Noninvasive Transcranial Brain Stimulation and Pain

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Transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS) are two noninvasive brain stimulation techniques that can modulate activity in specific regions of the cortex. At this point, their use in brain stimulation is primarily investigational; however, there is clear evidence that these tools can reduce pain and modify neurophysiologic correlates of the pain experience. TMS has also been used to predict response to surgically implanted stimulation for the treatment of chronic pain. Furthermore, TMS and tDCS can be applied with other techniques, such as event-related potentials and pharmacologic manipulation, to illuminate the underlying physiologic mechanisms of normal and pathological pain. This review presents a description and overview of the uses of two major brain stimulation techniques and a listing of useful references for further study.

Introduction

Noninvasive forms of cortical stimulation have the potential for illuminating mechanisms of pain in healthy subjects, treating intractable pain in patients, and predicting outcome in surgical intervention in patients with chronic pain. More in-depth descriptions of these techniques are available elsewhere [1••,2•,3]. Several recent review articles have discussed many of the topics described here in greater depth and are listed throughout and at the end of this paper. The literature cited thus focuses on key original papers, recent reviews, and work that has been published after the literature cited in these reviews. This article provides a general overview of noninvasive transcranial brain stimulation and pain and describes important, basic concepts to inform further reading. For example, one problem a clinician or new researcher faces is that most reviews have tables listing the clinical trials treating chronic pain with transcranial stimulation; however, the significance of the stimulation parameters listed in the tables is unclear. This paper discusses the stimulation parameters and terms typically listed in these tables so that a clinician will be able to integrate the results in a more meaningful way.

Noninvasive Transcranial Stimulation Techniques Described

The most commonly used noninvasive transcranial stimulation techniques are transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS). As in any treatment to ameliorate pain, there is the potential for clinical benefit due to a placebo response so that for both techniques, a critical aspect of clinical study design is that stimulation conditions be compared with a control (sham stimulation). Reviews of clinical interventions often restrict citations only to studies that include this type of control group. At present, only three published clinical trials in English use tDCS for the treatment of chronic pain [4–6], and more than 20 studies apply TMS [7,8••,9•,10•,11,12•]. Because tDCS has fewer risks than TMS and has beneficial effects on chronic pain, there will likely be more research on this technique. One key limit to both TMS and tDCS is that direct stimulation effects can only reach cortex. Although the sensorimotor cortex has been the most popular target region with regard to pain processing [12•], stimulation of other regions are theoretically possible, including the supplementary motor, medial prefrontal, dorsolateral frontal and parietal regions, and the cerebellar hemispheres. These techniques cannot directly penetrate deeper into the brain; therefore, direct stimulation of pain-related regions, such as the insula, cingulate, amygdale, thalamus, and hypothalamus, is not possible. The result is that surgical interventions will be needed when it is necessary to stimulate regions deeper in the brain.

There are several key concepts to understand in the various reviews of clinical efficacy of TMS [7,8••,9•,10•,

Figure 1. A figure-of-eight coil.

11,12•]. The basic principle of TMS is that an electrical current is passed through a magnetic coil. This current generates a brief, intense, magnetic field that passes through the scalp and induces an electrical field in the brain. The result is to depolarize neurons and to generate action potentials. One key advantage of TMS over tDCS is that TMS can be delivered to the brain in a more spatially focused way, particularly when a figure-of-eight coil is used (Fig. 1). Perhaps the most key TMS parameter is stimulation frequency. Stimulation rates at 1 Hz or below are described as slow (or low-frequency) repetitive TMS (rTMS), although some have also called this single-pulse TMS, a term generally used to describe TMS delivered every few seconds at random intervals. TMS delivered at higher frequency is described as fast (or high-frequency) rTMS. Generally, it is thought that there is a decrease in brain excitability if the stimulation frequency is slow (≤ 1 Hz), whereas at faster rates (≥ 5 Hz or more), there tends to be an increase [13]. These inhibitory and excitatory effects have been postulated to be akin to long-term potentiation and long-term depression [14]. Another approach is to deliver bursts of stimulation repeatedly, as is the case with theta-burst stimulation (TBS), so that the initial stimulation primes the system for the later stimulation [15,16].

Although the stimulation parameters can be consistent across individuals, for a given individual, there are differences in responsiveness to stimulation. One way in which the intensity of the stimulation has typically been calibrated across individuals is testing the person to derive the minimal intensity of stimulation applied to the motor cortex (often referred to as M1) that evokes a motor response. This motor threshold is generally reported at the intensity of stimulation defined in terms of a percentage of the device's available output or in Tesla. Even then, there is individual variability in the degree to which there is facilitation or inhibition, depending on stimulation frequencies [13]. Other TMS parameters include the inter-train interval (time between trains of stimulation), number of trains per session, and duration of the session. Special precautions are recommended when using rTMS because of the risk of seizures; however, since the safety guidelines for TMS were published in 1998 [17••], only two seizures have been induced [18,19]. The most common discomforts are headaches, scalp pain, nausea, and transient hearing difficulty (participants wear ear plugs to avoid this). In addition to the recent book on TMS by Wasserman et al. [1••], there are more concise tutorials [2•] and those with more explicit descriptions of transcranial stimulation techniques [3].

There are fewer parameters that vary across tDCS studies. The basic principle of tDCS is that weak electrical currents are applied to the scalp surface from the anode to cathode. Anodal stimulation typically depolarizes (hence excites) and cathodal stimulation typically hyperpolarizes (hence inhibits) neurons. The technique is reviewed in detail elsewhere [1••,20]. The typical levels administered are 1 or 2 mA of direct current applied for a maximum of 20 minutes in a given session. In contrast to TMS, this technique does not produce a strongly localized effect; however, the procedure has fewer risks and discomforts, and with repeated sessions the effects may be more enduring. A feeling of tingling under the electrodes is the most common complaint [21]. It is also possible to use tDCS before applying rTMS and enhance the effects of rTMS [8••].

Cortical Stimulation and Pain Treatment

The most common approach to the treatment of chronic pain with transcranial stimulation is to target the motor cortex [7,8••,9•,10•,11,12•]. One of the early uses of TMS in the treatment of pain grew out of the surgical implantation of motor cortex stimulation (MCS) [22]. TMS has been applied both as an alternative, noninvasive procedure and as a method of attempting to predict outcome for MCS. The MCS procedure continues to be used for treatment of pain and other disorders. There are reviews on the relative effectiveness and risks of MCS and TMS elsewhere [12•,23]. Early studies demonstrated that response to motor cortex TMS was both predictive of MCS outcome and could provide some pain relief [24–26]. There have been recent systematic reviews of the treatment of patients using TMS and tDCS to stimulate motor cortex [7,10•,12•]. A meta-analysis demonstrated that both invasive (ie, surgical, typically epidural MCS; 72% responder) and noninvasive (ie, TMS and tDCS; 45% responder) approaches can ameliorate pain; however, invasive treatments show significantly greater success [12•]. The effects of single-pulse TMS are too transient to be considered an effective treatment to ameliorate pain [8••]. Repetitive TMS was most effective when stimulation was more focal (ie, figure-of-eight rather than circular coil), applied

at a high rate (greater than 5 Hz), of long duration (at least 1000 pulses), and applied over repeated sessions [7]. Interestingly, pain relief is sometimes greater when stimulation is applied to the motor cortex region representing an area adjacent to the area in pain [27]. For example, patients with unilateral hand pain showed greater pain relief during stimulation of the motor cortex region representing face than for hand [27]. Image-guided delivery of TMS has recently been used to facilitate this functionally defined stimulation with good results [28].

There have been other noninvasive cortical stimulation approaches in the treatment of chronic pain, specifically stimulating other brain regions and the use of tDCS of other regions. Researchers have also targeted regions with rTMS other than the motor cortex and have ameliorated specific types of pain. For example, visceral pain, due to chronic pancreatitis, is considered particularly difficult to treat in general [29]. Fregni et al. [30] performed a small study of stimulation in somatosensory cortex with five patients with chronic visceral pain using frequencies of both 1 Hz and 20 Hz and demonstrated significant pain reduction. A small study of four patients targeted the right dorsolateral prefrontal cortex (DLPFC) with low-frequency rTMS (1 Hz) and ameliorated pain in patients with fibromyalgia [31]. Whereas several TMS studies demonstrate effects that last only 2 weeks, this study that targeted the DLPFC resulted in one of the longest durations of treatment responses (between 15 and 27 weeks). Another very different approach is to target regions other than the brain; this indirectly affects cortical excitability. Stimulation of neural structures outside the brain is described as repetitive magnetic stimulation (rMS), which can have indirect effects on the brain [32]. For example, targeting the cervical nerve root with rMS may alter motor cortex excitability, and this may be applied to the treatment of pain [33]. Transcranial DCS has also been applied to patients with chronic pain with some promising results [34,35].

Stimulation-Induced Correlates of Pain

One of the most commonly used approaches to measuring transcranial stimulation-induced changes in pain severity is to use a visual analogue scale (VAS). This measure provides an important source of validation of results because the ultimate goal of any treatment is to reduce pain; however, pain judgments are subjective and may have problems of reliability [36]. There are other measures derived using TMS that are associated with self-reported pain severity and also provide a source of concurrent validation that the brain system subserving the pain experience has been affected [37]. These correlates have also been used to predict treatment response to surgical intervention with MCS and to probe the mechanisms by which transcranial stimulation modulates pain.

One type of TMS-induced measure is the motor-evoked potential (MEP), a measure of motor cortico-spinal excitability. Motor cortico-spinal excitability refers to responsiveness to how excitable the motor pathway is to TMS stimulation. Various indicators of excitability, including the MEP, are described in detail elsewhere [1••,38]. The MEP is the most common dependent measure among various cortical and cortico-spinal excitability measures. It is an electrical muscular response generated by artificially stimulating a motor pathway above the spinal motor neuron, typically in the motor cortex, and commonly quantified using an electromyogram. With respect to changes in the MEP in response to provoked pain, healthy subjects usually generate depressed MEP when compared with instances when pain is not applied, which is consistent with an inhibitory response in the motor cortex. In contrast, many patients with chronic pain exhibit increased MEP amplitude on the affected extremity compared with the unaffected extremity, a pattern consistent with hyperexcitability of the motor cortex [8••]. In reviewing this literature, Lefaucheur [8••] advised that studies of patients with chronic pain include multiple measures of cortico-spinal excitability [1••,38] because the pattern of hyperexcitability is sometimes revealed by measures other than MEP.

MEP has been demonstrated to be reliable [39] and valid because it demonstrates patterns of changes similar to those observed with self-reported pain. For example, in a study that applied a VAS, Lefaucheur et al. [27] demonstrated that pain relief was more effective when TMS was applied to an area adjacent to the cortical representation of the painful zone rather than to the motor cortical area corresponding to the painful zone itself. On et al. [37] demonstrated a similar result with MEP, specifically that patients with knee pain showed enhanced MEP for the region in the motor cortex representing the muscle adjacent to the painful joint. In addition, changes in motor cortico-spinal excitability are associated with pain intensity ratings in healthy subjects, such that during induced pain from hypotonic saline, MEP inhibition was observed during the peak-pain [40].

Changes in detection thresholds for nonpainful stimuli occur with surgically implanted (MCS) and transcranial (TMS) motor cortex stimulation; this information may prove informative for treatment and pain research [8••]. For example, good responses to surgical MCS were associated with improvements in thermal thresholds when stimulators were turned on relative to when they were turned off [41]. Similarly, rTMS to the motor cortical representation of the painful zone was also associated with increases in sensitivity to temperature in the painful zone [42]. The effects of rTMS of motor cortex appeared to be selective for warm temperatures, not mechanical stimulation, which is consistent with the fact that pain and temperature are transmitted by the spinothalamic tract.

In addition, the TMS-induced change and not baseline differences in sensitivity was associated with the better treatment response.

Applying TMS and tDCS with event-related potentials (ERPs) may also assist in describing the underlying neurophysiologic mechanisms of normal and abnormal pain responses. One approach to evoking pain is briefly to apply a laser to the skin. The ERP response to this stimulation is described as the laser-evoked potential (LEP). Depending on the manner in which this stimulation is performed, it is possible to stimulate A delta fibers or C fibers, and TMS can be applied to modulate these evoked potentials [43]. LEP changes and subjective relief on VAS were also observed after tDCS treatments [44].

Transcranial Stimulation and Pain in Context: Combinations, Interactions, and Comorbidities

In the clinic, patients often have multiple illnesses and medications. This situation presents opportunities to combine treatments synergistically and to illuminate the pathophysiology of pain, but it also poses interpretive challenges.

Transcranial stimulation is being studied with pharmacologic interventions. Anesthetics can depress TMS-induced MEP amplitude [45], an important consideration if MEP were used to predict surgical MCS. At the same time, applying transcranial stimulation and medications together have great potential to illuminate the underlying mechanisms of their effects. For example, evidence supporting a role for endorphins in TMS-induced pain relief came from the finding that nalaxone blocked this effect [46]. Pergolide, a dopamine agonist, has been found to prolong the reduction of cathodal tDCS excitability as measured by LEP [47].

Transcranial stimulation provides revealing data about the relationship to pain and other associated symptoms. For example, low back pain and postural instability are known to be associated, and studies of cortical mapping using TMS suggest that there is cortical reorganization that may contribute to the association between these symptoms [48]. In addition, TMS treatments that target depression appear to ameliorate the unexplained pain that occurs comorbidly with the mood disorder [49].

Key Resources for Further Study

Whereas this paper focuses on general concepts and key original papers/studies from the past few years, there are many excellent review articles that cover many of the described topics in more depth-tracing studies from before this time. Wasserman et al. [1••] offer one of the most recent and authoritative series of tutorials on noninvasive transcranial stimulation techniques and related topics. Comprehensive reviews that cover both studies of induced pain in healthy subjects and patients with chronic pain are well discussed by Lefaucheur [8••] and Leo and Latif [11]. Lefaucheur suggests specific modifications in TMS stimulation to improve efficacy but also emphasizes the importance of repeated administrations and further study of tDCS in treatment. Transcranial stimulation and migraine were minimally described here but are also covered in depth elsewhere [1••]. With respect to the clinical use of transcranial stimulation in pain control, noninvasive techniques are compared with invasive surgical stimulation techniques in the guidelines from the European Federation of Neurological Societies [7,50]. Guidelines on the diagnostic utility of TMS in general have also been developed; however, there is minimal reference to pain management [51]. Several excellent reviews discuss factors that moderate the effectiveness of noninvasive transcranial stimulation techniques for the treatment of chronic pain [9•,10•]. Whereas studies of TMS allow focused stimulation of a particular brain region to modulate perception of pain, it is also possible to measure the consequences of this stimulation in other brain regions using other imaging and electrophysiologic techniques, such as electroencephalography and magnetoencephalography [43].

Conclusions

At this point, there are promising results from a series of clinical trials that transcranial stimulation (rTMS and tDCS) offers some relief and potential for improved prediction of outcome for surgical intervention; however, these transcranial stimulation techniques are research tools. The US Food and Drug Administration has approved TMS for use in the treatment of depression and peripheral nerve stimulation, so it is likely that it will be used as an off-label treatment for pain management. Repetitive TMS and tDCS are more effective for pain relief than single-pulse TMS but they must be applied over repeated sessions to have maximally prolonged effects. Transcranial stimulation has great potential to explain and characterize the physiology of normal and pathological pain responses, particularly when applied with other techniques, such as pharmacologic manipulation or ERP. This work may ultimately assist in differential diagnosis and prediction of response to more invasive measures; however, more research is needed.

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Disclosures

No potential conflicts of interest relevant to this article have been reported.

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- • Of importance
- •• Of major importance

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