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Non pharmacological treatment for neuropathic pain: invasive and non-invasive cortical stimulation.

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Abstract

The use of medications in chronic neuropathic pain may be limited with regard to efficacy and tolerance. Therefore, non-pharmacological approaches, using electrical stimulation of the cortex has been proposed as an alternative. First, in the early nineties, surgically-implanted epidural motor cortex stimulation (EMCS) was proven to be effective to relieve refractory neuropathic pain. Later, non-invasive stimulation techniques were found to produce similar analgesic effects, at least by means of repetitive transcranial magnetic stimulation (rTMS) targeting the primary motor cortex (M1). Following “high-frequency” rTMS (i.e. stimulation frequency ranging from 5 to 20 Hz) delivered to the precentral gyrus (i.e. M1 region), it is possible to obtain an analgesic effect via the modulation of several remote brain regions involved in nociceptive information processing or control. This pain reduction can last for weeks beyond the time of the stimulation, especially if repeated sessions are performed, probably related to processes of long-term synaptic plasticity. Transcranial direct current stimulation (tDCS), another form of transcranial stimulation, using low-intensity electrical currents, generally delivered by a pair of large electrodes, has also shown some efficacy to improve patients with chronic pain syndromes. The mechanism of action of tDCS differs from that of EMCS and rTMS, but the cortical target is the same, which is M1. Although the level of evidence of therapeutic efficacy in the context of neuropathic pain is lower for tDCS than for rTMS, interesting perspectives are opened by using at-home tDCS protocols for long-term management. Now, there is a scientific basis for recommending both EMCS and rTMS of M1 to treat refractory chronic neuropathic pain, but their application in clinical practice remains limited due to practical and regulatory issues.

Key words: brain stimulation, motor cortex stimulation, neuropathic pain, transcranial electrical stimulation, transcranial magnetic stimulation.

Introduction

Chronic neuropathic pain affects around 7% of the general population [1]. Less than 30% of patients with neuropathic pain have more than 50% pain relief with recommended medications [2]. Moreover, several side effects limit the use of these drugs, especially in vulnerable patients.

In the early 1990s, epidural motor cortex stimulation (EMCS) with surgically implanted electrodes over the dura mater was proposed as a treatment for drug-resistant, central neuropathic pain [3,4]. Since this first report, many studies have confirmed the beneficial effects of the EMCS procedure to treat chronic neuropathic pain of either peripheral or central origin [5].

In the late 1990s, it was shown that analgesia could also be obtained noninvasively by means of repetitive transcranial magnetic stimulation (rTMS) delivered at 10 Hz over the primary motor cortex (M1) [6]. Since this preliminary report, numerous studies have confirmed the value of “high-frequency” rTMS (i.e., delivered at a frequency ranging between 5 and 20 Hz) over M1 to relieve neuropathic pain [7,8]. Several years later, another technique of noninvasive cortical stimulation, transcranial direct current stimulation (tDCS), was also found to provide neuropathic pain relief when delivered anodally over M1 [9]. To date, it must be recognized that the level of evidence still remains higher for rTMS than for tDCS concerning the efficacy of noninvasive M1 stimulation in neuropathic pain [10,11].

Although these various invasive and non-invasive techniques can reduce neuropathic pain by stimulating the M1 cortical region, they do not share the same mechanisms of action and analgesic potential, as reviewed in the following sections and illustrated by Figure 1.

General principles and mechanisms of action of epidural motor cortex stimulation (EMCS)

The first report of EMCS for the treatment of chronic pain was published in 1991 in a set of 12 patients with pain secondary to central nervous system lesions, mostly thalamic stroke [3,4]. Two-thirds had continued significant effect of this therapy after one year, but all the published results are not so good [12]. A group of experts commissioned by the European Federation of Neurological Societies graded the recommendation of using EMCS to treat chronic refractory neuropathic pain as ‘weak’ [7], because of the heterogeneity and overall low quality of the reported data.

Usually, quadripolar leads with relatively wide electrode spacing are epidurally placed over the precentral gyrus under imaging and neurophysiological guidance [13]. Analgesic effects of EMCS are produced at a frequency comprised between 20 and 65Hz and weak intensity of stimulation, well below the motor threshold. Using such conditions, the induced current is only sufficient to excite the nerve fibers in the superficial cortical layers of the precentral gyrus. In most cases, a bipolar montage is used for chronic stimulation and the contact selected as the cathode (negative electrode) is right over the M1 cortical representation of the pain area [5]. Indeed, the cathode seems to play the key role in EMCS-induced analgesia, activating preferentially fibers that run parallel to it, whereas the anode activates perpendicular fibers [14,15]. From these observations, it can be concluded that EMCS induced-analgesia is mediated by horizontal interneuronal fibers in the superficial layers of the precentral gyrus and not by the corticospinal pyramidal tract itself [5]. This hypothesis is supported by the recording of late indirect I-waves as the main descending volleys elicited by the configuration of EMCS electrodes generating maximal pain relief [16].

However, all the mechanisms underlying the analgesic effects of EMCS remain incompletely elucidated. Several neuroimaging studies have shown that the hemodynamic changes induced into the brain by EMCS are not confined to the motor system, but concern various cortical and subcortical structures involved in pain processing and modulation [17–19]. In some (but not all) patients, the analgesic effects of M1 stimulation may also involve an inhibition of the spinal transmission of nociceptive signals [19]. In fact, the existence of motor cortex projections able to modulate the processing of sensory information at various anatomical levels has been demonstrated using tracing techniques [20]. Experimental animal studies showed that EMCS induces analgesia by activating cannabinoid and opioid systems via descending inhibitory pathways, leading to inhibit some thalamic sensory neurons, activate periaqueductal gray neurons, and produce spinal anti-neuroinflammatory effects [21–27]. The involvement of the endogenous opioid system in antinociceptive effects of EMCS has been confirmed in human patients treated for refractory neuropathic pain [28,29].

Despite technical progress in neurosurgical navigation, guided by neuroimaging and intraoperative electrophysiology to optimize electrode positioning [13], EMCS results are still variable, and validated criteria for selecting good candidates for implantation are lacking [30,31], except clinical response to preoperative rTMS. Repetitive TMS was initially developed to select good responders for EMCS [32,33]. It has now been proven that rTMS can predict EMCS efficacy with a very good positive predictive value [34–36]. However, it is important to note that non-responders to rTMS can respond to EMCS.

To summarize, one can say that the evidence in favor of this technique is sufficient to include it in the range of treatment options for refractory neuropathic pain. Although the link between M1 stimulation and pain relief is not obvious at first, M1 can be seen as an entry door into a larger network involved in pain modulation [37,38], as illustrated by Figure 2.

Repetitive transcranial magnetic stimulation (rTMS)

Repetitive transcranial magnetic stimulation (rTMS) relies on electromagnetic induction, first described by Faraday in 1831. Faraday's law of induction is a basic law of electromagnetism predicting how a rapidly changing magnetic field produces an electric current in a conducting material in the neighborhood, such a phenomenon being called electromagnetic induction. In the present case, a brief magnetic pulse is delivered by a coil placed on the scalp and passes through the skull with minimal attenuation, leading to axonal depolarization within the superficial cortical layers [39–41].

Several types of coils can be used to apply rTMS [42], but at the moment, almost all studies are performed with focal figure-of-eight coils, limiting the stimulated area to a few cm² at a depth of less than 2 cm. This focal stimulation makes the use of a neuronavigation system integrating individual brain imaging data helpful to allow comparable and reproducible stimulation targeting between sessions, especially for non-motor cortical targets [43,44]. Other types of double coils have been proposed to stimulate deeper brain structures [45,46], but the largest site of stimulation can be affected by means of Heschl coils (H-coils), nevertheless rarely used to produce neuropathic pain relief [47,48].

In practice, an rTMS session lasts about 15 to 30 minutes. Reducing session duration may lower the intensity of the analgesic effects [49]. When using a figure-of-eight coil, it must be handled parallel to the interhemispheric midline (anteroposterior or posteroanterior orientation) to provide optimal pain relief [50]. This coil orientation generates late I-waves, similarly to cathodal EMCS [16]. The intensity of stimulation is personalized, according to the motor threshold, which is precisely measured in each individual, but must be kept below this motor threshold. The stimulation pattern must be composed of trains of a hundred pulses delivered at a frequency ranging between 5 and 20 Hz spaced by pauses of several seconds (i.e. "high-frequency" rTMS, contrasting with "low-frequency" stimulation tonically delivered at 1 Hz or less). Train and intertrain durations, according to the frequency of stimulation, must remain within the safety limits, which have been proposed to reduce the risk of seizures [51].

For clinical routine, a neuro-navigation system is not mandatory to stimulate M1, but clearly helpful in the management of long-term treatment [52,53]. The minimum required material costs around 30,000 euros. Such a machine can also be used in the treatment of depression, based on the stimulation of the dorsolateral prefrontal cortex, at high-frequency on the left hemisphere or low-frequency on the right. In France, the cost of rTMS therapy for depression was evaluated to around 2,000 euros for a cure of 15 sessions [54]. Recent data showed that another type of rTMS protocol, called intermittent theta burst stimulation (iTBS), was non-inferior to high-frequency rTMS to produce antidepressant effects, when applied to the dorsolateral prefrontal cortex [55]. The advantage of iTBS is the shorter duration of each session compared to high-frequency rTMS (3 min vs. 37.5 min.). The potential interest of theta burst stimulation for pain treatment is under investigation [56], although not validated yet [57].

The mechanisms at the origin of the analgesic effects of high-frequency rTMS of M1 in neuropathic pain are very similar to those of EMCS, as shown by the predictive value of rTMS [34,35]. The stimulation of M1 modulates neural activity in pain networks and nociceptive inhibitory control structures not only locally but also in remote brain regions, leading to pain relief [38,58,59]. Again, various neurotransmitter systems have been implied, involving complex opioidergic, glutamatergic, or gabaergic modulations [60–62].

From now on, meta-analyses showed a rather beneficial impact of high-frequency rTMS of M1 on neuropathic pain [63,64], although there is some controversy regarding clinical meaningfulness [65]. A single rTMS session induces a maximal pain relief after two to three days and can last up to eight days [66]. For therapeutic purposes, repeated rTMS sessions are needed [67]. A few studies showed the value of a maintenance protocol of high-frequency M1-rTMS sessions to manage chronic neuropathic or non-neuropathic pain syndromes in clinical practice in the long term (at least six months) [49,52,53,68]. Therefore, recommendations now exist for the use of high-frequency rTMS of M1 to treat patients with chronic neuropathic pain syndrome [7,10]. Other cortical targets also have a potential analgesic interest, such as the dorsolateral prefrontal cortex or the insular cortex, but there is insufficient data to make any recommendation for the stimulation of these targets in the context of neuropathic pain control [10,65].

Transcranial direct current stimulation (tDCS)

Transcranial direct current stimulation (tDCS) is a type of electrical stimulation delivered continuously ("direct current") for 20-30 minutes at a low intensity, generally between 1 and 2 mA. Usually, two large electrodes are placed on the scalp, one anode and one cathode. For pain treatment, the conventional bipolar montage comprises the anode over M1 and the cathode over the contralateral supraorbital region. This produces a large current flow in various brain structures, such as the prefrontal cortex, the cingulate cortex, the insula, and even deeper structures (thalamic and brainstem nuclei) [69]. The focality of the stimulation can be enhanced by other types of montages such as Laplacian ones ("high-definition" tDCS) and the value of such montages are currently under investigation in pain syndromes [70,71]. The use of tDCS at the intensity of 1-2 mA is totally safe for brain structures, the only risk in clinical practice being to produce skin burns because of an inaccurate electrode-skin contact [72]. In addition, the device is small and easily portable. Therefore, this technique is especially suitable to be applied at home by the patient him(her)self for pain treatment in the long term [73]. The cheapest devices cost around 300 euros, making it possible for patients to buy their own device freely on the web, but without any guarantee about the reliability of the delivered current pattern. For clinical and research applications, CE-labeled and well-designed systems cost around 3,000 euros.

Contrarily to EMCS and rTMS, the intensity of current induced into the brain by tDCS is too low and not sufficient to elicit action potentials in cortical axons. However, tDCS is able to modulate the resting membrane potential of axons: a modification towards depolarization favors axonal excitability whereas hyperpolarization decreases it. Such an effect depends on electrode polarity and axonal orientation in the electric field induced by tDCS [74].

Since the first clinical report of the beneficial effect of anodal tDCS of M1 for the treatment of central pain secondary to spinal cord injury [9], numerous studies showed interesting perspectives for the use of tDCS to treat various pain syndromes [75]. However, the level of evidence of efficacy for anodal tDCS of the left M1 (with right orbitofrontal cathode) is higher in fibromyalgia (level B) than in chronic neuropathic pain (level C, only for lower limb pain secondary to spinal cord lesion) [11]. Overall, the level of evidence is higher for rTMS [10], but published data have been available for a longer time.

Only one study was conducted to compare the analgesic effects of tDCS vs. rTMS in patients with chronic neuropathic pain due to radiculopathy [76]. Using a randomized sham-controlled comparative design, each patient benefitted from three daily sessions of tDCS and three daily sessions of rTMS, in a random order, separated by a wash-out period. In these conditions, rTMS was superior to tDCS. However, it has been shown in a case study that anodal tDCS of

M1 could provide pain relief in the long term in a patient who was previously resistant to high-frequency rTMS of M1 [77]. This observation illustrates the fact that tDCS and rTMS do not share the same mechanisms of action for pain treatment, even if the stimulation is targeted over M1 in both cases.

There are other forms of low-intensity electrical stimulation delivered transcranially for clinical purposes, such as transcranial alternating current stimulation (tACS) or transcranial random noise stimulation (tRNS), but no evidence has been published to date regarding the analgesic potential of these techniques in neuropathic pain [78].

Finally, another modality of electrical stimulation, called cranial electrotherapy stimulation (CES), initially developed as an add-on treatment for anxiety and depression in the 1950s, has been tested for the treatment of neuropathic pain more recently [79]. The electrical current in CES is delivered via clip electrodes attached to patients' earlobes. To date, there is no evidence of a benefit of CES therapy in the context of chronic pain syndromes [65].

Conclusion

Invasive cortical stimulation can have a clear beneficial effect in patients with chronic refractory neuropathic pain. Even if surgical implantation of epidural electrodes has limited risks, complications do exist and there is a place for the development of non-invasive stimulation methods. Repetitive TMS is safe, well-tolerated and efficient in around half of chronic pain patients. However, the analgesic effects are limited both in magnitude and duration. Further improvement requires a better definition of maintenance protocols and maybe the development of new stimulation paradigms [80]. Another important point relies on the low accessibility of this new technique in routine clinical practice. Few hospitals can provide such innovative therapy, due to lack of funding for materials and trained staff, especially with regard to the great demand on human resources. Moreover, despite a good level of evidence for efficacy, rTMS is not listed in the French medical acts nomenclature (CCAM:classification commune des actes médicaux) as a pain therapy technique, precluding its reimbursement. Regarding tDCS, the level of evidence is too low to propose this approach in daily practice to date, but convincing data are currently in progression, opening interesting perspectives for the use of tDCS to treat chronic pain syndromes in the long term, especially by means of at-home protocols.

Disclosure of interest

The authors declare no conflict of interest concerning this article.

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Figures

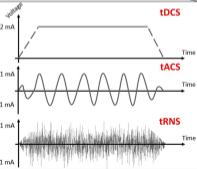
Figure 1: Non-invasive brain stimulation techniques proposed for neuropathic pain treatment. rTMS: repetitive transcranial magnetic stimulation; tACS: transcranial alternating current stimulation; tDCS: transcranial direct current stimulation; tRNS: transcranial random noise stimulation ; CES : cranial electrotherapy stimulation.

Figure 2: Main brain structures modulated by M1 stimulation and possibly involved in its analgesic effects. ACC: anterior cingulate cortex; DLPFC: dorsolateral prefrontal cortex; Hyp: hypothalamus; ISI: inter-stimulus interval; LC: locus coeruleus; M1: primary motor cortex; N Acc: Nucleus accumbens; RVM: rostral ventromedial medulla; SN: Substantia nigra; Thal: thalamus; VTA: ventral tegmental area; ZI: zona incerta. Adapted from [38].

Anode (+)



CES



High frequency rTMS (5 to 20Hz)

