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REVIEW
PAIN AND PHYSICAL MODALITIES

Cortical stimulation for chronic pain: from anecdote to evidence

Luis GARCIA-LARREA [1, 2] *, Charles QUESADA [1, 3]

[1]Central Integration of Pain (NeuroPain) Lab, Lyon Center for Neuroscience (CRNL), INSERM U1028, University Claude Bernard Lyon 1, Villeurbanne, France; [2]University Hospital Pain Center (CETD), Neurological Hospital, Hospices Civils de Lyon, Lyon, France; [3]Department of Physiotherapy, Sciences of Rehabilitation Institute (ISTR), University Claude Bernard Lyon 1, Villeurbanne, France

*Corresponding author: Luis Garcia-Larrea, Central Integration of Pain (NeuroPain) Lab, Lyon Centre for Neuroscience (CRNL), INSERM U1028, University Claude Bernard Lyon 1, Villeurbanne, France. E-mail: larrea@univ-lyon1.fr

ABSTRACT

Epidural stimulation of the motor cortex (eMCS) was devised in the 1990's, and has now largely supplanted thalamic stimulation for neuropathic pain relief. Its mechanisms of action involve activation of multiple cortico-subcortical areas initiated in the thalamus, with involvement of endogenous opioids and descending inhibition toward the spinal cord. Evidence for clinical efficacy is now supported by at least seven RCTs; benefits may persist up to 10 years, and can be reasonably predicted by preoperative use of non-invasive repetitive magnetic stimulation (rTMS). rTMS first developed as a means of predicting the efficacy of epidural procedures, then as an analgesic method on its own right. Reasonable evidence from at least six well-conducted RCTs favors a significant analgesic effect of high-frequency rTMS of the motor cortex in neuropathic pain (NP), and less consistently in widespread/fibromyalgic pain. Stimulation of the dorsolateral frontal cortex (DLPFC) has not proven efficacious for pain, so far. The posterior operculo-insular cortex is a new and attractive target but evidence remains inconsistent. Transcranial direct current stimulation (tDCS) is applied upon similar targets as rTMS and eMCS; it does not elicit action potentials but modulates the neuronal resting membrane state. tDCS presents practical advantages including low cost, few safety issues, and possibility of home-based protocols; however, the limited quality of most published reports entails a low level of evidence. Patients responsive to tDCS may differ from those improved by rTMS, and in both cases repeated sessions over a long time may be required to achieve clinically significant relief. Both invasive and non-invasive procedures exert their effects through multiple distributed brain networks influencing the sensory, affective and cognitive aspects of chronic pain. Their effects are mainly exerted upon abnormally sensitized pathways, rather than on acute physiological pain. Extending the duration of long-term benefits remains a challenge, for which different strategies are discussed in this review.

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KEY WORDS: Transcutaneous electric nerve stimulation; Pain; Motor cortex; Transcranial magnetic stimulation; Neuralgia.

Stimulating the motor cortex for pain relief: historical background

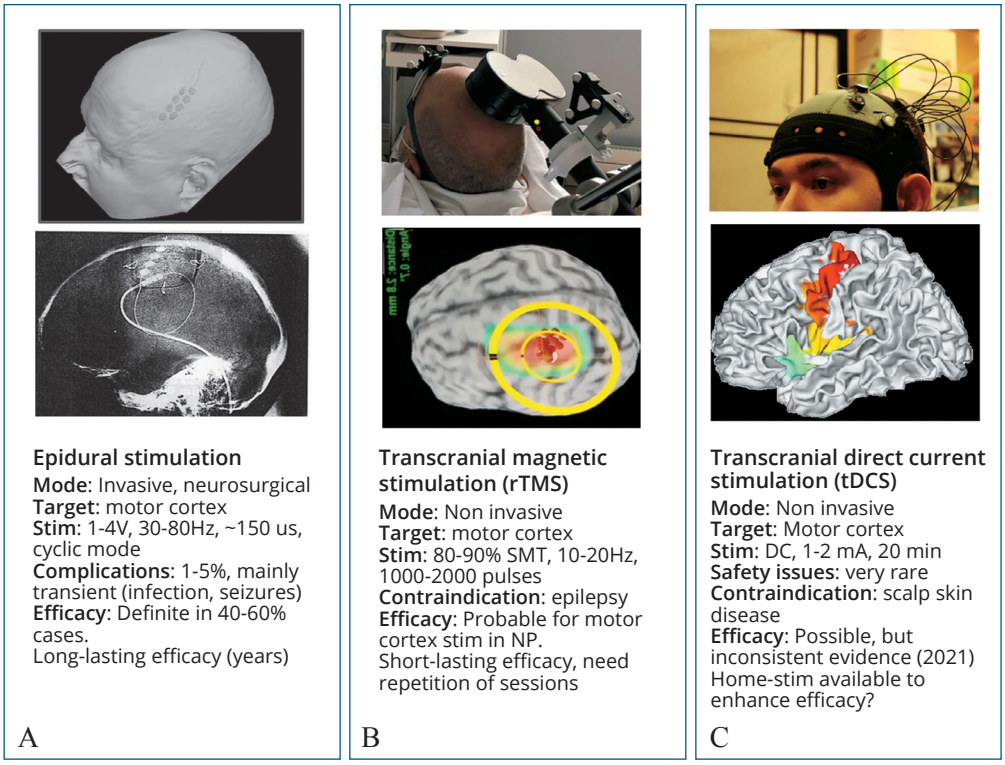
Reports on possible descending nociceptive controls activated by stimulation of the motor cortex date back to the middle of the last Century. In 1957, Lindblom *et al.*[1] described in cats the inhibition of dorsal horn spinal neurons during electrical stimulation of the pyramidal tract or motor cortex, and very shortly after it was suggested that this effect involved descending presynaptic inhibition.[2] Early attempts to apply these discoveries to the control of pain in humans via stimulation of the internal capsule obtained a relative success[3-5] but were discontinued due to surgical-related morbidity. In 1991, Tsubokawa *et al.*[6] described a relatively simple and safe technique of motor cortex stimulation using epidural plate electrodes (eMCS), and succeeded in alleviating central post-stroke pain in eight of 12 patients with thalamic or supra-thalamic lesions, with one year follow-up. The epidural technique was swiftly adopted by different neurosurgeons around

the world, and applied to different neuropathic pain (NP) conditions.[7-9] In parallel, non-invasive modes of cortical stimulation were rapidly developed, first with the aim of optimizing the selection of candidates to the epidural procedure, then gradually as analgesic techniques in their own right. In what follows, we will discuss the progression from anecdotal reports to evidence-based data, in relation to both neurosurgical approaches and non-invasive techniques.

Neurosurgically-implanted motor cortex stimulation (eMCS)

Although the stimulating devices and localization techniques have considerably evolved, the surgical procedure remains largely comparable to that described by Tsubokawa 30 years ago.[6, 10] After anesthesia and craniotomy, the stimulating electrodes are placed overlying the motor strip contralateral to the pain side, either parallel or orthogonal to and crossing the central sulcus (Figure 1A). The electrode wires are then tunneled under the skin down to the lateral neck and connected to the system antenna (a receiver activated by external radiofrequencies) in subclavicular or latero-abdominal position. Somatotopic concordance between the electrode position and the painful territory appears important for clinical effect,[6, 11, 12] therefore the stimulating electrodes are placed over the cortical convexity for upper limb/facial pain, and over its medial aspect for lower limb pain. Epidural is preferred to subdural position because of shorter operative time, and because subdural stimulation increases the risk of epileptic seizures and intracranial haematoma[13-16] without evidence of better results.[17] However, the subdural position is still preferred by some teams[16] and may be useful when the electrode needs to be positioned in the interhemispheric fissure.

The localization of the central sulcus is performed using MRI-based neuronavigation and neurophysiological testing with somatosensory evoked potentials, and its position compared with that suggested by MRI neuronavigation. Recording of motor responses can be also performed to ensure the optimal position of the electrodes. Correct determination of the Rolandic sulcus is crucial to avoid stimulation over the somatosensory cortex, which may enhance painful symptoms.[10, 18] Stimulation frequency is commonly set at 30–80 Hz, amplitude at 80% of the motor threshold to avoid contractions and seizures, and one week of testing under hospitalization is required to optimize the stimulation parameters.



Epidural stimulation
Mode: Invasive, neurosurgical
Target: motor cortex
Stim: 1-4V, 30-80Hz, ~150 us, cyclic mode
Complications: 1-5%, mainly transient (infection, seizures)
Efficacy: Definite in 40-60% cases.
Long-lasting efficacy (years)

A

Transcranial magnetic stimulation (rTMS)
Mode: Non invasive
Target: motor cortex
Stim: 80-90% SMT, 10-20Hz, 1000-2000 pulses
Contraindication: epilepsy
Efficacy: Probable for motor cortex stim in NP.
Short-lasting efficacy, need repetition of sessions

B

Transcranial direct current stimulation (tDCS)
Mode: Non invasive
Target: Motor cortex
Stim: DC, 1-2 mA, 20 min
Safety issues: very rare
Contraindication: scalp skin disease
Efficacy: Possible, but inconsistent evidence (2021)
Home-stim available to enhance efficacy?

C

Figure 1.—Summary of key-features of epidural, transcranial magnetic and direct-current procedures for cortical stimulation, as currently used in the treatment of chronic pain.

Mechanisms of action of eMCS

Studies in humans

Early hypotheses linking eMCS effects to activation of cortico-cortical fibers or interneurons within the motor cortex[10, 15, 19] were contradicted by the lack of metabolic changes within the motor cortex underneath the stimulating electrodes.[18, 20-23] Instead, a prominent metabolic enhancement during eMCS is found within the thalamus ipsilateral to the stimulated cortex,[18, 21, 23-25] and occasionally contralateral to it,[26] suggesting descending cortico-thalamic activation.[27, 28]

Thalamic activation is followed by activity changes in numerous cortico-subcortical areas, including the premotor, prefrontal and orbitofrontal cortices, perigenual cingulate, basal ganglia and periaqueductal grey matter (PAG).[23] High-order areas are thought to modulate the affective/motivational appraisal of pain, while activation of the PAG can trigger descending inhibition toward the spinal cord, and explain the attenuation of spinal nociceptive reflexes.[21] Most of these structures remain activated for hours after eMCS is discontinued,[20] which may explain the persistence of clinical effects beyond the stimulation periods. Long-lasting changes in neurotransmitters were also demonstrated using PET-scan, with potential secretion of endogenous opioids and a positive correlation between opioid receptors availability and clinical efficacy.[29, 30] Since endo-opioidergic changes and local CBF increase involved the same regions, both mechanisms may be related and concur to eMCS efficacy.

Studies in animals

MCS consistently alleviates neuropathic hypersensitivity in rodents and cats,[31-39] and also tonic pain in one study.[40] Most animal studies have confirmed the general mechanistic hypotheses driven from human data, with functional changes being reported in thalamus, cingulate, striatum, PAG and dorsal horn.[41] In convergence with human studies, descending inhibition and early thalamic involvement are the most reproducible results obtained in animals. Abnormal thalamic bursting during neuropathic pain is associated with a hypometabolic state,[42, 43] and MCS can both decrease thalamic bursting and increase thalamic metabolism.[34, 36, 44] These effects may be driven in part by a GABAergic pathway from the subthalamic *Zona incerta*.[33, 37, 38] Spread of thalamic activation and of c-Fos expression changes progressively appear in rodents after chronic stimulation,[45, 46] suggesting a time-dependent neural plasticity that may contribute to long-term efficacy.

MCS-related descending inhibition in rodents and cats is reflected by depressed activity in the superficial dorsal horn together with enhanced c-Fos reactivity in ACC and PAG.[2, 34, 36, 47, 48] It may involve different neurotransmitters and receptors, including endogenous opioids,[49, 50] catecholamines,[51] serotonin and its spinal 5-HT1A receptor,[32, 36, 52] dopamine through its D2 receptor,[53] and cannabinoids via the CB2 receptor.[50] Contradictory results also exist, including reports of either decrease or increase of GABAergic activity in the PAG,[39, 44] involvement *versus* lack of involvement of glutamate signaling in the same region,[39, 54] and activation *versus* lack of activation of locus coeruleus during MCS.[32, 52]

Clinical efficacy of epidural MCS

Loss of eMCS efficacy following battery exhaustion or broken wires were helpful anecdotes to establish confidence in the technique,[18, 55, 56] but definite clinical efficacy can only be established from controlled studies (RCTs). Pooled data from the literature indicates a 45-50% average success rate of eMCS in patients with drug-resistant, central or peripheral NP.[57-59] However, most clinical reports are subject to multiple bias such as lack of blinding, small sample size, heterogeneity of assessment tools, imprecision in reporting, and limited follow-up, which makes the evidence methodologically weak.[60] Very few randomized or blinded studies with >10 patients have been reported. While one of them was halted because of limited efficacy and adverse events (infections, panic attack),[61] six other trials reported positive results: Rasche *et al.*[62] and André-Obadia *et al.*[63] used blinded procedures to detect responders (>50% pain decrease or >30% decrease plus medication reduction), and reported good results in 47-50% of a total of 37 operated patients, with up to 10 years' follow-up. Other groups reported 40-60% success rate in randomized cross-over trials, with reversible pain increase when the stimulator was turned "off" and "on" in double-blinded conditions.[64-67] Even allowing for some decline of efficacy with time,[17, 63] data obtained under blinded and randomized conditions support the real efficacy of eMCS in a rough half of the patients with drug-resistant NP.

eMCS often displays delayed and fluctuating effects which can be underestimated in randomised trials. In one series, almost 20% of patients were considered as non-responders during the first month, but were relieved at 1 year.[66] Also, a number of patients with "insignificant" VAS changes noted an increase in pain after battery depletion and requested replacement of their device,[61] or declared themselves favorable to re-intervention for the same out-

come.[63, 68] These discordances, which have been also reported for spinal cord stimulation,[69] suggest that high values and preferences for neuromodulation therapy may be dissociated from quantitative VAS scales.

Prediction of eMCS clinical effects

Demographic, clinical, anatomical or pharmacological pre-operative data have not proven useful so far to predict the long-term efficacy of eMCS.[68, 70] Suggested but unconfirmed predictors include preservation of corticospinal function,[71] normal thermal thresholds,[72] relief of burning pain,[73] stimulation intensity,[74] susceptibility to ketamine,[75] and availability of brain opioid receptors.[30] Good efficacy at first month post-implantation predicted long-term efficacy in two independent studies.[68, 76] Small sample size, heterogeneity of evaluation methods and short follow-up probably explain the lack of reproducibility of such putative predictors, some of which might be confirmed in the future.

The only procedure consistently predicting the eMCS clinical effect is the response to transcranial repetitive magnetic stimulation (rTMS). A successful rTMS predicted subsequent efficacy of eMCS with ~90% accuracy.[17, 63, 70, 77-80] Although its negative predictive value is lesser, it increases with the length of follow-up and may approach 70% at 2 or more years.[63, 70] Since in most previous reports the patients were operated without consideration of predicting procedures, the clinical effect size of eMCS should increase significantly with a better selection of patients via preoperative rTMS assessment.

Take-home messages: eMCS

Implanted epidural stimulation is the original neurosurgical technique for motor cortex stimulation, which has now largely supplanted thalamic procedures. Its mechanisms of action involve activation of multiple cortico-subcortical areas, secretion of endogenous opioids, and descending inhibition toward the spinal cord. Clinical efficacy, including "on-off" effects, is supported by at least seven RCTs in more than 100 operated patients. Efficacy can persist up to 10 years, and can be reasonably predicted by preoperative use of rTMS.

Transcranial magnetic repetitive stimulation (rTMS)

High-voltage electrical pulses applied to the scalp can activate the motor cortex and thus mimic eMCS, but they are also very painful. This difficulty can be surmounted by activating the motor cortex *via* magnetic pulses. Short-lasting currents in a coil applied on the scalp (1000 A, 1 ms) create a magnetic field of ~1 T, which painlessly generates a secondary current in the brain via electromagnetic induction, according to Faraday's law. This secondary current has a magnitude similar to that used in direct cortical studies, and allows activation of the underlying motor cortex. These non-invasive techniques were initially intended to predict the effectiveness of epidural procedures, but their potential value as a pain therapy in their own right was soon envisaged. "Figure-of-eight" coils ensure precise millimetric cortical stimulation and are most widely used,[81, 82] and the technical settings to implement rTMS in clinical practice are discussed in Lefaucheur and Nguyen.[82]

rTMS mechanisms

Although rTMS stimulates cortical interneurons[83, 84] it remains unclear whether it entails sizeable changes in intracortical motor circuits under the conditions used to treat pain. Indeed, rTMS for pain relief threshold is applied at lower levels than the motor threshold, in conditions where local motor metabolic activation subsides or disappears.[85-87] Although a correlation was initially reported between intracortical motor inhibition (ICI) and rTMS-induced pain relief,[88] later studies failed to reproduce such effects,[89] perhaps because ICI changes in chronic pain depend on non-pain pathways.[90] Also, rTMS effects could be blocked pharmacologically in the absence of cortical excitability changes[91] and GABAergic drugs that modify intracortical inhibition[92] are not effective in neuropathic pain. Cortical motor inhibition appeared unrelated to pain relief in post-amputation or spinal cord injury pain,[93, 94] and in general the relevance of motor cortex excitability for rTMS analgesic effects remains largely unconfirmed.[95, 96]

In contrast, the activation of structures *distant* from the motor cortex has received consistent support. Subthreshold rTMS activates multiple areas that overlap the network activated during epidural MCS,[23] including the anterior cingulate (ACC), operculo-insular and dorsolateral prefrontal cortices (DLPFC), striatum and brainstem.[85-87] rTMS-induced input into the insula, operculum and ACC has been suggested by causal modelling studies[97] and enhancement of functional connectivity between these areas after rTMS has been shown in both human patients[98] and a nonhuman primate model of central pain.[99] rTMS in rats and mice also induced c-fos neural activation in regions distant from the stimulation including thalamus, ACC, striatum and hippocampus.[100-102] The clinical relevance of such multifocal changes is supported by the predictive

value of preserved thalamo-cortical and corticofugal motor tracts on rTMS clinical effects.[103, 104]

Contribution of endogenous opioids to these effects is supported by enhancement of serum beta-endorphin after successful rTMS,[105] naloxone blockade of rTMS analgesia,[106] and rTMS-induced increase in opioid receptor occupancy.[107] Enhanced dopamine striatal secretion was also described in rodents[108] and some human PET-scan studies[109] but not in others.[107] Since stimulus-related dopamine release returns rapidly to baseline, its secretion may be too short-lasting to account for clinical effects, but could have an indirect effect by its synergy with opioid-related activity. The potential contribution of NMDA glutamate receptors has also received indirect support from two studies in humans,[91, 110] while in rats rTMS effects were not blocked by NMDA antagonists.[101]

rTMS appears to influence abnormally hyperactive states, rather than physiological pain. Markers of acute nociception such as heat-pain detection and pain-evoked potentials, did not change after rTMS in healthy subjects,[107, 111-113] although cold pain was reported to be attenuated.[106, 114] Contrary to epidural stimulation, rTMS has not been shown to attenuate spinal nociceptive reflexes.[114, 115] This suggests a superior capacity of implanted eMCS to trigger descending mechanisms influencing spinal nociception, and would be in accordance with the enhanced degree of pain relief achieved with eMCS, relative to non-invasive procedures.[63, 79, 80]

rTMS as a predictive factor of epidural MCS

The suggestion that rTMS could be predictive of eMCS efficacy came very shortly after the first neurosurgical reports, but controlled studies on this matter were not available until 10 years later.[78, 79] Cumulative evidence from seven studies in 150 patients consistently indicates that a positive result of preoperative rTMS may be associated in ~90% of cases with satisfactory pain relief after epidural implantation.[17, 63, 70, 77-80] The negative predictive value, *i.e*. the probability that eMCS fails if rTMS is negative, was low at 6-12 months (~30-40%[78, 79]), but increased with longer follow-ups to reach ~70% or more in studies with 2-10 years follow-up.[63, 70, 80] A 70% chance of eMCS failure if preoperative rTMS is negative is often a reason to withhold operation.

rTMS as a pain-relieving procedure on its own right

A number of systematic reviews concluded to a statistical superiority of motor cortex rTMS relative to placebo to improve chronic neuropathic pain in the short or mid-term.[116-122] Other assessments were however much less optimistic, in particular in regard to the low quality of evidence included in some reviews due to low patient samples, absent blinding, defective handling, lack of follow-up, no report on withdrawals, etc.[60, 123, 124] In 2018, an influential Cochrane analysis examined the use of rTMS for chronic pain in 42 studies.[123] While underscoring the multiple biases due to the above-mentioned flaws, it also recognized "low-quality evidence" of rTMS effects on chronic pain and quality of life up to 6 weeks post-intervention. Since this account, at least six large and well-conducted studies (single/double-blinded, >20 patients in active group) have been reported on motor rTMS in chronic NP, with positive results in all but one of them.[96, 125-129] One further study reported significant effects in parkinsonian pain[130] and another negative results in fibromyalgia.[131] A recent report of the US Department of Veterans Affairs[119] using a "best-evidence approach" concluded that rTMS may reduce symptoms in NP, while in fibromyalgia it may not be better than sham interventions. Although the level of evidence was (again) limited by methodological drawbacks, this influential report concluded that rTMS, which has fewer side effects compared to most approved pharmaceuticals for NP, "could be a treatment option for patients who have exhausted other available options for treatment of chronic pain."[119]

Specific aspects of rTMS stimulation procedures.

Many practical details of rTMS remain controversial and are seldom analyzed specifically, although they can impact on the efficacy of rTMS procedures. Some of the effects of these variables are summarized in what follows, in the hope that they may serve to establish a minimum technical core set to be applied in a rehabilitation setting.

Stimulus frequency

Beneficial effects have been reported using "high frequencies" of 5, 10 or 20 Hz (commonly labelled "HF-rTMS") while low frequencies of 0.5 or 1 Hz were found useless in both patients and animal models.[78, 132, 133] Superiority of HF-rTMS was initially considered to depend on its ability to induce long-term potentiation (LTP) in the cortex; however, enhancement of LTP capacities with "theta burst" rTMS did not enhance analgesia.[96, 134, 135] A potentially important feature of rTMS is its relation with the neuronal oscillations of the underlying cortex. The transmission efficiency of neural networks increases when the stimuli match their intrinsic oscillatory frequency.[136, 137] Since rTMS synchronises oscillatory activity in the underlying

cortex,[138] and since human sensorimotor networks oscillate at around 10 and 20 Hz, this might underlie the superior efficacy of rTMS at these frequencies.

Stimulus intensity and number of pulses

Stimulus intensity is universally set at 80-90% of motor threshold; conversely, the optimal number of pulses per session has variously considered to be 1000,[60] 1200,[88] or even 3000 pulses.[82] One single comparative study reported that significant analgesia in NP was obtained with 2000 pulses, but not with 500.[139] An excessive number of stimuli, however, may reverse the effects of rTMS in humans,[140] and trigger allodynia in rodents,[141] hence more than 3000 stimuli per session are not advised. Independent of the number of stimuli, shortening the stimulation time from 20 to 10 min was reported to decrease analgesia.[142]

Somatotopy

Somatotopic match between the cortical stimulus and the painful region may be critical for epidural MCS,[12, 143] but appears much less relevant for rTMS. The pain-relieving effects of rTMS seem independent of any strict relation between pain location and rTMS placement over the motor homunculus.[144, 145] In patients with facial or leg pains the stimulation of the hand area proved as efficacious, or better, than that of the somatotopically corresponding area.[95, 139, 146, 147]

Alternative cortical targets

So far, only stimulation of the primary motor area (M1) has received consensus as to its efficacy in neuropathic pain (much less consistently in widespread pain/fibromyalgia). Stimulation of the postcentral gyrus (S1), premotor area (preM), or supplementary motor area (SMA) did not provide effective pain relief in comparative studies,[77, 148, 149] and rTMS over the posterior parietal cortex failed to perform beyond sham in experimental hyperalgesia.[150]

Stimulation of the left dorsolateral prefrontal cortex (DLPFC) has yielded controversial but overall disappointing results. Initial reports suggesting a decrease in postoperative morphine use[151] were later contradicted in large-scale studies.[152] Similarly, initially positive results of DLPFC stimulation in small series of NP patients[153] failed to be confirmed in larger samples,[129, 149] and had no effect on human models of neuropathic hyperalgesia.[112] In fibromyalgia/widespread pain two studies reported positive results[154, 155] while no difference from placebo was reported in four other studies of similar sample size.[156-160] M1 also showed superiority over DLPFC stimulation in opioid-resistant back pain[161] and peripheral neuropathic pain,[129] and only one small-sample study suggested the reverse in non-specific back/neck pain.[162] Recent systematic reviews have considered DLPFC rTMS as either ineffective *versus* sham,[119, 123, 163] less effective than M1 stimulation[121] or mildly effective in the short-term.[164] Other forms of DLPFC stimulation (bilateral, low-frequency)[165, 166] remain anecdotal and do not allow any conclusion. Caution is advised when dealing with high-order cortices such as DLPFC, whose stimulation may give rise to a wide array of unpredictable cognitive and emotional effects, including changes in sexual arousal or in craving for drugs.[167-169]

The posterior operculo-insular cortex may represent a unique area for pain modulation, as it receives a majority of ascending spinothalamic afferents in primates,[170] but reports on its stimulation are scarce. One sham-controlled study involving 17 patients with visceral pain was reported positive,[110] but has not been replicated. In neuropathic pain, positive results of S2 or posterior insula stimulation have been reported in small to medium-sized studies (15-31 patients),[171-173] while no significant relief beyond sham was obtained in a larger RCT recruiting 98 patients with central pain.[174] Despite its inherent relevance as a target, the multimodal nature of the insula makes this region more susceptible than M1 to adverse effects from stimulation. Two cases of epileptic seizures were reported during theta burst stimulation of the posterior operculo-insular cortex[175] perhaps due to current spread toward the anterior insula.[176]

Timing and repetition of sessions

The pain-relieving effects of a single rTMS session develop 1-3 days after the stimulation and fade away in less than 10 days. Repeated sessions over 5-10 days allow expanding their effect to up to one month,[82, 177] but this remains insufficient for chronic syndromes that persist for years. An initial series of 5-10 daily sessions followed by progressively spaced "maintenance" sessions achieved sustained efficacy for 6 months.[129, 142, 178] Other groups reported long-lasting efficacy of rTMS sessions repeated at long intervals of 2-4 weeks, without the need of an initial series of daily stimulation,[80, 125, 179-182] making of such "slow-pace" rTMS a potential avenue allowing long term efficacy with limited burden for patients and doctors. Solutions to implement rTMS at home

are under study using modified coils adapted for home use. Although some preliminary data have been published[182, 183] clinical systems are not yet operational to our knowledge.

Take-home messages: rTMS

rTMS can be used to predict the efficacy of implanted neurostimulation, but also as an analgesic procedure in its own right, with effects over both the sensory and affective pain domains. Reasonable evidence supports a significant analgesic effect of motor cortex HF-rTMS in neuropathic pain, and less consistently in widespread/fibromyalgic pain. Dorsolateral frontal stimulation has not proven efficacious so far, and the posterior operculo-insular cortex is an attractive target but evidence remains insufficient. rTMS acts preferentially upon abnormal hyperexcitable states rather than experimental pain. Short-term efficacy of rTMS in NP can be achieved with NNT ~2-3, but ensuring long-lasting efficacy remains a challenge.

Transcranial direct current stimulation (tDCS)

Direct current (galvanic) stimulation, *i.e*. a flow of electric charge that does not change direction, was empirically applied for medical purposes since the Roman antiquity,[184] then used for research and therapy in psychiatry during the 19th to early 20th centuries, until it was abandoned with the advent of electroconvulsive therapy.[185] Experimental studies in the second part of the 20th century showed that DC stimulation over the cortex influenced spontaneous neural firing in rodents and humans,[186-188] with surface anodal polarization increasing spontaneous unit discharges, and cathodal polarization decreasing them.[187, 189, 190] The use of transcranial DC stimulation appeared therefore as a promising tool to modulate cerebral excitability in a safe, painless, reversible and selective way, hence mimicking the analgesic effects of motor cortex stimulation.

Conventional tDCS procedures use a pair of surface electrodes (4 to 30 cm^2) connected to a stimulator delivering electrical direct current at 1-2 mA (Figure 1). Higher focalization of stimulation ("High-definition" tDCS, or HD-tDCS) can be achieved with one electrode surrounded by four others of opposite polarity.[191, 192]

Mechanisms of action

Although tDCS modifies the excitability of the underlying cortex, it also induces widespread metabolic alterations much beyond local motor excitability. Indeed, activity changes in cortical and subcortical regions have been documented in humans during or following tDCS,[193-195] and tDCS-induced analgesia was associated with distributed metabolic changes in a large array of brain areas,[194] while it was dissociated from motor excitability.[196-198] Changes in functional connectivity have been described between regions beneath the stimulation and distant areas including thalamus, striatum and parietal association cortices, but results are somewhat inconsistent and sometimes contradictory.[199-201] Although the notion of distributed activity has received robust evidence, the precise causal relation between such changes and the clinical effects should be considered cautiously in view of the inconsistencies in different reports. At a difference from both eMCS and rTMS, distributed neural activation in tDCS may come not only from neural connections between brain areas, but also from the direct current spread in distant brain structures, in particular when using widely separated anode and cathode.[202] In this respect, note that the terms "anodal" and "cathodal" do not capture the whole picture of tDCS, since both anodal and cathodal currents are in fact delivered,[203] and the effects should be understood as a compound of both.

In humans, neurotransmitter studies have reported GABA and glutamate concentration changes as well as a possible secretion of endogenous opioids during tDCS, mainly in the insula and ACC.[204, 205] In rodent models of neuropathic pain tDCS effects have been associated to virtually all neurotransmitter systems,[206] but the literature in this domain is confusing, rarely reproduced and sometimes contradictory. There remain significant unknowns about the influence on biochemical and behavioural effects of many tDCS parameters, including polarity, number, size and position of electrodes, duration of stimulation, etc. As in other forms of neurostimulation, part of the effects from tDCS might involve descending inhibitory mechanisms, since tDCS decreased spinal nociceptive reflexes in models of experimental hyperalgesia[207] and normalized BOLD responses in pain modulatory networks.[208] Evidence for descending modulation was also reported after motor anodal tDCS on a rodent model of neuropathic pain.[209]

tDCS has often failed to decrease experimental pain in healthy individuals,[191, 198, 210-212] whereas it reduced abnormal sensations (allodynia, hyperalgesia) induced by capsaicin,[213] suggesting that the procedure acts on abnormally sensitized pathways, rather than on physiological pain.[198] Similar conclusions have been proposed regarding rTMS.[113] On these premises, experimental studies in

healthy subjects should rather involve human models of neuropathic hyperalgesia (capsaicin, high-frequency stimulation, etc.) rather than simple acute physiological pain.[214]

tDCS clinical efficacy

From 2015 to date, no less than 120 articles, including 25 systematic reviews and meta-analyses have been proposed on the use of tDCS for pain, using diverse grading systems and providing inconsistent results. Because of the limited quality of many published reports, the level of evidence for pain remains low despite such a large number of studies.

While initial reviews cautiously concluded to a "possible pain-relieving efficacy,"[215, 216] more recent ones have uncritically stated that tDCS "successfully relieves NP."[122, 217-219] Other meta-analyses, however, concluded that tDCS had no effect in NP beyond sham stimulation,[124, 220] or found limited and conflicting evidence precluding reliable interpretations.[60, 221-224] Similar inconsistencies are found regarding widespread pain syndromes. While some systematic reviews concluded to "probable" or even "definite" efficacy in fibromyalgia,[215, 225-228] others found "tentative," "inconclusive," or simply absent evidence of pain reduction when compared to sham stimulation.[60, 123, 229] Such discrepancies are undoubtedly driven by the heterogeneity of reports in terms of sample size, randomization, procedures of stimulation, quality of blinding, control of bias, statistical thresholds, and so forth. Thus, the magnitude of clinical effects in fibromyalgia dramatically decreased with increased sample size, to become very often clinically insignificant or not better than sham.[230-233] As with every neuromodulation procedure, some subsets of patients may be more receptive to tDCS than others,[234] which underscores the importance of reporting precisely the percentage and clinical characteristics of responding subjects, along with numbers needed to treat (NNTs), rather than simply providing statistical group analyses.

tDCS addressed to the frontal cortex has not proved better than standard M1 stimulation, and in most cases, was inferior to it, both in NP[145, 235] and fibromyalgia.[226] There is a lack of head-to-head prospective studies comparing tDCS with conventional rTMS in neuropathic pain. One study contrasting their effects in patients with lumbosacral radiculopathy reported rTMS superiority;[236] however, patients unresponsive to conventional rTMS can also be alleviated by subsequent tDCS,[237] and two recent studies in different NP conditions reported similar global efficacy but a different subset of responding patients to each technique.[238] The use of tDCS as add-on therapy to invasive procedures was recently reported in a small randomised study, where combining tDCS with dorsal root ganglion (DRG) stimulation provided better results than DRG alone.[239]

A critical advantage of tDCS is the possibility of performing home-based therapy, hence allowing long-lasting maintenance of effects in responding patients. Although the development of systems for self-stimulation is technically simple, inadequate choice of targets, stimulation mode, electrode contact, or stimulus intensity can create significant harm[240, 241] including cognitive impairment,[242] which has lead major authors to issue notices of caution.[243] Remotely supervised systems can circumvent most of these problems by allowing online monitoring and control of the stimulation by clinical personnel. Such systems ensure that tDCS cannot be performed unless authorized by clinical staff, who follows in real time the procedure, can detect faulty or incomplete sessions, and communicate with patients in case of problems. Supporting clinical evidence remains weak, but real-life feasibility has been reported in a few sham-controlled pilot studies on small samples of NP patients, where about half of the patients were significantly improved with follow-up up to 6 months.[244, 245]

Take-home messages: tDCS

tDCS modulates the neuronal resting membrane state of the underlying cortex, induces activity changes in distributed brain networks, and can influence both cognitive-emotional and sensory aspects of pain. Lower cost relative to rTMS, few safety issues, and availability of home-based protocols are practical advantages; however, the limited quality of most published reports greatly lowers the level of evidence regarding its effects in chronic pain. Limited evidence suggests that: 1) M1 is superior to DLPFC stimulation for chronic pain; 2) repeated sessions over a long time may be necessary for clinically significant pain relief; 3) patients responsive to tDCS may differ from those improved by rTMS. Well-conducted RCTs are needed to gather conclusive evidence of its possible clinical relevance and NNTs.

Conclusions

Invasive and non-invasive cortical stimulation can be of significant benefit to patients with drug-resistant chronic pain. Noninvasive procedures are extremely safe when conducted by well-trained practitioners; they are being increasingly

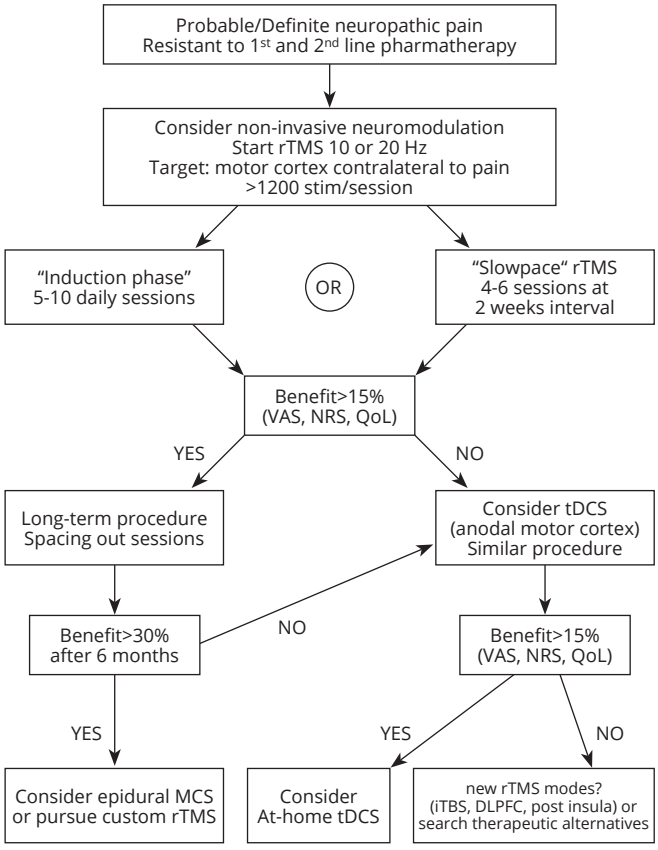


Figure 2.—A proposed therapeutic algorithm with options and paths for non-invasive cortical stimulation in chronic neuropathic pain patients.

used as either ancillary or last-resort treatments mainly in neuropathic pain, and may be successfully combined with rehabilitation. Although the potentialities are huge, evidence for successful clinical use in the long term remains low, in particular for tDCS, and extending the duration of beneficial effects beyond the first weeks post-treatment remains a challenge. Different strategies are being currently under investigation, and Figure 2 proposes an algorithm with pathways and options for long-term use of cortical stimulation in patients with chronic neuropathic pain.

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