NIH Public Access
Author Manuscript
J Pain Manag. Author manuscript; available in PMC 2010 June 21.

Published in final edited form as:
J Pain Manag. 2009 August ; 2(3): 339–352.

Brain stimulation for the treatment of pain: A review of costs, clinical effects, and mechanisms of treatment for three different central neuromodulatory approaches

Soroush Zaghi, BS, **Nikolas Heine, BS**, and **Felipe Fregni, MD, PhD**
Berenson-Allen Center for Noninvasive Brain Stimulation, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, United States of America

Abstract

Methods of cortical stimulation including epidural motor cortex stimulation (MCS), repetitive transcranial magnetic stimulation (rTMS), and transcranial direct current stimulation (tDCS) are emerging as alternatives in the management of pain in patients with chronic medically-refractory pain disorders. Here we consider the three methods of brain stimulation that have been investigated for the treatment of central pain: MCS, rTMS, and tDCS. While all three treatment modalities appear to induce significant clinical gains in patients with chronic pain, tDCS is revealed as the most cost-effective approach (compared to rTMS and MCS) when considering a single year of treatment. However, if a 5-year treatment is considered, MCS is revealed as the most cost-effective modality (as compared to rTMS and tDCS) for the neuromodulatory treatment of chronic pain. We discuss the theory behind the application of each modality as well as efficacy, cost, safety, and practical considerations.

Keywords

Chronic pain; brain stimulation; cost-effect analysis; motor cortex stimulation; repetitive transcranial magnetic stimulation; transcranial direct current stimulation; brain polarization

INTRODUCTION

> "Chronic pain is a thief. It breaks into your body and robs you blind. With lightning fingers, it can take away your livelihood, your marriage, your friends, your favorite pastimes and big chunks of your personality. Left unapprehended, it will steal your days and your nights until the world has collapsed into a cramped cell of suffering." (Claudia Willis, Time Magazine).

Central pain syndrome is a prevalent, costly, and disabling neurological disorder that causes unrelenting suffering and disability. The pain ranges in intensity from moderate to severe and is often described as a burning, pressing, lacerating, or aching pain, occasionally accompanied by brief, intolerable bursts of sharp pain (1). Analgesics often provide some relief and treatment with tricyclic antidepressants (e.g. nortriptyline) or anticonvulsants (e.g. gabapentin) may be helpful, but pharmacologic interventions for central pain are nonspecific in focality and at target doses may cause drowsiness, impaired memory, and decreased capacity to carry out activities that require high executive functioning. These side effects result in administration of

Correspondence: Felipe Fregni, MD, PhD, Berenson-Allen Center for Non-invasive Brain Stimulation, 330 Brookline Ave, KS 452, Boston, MA 02215 United States. Tel: 617–667-5272; ffregni@bidmc.harvard.edu.

NIH-PA Author Manuscript
NIH-PA Author Manuscript
NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

doses that are often insufficient or ineffective. Other limitations to pharmacologic intervention include concerns of organ toxicity and risk of abuse or addiction (2). Thus, central pain remains inadequately treated, affecting up to 2.6% of women and 1.9% men for an average duration of 9.5 to 11.2 years (3). Indeed, the ensuing chronic pain results in significant loss of function and productivity, and is relatively expensive in terms of health care use. Thus, there remains an unmet clinical need for the development of new therapeutic approaches for the treatment of central pain.

In this setting, cortical stimulation has emerged as an interesting, effective, and promising modality in the investigation of novel approaches for pain relief. Cortical stimulation is based on the delivery of electric current to the motor cortex (among other cortical areas) of the brain; this delivery of current can be accomplished directly via epidural electrodes (as in epidural motor cortex stimulation, MCS) or indirectly and non-invasively via transcranial application of rapidly varying magnetic fields (as in repetitive transcranial magnetic stimulation, rTMS) or weak electrical currents (as in transcranial direct current stimulation, TDCS). A recent meta-analysis has shown that both direct and noninvasive means of motor cortical stimulation can be highly effective in the treatment of chronic pain (4) (5)). Sites of stimulation beyond the motor cortex, such as the dorsal lateral prefrontal cortex, may also be effective. Here we discuss the principles and mechanism in the use of brain stimulation for the treatment of central pain, and we discuss safety and practical considerations, as well as cost, in the application of these modalities.

Mechanisms and components of central pain

Central pain is, by definition, damage to or dysfunction of the central nervous system (brain, brainstem, and spinal cord) that results in long-lasting pain. It can be caused by stroke, multiple sclerosis, tumors, epilepsy, brain or spinal cord trauma, or Parkinson's disease, among other etiologies. However, central pain can also be caused by peripheral nerve injury, as with limb amputation, chemical injury, blunt trauma, or neuropathy that secondarily affects the central nervous system. Central pain often begins shortly after the causative injury or damage, but may be delayed by months or even years, especially if it is related to post-stroke pain (1).

Pain, in general, is mediated by a specific network of peripheral and central neurons that alarm us to the presence of potentially harmful stimuli. Normally, the perception of pain diminishes after resolution of the insult. In chronic pain, however, the nociceptive neural network responsible for pain conduction and processing sustains a hypersensitive state. The result is a hypersensitive network with lowered neural thresholds for sensory stimuli such that noxious stimuli produce an exaggerated and prolonged response to pain and non-noxious stimuli that are normally not painful become more likely to induce pain (6). Indeed, dysfunctional central sensitization is the hallmark of central pain, and a disturbance of pain-related thalamocortical transmission and processing is now acknowledged to be one of the main engines of this dysfunctional state (7).

The sensation commonly referred to as “pain” can be divided into a sensory-discriminative and an affective-motivational component (8). The sensory-discriminative component of pain (i.e. nociception or sensory pain) provides information about the location, modality, and intensity of painful stimuli. Pathways involved in this aspect of pain involve the spinothalamic tract (9) and result in preferential activation of the lateral thalamus and somatosensory cortices (S1 and S2), as well as the posterior insular cortex (10). On the other hand, the affective-motivational component of pain (i.e. the moment-by-moment unpleasantness of pain) refers to the emotional responses elicited by a painful stimulus—that is, painful stimuli invoke feelings of suffering, fear, exhaustion, disgust, sadness, and anxiety, among others, that motivate the individual to escape or reduce the source of pain. Indeed, this emotional pain preferentially activates the anterior cingulate cortex and the anterior insular cortex, which in

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

turn activate other components of the limbic system (i.e. areas of executive processing, such as the medial and dorsolateral prefrontal cortex), (10) which play an integral role in focusing attention to salient stimuli.

Interestingly, this affective dimension of pain relies on neurophysiological systems that are at least partly anatomically distinct from those involved in the sensory perception of pain (11). Even so, the cortico-limbic pathway is known to integrate nociceptive input with information about overall status of the body, in turn regulating (and sometimes amplifying) the affect attributed to pain (12). The cortical perception of pain is then intimately linked with areas of the brain involved in autonomic and neuroendocrine regulation (amygdala, hypothalamus, thalamic reticular nucleus, ventral tegmental area, locus coeruleus, laterodorsal tegmental nucleus), such that the perception of pain manifests physically with changes in blood pressure, heightened reflexes, and skin galvanomic response, among other changes (13). In addition, this integrated system might indicate that pain is not only part of an afferent system in which the final product is a change in behavior, but that the perception of pain itself may be part of a complex two-way afferent-efferent system in which the chronic pain might have profound changes in immune system function and endocrine regulation(14).

Thus, the perception of pain involves a large and complex interconnected network of neural structures, and central pain may result from a dysfunction in any part of this system. That is, lesions or injuries affecting any part of the network that processes sensation, emotion, or attention may all in turn contribute to the genesis of central pain. This is important to consider when discussing focal therapies (as with brain stimulation) because not all types of central pain are caused by a similar etiology, and so not all patients with central pain may benefit from a single, unique parameter of stimulation. Even so, cortical stimulation promises an interesting alternative in the treatment of central pain.

Cortical stimulation for the treatment of central pain

The mechanism of cortical stimulation for the relief of pain is based on the excitability modification of neuronal activity intimately involved in the neural circuits responsible for pain processing and perception. In this way, it is believed that stimulation of the cerebral cortex either inhibits or interrupts and interferes with pain signals that originate from the thalamus and other hyperactive areas in the pain networks of the brain. Thus, stimulation of the cortex may merely be an entry port for the complex pain-related neural network. We discuss two targets for cortical stimulation: motor cortex and prefrontal cortex.

Electrical stimulation of the primary motor cortex has been heralded as an extremely promising technique (15), and indeed the motor cortex has been the primary target for cortical stimulation for pain relief. The role of motor cortex stimulation in the relief of central pain has been best demonstrated for pain of thalamic origin. Animal studies show that transection of the spinal cord results in burst hyperactivity of VPL thalamic neurons that can be decreased by motor, but not sensory, cortex stimulation (7). Furthermore, epidural stimulation of the primary motor cortex has been found to relieve both thalamic hyperactivity and pain in human spinal cord injury pain patients (16). These findings suggest that motor cortex stimulation modulates abnormal thalamic activity via cortico-thalamic fibers to relieve pain in certain chronic pain syndromes (17,18). One possibility is that enhancement of motor cortex activity may result in direct inhibition of thalamic activity through inhibitory cortico-thalamic fibers. The secondary modulation of the thalamic nuclei may perhaps underlie the pain-alleviating attribute of motor cortex stimulation.

The prefrontal cortex is an alternate target of stimulation for the relief of pain, one that may be especially helpful in modulating the emotional, attentional, and affective dimensions of pain. Simulation of the prefrontal cortex has been associated with a modification of a large

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

extensive neural network associated with the limbic system such as the cingulate gyrus and parahippocampal areas (19,20). In fact, stimulation of prefrontal cortex areas is associated with working memory, attentional control, reasoning and decision-making modulation, as well as temporal organization of behavior, and emotional processing (21). Indeed, stimulation of the prefrontal cortex with rTMS has been shown to increase thermal pain thresholds in healthy adults (22) and to reduce of pain in fibromyalgia (23), further suggesting that this area may indeed be a potent target for brain stimulation in the treatment of central pain.

Stimulation of the primary motor cortex (M1) and dorsolateral prefrontal cortex (DLFPC) may both reduce the perception of pain, but recent studies suggest that they likely do so by different mechanisms. Pain and perception thresholds to electrical stimulation were assessed in 20 healthy volunteers before and during anodal TDCS. Four conditions of stimulation were compared: M1, DLPFC, occipital cortex, and sham. Anodal tDCS of M1 increased both perception and pain thresholds, while stimulation of DLPFC increased pain thresholds only. The results suggested that 1) anodal stimulation of M1 but not DLPFC could induce analgesia by modulating sensory discrimination and 2) stimulation of DLPFC could modulate the perception of pain via a mechanism independent of sensory perception (21). An adjunctive study with 22 healthy volunteers showed that anodal tDCS of the DLPFC (but not M1, occipital, or sham) could decrease the perception of unpleasantness and reduces emotional discomfort/pain while subjects viewed emotionally aversive images demonstrating human pain. It is indeed quite interesting that subjects perceived the aversive images as less unpleasant and reported lower levels of emotional discomfort during DLPFC tDCS, as compared to baseline and sham, and that motor cortex stimulation had no effect (22).

Together, these results suggests that while motor cortex stimulation may mediate its analgesic effects by decreasing the somatosensory-discriminative aspect of pain, stimulation of DLPFC may effect the affective-emotional aspect of pain, reducing the unpleasantness of a perceived stimulus. Interestingly, stimulation of DLPFC has also been effective in the treatment of depression and anxiety disorders, as well as the enhancement of attention and memory on cognitive tasks.

METHODS OF STIMULATION

Here we consider the three methods of brain stimulation that have been investigated for the treatment of central pain: MCS, rTMS, and tDCS.

Epidural motor cortex stimulation

MCS is a method of introducing electric current to the motor cortex via the surgical implantation of epidural electrodes. Preoperative and intraoperative localization of the motor cortex is achieved through neuronavigation, which includes fMRI and somatosensory evoked potentials, among other neurosurgical mapping techniques. During the neurosurgical procedure, a paddle lead with four electrodes is placed beneath the periosteum of the skull and above the dura mater. The paddle lead is adjusted so that all four contact points cover the precentral gyrus of the brain. Proper positioning is ensured by the application of suprathreshold stimulation to induce contralateral motor response without the induction of parasthesia or other sensory phenomena (24). After the operation, an individualized test trial is performed for each patient to identify the electrode combination and stimulation parameters that generate the greatest pain-relieving effect. The most commonly used settings are 2–3 V (range 0.5–9.5 V) of intensity, 25–50 Hz (range 15–130 Hz) of frequency, and 200 μsec (range 60–450 μsec) for pulse width. In all cases, the stimulation is sub-threshold and bipolar, and the parameters of stimulation (i.e. elevated frequency and intensity) are targeted to cause a disruption in the area of stimulation where the electrodes are placed. Stimulation is provided off-and-on throughout

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

the day according to a cyclic program, where most patients receive about 12 hrs of stimulation daily (25).

According to a recent systematic review the mean weighted responder rate for studies with epidual MCS is 72.6% (95% CI, 67.7-77.4) (4). Another similar review also confirmed the high response rate for this procedure: about 56.7% of patients experience a “good outcome” (= 40–50% improvement) after the implantation of a motor cortex stimulator. In studies where follow-up = 1 year was considered, 45.4% had a “good postoperative outcome.” In the 2 studies with the longest follow-up period (49 months in both), 47 and 22.6% of the patients experienced a long-term pain relief of = 50%. Among the subset of patients with less favorable results, for many it has been possible to reduce medication doses and still others are noted to experience substantial yet less significant pain relief and improvements in quality of life. Nevertheless, many neurosurgeons anecdotally suggest that MCS results are not consistent and often disappointing (25).

Repetitive transcranial magnetic stimulation

Transcranial magnetic stimulation (TMS) is a non-invasive technique of brain stimulation based on the principle of electromagnetic induction. A coil of copper wire encased in plastic is rested on the subject's scalp overlying the area of the brain to be stimulated. As current passes through the coil, a magnetic field is generated in a plane perpendicular to the coil. The current passed is strong but extremely brief, thus generating a magnetic field that changes rapidly in time. In fact, the magnetic field reaches 2 Tesla in about 50 μs, but then decays back to 0 in the same amount of time. This very rapidly changing magnetic field penetrates the skin and skull of the subject unimpeded, without causing any discomfort. Due to the rapid change in time, it induces a secondary electrical current in the subject's brain that is strong enough to depolarize neurons. The peak of this induced current is limited to a small volume of brain cortex (1-4 cm3) (26). The stimulation does not penetrate further because the magnetic field decays rapidly in intensity with square of the distance. Even so, depolarization of cortical neurons may result in secondary activation or inhibition of other brain areas, including the contralateral hemisphere and thalamic nuclei, among other cortical and subcortical regions.

If the TMS stimulus is repeated over and over again in trains of stimulation, this is referred to as repetitive transcranial magnetic stimulation (rTMS). A train of rTMS can modulate cortical excitability in manner that lasts beyond the duration of the rTMS itself. This effect may range from suppression to facilitation of activity in an underlying brain area, depending on the stimulation parameters, particularly stimulation frequency. For instance, in the motor cortex, lower rTMS frequencies in the 1 Hz range can usually suppress cortical excitability, while 20 Hz stimulation trains seem to lead to a temporary increase in cortical excitability in most subjects. Although these effects are relatively consistent, other parameters (such as baseline cortical excitability) do play an important role. Indeed, in epileptic patients with chronic valproate use, a study shows that when serum concentration of valproate are low, 1 Hz rTMS has a similar inhibitory effect on corticospinal excitability as in healthy subjects; but, when the serum valproate concentration are high (in the same patients), 1 Hz rTMS paradoxically increases the corticospinal excitability (27). Therefore the therapeutic use of rTMS should take into consideration the interaction between rTMS and drugs that change cortical excitability.

In rTMS, the site of stimulation can be approximated by using brain landmarks and then confirmed by identification of motor or sensory evoked potentials. Motor cortex stimulation is reliable with such an approach, because motor evoked potentials can be appreciated. DLPFC stimulation, on the other hand, is limited, however, because the technician can only approximate and never be entirely sure whether an exact location is being stimulated. Here, it is debatable whether this represents a real limitation as the focality of rTMS is also limited. Alternatively, the use of a frameless stimulation guiding device allows targeting specific areas

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

of the subject's brain by using the subject's own brain MRI to guide placement of the TMS coil on the subject's head (28). Nevertheless, accurate localization and focalization of stimulation area with TMS clearly has greater limitations when compared to direct epidural stimulation.

In patients with chronic neuropathic pain, motor cortex stimulation with rTMS applied at 5-20 Hz for at least 1000 pulses reduces pain scores by about 25-30% (5). In fact a recent meta-analysis, has shown that the mean responders rate is 36.8% (95% C.I., 30. 5– 43. 0 %) (4). Following a single rTMS session, analgesic effects are optimal a few days later and last for less than one week. Repeated daily stimulation sessions appear to increase and prolong the pain-relieving effects, and there may be some role for treatment with maintenance therapy (see Case Report by Zaghi et al. in this journal). Of note, although stimulation of DLPFC has been shown to be effective in depression and anxiety syndromes, including fibromyalgia and PTSD, to our knowledge, the investigation of stimulation of DLPFC stimulation for pain has been limited to healthy volunteers.

Transcranial direct current stimulation

tDCS is based on the application of low-amplitude electric current to the scalp. A battery-powered current generator (capable of delivering up to 2 mA of constant current flow) is attached to two sponge-based electrodes (20-35 cm^2). The sponge electrodes are then soaked, applied to the scalp, and held in place by a non-conducting rubber montage affixed around the head. During tDCS, low amplitude direct currents penetrate the skull to enter the brain. Although there is substantial shunting of current at the scalp, sufficient current penetrates the brain to modify the transmembrane neuronal potential (29,30) and, thus, influence the level of excitability and modulate the firing rate of individual neurons. However, it should be noted that the effects of tDCS are strongly dependent on electrode montage and parameters of stimulation (i.e. intensity and duration of stimulation). Furthermore, DC currents do not induce action potentials; rather, the current appears to modulate the spontaneous neuronal activity in a polarity-dependent fashion: for example, anodal tDCS applied over the motor cortex increases the excitability of the underlying motor cortex, while cathodal tDCS applied over the same area decreases it (31,32). Similarly, anodal tDCS applied over the occipital cortex produces short-lasting increases in visual cortex excitability (33,34). Hence, TDCS is believed to deliver its effects by polarizing brain tissue, and while anodal stimulation generally increases excitability and cathodal stimulation generally reduces excitability, the direction of polarization depends strictly on the orientation of axons and dendrites in the induced electrical field.

It has been demonstrated that the functional effects of tDCS are generally restricted to the area under the electrodes (35,36). However, of significant interest are recent studies that show that TDCS can induce effects beyond the immediate site of stimulation (37,38). This supports the notion that TDCS has a functional effect not only on the underlying cortico-spinal excitability but also on distant neural networks (39). In addition, fMRI studies reveal that tDCS not only has effects on the underlying cortex (40), but that it moreover provokes sustained and widespread changes in regional neuronal activity (41). EEG studies support these findings showing that stimulation induces synchronous changes to oscillatory activity (42,43). Hence, the effects of DC stimulation are likely perpetuated throughout the brain via networks of inter-neuronal circuits (44). But, this raises an interesting question as to whether the observed clinical effects (e.g. pain, depression alleviation) are mediated primarily through the cortex or secondarily via activation or inhibition of other cortical and/or sub-cortical structures (21,45).

tDCS has been valuable in exploring the effect of cortical modulation on various neural networks implicated in decision-making (46), language (47), memory (48), among other high-order cortical processes, including sensory perception and pain (45). Furthermore, preliminary small sample-size studies with TDCS have shown initial positive results in modulating chronic

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

pain (49). For chronic central pain due to traumatic spinal cord injury, 5 daily sessions of TDCS (20 min, 2 mA, motor cortex) resulted in a reduction of pain scores of at least 50% in 6/11 patients receiving active treatment (50). For pain due to fibromyalgia, our studies suggest an approximate improvement of 20-30% with 10 daily sessions among all subjects receiving motor cortex or DLPFC stimulation.

tDCS has some advantages over rTMS because it has longer-lasting modulatory effects on cortical function and is less expensive to administer. The primary limitation is that the sites of stimulation in tDCS are identified based on the cranial landmarks used in 10-20 system for EEG electrode placement. Clearly, because there is great variety in true brain anatomy among subjects, this means that in many cases, the electrode placement may not exactly correspond to the target site of stimulation. Coincidentally, it appears that certain subjects appear more susceptible to the effects of tDCS per the current protocol, and indeed subjects who do respond to treatment with tDCS appear to do quite well when supported with repeated maintenance tDCS sessions (51).

Cost-effectiveness analysis

We performed a preliminary cost-effectiveness analysis involving the three main modalities of brain stimulation (MCS, rTMS and tDCS) for the treatment of chronic pain.

Study population

The target population for this study was patients with chronic pain (see list of conditions in table 1) undergoing cortical stimulation. In carrying out this analysis, we considered the sub-acute effects of the treatments as described in the studies, but we furthermore adopted extrapolative assumptions in the consideration of these modalities for long term-use. In order to obtain estimates of treatment effects, we conducted a systematic investigation throughout MEDLINE and other databases and collected Visual Analogue Scale (VAS) assessments from studies that evaluated the effects of any of these techniques on pain.

Effectiveness measures

For the purpose of evaluation, we decided to use VAS of pain as the primary measure of effectiveness. Quality-Adjusted Life Years (QALYs) were used as a secondary measure of effectiveness and were derived from the VAS of pain using a transformation function to convert VAS values (V) to Standard Gamble (SG) utility scores (U). Several studies found a discrepancy between V and U values due to a well known end-aversion bias of VAS and a slightly concave curve pattern in a direct and systematic relationship of SG and VAS. Despite the fact that this relationship may not be stable at the individual level, comparative group analysis have demonstrated a highly accurate relationship once the VAS values are converted by a transformation function into SG utility scores.

Cost measures

We decided to include only costs from the perspective of the health care system. We did not include future or societal costs due to the short time frame of our model. Therefore, we only included direct fixed costs associated with treatment such as: room utilization, equipment maintenance, supplies, technician, neurologist coverage for each session and/or consultation, administrative fees, hospitalization costs, surgeon fee, anesthesiologist fee, surgical fee, electrode costs.

The costs of rTMS and tDCS treatment administration were estimated using data on capital costs (including the treatment suite and machines used during treatment) and cost of professionals' time related to treatment. We searched for these costs in several cities US cities.

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

For the estimation of costs associated with the treatment suite, we searched for the rental of medical office space with a size of 200 square feet – including utilities. The costs of machinery used in treatment were obtained from suppliers, and the market value of the equipment annuitized at 3.0% over 10 years plus any associated maintenance costs. The annual costs of the treatment suite and machinery were then divided by the number of administrations of treatments for the year – we estimated an average of 400 treatments per year.

To measure staff time, we recorded the profession and grade of the staff involved in the treatment; we estimated the annual salary of the technician over the different US cities and divided by the number of treatments (400 a year). For the neurologist, we estimated his/her annual salary and divided by 8 (estimating that he would dedicate 1/8 of his time to follow-up these patients and then divided by the number of treatments in a year [400]. We then estimated the costs of administrative overhead calculating 10% of the total costs per session for each modality.

To estimate costs of the surgery, we gathered data across the U.S. on hospitalization-related costs, including admission; room and board; operating room; pharmacy; radiology; laboratory; medical and surgical supplies; and other charges (i.e., anesthesia, blood, etc.).

Economic evaluation

A cost-effectiveness analysis summarizes the additional resources consumed for an improvement in the effects (in our study measured as decrease in pain as indexed by VAS) associated with one intervention compared to another. The result can be summarized as an incremental cost-effectiveness ratio (ICER) – a measure of the additional cost per unit of health gain. The underlying calculation for the ICER comparing for instance MCS vs. rTMS in patients with chronic pain was:

$$\text{ICER} = \frac{\text{Average Cost}_{\text{MCS}} - \text{Average Cost}_{\text{rTMS}}}{\text{Average Effect}_{\text{MCS}} - \text{Average Effect}_{\text{rTMS}}}$$

where costs were measured in US dollars and effects were measured in VAS changes. A cost-effective analysis was conducted by comparing MCS vs. rTMS, MCS vs. tDCS and rTMS vs. tDCS. For each comparison, we calculated the incremental cost per unit of VAS decreased and incremental cost per quality-adjusted life-year (QALY) gained. Incremental cost-effectiveness ratios were not calculated if one treatment strategy dominated the other (i.e., lower costs, better outcomes).

Preliminary results

The demographic and clinical characteristics of the subjects at baseline are shown in table 2. MCS treatment was associated with a mean reduction in VAS of 3.44 and an increase in Standard Gambles Utilities Score of 0.41. rTMS had the lowest reduction in VAS and lowest increase in Utilities Score, respectively 2.14 and 0.25. On the other hand, tDCS was intermediate in effect with 2.84 for VAS and 0.30 for Utilities Score.

Costs of treatment

Our analysis showed that the cost per tDCS session is lower than rTMS session (US$167.72 vs. US$207.24). The mean cost of the first treatment (given 10 sessions of non-invasive brain stimulation) is US$ 1677.20 for tDCS, US$ 2072.40 for rTMS and US$ 42,000.00 for MCS (mean cost of neurosurgical procedure including electrodes to implant the cortical stimulation). We then analyzed costs over 1 year and over 5 years. For tDCS and rTMS, we calculated one maintenance session per week – starting 2 weeks after treatment and including two sets of

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

booster treatments of 5 sessions per year – then 70 sessions are needed per year for both treatments, therefore an annual treatment for these two techniques would cost US$ 11,740.40 for tDCS and US$ 14,506.80 for rTMS. For MCS, one monthly visit is necessary to check the parameters of stimulation – therefore, the annual costs of MCS are US$ 3,600.00 (given US$ 300 dollars the cost of one appointment to check parameters of stimulation).

Stipulating a time horizon of 1 year, the costs of treatment are US$45,600.00 for MCS, US$ 11,740.40 for tDCS and US$ 14.506.80 for rTMS treatment. For a time horizon of 5 years, we discounted the costs of years after the first year, adjusting to the beginning of the first year, following a discount rate of 3.0 percent per year. For MCS, with the monthly visit of the second through the fifth year properly discounted and added to the surgery costs, totalized US$ 58591.91. All rTMS discounted costs summed with the first year is US$ 68.311.00. For tDCS the total amount correctly discounted is US$ 55.284.00.

Cost-effectiveness

The main outcome for the cost-effectiveness analysis was the incremental cost per unit of VAS. Because MCS was associated with the best outcome but was also the most expensive treatment, we compared MCS vs. tDCS and MCS vs. rTMS. We performed this analysis for two scenarios: 1 and 5 years of treatment. This comparison was not done for rTMS vs. tDCS as the response to tDCS was larger and less costly than rTMS; therefore, tDCS is always more cost-effective as compared to rTMS.

Scenario 1: 1-year treatment

Initially, we compared rTMS vs. MCS during the first year of treatment. For the first year, rTMS is a less costly procedure but induces less benefit as compared to MCS. The ICER when comparing these two procedures is US$ 23819.84 per unit of VAS. We then performed similar analysis, but used tDCS instead of rTMS. The comparison showed that ICER is US$ 56432.66 per unit of VAS. Therefore, rTMS and tDCS are less costly but also less effective than MCS, and an additional gain of 1.3 or 0.6 units of VAS conferred by MCS would cost US$30,964.70 and US$33,859.60 respectively as compared with rTMS and tDCS.

Scenario 2: 5-year treatment

We then performed similar analysis, but considered the 5-year scenario. The ICER when comparing MCS and rTMS shows a negative value (−9,358.66 dollars); therefore showing that MCS would be a more effective and cost-saving procedure compared to rTMS. However the comparison between MCS and tDCS showed that ICER is US$3,667.95 per unit of VAS, such that the additional gain of 0.6 units of VAS conferred by MCS would cost US$2,200.77.

SUMMARY AND FUTURE DIRECTIONS

MCS is an invasive technique of brain stimulation that requires neurosurgery and therefore carries significant risk of injury or death. While the procedure is quite expensive, the major benefit is that it allows for a prolonged duration of stimulation (hours a day for years) and in fact might induce the largest benefits as compared to rTMS and tDCS. rTMS, on the other hand, is similarly excellent in targeted brain stimulation and it offers a non-invasive manner of inducing electric current. Even so, the technique is quite challenging requiring a trained technician to be present for the entire duration of stimulation, and so rTMS is relatively more expensive in comparison to tDCS. Furthermore, specific parameters of stimulation must be followed (and certain subjects excluded) to prevent risk of seizure with the application of rTMS. Finally, tDCS offers a less focal method of brain stimulation that is much easier to apply and carries almost no risk of seizure. Indeed, it may be possible to design tDCS devices for home use, so that patients can use the device for extended durations at little or no extra cost. This

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

would make this technique the most cost-effective modality as compared to all the other methods of stimulation. tDCS is limited with respect to the intensity of stimulation that can be applied, such that it generally involves a diffuse spread of electric current. It is not clear whether the efficacy of these treatments is based on accurate localization of brain targets, intensity of stimulation, and duration. If it is, then it should be expected that MCS would deliver the greatest efficacy followed in turn by tTMS and tDCS. In the future, chronic pain patients who respond beneficially but only transiently to rTMS, may then be offered a trial of tDCS, or as a last resort they may be referred for consideration of epidural motor cortex stimulation. In addition, in the future, we can hope that more sophisticated regimens and parameters of stimulation will be developed that may be able to dynamically stimulate various brain regions at different frequencies and intensities during a single session. In this way, non-invasive brain stimulation might be physiologically tailored to suit the brain state of each patient in an attempt to maximize efficacy.

REFERENCES

1. NINDS. NINDS Central Pain Syndrome Information Page. National Institute of Neurological Disorders and Stroke. 2009. http://www.ninds.nih.gov/disorders/central_pain/central_pain.htm
2. Katz NP, Adams EH, Chilcoat H, Colucci RD, Comer SD, Goliber P, et al. Challenges in the development of prescription opioid abuse-deterrent formulations. Clin J Pain 2007;23(8):648–60. [PubMed: 17885342]
3. Tunks ER, Crook J, Weir R. Epidemiology of chronic pain with psychological comorbidity: prevalence, risk, course, and prognosis. Can J Psychiatry 2008;53(4):224–34. [PubMed: 18478825]
4. Lima MC, Fregni F. Motor cortex stimulation for chronic pain: systematic review and meta-analysis of the literature. Neurology 2008;70(24):2329–37. [PubMed: 18541887]
5. Lefaucheur JP. Use of repetitive transcranial magnetic stimulation in pain relief. Expert Rev Neurother 2008;8(5):799–808. [PubMed: 18457536]
6. Woolf CJ, Ma Q. Nociceptors--noxious stimulus detectors. Neuron 2007;55(3):353–64. [PubMed: 17678850]
7. Canavero S, Bonicalzi V. Central pain syndrome: elucidation of genesis and treatment. Expert Rev Neurother 2007;7(11):1485–97. [PubMed: 17997698]
8. Treede RD, Kenshalo DR, Gracely RH, Jones AK. The cortical representation of pain. Pain 1999;79 (2-3):105–11. [PubMed: 10068155]
9. Ohara PT, Vit JP, Jasmin L. Cortical modulation of pain. Cell Mol Life Sci 2005;62(1):44–52. [PubMed: 15619006]
10. Moisset X, Bouhassira D. Brain imaging of neuropathic pain. Neuroimage 2007;37(Suppl 1):S80–8. [PubMed: 17512757]
11. Duquette M, Roy M, Lepore F, Peretz I, Rainville P. Cerebral mechanisms involved in the interaction between pain and emotion. Rev Neurol (Paris) 2007;163(2):169–79. [PubMed: 17351536]
12. Price DD. Central neural mechanisms that interrelate sensory and affective dimensions of pain. Mol Interv 2002;2(6):392–403. [PubMed: 14993415]
13. Blackburn-Munro G. Hypothalamo-pituitary-adrenal axis dysfunction as a contributory factor to chronic pain and depression. Curr Pain Headache Rep 2004;8(2):116–24. [PubMed: 14980146]
14. Fregni F, Pascual-Leone A, Freedman SD. Pain in chronic pancreatitis: a salutogenic mechanism or a maladaptive brain response? Pancreatology 2007;7(5-6):411–22. [PubMed: 17898531]
15. Saitoh Y, Hirayama A, Kishima H, Oshino S, Hirata M, Kato A, et al. Stimulation of primary motor cortex for intractable deafferentation pain. Acta Neurochir Suppl 2006;99:57–9. [PubMed: 17370765]
16. Lenz FA, Kwan HC, Dostrovsky JO, Tasker RR. Characteristics of the bursting pattern of action potentials that occurs in the thalamus of patients with central pain. Brain Res 1989;496(1-2):357–60. [PubMed: 2804648]
17. 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. [PubMed: 1705329]

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

18. Tsubokawa T, Katayama Y, Yamamoto T, Hirayama T, Koyama S. Chronic motor cortex stimulation for the treatment of central pain. Acta Neurochir Suppl (Wien) 1991;52:137–9. [PubMed: 1792954]
19. Mottaghy FM, Krause BJ, Kemna LJ, Topper R, Tellmann L, Beu M, et al. Modulation of the neuronal circuitry subserving working memory in healthy human subjects by repetitive transcranial magnetic stimulation. Neurosci Lett 2000;280(3):167–70. [PubMed: 10675787]
20. Catafau AM, Perez V, Gironell A, Martin JC, Kulisevsky J, Estorch M, et al. SPECT mapping of cerebral activity changes induced by repetitive transcranial magnetic stimulation in depressed patients. A pilot study. Psychiatry Res 2001;106(3):151–60. [PubMed: 11382537]
21. Boggio PS, Zaghi S, Fregni F. Modulation of emotions associated with images of human pain using anodal transcranial direct current stimulation (tDCS). Neuropsychologia 2009;47(1):212–7. [PubMed: 18725237]
22. Borckardt JJ, Smith AR, Reeves ST, Weinstein M, Kozel FA, Nahas Z, et al. Fifteen minutes of left prefrontal repetitive transcranial magnetic stimulation acutely increases thermal pain thresholds in healthy adults. Pain Res Manag 2007;12(4):287–90. [PubMed: 18080048]
23. Sampson SM, Rome JD, Rummans TA. Slow-frequency rTMS reduces fibromyalgia pain. Pain Med 2006;7(2):115–8. [PubMed: 16634724]
24. Rasche D, Ruppolt M, Stippich C, Unterberg A, Tronnier VM. Motor cortex stimulation for long-term relief of chronic neuropathic pain: a 10 year experience. Pain 2006;121(1-2):43–52. [PubMed: 16480828]
25. Fontaine D, Hamani C, Lozano A. Efficacy and safety of motor cortex stimulation for chronic neuropathic pain: critical review of the literature. J Neurosurg. in press.
26. Wagner T, Gangitano M, Romero R, Theoret H, Kobayashi M, Anschel D, et al. Intracranial measurement of current densities induced by transcranial magnetic stimulation in the human brain. Neurosci Lett 2004;354(2):91–4. [PubMed: 14698446]
27. Fregni F, Boggio PS, Valle AC, Otachi P, Thut G, Rigonatti SP, et al. Homeostatic effects of plasma valproate levels on corticospinal excitability changes induced by 1Hz rTMS in patients with juvenile myoclonic epilepsy. Clin Neurophysiol 2006;117(6):1217–27. [PubMed: 16644277]
28. Gugino LD, Romero JR, Aglio L, Titone D, Ramirez M, Pascual-Leone A, et al. Transcranial magnetic stimulation coregistered with MRI: a comparison of a guided versus blind stimulation technique and its effect on evoked compound muscle action potentials. Clin Neurophysiol 2001;112(10):1781–92. [PubMed: 11595135]
29. Wagner T, Valero-Cabre A, Pascual-Leone A. Noninvasive human brain stimulation. Annu Rev Biomed Eng 2007;9:527–65. [PubMed: 17444810]
30. Miranda PC, Lomarev M, Hallett M. Modeling the current distribution during transcranial direct current stimulation. Clin Neurophysiol 2006;117(7):1623–9. [PubMed: 16762592]
31. Wassermann EM, Grafman J. Recharging cognition with DC brain polarization. Trends Cogn Sci 2005;9(11):503–5. [PubMed: 16182596]
32. Nitsche MA, Paulus W. Sustained excitability elevations induced by transcranial DC motor cortex stimulation in humans. Neurology 2001;57(10):1899–901. [PubMed: 11723286]
33. Antal A, Kincses TZ, Nitsche MA, Paulus W. Manipulation of phosphene thresholds by transcranial direct current stimulation in man. Exp Brain Res 2003;150(3):375–8. [PubMed: 12698316]
34. Lang N, Siebner HR, Chadaide Z, Boros K, Nitsche MA, Rothwell JC, et al. Bidirectional modulation of primary visual cortex excitability: a combined tDCS and rTMS study. Invest Ophthalmol Vis Sci 2007;48(12):5782–7. [PubMed: 18055832]
35. Nitsche MA, Liebetanz D, Lang N, Antal A, Tergau F, Paulus W. Safety criteria for transcranial direct current stimulation (tDCS) in humans. Clin Neurophysiol 2003;114(11):2220–3. [PubMed: 14580622]
36. Nitsche MA, Niehaus L, Hoffmann KT, Hengst S, Liebetanz D, Paulus W, et al. MRI study of human brain exposed to weak direct current stimulation of the frontal cortex. Clin Neurophysiol 2004;115 (10):2419–23. [PubMed: 15351385]
37. Boros K, Poreisz C, Munchau A, Paulus W, Nitsche MA. Premotor transcranial direct current stimulation (tDCS) affects primary motor excitability in humans. Eur J Neurosci 2008;27(5):1292–300. [PubMed: 18312584]

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

38. Vines BW, Cerruti C, Schlaug G. Dual-hemisphere tDCS facilitates greater improvements for healthy subjects' non-dominant hand compared to uni-hemisphere stimulation. BMC Neurosci 2008;9(1): 103. [PubMed: 18957075]
39. Nitsche MA, Seeber A, Frommann K, Klein CC, Rochford C, Nitsche MS, et al. Modulating parameters of excitability during and after transcranial direct current stimulation of the human motor cortex. J Physiol 2005;568(Pt 1):291–303. [PubMed: 16002441]
40. Kwon YH, Ko MH, Ahn SH, Kim YH, Song JC, Lee CH, et al. Primary motor cortex activation by transcranial direct current stimulation in the human brain. Neurosci Lett 2008;435(1):56–9. [PubMed: 18325666]
41. Lang N, Siebner HR, Ward NS, Lee L, Nitsche MA, Paulus W, et al. How does transcranial DC stimulation of the primary motor cortex alter regional neuronal activity in the human brain? Eur J Neurosci 2005;22(2):495–504. [PubMed: 16045502]
42. Marshall L, Molle M, Hallschmid M, Born J. Transcranial direct current stimulation during sleep improves declarative memory. J Neurosci 2004;24(44):9985–92. [PubMed: 15525784]
43. Ardolino G, Bossi B, Barbieri S, Priori A. Non-synaptic mechanisms underlie the after-effects of cathodal transcutaneous direct current stimulation of the human brain. J Physiol 2005;568(Pt 2):653–63. [PubMed: 16037080]
44. Lefaucheur JP. Principles of therapeutic use of transcranial and epidural cortical stimulation. Clin Neurophysiol 2008;119(10):2179–84. [PubMed: 18762449]
45. Boggio PS, Zaghi S, Lopes M, Fregni F. Modulatory effects of anodal transcranial direct current stimulation on perception and pain thresholds in healthy volunteers. Eur J Neurol. in press.
46. Fecteau S, Pascual-Leone A, Zald DH, Liguori P, Theoret H, Boggio PS, et al. Activation of prefrontal cortex by transcranial direct current stimulation reduces appetite for risk during ambiguous decision making. J Neurosci 2007;27(23):6212–8. [PubMed: 17553993]
47. Floel A, Rosser N, Michka O, Knecht S, Breitenstein C. Noninvasive brain stimulation improves language learning. J Cogn Neurosci 2008;20(8):1415–22. [PubMed: 18303984]
48. Fregni F, Boggio PS, Nitsche M, Bermpohl F, Antal A, Feredoes E, et al. Anodal transcranial direct current stimulation of prefrontal cortex enhances working memory. Exp Brain Res 2005;166(1):23–30. [PubMed: 15999258]
49. Fregni F, Gimenes R, Valle AC, Ferreira MJ, Rocha RR, Natalle L, 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. [PubMed: 17133529]
50. Fregni F, Boggio PS, Lima MC, Ferreira MJ, Wagner T, Rigonatti SP, 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. [PubMed: 16564618]
51. Cecilio SB, Zaghi S, Cecilio LB, Correa CF, Fregni F. Exploring a novel therapeutic approach with noninvasive cortical stimulation for vulvodynia. Am J Obstet Gynecol 2008;199(6):e6–7. [PubMed: 19084092]

NIH-PA Author Manuscript
NIH-PA Author Manuscript
NIH-PA Author Manuscript

Table 1

Etiology of pain syndrome (number of patients)

Treatment	Causative Lesion	Number of Patients	Treatment	Causative Lesion	Number of Patients
MCS	Deep brain hematoma	5	**rTMS**	Trigeminal neuralgia	24
	Ischemic Stroke	25		Post-stroke pain	24
	Arteriovenous malformation	1		Fibromyalgia	8
	Avulsion	4		Spinal Cord injury	6
	Haemorrhagic stroke	16			
	Dental surgery	3			
	Trigeminal pain	22	**tDCS**	Fibromyalgia	11
	Thalamic abscess	1		Spinal Cord injury	11
	Trauma	8			
	Herpetic pain	3			
	Nerve injury	6			
	No clear cause	2			

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

Table 2

Demographic characteristics

	MCS	rTMS	tDCS
Number of patients	96	35	22
Age (mean)	58.14215	56	45.4
Duration of pain (years)	6.433333	4.283333	6.85
Baseline pain (VAS)	8.59	6.666667	7.34

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

Table 3

Changes in VAS and utilities

	Change in VAS (amount decreased from baseline)	VAS (% change)	Change in Utilities Scores (amount increased from baseline)
MCS	3.44	41.7%	0.41
TMS	2.14	33.5%	0.25
TDCS	2.84	37.3%	0.30

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

Table 4

tDCS and rTMS costs per session.

	tDCS	rTMS
Room Utilization(US$)	$16.25	$16.25
Equipment maintenance/leasing (US$)	$1.68	$32.60
Supplies (US$)	$5.00	$10.00
Technician (US$)	$111.57	$111.57
Licensed physician (US$)	$17.98	$17.98
Administrative costs (US$)	$15.24	$18.84
Total	$167.72	$207.24