessions is also subject of debate. In a recent study by Pommier et al., 40 patients underwent rTMS for central, neuropathic pain. Of the 31 patients that responded to rTMS, a mean number of 13 sessions was performed, with an average of 29 days between sessions. For responders, this protocol was sustainable, with patients averaging a mean pain relief of 41% for a duration of 16 days and 90% continuing to respond at 1 year [55••].

rTMS may help identify responders to MCS. In a recent study of post-stroke pain patients by Zhang et al., a significant association was observed between responders to rTMS and patients who benefited from MCS, with a positive predictive value of 0.86 [32•]. Type of stroke, stroke location, or electrode placement above or below the dura did not affect the pain relief. These results, reinforced by earlier research [47, 49], support rTMS as a potentially useful screening tool to identify patients who may benefit from MCS.

Transcranial Direct Cortical Stimulation

Transcranial direct cortical stimulation (tDCS), although initially investigated as early as 200 years ago [56], is a relatively new, non-invasive technique for treatment of chronic pain. Even though it is potentially less expensive and easier to use than rTMS, tDCS has been much less studied, and its benefits remain unproven [49]. tDCS functions by increasing cortical excitability using direct, weak, continuous electric current, in contrast to rTMS which provides repetitive impulses at higher intensities [56].

In most studies for chronic pain, tDCS involves stimulation at an intensity of 2 mA with an electrode size of 35cm^2 for 10–20 min [57]. Up to 20 sessions are performed, with the primary motor cortex or dorsolateral prefrontal cortex being the most common targets [57]. Initial studies of anodal tDCS over the primary motor cortex found tDCS to be effective in reducing pain perception in patients with spinal cord injury [58] and fibromyalgia [59] when compared with a sham stimulation. Maximal relief reached 1 week after stimulation and present for 3 weeks after the treatment.

More recent studies investigated the effectiveness of tDCS for pain from lumbar radiculopathy [60], temporomandibular pain [61], trigeminal neuralgia [62], and multiple sclerosis [63], and other chronic pain conditions. Based on existing literature to date, however, current recommendations support tDCS for fibromyalgia, depression, and addiction only (Level B evidence), although further research is underway for this emerging technique [57].

The analgesic effect of tDCS remains unproven. A recent paper comparing tDCS and rTMS in a randomized, double-blind, sham-controlled, crossover trial revealed rTMS to be superior to tDCS in controlling pain intensity from neuropathic radicular pain, with tDCS not superior to sham. Analgesia from tDCS closely correlated with rTMS, however, which the authors attributed to a common mechanism of action [60].

Future Directions

Since initially proposed by Tsubokawa in 1991 [6], MCS for deafferentation pain has evolved considerably, with new indications, stimulation techniques, and surgical nuances expanding its use. Multiple areas are currently under investigation, however, holding a promise for more effective therapy. Closed-loop devices [64], for example, are capable of recording cortical activity, analyzing, and then stimulating appropriately, but this approach is hindered by significant recording artifacts during stimulation. Design of new, MCS-specific electrode arrays with a greater quantity of smaller, more closely spaced contacts may have a potential to improve the efficacy of stimulation [42].

Initial trials of rTMS or tDCS for patients anticipated to have short duration of symptoms, with conversion to MCS when non-invasive methods are no longer effective, are a potential therapeutic strategy [42]. Identifying patients that will have a favorable response to MCS is another opportunity: in patients with longstanding chronic pain, preoperative trials with rTMS to identify optimal MCS candidates, as discussed previously, appear increasingly more worthwhile [32•, 47, 49].

Improvements in device design and integration with neuronavigation are allowing for more effective treatment with rTMS and tDCS. rTMS paired with image-guided neuronavigation using functional brain imaging allows for more precise localization of stimulation targets and greater interoperator reliability between stimulation sessions [42, 65]. While initial studies have revealed better analgesia with image-guided rTMS targeting of the motor cortex [66], the value of pairing rTMS with navigation deserves further investigation.

A new tDCS method, so-called high-definition tDCS (HD-tDCS), involves a montage of four cathodes arrayed around an anode, the active electrode, which increases focal delivery of energy to specific areas of the cortex [67]. Initial studies of HD-tDCS targeting the primary motor cortex revealed a decreased sensitivity to hot and cold noxious stimuli in healthy volunteers [67], and improvement in pain of patients with chronic temporomandibular pain that persisted at 4 weeks [68].

Conclusions

Deafferentation pain is a severe, disabling condition that persists as an unyielding challenge for patients and clinicians. When refractory to pharmacotherapy, MCS provides a unique treatment option that can be effective for patients with pain from multiple causes. Over the last several years, the MCS literature has been revitalized with studies exploring the mechanism of neuropathic pain, new surgical technologies and techniques, and intriguing neuroanatomic data that hold promise as future therapeutic targets. At the same time, a growing number of studies and meta-analyses continue to demonstrate the effectiveness of MCS, with recent research providing better guidance in identifying MCS responders.

rTMS and tDCS, two established non-invasive stimulation techniques, are considered a new opportunity in the management of deafferentation pain and may become useful in treatment of certain conditions. rTMS and tDCS are becoming more attractive and accessible for patients that are less disabled or have a shorter duration of pain and may be useful in identifying good candidates for the long-term treatment with MCS implantation. As the number of potential therapies grows, the clinician's role shifts to the personalization of treatment with a unique plan for each individual pain patient. With introduction of new treatment modalities, this form of personalized medicine will gradually become a reality.

Source of Financial Support/Industry Affiliations Ahmed E. Hussein—None; Darian R. Esfahani—None; Galina I. Moisak—None; Jamil A. Rzaev—None; Konstantin V. Slavin—Consultant: Abbott, Boston Scientific, Medtronic, Neuramodix, Nevro, Nuvectra, SPR Theraputics, Stimwave; Stockholder/Stock options: Vycor Medical, Neuramodix and Stimwave

Compliance with Ethical Standards

Conflict of Interest Ahmed E. Hussein, Darian R. Esfahani, Galina I. Moisak, Jamil A. Rzaev, and Konstantin V. Slavin declare no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. Hanakawa T. Neural mechanisms underlying deafferentation pain: a hypothesis from a neuroimaging perspective. J Orthop Sci. 2012;17(3):331–5.
2. Osenbach RK. Motor cortex stimulation for intractable pain. Neurosurg Focus. 2006;21(6):E7.
3. May A. Chronic pain may change the structure of the brain. Pain. 2008;137(1):7–15.
4. Naro A, Milardi D, Russo M, et al. Non-invasive brain stimulation, a tool to revert maladaptive plasticity in neuropathic pain. Front Hum Neurosci. 2016;10:376.
5. Woolf CJ, Salter MW. Neuronal plasticity: increasing the gain in pain. Science. 2000;288(5472):1765–9.
6. Tsubokawa T, Katayama Y, Yamamoto T, Hirayama T, Koyama S. Treatment of thalamic pain by chronic motor cortex stimulation. Pacing Clin Electrophysiol. 1991;14(1):131–4.
7. Carroll D, Joint C, Maartens N, Shlugman D, Stein J, Aziz TZ. Motor cortex stimulation for chronic neuropathic pain: a preliminary study of 10 cases. Pain. 2000;84(2–3):431–7.
8. Esfahani DR, Pisansky MT, Dafer RM, Anderson DE. Motor cortex stimulation: functional magnetic resonance imaging-localized treatment for three sources of intractable facial pain. J Neurosurg. 2011;114(1):189–95.
9. Brown JA, Pilitsis JG. Motor cortex stimulation for central and neuropathic facial pain: a prospective study of 10 patients and observations of enhanced sensory and motor function during stimulation. Neurosurgery. 2005;56(2):290–7.
10. Sol JC, Casaux J, Roux FE, et al. Chronic motor cortex stimulation for phantom limb pain: correlations between pain relief and functional imaging studies. Stereotact Funct Neurosurg. 2001;77(1–4):172–6.
11. Brasil-Neto JP. Motor cortex stimulation for pain relief: do corollary discharges play a role? Front Hum Neurosci. 2016;10:323.
12. Goto T, Saitoh Y, Hashimoto N, et al. Diffusion tensor fiber tracking in patients with central post-stroke pain; correlation with efficacy of repetitive transcranial magnetic stimulation. Pain. 2008;140(3):509–18.
13. Ohn SH, Chang WH, Park CH, et al. Neural correlates of the antinociceptive effects of repetitive transcranial magnetic stimulation on central pain after stroke. Neurorehabil Neural Repair. 2012;26(4):344–52.
14. Rojas-Piloni G, Martinez-Lorenzana G, Condes-Lara M, Rodriguez-Jimenez J. Direct sensorimotor corticospinal modulation of dorsal horn neuronal C-fiber responses in the rat. Brain Res. 2010;1351:104–14.
15. Senapati AK, Huntington PJ, Peng YB. Spinal dorsal horn neuron response to mechanical stimuli is decreased by electrical stimulation of the primary motor cortex. Brain Res. 2005;1036(1–2):173–9.
16. Peyron R, Garcia-Larrea L, Deiber MP, et al. Electrical stimulation of precentral cortical area in the treatment of central pain: electrophysiological and PET study. Pain. 1995;62(3):275–86.
17. Garcia-Larrea L, Peyron R, Mertens P, et al. Electrical stimulation of motor cortex for pain control: a combined PET-scan and electrophysiological study. Pain. 1999;83(2):259–73.
18. Nguyen JP, Nizard J, Keravel Y, Lefaucheur JP. Invasive brain stimulation for the treatment of neuropathic pain. Nat Rev Neurol. 2011;7(12):699–709.
19. Behbehani MM, Fields HL. Evidence that an excitatory connection between the periaqueductal gray and nucleus raphe magnus mediates stimulation produced analgesia. Brain Res. 1979;170(1):85–93.
20. Buckett WR. Pharmacological studies on stimulation-produced analgesia in mice. Eur J Pharmacol. 1981;69(3):281–90.
21. Maarrawi J, Peyron R, Mertens P, et al. Motor cortex stimulation for pain control induces changes in the endogenous opioid system. Neurology. 2007;69(9):827–34.
22. Peyron R, Faillenot I, Mertens P, Laurent B, Garcia-Larrea L. Motor cortex stimulation in neuropathic pain. Correlations between analgesic effect and hemodynamic changes in the brain. A PET study. NeuroImage. 2007;34(1):310–21.
23. Ito M, Kuroda S, Shiga T, Tamaki N, Iwasaki Y. Motor cortex stimulation improves local cerebral glucose metabolism in the ipsilateral thalamus in patients with poststroke pain: case report. Neurosurgery. 2011;69(2):E462–9.
24. Jiang L, Ji Y, Voulalas PJ, et al. Motor cortex stimulation suppresses cortical responses to noxious hindpaw stimulation after spinal cord lesion in rats. Brain Stimul. 2014;7(2):182–9.
25. Henssen DJ, Kurt E, Kozicz T, van Dongen R, Bartels RH, van Cappellen van Walsum AM. New insights in trigeminal anatomy: a double orofacial tract for nociceptive input. Front Neuroanat. 2016;10:53.
26. Jantsch HHF, Kemppainen P, Ringler R, Handwerker HO, Forster C. Cortical representation of experimental tooth pain in humans. Pain. 2005;118(3):390–9.
27. Weigelt A, Terekhin P, Kemppainen P, Dorfler A, Forster C. The representation of experimental tooth pain from upper and lower jaws in the human trigeminal pathway. Pain. 2010;149(3):529–38.
28. Jung HH, Shin J, Kim J, et al. Rostral agranular insular cortex lesion with motor cortex stimulation enhances pain modulation effect on neuropathic pain model. Neural Plast. 2016;2016:3898924.
29. Taylor JJ, Borckardt JJ, Canterberry M, et al. Naloxone-reversible modulation of pain circuitry by left prefrontal rTMS. Neuropsychopharmacology. 2013;38(7):1189–97.
30. Wood CC, Spencer DD, Allison T, McCarthy G, Williamson PD, Goff WR. Localization of human sensorimotor cortex during surgery by cortical surface recording of somatosensory evoked potentials. J Neurosurg. 1988;68(1):99–111.
31. Pirotte B, Voordecker P, Neugroschl C, et al. Combination of functional magnetic resonance imaging-guided neuronavigation and intraoperative cortical brain mapping improves targeting of motor cortex stimulation in neuropathic pain. Neurosurgery. 2005;56(2 Suppl):344–59.
32.• Zhang X, Hu Y, Tao W, Zhu H, Xiao D, Li Y. The effect of motor cortex stimulation on central poststroke pain in a series of 16 patients with a mean follow-up of 28 months. Neuromodulation. 2017;20(5):492–6. **This retrospective study of 16 patients receiving MCS for post stroke pain reveals good responses to MCS, with treatment reducing mean VAS scores from 8 to 3.8 one month after surgery, although this increased to 5.3 at last followup. The study also identifies rTMS as an effective predictor of MCS responders.**

33. O'Brien AT, Amorim R, Rushmore RJ, et al. Motor cortex neurostimulation technologies for chronic post-stroke pain: implications of tissue damage on stimulation currents. Front Hum Neurosci. 2016;10:545.
34. Colloca L, Ludman T, Bouhassira D, et al. Neuropathic pain. Nat Rev Dis Primers. 2017;3:17002.
35. Velasco F, Arguelles C, Carrillo-Ruiz JD, et al. Efficacy of motor cortex stimulation in the treatment of neuropathic pain: a randomized double-blind trial. J Neurosurg. 2008;108(4):698–706.
36. Holsheimer J, Lefaucheur JP, Buitenweg JR, Goujon C, Nineb A, Nguyen JP. The role of intra-operative motor evoked potentials in the optimization of chronic cortical stimulation for the treatment of neuropathic pain. Clin Neurophysiol. 2007;118(10):2287–96.
37. Lefaucheur JP, de Andrade DC. Intraoperative neurophysiologic mapping of the central cortical region for epidural electrode placement in the treatment of neuropathic pain by motor cortex stimulation. Brain Stimul. 2009;2(3):138–48.
38. Fontaine D, Hamani C, Lozano A. Efficacy and safety of motor cortex stimulation for chronic neuropathic pain: critical review of the literature. J Neurosurg. 2009;110(2):251–6.
39. Lima MC, Fregni F. Motor cortex stimulation for chronic pain: systematic review and meta-analysis of the literature. Neurology. 2008;70(24):2329–37.
40. Nguyen JP, Lefaucheur JP, Raoul S, Roualdes V, Pereon Y, Keravel Y. Treatment of trigeminal neuropathic pain by motor cortex stimulation. Neurochirurgie. 2009;55(2):226–30.
41. Nuti C, Peyron R, Garcia-Larrea L, et al. Motor cortex stimulation for refractory neuropathic pain: four year outcome and predictors of efficacy. Pain. 2005;118(1–2):43–52.
42. Lefaucheur JP. Cortical neurostimulation for neuropathic pain: state of the art and perspectives. *Pain*. 2016;157(Suppl 1):S81–9.
43. Rainov NG, Heidecke V. Motor cortex stimulation for neuropathic facial pain. Neurol Res. 2003;25(2):157–61.
44. Anderson WS, Kiyofuji S, Conway JE, Busch C, North RB, Garonzik IM. Dysphagia and neuropathic facial pain treated with motor cortex stimulation: case report. Neurosurgery. 2009;65(3):E626.
45. Henderson JM, Boongird A, Rosenow JM, LaPresto E, Rezai AR. Recovery of pain control by intensive reprogramming after loss of benefit from motor cortex stimulation for neuropathic pain. Stereotact Funct Neurosurg. 2004;82(5–6):207–13.
46. Hosomi K, Saitoh Y, Kishima H, et al. Electrical stimulation of primary motor cortex within the central sulcus for intractable neuropathic pain. Clin Neurophysiol. 2008;119(5):993–1001.
47. Andre-Obadia N, Peyron R, Mertens P, Mauguiere F, Laurent B, Garcia-Larrea L. Transcranial magnetic stimulation for pain control. Double-blind study of different frequencies against placebo, and correlation with motor cortex stimulation efficacy. Clin Neurophysiol. 2006;117(7):1536–44.
48. Lefaucheur JP, Drouot X, Menard-Lefaucheur I, et al. Neurogenic pain relief by repetitive transcranial magnetic cortical stimulation depends on the origin and the site of pain. J Neurol Neurosurg Psychiatry. 2004;75(4):612–6.
49. Lefaucheur JP, Menard-Lefaucheur I, Goujon C, Keravel Y, Nguyen JP. Predictive value of rTMS in the identification of responders to epidural motor cortex stimulation therapy for pain. J Pain. 2011;12(10):1102–11.
50. Lefaucheur JP, Antal A, Ahdab R, et al. The use of repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS) to relieve pain. Brain Stimul. 2008;1(4):337–44.
51. Saitoh Y, Maruo T, Yokoe M, Matsuzaki T, Sekino M. Electrical or repetitive transcranial magnetic stimulation of primary motor cortex for intractable neuropathic pain. Conf Proc IEEE Eng Med Biol Soc. 2013;2013:6163–6.
52.• DosSantos MF, Ferreira N, Toback RL, Carvalho AC, DaSilva AF. Potential mechanisms supporting the value of motor cortex stimulation to treat chronic pain syndromes. Front Neurosci. 2016;10:18. **This well-written review paper illustrates and discusses multiple proposed mechanisms by which MCS may provide relief for chronic pain. Emphasis is placed on recent MCS studies as well as non-invasive techniques such as tDCS and rTMS.**
53. Saitoh Y, Hirayama A, Kishima H, et al. Reduction of intractable deafferentation pain due to spinal cord or peripheral lesion by high-frequency repetitive transcranial magnetic stimulation of the primary motor cortex. J Neurosurg. 2007;107(3):555–9.
54.• Hodaj H, Alibeu JP, Payen JF, Lefaucheur JP. Treatment of chronic facial pain including cluster headache by repetitive transcranial magnetic stimulation of the motor cortex with maintenance sessions: a naturalistic study. Brain Stimul. 2015;8(4):801–7. **This retrospective, naturalistic study of 55 patients demonstrates rTMS as effective in reducing several types of facial pain, including cluster headache, trigeminal neuropathic pain, and atypical facial pain. 73% of patients responded (defined as a decrease in pain of ≥30%) by day 15, decreasing to 40% at day 180, suggesting a rTMS maintinence protocol is effective at providing long-term analgesia, but only in a subset of patients. 20 minutes was also identified as a preferable session length, with decreased analgesia in a 10 minute subgroup.**
55.•• Pommier B, Creac'h C, Beauvieux V, Nuti C, Vassal F, Peyron R. Robot-guided neuronavigated rTMS as an alternative therapy for central (neuropathic) pain: clinical experience and long-term follow-up. Eur J Pain. 2016;20(6):907–16. **This prospective study of 440 rTMS therapy sessions across 40 patients identifies rTMS as an effective technique in producing a mean pain relief of 41% in 31 of 40 patients with refractory neuropathic pain. Excellent followup and experimental design strengthen this study, which provides convincing evidence of rTMS as an effective analgesic technique for a subset of patients wih refractory neuropathic pain.**
56. Parent A. Giovanni Aldini: from animal electricity to human brain stimulation. Can J Neurol Sci. 2004;31(4):576–84.
57. Lefaucheur J-P, Antal A, Ayache SS, et al. Evidence-based guidelines on the therapeutic use of transcranial direct current stimulation (tDCS). Clin Neurophysiol. 2017;128(1):56–92.
58. Fregni F, Boggio PS, Lima MC, et al. A sham-controlled, phase II trial of transcranial direct current stimulation for the treatment of central pain in traumatic spinal cord injury. Pain. 2006;122(1–2):197–209.
59. Fregni F, Gimenes R, Valle AC, et al. A randomized, sham-controlled, proof of principle study of transcranial direct current stimulation for the treatment of pain in fibromyalgia. Arthritis Rheum. 2006;54(12):3988–98.
60. Attal N, Ayache SS, Ciampi De Andrade D, et al. Repetitive transcranial magnetic stimulation and transcranial direct-current stimulation in neuropathic pain due to radiculopathy: a randomized sham-controlled comparative study. Pain. 2016;157(6):1224–31.
61. Oliveira LB, Lopes TS, Soares C, et al. Transcranial direct current stimulation and exercises for treatment of chronic temporomandibular disorders: a blind randomised-controlled trial. J Oral Rehab. 2015;42(10):723–32.
62. Hagenacker T, Bude V, Naegel S, et al. Patient-conducted anodal transcranial direct current stimulation of the motor cortex alleviates pain in trigeminal neuralgia. J Headache Pain. 2014;15:78.
63. Mori F, Codeca C, Kusayanagi H, et al. Effects of anodal transcranial direct current stimulation on chronic neuropathic pain in patients with multiple sclerosis. J Pain. 2010;11(5):436–42.
64. Beuter A, Lefaucheur JP, Modolo J. Closed-loop cortical neuromodulation in Parkinson's disease: an alternative to deep brain stimulation? Clin Neurophysiol. 2014;125(5):874–85.

65. Lefaucheur JP. Principles of therapeutic use of transcranial and epidural cortical stimulation. Clin Neurophysiol. 2008;119(10): 2179–84.
66. Hirayama A, Saitoh Y, Kishima H, et al. Reduction of intractable deafferentation pain by navigation-guided repetitive transcranial magnetic stimulation of the primary motor cortex. Pain. May 2006;122(1–2):22–7.
67. Borckardt JJ, Bikson M, Frohman H, et al. A pilot study of the tolerability and effects of high-definition transcranial direct current stimulation (HD-tDCS) on pain perception. J Pain. 2012;13(2): 112–20.
68. Donnell A, D'Nascimento T, Lawrence M, et al. High-definition and non-invasive brain modulation of pain and motor dysfunction in chronic TMD. Brain Stimul. 2015;8(6):1085–92.