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Brain Stimulation in the Treatment of Chronic Neuropathic and Non-Cancerous Pain

EB Plow[1,2], **A Pascual-Leone**[3,4], and **A Machado**[5,6]

[1]Department of Biomedical Engineering, Lerner Research Institute, The Cleveland Clinic Foundation, Cleveland, OH, USA

[2]Department of Physical Medicine and Rehabilitation, Neurological Institute, The Cleveland Clinic Foundation, Cleveland, OH, USA

[3]Berenson-Allen Center for Noninvasive Brain Stimulation, Department of Neurology, Beth Israel Deaconess Medical Center, Harvard Medical School. Boston, MA, USA

[4]Instituto Guttmann de Neurorrehabilitación, Universidad Autónoma de Barcelona, Badalona, España

[5]Center for Neurological Restoration, Department of Neurosurgery, Neurological Institute, The Cleveland Clinic Foundation, Cleveland, OH, USA

[6]Department of Neurosciences, Lerner Research Institute, The Cleveland Clinic Foundation, Cleveland, OH, USA

Abstract

Chronic neuropathic pain is one of the most prevalent and debilitating disorders. Conventional medical management, however, remains frustrating for both patients and clinicians owing to poor specificity of pharmacotherapy, delayed-onset of analgesia and extensive side-effects. Neuromodulation presents as a promising alternative, or at least an adjunct, as it is more specific in inducing analgesia without associated risks of pharmacotherapy. Here, we discuss common clinical and investigational methods of neuromodulation. Compared to clinical spinal cord stimulation (SCS), investigational techniques of cerebral neuromodulation, both invasive [deep brain stimulation (DBS) and motor cortical stimulation (MCS)] and noninvasive [repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS)], may be more advantageous. By adaptively targeting the multi-dimensional experience of pain, subtended by integrative pain circuitry in the brain, including somatosensory and thalamocortical, limbic and cognitive, cerebral methods may modulate the sensory-discriminative, affective-emotional and evaluative-cognitive spheres of the pain neuromatrix. Despite promise, the current

Corresponding Author: Andre Machado MD PhD, Director, Center for Neurological Restoration, Assistant Professor of Surgery, Department of Neurosurgery, Cleveland Clinic, 9500 Euclid Ave, S-31, Cleveland, OH 44195, Phone: 216-444-4270, Fax: 216-444-1015, machada@ccf.org.

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state of results alludes to the possibility that cerebral neuromodulation has thus far not been effective in producing analgesia as intended in patients with chronic pain disorders. These techniques, thus, remain investigational and off-label. We discuss issues implicated in inadequate efficacy, variability of responsiveness and poor retention of benefit, while recommending design and conceptual refinements for future trials of cerebral neuromodulation in management of chronic neuropathic pain.

Keywords

Neuropathic Pain; Deep Brain Stimulation (DBS); Motor Cortical Stimulation (MCS); repetitive Transcranial Magnetic Stimulation (rTMS); Transcranial Direct Current Stimulation (tDCS); Neuromodulation

Introduction

Chronic neuropathic pain of non-cancerous origin is one of the most prevalent disorders, affecting about 8% of the general population.[133] Patients with neuropathic pain report the poorest health and highest disability.[130] The direct medical and societal costs are staggering. Patients not only incur 3 times higher expenditures than those without neuropathic pain[12] but 43% report disruption of employment status, while 80% note reduction in work productivity.[80] The consequent loss in earnings can be significant, ranging between $US45,000 and $US89,000, for certain diagnoses.[101]

Medical treatment of chronic neuropathic pain remains frustrating for both patients as well as clinicians. Response to drugs is unpredictable and varies considerably from one condition to another.[7] Despite advancements, pharmacotherapy demonstrates poor specificity, owing to limited knowledge on pain syndrome-specific pathophysiology. Further, high degree of side effects impact cognition, particularly executive functions, affecting individual's ability to work,[78] and also raise concerns about organ toxicity and addiction potential. In light of evidence that supports only partial, inconsistent efficacy of conventional management in 40–60% of patients,[34, 124] there is a clear need for therapeutic approaches that provide specific, predictable, effective pain relief while mitigating risks associated with pharmacotherapy.

Neuromodulation: novel, specific therapeutic technique

Neuromodulation may represent a more specific adjunct or in some cases an alternative to current medical management. As a means of supplanting conventional medical management in chronic pain originating from spinal degenerative and peripheral neuropathy causes, implanted spinal cord stimulation (SCS) has been, traditionally, the most common clinical method of neuromodulation.[56] It is an effective adjunct in failed back surgery syndrome[56] and safe and efficacious in complex regional pain syndrome.[81, 127] However, even in failed back surgery syndrome, the most common indication for SCS, 50% of patients fail to respond to SCS and are left with limited therapeutic options.

Poor outcomes of SCS may result from inadequate targeting of the multidimensional experience of pain, patterns of which are ultimately believed to originate from neural networks in the brain.[82] Neuromodulation that adaptively targets brain activity may be a promising, focused method of modifying experience associated with multiple facets of pain. This idea bears origin in Melzack's theory that '*brain….(acts) as an active system that filters, selects and modulates inputs'*, which founded the theoretical framework for pain experience, called the *neuromatrix*. Envisioned as a matrix of neural circuits with cyclical processing and integrated activity of somatosensory system, limbic and cognitive pathways as well as thalamocortical interactions,[82] the neuromatrix, correspondingly, processes 3

main spheres of pain experience: sensory-discriminative, affective-motivational and evaluative-cognitive. Over time, however, repeated central or peripheral sensitization of these components leads to chronification of pain experience,[6, 128] further complicating diagnosis and treatment selection.

In the present article, we focus on methods of cerebral neuromodulation, which show promise in addressing limitations of traditional methods in pain management, pharmacotherapy and SCS. By targeting components subtending different spheres of pain, including suppressing activity of sensitized structures and facilitating adaptive compensatory synergists within the neuromatrix, focused cerebral neuromodulation may produce generalized benefits, interrupting the vicious cycle of sensitization-chronification. We focus on invasive [deep brain stimulation (DBS) and motor cortical stimulation (MCS)] and noninvasive [repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS)] methods and their nodes within pain circuits. Despite promise, cerebral neuromodulation remains investigational and off-label in pain management; the following sections discuss the evidence in support of as well as factors that diminish confidence in the efficacy of these techniques.

INVASIVE CEREBRAL NEUROMODULATION

Deep Brain Stimulation: Thalamic Nuclei, Periventricular gray (PVG), Periaqueductal gray (PAG)—In the management of pain, traditionally, the sensory nuclei of the thalamus are targeted for neuropathic, while periventricular gray (PVG) and periaqueductal gray (PAG), both endorphin-releasing regions,[1, 116] are stimulated in nociceptive syndromes (such as low back pain). Despite evidence of efficacy,[27, 45, 75, 104] DBS remains off-label for chronic pain management although it has now become a standard of care for the management of advanced movement disorders.[33, 43, 58]

Long-term outcome of DBS in chronic pain varies considerably across study designs that affects its therapeutic utility.[24] Preliminary reports support its efficacy and safety in chronic pain,[68, 113, 116, 135] whereas large-scale studies demonstrate mixed results. Levy et al.[69] reviewed the long-term outcomes of 141 patients (84 with deafferentation pain mainly treated with sensory thalamic stimulation and 57 with nociceptive pain managed with PAG/PVG stimulation) following implantation of DBS for an externalized trial. Approximately 60% of the total sample responded favorably and subsequently received a fully-internalized system. At post-6 year follow-up, however, less than a third of responders retained significant pain relief. Prospective multi-center clinical trials, similarly, report retention of >50% relief in only 14% of sample.[24]

Although large-scale prospective and retrospective trials[24, 69] are critical, we posit that inclusion of a mix of etiologies and DBS loci introduces high variability. Our speculation originates from evidence of higher retention in studies using homogenous samples. Kumar et al.[57] evaluated a sample of 68 patients, predominantly comprised of patients with failed back surgery syndrome. At an average 6-year follow-up, approximately 75% of patients transitioned from externalized to fully-internalized systems, of which 80% retained analgesia at the last follow-up. Contrarily, heterogeneity of sampling obscures efficacy and retention owing to the differential responsiveness of varying chronic pain conditions. Reports of greater benefit in failed back surgery syndrome versus chronic pain of central origin[45, 57, 69, 113] (thalamic pain syndrome or spinal cord injury) are instances of variable success of DBS applications across conditions. The differences in response arguably originate from maladaptive central reorganization and neuroplastic changes in the pain pathways as well as pain-inhibiting structures that follow deafferentation in brain and spinal cord lesions.[113] The issue of heterogeneity is only complicated further by types of surgical target selected.[24] Classical evidence indicates that for neuropathic pain, response to thalamic

stimulation is more favorable than PAG/PVG stimulation,[45] but more recent evidence indicates otherwise. [104] Therefore, design limitations, such as aggregating multiple pain etiologies and targets without investigating the potential benefit of etiology-specific loci, diminish the confidence in the efficacy of DBS in chronic pain. This evidence is in contraposition to that supporting clinical utility of DBS for movement disorders, where singular, individualized targets are selected for uniform diagnoses.[10–11, 33, 58] We would like to acknowledge, however, that inferences about differential responsiveness of various pain conditions and surgical loci are only exploratory, retrospective and preliminary at best. [45, 57, 113] Analysis of enrolled and treated patients has been used to draw inferences *a posteriori* about response of one condition or one target versus another but such attempts have been grossly under-powered. Thus, transitioning from retrospective to prospective systematic comparisons is critical to truly draw valid conclusions about efficacy of specific DBS targets for specific chronic pain conditions.

DBS: Alternate Cerebral Targets—The field of DBS in chronic pain has recently begun to re-evaluate the "dogmatic" management with fixed cerebral loci. Aziz and collaborators[13] tested both PVG and sensory thalamic leads in patients with phantom limb pain; contrary to the typical hypothesis, one of 3 patients benefitted considerably from a combination of sensory thalamic and PVG stimulation. Analogously, in a set of studies of post-stroke central pain,[90, 104] the majority of patients benefitted either from PAG/PVG stimulation or its combination with standard sensory thalamic stimulation, which again challenged the treatment convention. The evidence discussed here, albeit preliminary, alludes to the significance of exploring novel areas in light of emerging evidence in mechanisms of pain control.

Acceptance of the neuromatrix theory[82] over the gate-control theory[83] represents a key milestone in understanding of the mechanisms. Classical DBS modulated sensory-discriminative aspects of pain, which, in severe central anesthesia-dolorosa syndromes,[57, 69] has been frustrating due to natural or iatrogenic destruction of the sensory-discriminative ascending pathways. Neuromatrix theory suggests remedial alternatives. DBS targeting networks that process affective behavior may be functionally-adaptive. Based on strong correlations between depression and chronic pain[2, 48] and the success of DBS [ventral striatum and ventral capsular area (VC/VS)] in refractory depression,[74, 77] stimulation of VC/VS may modulate the 'suffering' component of chronic intractable central pain. This is the subject of an ongoing investigation (http://clinicaltrials.gov/ct2/show/NCT01072656).

Epidural Motor Cortical Stimulation (MCS)—The frustrating outcomes associated with traditional DBS in chronic pain, especially in central pain syndromes,[138] marked the advent of a novel, and *'less invasive'* alternative, epidural Motor Cortical Stimulation (MCS), in the early 1990s. The reasoning was based on observations that MCS reduced thalamic hyperactivity via corticothalamic tracts in feline[47] and rodent[143] models of spinal cord deafferentation. Clinical application of epidural MCS followed soon after, first pioneered in 1991 by Tsubokawa and colleagues in patients with chronic pain due to central or peripheral deafferentation.[136–138] The initial results in both sets of patients were very encouraging.[136–137]

In a subsequent series, however, at the Karolinska Institutet, improvements with MCS were only witnessed among patients with peripheral syndromes.[85] Several groups around the world similarly report mixed results with trends favoring pain of peripheral etiology[76, 91, 93, 121] with poor response rates of 40–50% in central pain[52] potentially due to damage to the central pain transmission pathways.[114] The apparent disadvantage for central pain syndromes versus peripheral has, however, only been demonstrated through subgrouping in retrospective trials, as in the case of DBS.[45, 57, 113] Nguyen et al.[94] discuss

favorable response of MCS in peripheral pain syndromes compared to post-stroke pain, but only in small samples. Similarly, Saitoh et al.[121] report poorer outcomes in post-stroke central compared to peripheral deafferentation pain across 4 subjects each, while Rasche et al.[114] reveal greater responsiveness in TNP (5/10) than in post-stroke pain (3/7). Owing to their elemental nature, it is problematic to make broad generalizations from findings of peripheral vs. central responsiveness since smaller subsamples affect validity as well as the statistical power.

Key prognostic factors, such as functional-neurological, have been implicated in the potentially intractable nature of central pain. Patients with preserved or significantly-recovered motor function on the affected side present with better outcomes following MCS than those with severe hemiparesis,[51, 100] which indicates that corticofugal pathways may be important substrates for MCS efficacy. Since larger subcortical lesions may invariably impair a majority of the motor descending pathways, including cortico-thalamic tracts implicated in mechanism of action of MCS,[47, 73, 143] neuropathologic markers based on motor function seem valid. Preservation of critical tracts can also be inferred by incorporating trial stimulation in study designs; those who fail to respond during the externalized period of trial stimulation are less likely to have good long-term results.[73, 114] Although functional-structural markers seem promising, again, they are based on retrospective analysis [51, 100] of subjective observations of motor functional state instead of quantitative neuro-radiologic confirmation. The evidence favoring use of prognostic indicators of MCS, thus, requires substantiation in future systematic investigations.

Besides differences in etiology, methodologic issues related to application of MCS may introduce variability in efficacy across studies. Broadly, these issues can be categorized into 1) methods to expose the motor cortex (M1) via craniotomy or placement of the leads via burr holes, 2) intra-operative mapping, and 3) determination of optimal polarity and stimulation parameters. Some centers prefer use of flap craniotomy (usually 4–5cm) to expose M1 as it allows extensive electrophysiological mapping, [92–93, 100, 121] versus the traditionally-used, less invasive burr hole[136] procedure that could require several repositioning attempts with the [92] associated risk of epidural hematomas. Recently though, combining burr hole procedure with image-guided neuronavigation has been reported to facilitate accurate placement of leads while still allowing time for recording of electrophysiological data.[113] Sophisticated intra-operative mapping also aids accurate localization, the experience for which has evolved, and may have introduced variability in responsiveness across studies over years.[92–93, 100, 114, 121] The process of determining optimal stimulation parameters also varies. While several centers prefer complete internalization of leads in a single procedure, followed by empirical post-operative re-adjustments,[93, 100] others prefer to conduct externalized test stimulation post-operatively over weeks to define the best parameters and polarities generating greatest pain inhibition.[23, 114, 138] Another detailed yet unique way of determining optimal parameters involves a two-stage procedure where initially a 20- or 40- electrode array is implanted to test various geometric patterns of stimulation and polarities before the final arrays are implanted for long-term purposes. Response rates appear to be higher in such a trial potentially due to identification of best stimulation target, but these speculations await further confirmation.[121] With continued advancements in the application of MCS across centers, perhaps, consistency in delivery and utility can be achieved.

Despite sophistication in application and experience, use of MCS is still considered off-label[76] as reliable outcomes across etiologies are lacking.[100] Besides, it is costly, invasive, requiring at least a burr hole or craniotomy even for placement of trial leads, and carries risks associated with surgical implantation, such as intracranial hemorrhages and infections.[60] Noninvasive cortical stimulation holds promise as a safer and inexpensive

alternative to identify responders to implantable neuromodulation[66] in pain and, potentially, in emerging therapeutic applications as well.

NONINVASIVE CEREBRAL NEUROMODULATION

Repetitive Transcranial Magnetic Stimulation (rTMS)—Using a time-varying magnetic field that induces electrical currents in focused parts of the brain, repetitive TMS (rTMS) can modulate activity of underlying networks[8] for periods outlasting the duration of the stimulation,[108, 142] steering cortical reorganization to promote functional re-mapping.[106] This characteristic of rTMS has been exploited for more than a decade in the field of chronic neuropathic pain.

In drawing inspiration from contemporary MCS evidence,[85, 91] the predominant use of rTMS in chronic neuropathic pain involves high-frequency M1 stimulation.[3, 46, 53, 60–63] In a pioneering placebo-controlled trial, patients with chronic neuropathic pain immediately benefitted from a single session of sub-threshold high frequency (10Hz) rTMS.[60] The effect, however, was small [(average reduction of 2 points on the Visual Analogue Scale (VAS)] and manifested in only 7 of 18 patients (~39% of sample). In subsequent studies, the long-term benefit of rTMS[67] has not been clinically meaningful either.[60, 62] The outcomes are variable,[37, 67] transient,[118] and indistinguishable from placebo.[31, 50, 118]

Variance in responsiveness with rTMS can be potentially linked to similar clinico-pathologic factors as in the case of DBS[57, 113] and MCS.[114, 121] Patients with peripheral trigeminal neuropathic pain (TNP) experience good-to-excellent[92] pain relief (58% response rate),[63] benefits that are greater than those found in patients with central thalamic stroke pain.[63–64] Site of pain also exaggerates differential responsiveness; facial pain appears to benefit the most (64.3% response rate), while brainstem stroke with limb pain is associated with the worst prognosis, likely due to thalamocortical deafferentation.[63] Unlike in studies of DBS and MCS, however, where clinico-pathologic predictors have been inferred from retrospective subgroup analyses, [57, 113–114, 121] rTMS has offered the opportunity for prospective, planned comparisons between different pain conditions that has generated adequate statistical power to illustrate differences across etiologies.[63] Besides power, prospective studies have allowed creation of homogenous samples that permit study of etiology-specific mechanisms of response to neuromodulation. For instance, a recent clinical trial in post-stroke central pain concluded that greater patency of superior thalamocortical tracts (TCT)[41, 102] in the ipsilesional hemisphere predicted greater response to high frequency rTMS targeting M1.[102]

Despite systematic homogenous sampling, the efficacy of rTMS still varies across studies; besides clinico-pathologic markers, we believe methodologic factors associated with application of rTMS may be implicated. In facial pain in TNP, response can be as high as 44% when the hand M1 area is targeted, while in cases of hand pain, response can reach up to 61% when rTMS is delivered to the neighboring facial M1 area.[65] Efficacy of reciprocal rTMS, thus, appears to be greater compared to traditional somatotopy-specific application (with benefits ranging from 27% to 37%) where M1 representation corresponding to painful site is targeted.[60, 63] Such reciprocal efficacy, that is also in direct contrast with somatotopic-specificity emphasized with MCS,[92] speculatively normalizes lesion-induced imbalance between[65] deafferented representations of pain-afflicted sites and those of adjacent, less-affected sites in M1.[84, 99, 145–146] An important caveat, nevertheless, should be considered. Efficacy of reciprocal (or somatotopic-adjacent) rTMS could simply be an artifact of poor spatial specificity of TMS delivery,[9] a factor that critically influences trajectory of corticospinal and cortico-cortical stimulation,[89] but has received little attention in pain modulation literature.[46] Thus, MRI-guided stereotaxic navigation, which forms the

mainstay of accurate MCS delivery,[92] when utilized similarly for rTMS, will truly differentiate between efficacy of somatotopic-specificity versus -adjacency.

Unlike response, maintenance of response to rTMS has hardly been studied until more recently. As effects of single[64] and monthly sessions[62] have only been shown to last a week at a time, increasing frequency[144] and overall length of treatment can extend cumulative benefits up to 2 weeks.[54] Most investigations, however, have used case-study designs; systematic, rigorous exploration of potential for retention is lacking.

rTMS: Alternate Cerebral Targets—In light of inconsistent evidence regarding effectiveness and long-term benefit of rTMS targeting M1, modulating other key components of the neuromatrix[82, 112] may serve to alter perception of pain. This rationale is not distant from our ongoing approach involving DBS of the VC/VS for central pain syndromes.

Dorsolateral prefrontal cortex (DLPFC) is now beginning to be identified for its potential top-down influence in pain.[21–22, 42, 88] Its structural connections with PAG[44] establish its place in the circuitry, while its interactions with basal ganglia, amygdala, anterior cingulate cortex (ACC) and thalamus allude to its control over emotional-affective[6, 70, 147] and evaluative-cognitive[103] percept of pain.

The evidence regarding potential clinical benefit of targeting DLPFC in chronic neuropathic pain and pain emerging from other non-cancerous conditions is still in the elementary stages though. Only experimental models of pain research and a few pilot attempts in clinical paradigms, thus far, have suggested DLPFC's role in analgesia. Empirically, facilitation of left DLPFC [20–21] or suppression of right DLPFC activity,[42] using high frequency and low-frequency rTMS, respectively, increases tolerance to experimentally-induced pain. The antinociceptive effect exerted by modulation of either DLPFC is based upon the idea of interhemispheric rivalry, wherein suppression on the right side would indirectly activate the left or vice versa to produce comparable analgesia.[21] First-stage evidence for therapeutic utility only comes from open trials[122] or pilot exploratory studies.[19, 123] While right-sided, suppressive rTMS appears to benefit pain in fibromyalgia[123] as well as that in central and peripheral deafferentation,[122] left-sided facilitation alleviates chronic pain of peripheral neuropathic etiology.[19] It cannot be excluded that the pain alleviating mechanism associated with stimulation of one or both DLPFC is related to the affective sphere of pain rather than analgesia per se. The experience of DLPFC rTMS for depression – the only indication for which it is clinically-labeled – corroborates this possibility.

However, several controversies in relation to rTMS delivered to DLPFC have prevented its widespread application as an alternative site to M1 in neuromodulation in chronic neuropathic pain. The issue of whether left DLPFC should be facilitated or right DLPFC should be inhibited, using high frequency or low frequency rTMS, has not been resolved[18, 20–21, 42] and has only been weakly linked to inter-hemispheric rivalry without concrete evidence. The durability of antinociceptive benefit, i.e. its transience[42] or retention,[18, 21, 122–123] varies considerably across studies. Clinically, changes in pain ratings are not remarkable, perhaps owing to heterogenous pain etiologies,[19] which may also be associated with significantly low response rates, such as in 4 out of 9[122] or 2–3 out of 4 patients.[19, 123] Further, although fundamental efficacy of rTMS involving DLPFC has been tested by incorporating sham-controlled phases, the design of trials has been weak[123] and, in a repeated measures cross-over study, may have been influenced by inadequate time for wash-out created between sham and active rTMS conditions.[19]

Role of DLPFC stimulation thus remains to be rigorously confirmed in chronic neuropathic pain management. Further, its distinctiveness from stimulation of M1 needs to be elaborated upon. Empirical findings suggest that unilateral DLPFC stimulation seemingly modulates pain perception bilaterally, which is different from the strict contralateral effect noted with unilateral M1 stimulation, reinforcing the idea that pathways other than somatotopic sensory-discriminative are influenced by DLPFC.[21, 42] In small pilot studies or open trials, with long-term application, significant retention of benefit has been noted for weeks,[19] and in certain cases for 2–3 months.[122] If confirmed in systematic comparisons in the future, this advantage of DLPFC could potentially outlast maximal retention noted with long-term rTMS application of M1. [54, 144]

Transcranial Direct Current Stimulation (tDCS)—Another noninvasive neuromodulation strategy that is fast gaining popularity and may serve as a useful adjunct, if not an alternative, to rTMS in pain management is Transcranial Direct Current Stimulation (tDCS). Through application of weak, low-level direct currents, tDCS alters spontaneous neuronal excitability in a polarity-specific manner in targeted cortical[4, 35, 96] and interconnected regions[59, 132] even when applied for few to several minutes.[95, 98] TDCS is appealing as it is easy-to-apply and administer, safe, and less expensive than rTMS and invasive cerebral neuromodulation. In clinical trials, tDCS offers the advantage of a reliable placebo condition.[37, 39]

In sham-controlled designs, effectiveness of anodal tDCS [(polarity that enhances cortical excitability,[97] analogous to high frequency rTMS and invasive MCS)] over M1 has been explored in patients with neuropathic pain of varying etiologies,[5] that which resulted from spinal cord injury (SCI),[36] multiple sclerosis[87] and fibromyalgia.[38] Although the response rate following tDCS[36] (~63%) is slightly lower than that following ultra-high frequency (20Hz) rTMS (~71%)[54], retention at follow-up is comparable [33.33%[5, 36] to 60%[87] considered responders following tDCS versus 35% to 50%[54] following rTMS]. Importantly, however, the mean reduction in pain, appears to be greater following 5-days of tDCS [58 to 63%[36, 87, 117]] versus 5-days of rTMS [20 to 45%,[54, 64] respectively]. In fact, longer treatment protocols generate even greater cumulative effects of consecutive sessions, with retention of benefit lasting almost up to 60 days.[140]

These seemingly advantageous applications of tDCS, versus rTMS, should, however, be interpreted with some caution. Effects of tDCS have been demonstrated in studies of single etiology,[36, 38, 87] whereas those of rTMS have been investigated in more heterogeneous patient groups,[54] resembling failed trials of DBS for pain.[69] Even if effects of tDCS in chronic neuropathic pain may only be comparable to those of rTMS, it may act as an important therapeutic adjunct or alternative to promoting maintenance especially since it is easy to apply as an adjunct to concurrent rehabilitation[14] or behavioral therapies.[131]

tDCS: Alternate Cerebral Targets—Traditionally, in line with studies using rTMS and MCS, tDCS has commonly been delivered to the region of M1 in management of chronic neuropathic pain.[5, 36, 87] In recent studies,[15–16, 38, 140] however, there has been a growing interest in the prospect of targeting DLPFC,[70] along similar rationale as in rTMS studies[18–21, 42, 122–123] and DBS trials targeting affective-emotional spheres of the neuromatrix. The evidence documenting potential benefits of targeting DLPFC with tDCS is still evolving even as compared to elementary studies in rTMS. In clinical populations, such as fibromyalgia, long-term application of tDCS lasting 10 days shows favorable results for pain as well as quality of life,[140] though in short-term trials, tDCS delivered to DLPFC, unlike M1, does not appear to exert anti-nociception.[38] Irrespective of the promise witnessed with longer treatment involving DLPFC, retention, intriguingly, still appears to favor tDCS targeting M1 versus DLPFC.[140] Experimental models of pain shed light upon the possible

distinctive effects of stimulating M1 versus DLPFC. Anodal tDCS of M1 increases pain as well as sensory perception thresholds, while stimulation of DLPFC only alters pain perception,[16] while simultaneously attenuating unpleasantness and emotional discomfort evoked by aversive painful stimuli.[15]

It is important to note that distinctive roles of M1 and DLPFC in pain modulation still require confirmation in clinical studies. If empirical findings are substantiated, the choice of locus of stimulation can be individualized to the intended effect of the intervention. However, an important drawback of current tDCS technique may confound the investigation of distinctive effects of loci. The standard tDCS electrodes (sponge-based) are spatially crude, usually measuring 5×7 cm^2 in size. DLPFC, traditionally, in the absence of neuronavigation, has been localized based on a general rule; once representation of intrinsic hand muscles in the M1 is identified with evaluative TMS, a region 5 cm anterior to that location is chosen as site for DLPFC stimulation.[21, 42, 107] It can thus be appreciated that standard tDCS electrodes may not allow optimal differentiation between M1 and DLPFC effects. In such cases, use of high-definition tDCS (HD-tDCS,)[28] in combination with image-guided neuronavigation, may serve a useful advantage. As a safe and tolerable technique, consisting of array configurations of compact cathodal and anodal scalp electrodes, HD-tDCS may provide targeted neuromodulation allowing precise study of mechanisms, a prospect that has been discussed in experimental model of pain recently.[17]

Mechanisms of Relief of Chronic Neuropathic Pain with Cerebral Neuromodulation

Understanding how different neuromodulatory modalities at various targets affect unique mechanisms of pain will help draw conclusions about relative efficacy of existing methods and guide development of individualized applications for future. The totality of human experience with pain ranging from perception of intensity to unpleasantness and the affect that shapes the experience and memory trace, is represented by the most complex parallel and serial, central, circuitry,[112] the ‘neuromatrix’, conceptualized as integration of myriad of neural networks in the brain subtending the multidimensional experience of pain. A better understanding of this neural circuitry will be important to realize the differential success associated with various techniques, while the knowledge of mechanisms to be gained will inform opportunities for potential synergism.

Whether targeted by invasive and/or noninvasive cerebral neuromodulation, the loci discussed in the present article are speculated to initiate unique mechanisms in association with pain management (Fig. 1). Notably, the discussion of the processes is consistent across the literature, but their speculative nature has been uniformly acknowledged.

1. PVG and PAG, targeted using DBS, have traditionally been implicated in descending opioid-based anti-nociception.[49]
2. Stimulation of thalamic nuclei, targeted directly using DBS, may act by way of suppressing hyperactivity of spinal sensory pathways.[57, 134]
3. Targeting M1, a popular locus for invasive as well as noninvasive stimulation, speculatively affects GABAergic divisions of thalamus[71] via cortico-thalamic pathways,[41, 102] inhibiting hyperactive thalamic nuclei.[47, 143] Thus, by blocking somatosensation and nociception,[16] M1-thalamic projections are believed to influence the sensory-discriminative sphere of the neuromatrix of pain.
4. Unlike M1, DLPFC stimulation alters pain thresholds only, without affecting somatosensation.[16] DLPFC stimulation arguably operates by directing medial pain pathways,[16] dampening the association between midbrain-thalamus in perception

of noxious stimuli[70] and controlling emotion and behavior[86] through cortical-striatal-thalamic-cortical (CSTC) loop.[32, 139] Through such interactions, stimulation of DLPFC may process the affective component of chronic pain,[70] attenuating unpleasantness/emotional discomfort[15] while relating to historical personal experience[103] via its cognitive-evaluative role.

Despite distinct modes of action, we argue that the ultimate mechanism of attenuating experience of pain may also share commonality across loci (Fig. 1), even though it may deviate from the widely-accepted mechanisms discussed above. For instance,

1. Besides descending, PVG/PAG stimulation may also possess an ascending mechanism of pain relief. Via dorsal medial thalamic nucleus, PAG is associated with limbic regions- ACC,[115] insula and amygdala,[13] evidence suggesting that targeting PAG may reduce emotional overtones related to pain.
2. Similarly, thalamic DBS, besides modulating activity of the sensory pathways, may exert pain relief via activation of limbic ACC.[29]
3. M1 stimulation can affect descending opioid-based anti-nociception[72] via its relation to PAG.[105] More importantly, besides the sensory-discriminative role, M1 stimulation may influence affective-emotional component of pain through its connections to the limbic system,[40, 55] ACC and amygdala.
4. Last, prefrontal areas can regulate ascending spinal nociceptive information and assist in spatial discrimination of pain based on personal experience,[103] functions that deviate from their purely ‘affective-emotional’ role in CSTC loop.

It, therefore, becomes difficult to argue that modalities of neuromodulation in pain operate via exclusive mechanisms. The ultimate success of a modality may instead be based on interaction of the proposed mechanisms with several other factors. First, efficacy of a method may depend upon how direct and timely it is in relation to the continuum of pain experience. For instance, although based on theoretical premise only, pain associated with deafferentation injuries may initially benefit from M1 stimulation, owing to its purported effect on thalamic hyperactivity. In chronic situations, however, targeting DLPFC or its CSTC synergists to modulate affective-emotional aspects of experience of pain, which add refractoriness to management, may present as a more viable option or at least a critical adjunct. Second, pre-stimulation state of targeted node[129] may precipitate variability of effect of the same technique across patients and etiologies. Instead of choosing a ‘one-size-fits-all’ stimulation pattern (frequency, duration, intensity), patient-specific models may optimize the degree of stochastic resonance[126] or other neurobiologic effects that underlie efficacy. Third, besides the node, the final effect upon the entire network may be as important. Unlike in other applications of neuromodulation, such as stroke,[141] in chronic neuropathic pain, it is unknown whether facilitating a target/node in a network is as effective, or at least synergistic, with inhibiting another. Connectivity-based imaging may be a useful precursor; early approaches along such ideas seem promising and warrant careful and more extensive follow-up investigation.[41, 44, 70, 102–103]

Finally, despite efforts, if benefits of neuromodulation remain modest and transient, clinical-applicability may be improved by supplementing with existing or novel strategies. Addition of noninvasive neuromodulation to standard pharmacological management,[110] physical rehabilitation[14] and neuro-behavioral visual imagery[131] are some of the existing examples. Synergism of neuromodulation with adjunctive methods may operate by enhancing key mechanisms, such as release of endogenous opioids,[30, 72] sensori-motor gating of pain,[14] corticospinal excitability and reduction of intracortical inhibition.[131]

Future Directions in the Study of Relief of Chronic Neuropathic Pain with Cerebral Neuromodulation

Despite promise, the clinical findings, thus far, do not unequivocally substantiate the therapeutic utility of cerebral neuromodulation in pain management; we argue that limitations in design and analyses may be implicated. Re-evaluating the study methods to generate robust data with randomized, blinded clinical trials in line with CONSORT (Consolidated Standards of Reporting Trials) guidelines[125] is critical to assessing and validating efficacy of neuromodulatory therapies. We discuss below design refinements that may help meet the stated goal.

Diagnostic Consistency

Future trials would provide more meaningful information if specific pain etiologies could be studied in segregated groups[26] and targets are selected based on a rationale that anticipates efficacy for specific diagnoses. Studies should be adequately powered and multiple intervention options (such as multiple targets) should be avoided unless planned - *a priori* - for separate and individually powered samples.

Creating Randomized, Placebo-controlled Double-blinded designs

Due to the subjectivity of pain, investigations of neuromodulatory therapies lend themselves to confounds, such as placebo effect, therapeutic confusion within investigative team and unintentional cues etc.[26] Although challenging, developing randomized, double-blinded, placebo-controlled trials offer reliable means of controlling confounds.

In invasive cerebral neuromodulation research, although introducing control groups is associated with ethical ramifications, the benefits of rigorous systematic exploration of efficacy outweigh these limitations. Patients, even if randomized to, subthreshold or placebo (stimulator off) conditions, could retain the option of crossing over to the stimulation group once the blinded phase of study is complete.[26] Randomized-controlled design was introduced in at least one study using thalamic DBS[79] and in two studies of MCS.[93, 114] With a randomized-controlled design, issue of dual experimental blinding becomes crucial. Creating blinded placebo is challenging with sensory thalamic DBS owing to paresthesias,[79] while it is more easily accomplished with MCS. By introducing 'harmless deception'[26] in terms of paresthesias,[79] and by assigning a neutral evaluator to test parameters, double blinding can be implemented[93, 114] with DBS[79] and MCS.[93, 114]

Noninvasive neurostimulation offers appealing alternatives to surgically-implanted systems for conducting randomized, controlled, double-blinded clinical trials as placebo stimulation can be accomplished consistently with the existing armamentarium. Interestingly, confound of placebo associated with rTMS is greater than that with tDCS. This could be related to poor placebo protocols created with rTMS in studies of chronic pain, which usually involve a simple tilt of the TMS coil away from the head,[54, 118, 120] instead of employing optimal sham coils.[63, 65] Additionally, higher technical effort involved in delivery of rTMS versus tDCS may also contribute to higher placebo effect with the former.[5] TDCS creates low placebo effect [ranging from −18.9% to + 9.8%[36] to (23.7%) at greater intensity[87]], an important advantage compared to most invasive and noninvasive neuromodulation techniques.

Adverse effects

Evaluation of adverse effects will help understand the risk-to-benefit ratio, which can be highly informative for design of future trials. Adverse effects noted in studies of MCS and DBS in chronic pain include, among the usual risks of major organ surgery, intracerebral or

extra-axial hematomas, seizures, infection, hardware failure and complications related to hardware maintenance such as battery replacements, replacement of failed leads and MRI safety concerns. As safer, noninvasive, alternatives, rTMS and tDCS carry risks that are mild and rare. High-frequency rTMS carries a rare risk of seizures;[119, 142] although most studies have not reported such a serious negative effect,[54, 62, 65, 120] one generalized seizure was noted in a subject undergoing rTMS for complex regional pain syndrome.[110] Other effects may include muscle twitches or paresthesias,[60] and occasional minor headache,[20, 30] neck pain,[110] dizziness,[30, 111] discomfort at treatment site,[122] transient tinnitus or nausea.[109] These side effects of rTMS have occasionally resulted in voluntary withdrawal of subjects[118] or attrition.[122] The incidence of adverse events with tDCS is even lower.[38] Usual adverse effects with tDCS are very mild, including headache,[5, 36] fatigue,[5] itching underneath the electrodes[5, 36] and sleep problems.[5]

Predicting Response

To help identify ideal candidates for existing neuromodulatory therapies, neurological markers, such as degree of paresis, as discussed earlier, carry predictive value for response to treatments, such as MCS[51, 100] and rTMS.[102] Residual state, both anatomical and functional, of the targeted networks[25] and of areas somatotopically-adjacent to painful site[65] as well as patency of implicated pathways[41] may correlate with outcomes. Structural neuroimaging,[41, 102] as well as neurophysiologic responsiveness to noninvasive rTMS[66] may add to the predictive value of subsequent surgical implantation with MCS.

Conclusions

The evidence, thus far, we argue, may not be rigorous enough to illustrate clinical applicability of cerebral neuromodulation in chronic neuropathic pain and pain of non-cancerous origin. The present article discusses factors diminishing confidence in the clinical applicability of cerebral neuromodulation in the management of chronic neuropathic pain. We posit that clinical studies of invasive (DBS and MCS) and noninvasive (rTMS and tDCS) brain stimulation suffer from key limitations. 1) Heterogenous study groups with mix of etiologies and cerebral targets create variability, 2) dogmatic management using fixed cerebral loci across etiologies impedes progress in the field, 3) little attention has been given to clinico-pathologic factors, such as viability of candidate substrates/pathways, 4) operative mechanisms in ‘responders’ versus ‘non-responders’ have hardly been compared, 5) consensus on optimal methodological application of certain techniques is lacking and 6) the field suffers from over-reliance on modulating sensory-discriminative percept of pain. Our recommendations include creating uniform study groups, illustrating etiology-specific mechanisms of recovery, identifying patient-centered loci customized to etiology, as well as state of recovery, modifying affective-emotional and cognitive-evaluative dimensions of pain besides sensory-discriminative sphere of the neuromatrix, utilizing randomized-controlled, blinded trials or surrogate techniques better suited to blinding and placebo as well as supplementing modest effects with rehabilitative and neuro-behavioral therapies.

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PERSPECTIVE

This critical review focuses on factors contributing to poor therapeutic utility of invasive and noninvasive brain stimulation in the treatment of chronic neuropathic and pain of non-cancerous origin. Through key clinical trial design and conceptual refinements, retention and consistency of response may be improved, potentially facilitating the widespread clinical applicability of such approaches.

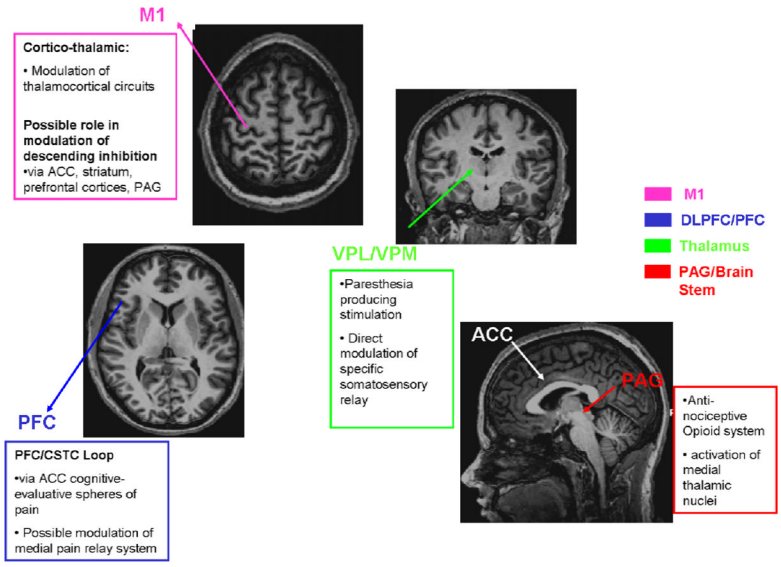

Figure 1.

Illustration depicting the most common cerebral targets of neuromodulation in treatment of chronic neuropathic pain. Different colors are associated with various loci targeted using invasive and noninvasive methods of neuromodulation. Textboxes summarize the mechanisms most commonly associated with stimulation of individual targets. As can be noted, distinct loci can operate via overlapping mechanisms, besides their specific substrates. Abbreviations: M1- Primary Motor Cortex; ACC- Anterior Cingulate Cortex; VPL- Ventral Posterior Lateral Nucleus; VPM- Ventral Posterior Medial Nucleus; DLPFC/PFC- Dorsolateral Prefrontal Cortex/Prefrontal Cortex; PAG- Peri-aqueductal Gray; CSTC- cortical-striatal-thalamic-cortical.