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The use of repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS) to relieve pain

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Summary

Chronic pain resulting from injury of the peripheral or central nervous system may be associated with a significant dysfunction of extensive neural networks. Noninvasive stimulation techniques, such as repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS) may be suitable to treat chronic pain as they can act on these networks by modulating neural activities not only in the stimulated area, but also in remote regions that are interconnected to the site of stimulation. Motor cortex was the first cortical target that was proved to be efficacious in chronic pain treatment. At present, significant analgesic effects were also shown to occur after the stimulation of other cortical targets (including prefrontal and parietal areas) in acute provoked pain, chronic neuropathic pain, fibromyalgia, or visceral pain. Therapeutic applications of rTMS in pain syndromes are limited by the short duration of the induced effects, but prolonged pain relief can be obtained by repeating rTMS sessions every day for several weeks. Recent tDCS studies also showed some effects on various types of chronic pain. We review the evidence to date of these two techniques of noninvasive brain stimulation for the treatment of pain.

Keywords chronic pain; motor cortex; neuropathic pain; neuroplasticity; repetitive transcranial magnetic stimulation; transcranial direct current stimulation

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Chronic motor cortex stimulation (MCS) with surgically implanted epidural electrodes was first performed in the early nineties and was found to produce significant analgesic effects in patients who had chronic, drug-resistant, central pain.[1] Since this first report, numerous studies confirmed the beneficial effects of epidural MCS for the treatment of chronic neuropathic pain of either peripheral or central origin, as discussed by Nguyen et al.[2] However, such treatment is invasive and associated with a significant interindividual variability in the outcome. On the basis of these initial findings, several studies have tested and shown that sessions of noninvasive brain stimulation using the technique of repetitive transcranial magnetic stimulation (rTMS) could also relieve chronic neuropathic pain at least transiently.[3-5] Nevertheless, others found the effect to be small and not significant.[6,7] At present, about 20 studies have assessed the efficacy of rTMS in more than 300 patients with drug-resistant chronic pain (poststroke pain, complex regional pain syndrome, visceral pain, fibromyalgia, trigeminal neuralgia, phantom limb pain, or pain related to lesion of the spinal cord, brachial plexus, or nerve trunks). A recent meta-analysis showed that rTMS was associated with a significant reduction in pain.[8] Another noninvasive method of cortical stimulation—transcranial direct current stimulation (tDCS)—may also produce beneficial effects on pain and has been favored in a recent editorial.[9] Compared with rTMS, tDCS appears to be less expensive and easier to use in daily practice, but its effects are less well studied to date. Actually, only two studies have assessed the efficacy of tDCS in patients with chronic pain (neuropathic pain related to spinal cord lesion and fibromyalgia).[10,11]

rTMS and experimentally induced pain

Although the major focus of this study is the review of the potential of rTMS in the treatment of chronic pain, it is relevant to consider first the effects of this technique that have been reported on various types of experimentally provoked pain.

High-frequency rTMS (20 Hz) administered over M1 was found to reduce susceptibility to cold pain (that is a decrease in temperature for cold pain thresholds) both in healthy volunteers[12] and in patients with chronic low back pain.[13] In this latter series of patients, 20-Hz rTMS also reduced susceptibility to heat pain (that is an increase in temperature for heat pain thresholds).[13] Cold pain is mostly mediated by A-delta fibers and heat pain by C fibers. In normal subjects, low-frequency rTMS (1 Hz) delivered over M1 also decreased C fiber-mediated pain produced by intradermal capsaicin application,[14] but it increased A-delta fiber-mediated pain induced by cutaneous laser stimulation.[15] Finally, bursts of low intensity magnetic stimuli repeated at a theta frequency for 40 seconds over M1 (continuous theta burst stimulation, cTBS) attenuated pain perception evoked by laser stimulation of the dorsum of the contralateral hand.[16] Thus, cTBS and low-frequency rTMS produce opposite changes on laser-induced pain, although both of these protocols are known to reduce motor evoked potential (MEP) amplitude.[17] It is therefore conceivable that the analgesia provided by TMS techniques is not mediated by a modulation of the motor corticospinal output.

The effects of 10-Hz rTMS applied to M1 were also assessed on electrically induced pain, using alternating currents with sinusoid waveform (Neurometer device)[18] or brief trains of five pulses at a frequency of 250 Hz (generating a nociceptive flexion reflex).[19] These studies reported conflicting results, because rTMS increased the tolerance to pain in the first study and the scores of pain unpleasantness in the second study. These observations are difficult to interpret because the parameters of painful electrical stimulation differed between the studies, as well as the investigated feature of pain (tolerance vs unpleasantness).

Several studies also assessed the value of TMS protocols applied to targets other than M1 to modulate provoked pain. Kanda et al[20] studied the variation of CO_2 laser-induced acute pain perception after paired-pulse rTMS (interpulse interval of 50 milliseconds and stimulation intensity above motor threshold) applied to various cortical regions. When cortical stimulation was applied to primary sensorimotor areas, the stimulus was perceived as more painful than in a control condition. In contrast, stimulation of the medial frontal cortex (MFC), which is close to the anterior cingulate cortex (ACC), reduced pain perception. This study supports the importance of the ACC in pain processing. In contrast, Mylius et al[21] reported that a similar paired-pulse TMS protocol applied over the MFC increased the verbal pain report to a painful electrical stimulation that was able to elicit a nociceptive flexion reflex. In the same way, Yoo et al[18] showed that 10-Hz rTMS applied over the MFC reduced pain tolerance threshold to electrical stimulation.

Amassian et al[22] found that rTMS applied at 20 Hz over the primary somatosensory cortex (S1) resulted in a significant attenuation of acute pain provoked by transient circulatory occlusion of the arm with a tourniquet, contralaterally to the site of cortical stimulation. This effect was reversed by naloxone, suggesting an endorphin-mediated process. When targeted over S1 using a dedicated navigation system, various active TBS protocols (cTBS, intermittent, or intermediate TBS), but not sham TBS, significantly diminished the amplitude of the N2 component of the laser-evoked potentials (LEPs) produced by Tm:YAG laser stimulation of the hand, contralaterally to the site of TBS.[23] However, the subjective pain perception decreased after both active and sham TBS conditions. Finally, Töpper et al[24] found no significant effect of rTMS administered over the parietal cortex on acute pain provoked by hand immersion in cold water (cold pressor test).

In a large series of healthy volunteers, Graff-Guerrero et al[25] studied the effect of low-frequency (1 Hz) rTMS on

pain threshold and tolerance during the cold pressor test. The rTMS targets were M1 and the dorsolateral prefrontal cortex (DLPFC) of the right and left hemispheres. An increased tolerance to cold-induced pain after right DLPFC stimulation was the only significant change induced by low-frequency rTMS. In healthy adults with no history of depression or chronic pain, Borckardt et al[26] found that high-frequency (10 Hz) rTMS of the left DLPFC increased heat pain thresholds. These two studies support the idea that DLPFC may be a relevant TMS cortical target to induce analgesia.

However, some of these results are in conflict. It can be speculated that TMS enables different effects on experimental pain depending on the protocol of stimulation (such as frequency or train duration), the type of nerve fibers or neural pathways that are involved in pain processing, and the cortical target. No firm conclusion can be drawn for the MFC and S1 targets, in contrast to the DLPFC and M1 targets. Regarding DLPFC, analgesic effects were obtained when rTMS was applied at low frequency on the right area or at high frequency on the left area. This observation is in line with the antidepressant effects produced by DLPFC stimulation with respect to the side of stimulation. Regarding M1 stimulation in healthy subjects, phasic pain mediated by A-delta fibers was enhanced by paired-pulse or 1-Hz rTMS but reduced by cTBS or 20-Hz rTMS, whereas tonic pain mediated by C fibers was attenuated by 1-Hz rTMS. These results were not strictly in agreement with those obtained in cases of chronic neuropathic pain. In fact, acute provoked pain may not be an optimal model for patients with chronic pain caused by neurologic lesion. Neural networks involved in the processing of acute versus chronic pain are not the same (review in[27,28]). For example, chronic pain is associated with a decreased perfusion of the thalamus at the resting state, whereas experimental pain induced in healthy subjects is associated with an increased perfusion of the thalamus and ACC.[29,30]

tDCS and experimentally induced pain perception

Only a few studies have evaluated the effect of tDCS on acute perception of provoked pain. In a recent investigation, LEPs were recorded before and after anodal, cathodal, or sham tDCS delivered over S1.[31] Cathodal tDCS resulted in a concomitant reduction of pain perception and of the amplitude of the N2 LEP component in response to Tm:YAG laser stimulation of the contralateral hand. In contrast, anodal and sham stimulations had no significant effect.

The recording of LEPs is a frequently used method in pain research.[32,33] One early negative component (N2) is partly generated in the operculoinsular region, representing sensory discrimination of pain. The later positive component (P2) arises mainly from the ACC and reflects endogenous, cognitive, attentional, and affective factors. Specific attenuation of the N2 component could reveal that cathodal tDCS of S1 affects sensoridiscriminative rather than cognitive aspects of pain.

In a separate sham-controlled study,[34] cathodal tDCS of M1 also diminished pain sensation and the N2-P2 amplitude of the LEPs produced by laser stimulation contralateral to the side of tDCS. A subsequent study showed that the analgesic efficacy of cathodal tDCS applied to M1 could be increased when combined with pergolide intake.[35] Pergolide enhances dopamine D2, and to a much lesser degree, D1 receptor activity, and was shown to consolidate the reduction of motor cortex excitability induced by cathodal tDCS for up to 24 hours.[36] Subjective pain perception was significantly lowered only up to 40 minutes after cathodal tDCS and pergolide intake prolonged analgesic effects up to 2 hours after the stimulation. In parallel, amplitude reduction of the N2 LEP component produced by cathodal tDCS of M1 was still observed after 24 hours in case of pergolide administration.

In another study, pain and perception thresholds to electrical stimulation were assessed in 20 healthy subjects before and during anodal tDCS.[37] Four conditions of stimulation were compared: anodal tDCS of M1, DLPFC, occipital cortex (V1), and sham tDCS. A significant increase in pain threshold was observed during either M1 or DLPFC stimulation (but not during V1 or sham stimulation). The analgesic effect produced by M1 stimulation was concomitant with an increase in stimulus perception threshold. This was not the case during DLPFC stimulation. Anodal stimulation of M1 but not of DLPFC could induce analgesia by modulating sensory discrimination.

All these observations support the analgesic potential of tDCS that can be further reinforced by pharmacologic procedures. Analgesic effects were produced by cathodal tDCS of S1 and both cathodal and anodal tDCS of M1. The fact that either cathodal or anodal tDCS applied to M1 were efficacious could be possibly explained by differences in the mechanisms of pain provoked by painful laser versus electrical stimuli. Nevertheless, it suggests above all that analgesia induced by tDCS, as for rTMS, does not strictly relate to the modulation of the motor corticospinal output. Actually, anodal and cathodal tDCS of M1 can produce similar analgesic effects but opposite changes in MEP amplitude.[38]

rTMS and chronic pain

About the analgesic efficacy of rTMS in chronic pain, several factors need to be considered: (1) the frequency of stimulation, (2) the site of stimulation, (3) the duration of stimulation, and (4) the delay between the time of stimulation and the clinical effects.

Stimulation frequency governs excitability changes that are induced by rTMS: high-frequency stimulation (5 Hz or

more) is generally excitatory, whereas low-frequency stimulation (1 Hz or less) reduces cortical network excitability in most of the conditions. However, opposite effects can be observed depending on the nature of the rTMS targets and the prior state of activation of the recruited circuits.[39]

First, Migita et al[40] applied rTMS at 0.2 Hz in two patients with central pain, using a nonfocal, circular coil that was centered over M1, contralateral to the painful side. The first patient experienced 30% pain relief for 1 hour, whereas rTMS was ineffective in the second patient. TMS effects paralleled the therapeutic outcome of subsequent chronic epidural MCS. Later, Canavero et al[41] also applied repeated TMS pulses at 0.2 Hz in a series of patients with chronic pain secondary to stroke or spinal cord lesion, using a figure-of-eight coil for arm area stimulation or a double-cone coil for leg area stimulation. Among the nine patients enrolled in this placebo-controlled study, one patient was relieved from allodynia and four patients from both spontaneous pain and allodynia. Pain relief lasted 16 hours in one case.

However, most studies have been performed at higher frequencies. In a controlled trial, Lefaucheur et al[3] demonstrated that rTMS was able to relieve neuropathic pain when administered over M1 at 10 Hz but not at 0.5 Hz. A second group showed that rTMS provided better alleviation of pain at 20 Hz than at 1 Hz.[42] A third group found that 10-Hz rTMS was more efficacious than 5-Hz rTMS, whereas 1-Hz rTMS did not produce significant effects.[43] Therefore, the use of too low frequencies of stimulation 1 and 5 Hz may explain the lack of efficacy of rTMS administered over M1 to induce significant analgesic effects in one study.[7]

The efficacy of rTMS also seems to depend on a precise targeting, at least regarding M1 stimulation. High-frequency rTMS failed to produce significant analgesia when it was nonfocally applied with a circular coil.[6] In a series of 60 patients with chronic neuropathic pain of various origins and locations, Lefaucheur et al[4] found that facial pain better improved than hand pain when the hand motor area was stimulated. In another study, rTMS was found more effective when the stimulation site was adjacent to the cortical representation of the painful zone rather than within the painful zone itself.[44] In contrast to the heterotopic efficacy of rTMS, the efficacy of chronic electrical stimulation of the cortex using epidural electrodes implanted over M1 is homotopic.[45] Targeting differences between these techniques are likely because of the differences in the geometry of the induced electric field. Because fibers are more prone to be stimulated than cell bodies,[46] it is critical to consider the relationships between the magnitude and polarity of the current and the depth and orientation of the fibers that are amenable to activation within the cortical layers.[47,48] In fact, analgesic effects are likely mediated via the activation of horizontal fibers in the superficial layers of M1.[49] Epidural stimulation and rTMS may differ by the way they recruit such fibers.

Regarding cortical sites of stimulation other than M1, negative results have been reported in chronic neuropathic pain of various origins after high-frequency rTMS administered over S1 or premotor areas.[50] In contrast, significant analgesic effects have been obtained with 20-Hz rTMS delivered over the secondary somatosensory cortex (S2) in patients with chronic visceral pain caused by pancreatitis.[51] Like for experimental pain, the DLPFC may be one of the most promising TMS cortical target for the management of chronic pain with respect to the side and frequency of stimulation. Sampson et al[52] reported a complete resolution of fibromyalgia-associated pain in four women treated for depression by low-frequency (1 Hz) rTMS applied to the right DLPFC. Pain relief was unrelated to antidepressant effects. A reduction in pain, not explained by the antidepressant effects, was also shown by Avery et al[53] in patients with drug-resistant depression and pain who received high-frequency (10 Hz) rTMS delivered over the left DLPFC. Reid and Pridmore[54] reported the efficacy of repeated sessions of 20-Hz rTMS delivered over the left DLPFC in a depressive patient with drug-resistant facial pain caused by teeth removal. Pain decreased by 42% during the second week of stimulation and maintained 4 weeks after the end of treatment, unrelated to mood changes. O'Reardon et al[55] observed in two patients that DLPFC stimulation for major depressive disorder could also reduce daily headaches. Brighina et al[56] further showed in a controlled trial that a series of 12 daily sessions of high-frequency rTMS delivered over the left DLPFC could ameliorate chronic migraine, during and in the month after the treatment as compared with the month before treatment. Finally, in a series of 20 patients who underwent gastric bypass surgery, Borckardt et al[57] found that a single session of high-frequency rTMS applied immediately after surgery at 10 Hz over the left DLPFC for a total of 4000 pulses was associated with a 40% reduction in total morphine use during the first 2 days after surgery. This reduction corresponded to the effect of active rTMS minus that of sham stimulation. This finding has been recently replicated by the same team.[58] Postoperative analgesic effects induced by active rTMS of DLPFC were not driven by antidepressant effects.

Another important issue is the latency of the analgesic effects. Following a single session of rTMS administered over M1, Lefaucheur et al[59] found that the maximal analgesic effect was delayed for 2 to 4 days and that pain level could remain significantly reduced for about a week. This time course is similar to what is observed for chronic epidural MCS: clinical changes are delayed for several days after switching "on" or "off" the stimulator or after modifying the parameters of stimulation.[45] Expression of secondary messengers and time-consuming processes of synaptic plasticity in cortical circuitry could not explain why the effects are delayed but rather why they last and are stabilized beyond the time of stimulation. Nevertheless, analgesic effects resulting from a single rTMS session are

too short-lived to be compatible with a durable control of chronic pain. Repeated rTMS sessions on consecutive days are able to produce cumulative effects, lasting for at least a couple of weeks beyond the time of stimulation.[5,60] However, further trials are needed to better determine whether a noninvasive cortical stimulation technique should induce sufficient long-term effects to be relevant for chronic treatment in clinical practice. Until more data are available, invasive techniques of brain stimulation are still preferable to induce long-lasting effects.

tDCS and chronic pain

Only two placebo-controlled studies have been published to date assessing the effects of tDCS on chronic pain. These studies showed positive results. In the first study, patients with pain caused by a spinal cord lesion were randomly assigned to receive sham or active anodal tDCS over the left or right M1 (2 mA, 20 minutes) for 5 consecutive days.[10] Pain was reduced significantly after anodal stimulation, but not after sham stimulation. A second study of the same group showed that the same protocol of stimulation (anodal tDCS over M1) produced similar decrease in pain perception in patients with fibromyalgia.[11] Pain relief was maximal at the end of the week of stimulation and was still significant 3 weeks later. Finally, a case report suggested that anodal tDCS of M1 may also induce analgesic effects in cancer pain.[61] The patient in this study had severe pain for several months and responded well to active, but not sham, anodal tDCS of M1. These findings provide initial evidence of a beneficial effect of anodal tDCS applied over M1 in various types of chronic pain, thus encouraging further trials.

Interestingly, in contrast to tDCS, it has been demonstrated that chronic MCS with surgically implanted epidural electrodes was more efficacious when the contacts placed over M1 were selected as cathodes.[45,49] In chronic MCS, the anode needs to be located over the central sulcus or the postcentral gyrus (S1).[45,49] This observation relative to epidural stimulation cannot be considered to be in opposition to the results obtained with tDCS because the physical characteristics of these two modes of cortical stimulation are totally different.

Finally, because cathodal tDCS trials applied to M1 or S1 were found efficacious in experimental pain studies, such protocols should be tested on chronic pain. However, as discussed previously, acute provoked pain and chronic neuropathic pain may be not equally sensitive to a given protocol of cortical stimulation.

Mechanisms of action

The mechanisms underlying the analgesic effects elicited by transcranial cortical stimulation are not fully understood yet and the exact nature of the involved pathways remains hypothetical. Transcranial stimulation of M1 might affect intracortical motor circuitry, as suggested by rTMS-induced changes in cortical excitability parameters measured in the stimulated hemisphere, contralaterally to the painful side.[62] Active 10-Hz rTMS was found to restore intracortical inhibition in parallel with pain relief. The inhibition of M1 activity was associated with the existence of 20-Hz frequency cortical oscillations that are abolished in the presence of chronic or provoked pain.[63] By restoring such oscillatory activity, transcranial stimulation could restore defective inhibitory mechanisms, and decrease pain perception.

However, the site of action may be also situated at a distance from the site of stimulation. Positron emission tomography (PET) study of patients with neuropathic pain treated by epidural MCS showed that switching "on" the stimulation resulted in the activation of various brain regions, including thalamus, anterior insula, periaqueductal grey matter (PAG), and upper brainstem.[64-66] In these structures, all implicated in pain processing, neural activity changes could mediate the concomitant effects of transcranial or epidural MCS on both nociceptive and non-nociceptive thermal sensory discrimination.[67,68]

PET studies also revealed MCS-induced activation in limbic and associative structures that are ACC, orbitofrontal, and prefrontal cortices.[65,66] Via corticocortical projections, MCS would entail a cascade of synaptic events in structures involved in the affective and emotional aspects of pain. The clinical characterization of the features of pain relief provided by either noninvasive or invasive MCS seems to confirm such a hypothesis.[60,69] In addition, ACC and PAG contain a high density of opioid receptors, supporting the activation of the endogenous opioid system by chronic MCS.[70]

The mechanism of action of tDCS should differ from that of rTMS. In fact, tDCS is a purely neuromodulation technique, whereas rTMS exerts both neurostimulatory and neuromodulatory effects.[9] Long-lasting changes of cortical excitability and activity can be induced by tDCS, reversibly, painlessly and safely.[38,71,72] In fact, tDCS causes polarity-dependent shifts of the resting membrane potential and consequently could change neuronal excitability at the site of stimulation and in the connected areas.[73,74] If the stimulation lasts long enough, tDCS induces after-effects, which depend on synaptic plasticity changes related to transient activation of glutamatergic NMDA receptors.[75,76] In humans, the modulatory effect of tDCS has first been demonstrated in the motor system,[38] but it can influence visual, somatosensory, and prefrontal functions as well.[77-79] Therefore, tDCS modulation could also affect the processing of pain.

A PET study showed that tDCS applied over M1 was associated with significant metabolic changes in distant brain regions such as thalamus.[80] These changes may last up to 50 minutes beyond the time of stimulation. In addition, a functional magnetic resonance imaging (fMRI) study revealed that anodal tDCS applied to M1 could result

in not only the activation of the underlying cortex, but also of the ipsilateral supplementary motor area and the contralateral posterior parietal cortex.[81] The mechanisms of action of tDCS likely include effects on remote structures as compared with rTMS. Therefore, depending on the site of stimulation, tDCS modulation could occur in various neural circuits, involved in sensoridiscriminative, cognitive, or emotional aspect of chronic pain.

Summary

Significant analgesic effects of rTMS and tDCS have been found in several studies of patients with chronic pain of various origins, even when the placebo effect was appropriately controlled. Concerning rTMS, M1 stimulation at high frequency was shown to reduce pain scores by 20% to 45% after active stimulation and by less than 10% after sham stimulation. Regarding individual results, 35% to 60% of the published patients have been considered as good responders to rTMS (more than 30% pain relief after active rTMS). Concerning tDCS, repeated daily sessions of anodal tDCS over M1 used alone as an alternative technique to rTMS, were found to decrease pain scores by 58%, that is a larger result as compared with most of rTMS studies.[10,11]

Analgesic effects were obtained whatever the origin of pain, including the usual indications of surgically-implanted MCS that are poststroke pain (mainly thalamic stroke) and facial pain caused by trigeminal neuropathy,[5,59] as well as other causes of neuropathic pain, such as spinal cord injury, root or brachial plexus avulsion, or peripheral nerve trunk lesion.[3,4,10,42,50] Actually, it is not possible to determine an overall order of efficacy of noninvasive cortical stimulation on pain diagnoses. Good results have been reported with either rTMS or tDCS administered over M1, S2, or DLPFC in chronic pain syndromes that are not typically "neuropathic," such as visceral pain,[51] cancer pain,[61] migraine,[55,56] fibromyalgia,[11,52,60] or complex regional pain syndrome type I.[82]

However, therapeutic strategies of cortical stimulation for chronic pain still remain to be optimized in the future. It is accepted that negative rTMS results can be attributed to a too low frequency of stimulation (5 Hz or less) or number of pulses (500 or less). Increasing the total number of pulses per session and repeating the sessions for several days or weeks enhance and prolong rTMS-induced analgesia.[5] Another critical point is the intensity of stimulation: it seems better to use it below the motor threshold. Stimulations performed above motor threshold were not associated with a better efficacy.[83] Furthermore, the experience of chronic epidural MCS showed that analgesic effects are produced at a low intensity of stimulation, sufficient to stimulate the superficial cortical layers. Therefore, clinical results cannot be substantially improved by increasing stimulus intensity.

Experience with tDCS in chronic pain is limited to two studies. On the basis of these results, tDCS might represent another promising approach for relieving chronic pain. Compared with rTMS, tDCS has some advantages, in particular because it can be used as a portable device. Within the safety limits of this technique,[72] the influence of various parameters of stimulation in the production of tDCS-induced analgesic effects should be assessed in future studies.

Regardless the method of cortical stimulation, the optimally suited site of stimulation remains an open question. Targeting procedures are improving with the development of image-guided navigation using morphologic or functional brain imaging. Navigation is especially useful when the target is located outside the M1.[50] Future investigation should also address the issues of interindividual variability of the analgesic effects provided by cortical stimulation, priming influence of various analgesic medications, and characterization of the significant predictors of efficacy. However, for these studies, large sample sizes are essential.

Finally, despite their significance, rTMS and tDCS effects are quite short and this is a major limit for routine therapeutic use of these techniques in patients with chronic pain. Invasive epidural stimulation can still be considered as the best approach for long-term treatment, at least until long-term benefits of maintenance treatment are demonstrated by using transcranial stimulation. However, a potential new direction of noninvasive cortical stimulation could be the management of some acute or transient pain syndromes, such as postoperative pain.[57,58]

Another important point is that rTMS could predict the outcome of chronic stimulation performed with implanted epidural electrodes.[40-42,84] A positive response to rTMS appears to be closely related to a good efficacy of chronic MCS. In contrast, the absence of prior response to sessions of rTMS administered over M1 is not indicative of a subsequent failure of epidural MCS.

The indication and results of different techniques of neurostimulation therapy for neuropathic pain have been recently reappraised by a committee of European experts.[85] The place of noninvasive cortical stimulation has not been firmly defined because of the lack of long-term results. Conclusions were that rTMS effects were rather modest and short-lasting on clinical grounds, and therefore rTMS could not be considered as a therapeutic method, except if the sessions of stimulation were repeated for several days or weeks. In this review, it was concluded that rTMS can be used as a noninvasive preoperative therapeutic test for patients with drug-resistant chronic pain who are candidates for surgically implanted chronic MCS.

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