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Non-invasive Cortical Stimulation for the Treatment of Pain

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Non-invasive cortical stimulation techniques are promising tools in the arsenal against refractory chronic pain. Repetitive transcranial magnetic stimulation can produce analgesic effects, leading to consideration of this technique as a therapeutic tool per se or as a prognostic tool to select candidates for subsequent implanted epidural motor cortex stimulation. This review focuses on the optimal parameters of stimulation, including the cortical target, coil orientation, stimulation intensity and frequency. The long-lasting effects of consecutive daily sessions and the possibility for ameliorating specific components of pain are also discussed.

K e y w o r d s: transcranial magnetic stimulation, TMS trials, analgesic effects, motor cortex stimulation

1. Introduction

Recent works have promoted the therapeutic potential of non-invasive cortical stimulation (NICS) techniques such as repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS) for the management of various pain syndromes [1]. These techniques are employed to generate an electric current into the brain that is able to modulate neuronal activity in pain processing pathways.

A TMS machine produces a brief magnetic pulse [2], which is delivered through a coil that can be placed on a scalp site. This time-varying magnetic pulse is able to cross the skull and to induce an electric current in the underlying cortical structure,

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a few centimeters away from the coil, in accordance with Faraday's law. The electrical field can depolarize specific populations of neurons with respect to current direction and nerve fibre orientation. The main parameters of stimulation are the waveform of the magnetic pulse (monophasic versus biphasic) and the intensity and frequency of discharge. These parameters clearly influence the clinical changes produced by rTMS procedures. The depth of stimulation and region of activation, and therefore the clinical effects, vary with the type of coil used and its orientation. For therapeutic effects, TMS is performed repetitively (rTMS), generally using a figure-eight coil. The duration of therapeutic effects depends on the number of pulses per session and the number of sessions.

One of the first therapeutic applications of rTMS was to treat depressive patients as an alternative to electro-convulsive therapy [3]. Later on, rTMS was proposed for use as a predictive tool to select candidates for surgical treatment of chronic neuropathic pain by epidural motor cortex stimulation (EMCS) [4, 5]. Recent studies also suggested the use of rTMS as an adjunctive therapy to control various chronic pain conditions such as fibromyalgia [6].

2. Mechanisms of Action

Studying the mechanisms of action by which rTMS relieves chronic pain continues to be an expanding field of research. Most rTMS pain studies targeted the primary motor cortex (M1); however, it is very unlikely that the analgesic effects directly result from a modulation of M1 activity. These effects are rather mediated through the activation of various brain regions structurally connected to M1 but distant from the stimulated area. In neuropathic pain patients, positron emission tomography (PET) scans revealed that EMCS was able to activate the thalamus (lateral or medial), some limbic cortical areas (orbitofrontal, prefrontal, or anterior cingulate cortex), and the periaqueductal grey matter, all implicated in pain processing [7]. For instance, by influencing the lateral thalamus via cortico-thalamic projections, EMCS would initiate a cascade of synaptic events in structures receiving afferents from this nucleus. In particular, activation of the anterior cingulate cortex and periaqueductal gray is relevant, because these structures contain a high density of opioid receptors and pertain to the cortical-subcortical network activated during opioid analgesia in humans. Indeed, the activation of the endogenous opioid system was shown to take place during chronic EMCS sessions [8]. Experimental data show that μ-opioid receptors increase the release of dopamine in the ventral tegmental area by modulating GABAergic transmission [9–12]. This finding is in line with imaging studies showing that dopamine is released after a single session of rTMS over M1 [13, 14] and that chronic pain patients have a defective GABA-a-dependent intracortical inhibition that can be restored by rTMS delivered to M1 in correlation with its analgesic effects [15].

It is known that rTMS mainly activates axons rather than cell bodies of cortical neurons [16]. High-frequency rTMS (≥5 Hz) is thought to potentiate, while low-frequency rTMS (≤1 Hz) is thought to depress synaptic transmission in neural pathways. However, the resulting clinical effect may be more complicated to design, since inhibition of inhibitory systems may lead to a net excitatory effect and vice-versa. Other parameters of stimulation can modulate the effects of rTMS. For instance, coil orientation can preferentially produce direct or indirect waves (D- or I-waves), depending on the direction of the electric current induced into the brain [17]. This has been shown to influence the analgesic efficacy of rTMS in neuropathic pain [18].

3. The Use of rTMS as a Therapeutic Tool in Pain Syndromes

Therapeutic efficacy of EMCS in neuropathic pain patients not responsive to medical treatment was first reported in the early nineties [19]. It opened new perspectives for neuromodulation techniques to treat refractory chronic pain. A few years later, M1 TMS testing was performed before surgery in two patients and the results were found to predict the long-term analgesic response to EMCS [4]. In the years that followed, other studies confirmed the value of the response to preoperative rTMS tests in predicting surgical EMCS outcome [20, 21].

The analgesic effects provided by a single session of high-frequency rTMS delivered to M1 were found to be enhanced and prolonged by repeated sessions on consecutive days [22]. More recently, impressive rTMS effects were observed on pain syndromes other than neuropathic ones [6]. These findings suggested that rTMS could be employed as a therapeutic tool *per se*, to control refractory pain syndromes in the clinical setting.

We will briefly review the main parameters known to influence the analgesic effect of rTMS for neuropathic pain in the light of the sham-controlled, double-blind studies published to date. Then, we will report available data on non-neuropathic pain syndromes that contain some interesting reports on the use of tDCS.

3.1. Neuropathic Pain

In most rTMS studies performed in chronic pain, the intensity of stimulation of M1 was maintained below the motor threshold measured in one hand muscle at rest (rest motor threshold, RMT). The great majority of clinical studies used subthreshold stimulation, usually performed at 80 or 90% of the RMT.

3.1.1. Targeting

According to EMCS results, M1 has been the preferred target of stimulation in most rTMS studies, and to date, M1 has been the target in all studies showing a positive

effect of rTMS in neuropathic pain. One study compared the efficacy of various cortical sites of stimulation (M1, premotor areas, and postcentral gyrus) to relieve neuropathic pain [23]. Analgesic effects were observed only when rTMS was delivered to M1, with 50% of patients recording a pain level reduction greater than 30% and lasting up to three hours after the end of the stimulation.

Objective responses to cortical stimulation can be provided only by stimulation of M1 or the occipital cortex (production of motor evoked potentials or phosphenes, respectively). For other cortical targets, the localization is based on standardized anatomical landmarks, according to motor hotspot location. Image-guided neuronavigation systems, dedicated to rTMS practice, recently become available. They integrate individual magnetic resonance imaging data. An infrared camera detects reflectors placed on both the coil and the head of the patient, then the location and orientation of the TMS coil can be visualized, relative to the head of the patient, in real-time and on the three-dimensional reconstruction of the brain on a computer screen. The possibility to precisely target any cortical area opens a new exciting era in NICS studies. It remains to be determined, however, whether such precise targeting will have any significant clinical impact on the therapeutic efficacy of rTMS.

It has been shown that the analgesic effects of EMCS are homotopic: the stimulation must be performed on the motor cortical area corresponding to the painful region of the body. Therefore, neuroradiological and neurophysiological techniques are performed during surgery to ensure an accurate placement of the epidural leads on the desired M1 region. However, for rTMS, targeting the cortical area immediately adjacent to the corresponding painful region (e.g., targeting the hand cortical area for facial pain) might provide a stronger analgesic effect [24, 25]. This phenomenon could be related to the geometry of the electrical field induced by a TMS coil, which differs from that induced by epidurally-implanted electrodes.

3.1.2. Frequency of Stimulation

The frequencies of stimulation usually applied in pain treatment by EMCS range from 25 to 60 Hz. Regarding rTMS, lower frequencies were tested, ranging from 0.2 to 20 Hz. Stimulation frequency is thought to play a major role on the analgesic efficacy of M1 stimulation. To date, all the studies using 10 Hz stimulation showed significant effects of M1 rTMS on neuropathic pain [5, 15, 20, 25, 26]. In the range of so-called high-frequency rTMS, 5 and 20 Hz procedures provided conflicting results, either positive [22, 23, 27] or negative [28, 29]. In contrast, the results of low-frequency rTMS ($\leq$1 Hz) were consistently negative in relation to pain score reduction [5, 15, 21, 27, 29]. There is growing cumulative data to support a stronger analgesic efficacy of 10 or 20 Hz stimulation when compared to lower frequencies. This may be related to the existence of 10 or 20 Hz cortical oscillatory activity, which is abolished in the presence of chronic or provoked pain [30] and could be restored by cortical stimulation.

3.1.3. Duration of Effect

An important issue regarding the use of rTMS to treat neuropathic pain is the ability of rTMS sessions to produce durable changes in pain processing and clinical improvement that can last beyond the time of the stimulation. A single rTMS session was found to relieve pain for less than a week, with a peak of analgesic efficacy between two and four days after the stimulation [5].

The cumulative effect of repeated daily rTMS sessions was evaluated by Khedr et al. [22]. They studied 48 patients suffering from central or trigeminal pain and found that analgesic effects could last up to 14 days after five daily sessions of 20 Hz rTMS delivered over M1. Other studies of repeated rTMS sessions applied to patients with neuropathic pain condition produced no positive results [28, 29], but their methodology differed from that of Khedr et al. regarding the frequency of stimulation, the clinical profile of the patients, or the type of coil employed [22].

3.1.4. Type of Coil and Direction of Induced Current

Type of coil is an important factor in rTMS studies because it determines the focus and depth of the induced electric field. A "figure-of-eight" coil provides a more focal and superficial stimulation than a "circular" or a "double cone" coil and is therefore more suitable for therapeutic applications of rTMS. Current generated by the coil flows perpendicular to the scalp, and creates an electric field with a preferential direction into the brain. Current flowing in the posterior-anterior (PA) direction generates descending indirect volleys in the corticospinal tracts, whereas direct volleys are produced by latero-medial (LM) stimulation [17]. There is some evidence that the current direction may play an important role in the analgesic and long-term effects of rTMS: most of the positive studies in neuropathic pain used PA stimulations. Moreover, analgesic efficacy of rTMS delivered over M1 with a PA-oriented coil can be lost if the coil has an LM orientation, even at the same site of stimulation [18].

3.1.5. Total Number of Pulses

The total number of pulses necessary to obtain a significant analgesic effect after an rTMS session has never been specifically studied. It has been proposed [31] that at least 1200 pulses would be required, but this assertion remains a matter of debate [32]. Among studies using 1000 or more pulses, there is only one negative report to date [21]. However, positive results have been found in studies using 500 [23, 27] and even 200 pulses [33] per session.

Interestingly, in a study performed in healthy volunteers, Jung et al. [34] compared changes in cortical excitability parameters after 1000 or 300 pulses of 10 Hz stimulation over M1. They found that 1000 pulses, but not 300, were able to modify

cortical excitability parameters in both hemispheres up to 90 minutes after stimulation. Despite the obvious differences between healthy volunteers and neuropathic pain patients, this study suggests that the number of pulses can play an important role in the magnitude of rTMS effects.

3.1.6. End-points

Most rTMS studies on neuropathic pain have assessed pain level changes scored on a visual analogue scale as the primary end-point. A few studies used multi-dimensional scales, including cognitive-motivational and emotional-affective components of the painful experience [23, 27, 28]. The respective effects of rTMS on the various sensory-discriminative aspects of pain, such as the presence of pain paroxysms, continuous pain, allodynia, hyperalgesia and hyperpathia, have also rarely been characterized. One of the few reports assessing such features found that mechanical allodynia was reduced in 44% of patients after low-frequency rTMS [33].

Other ways of assessing rTMS effects on pain include cortical excitability measurements and sensory threshold quantification. One study assessed the modifications of cortical excitability parameters after rTMS in neuropathic pain patients [15]. In this study, intra-cortical inhibition (ICI), a parameter evaluating GABAergic transmission, was reduced in the cerebral hemisphere contralateral to the painful area. After subthreshold rTMS performed at 10 Hz over M1, responders presented an increase in ICI that correlated to pain relief. The analgesic response to M1 rTMS was also associated with an improved thermal sensory perception in the painful zone following cortical stimulation [35]. A similar correlation was observed between the therapeutic efficacy of EMCS on pain in the long term and a preserved thermal sensory perception in the painful zone or an improved perception when the stimulator was switched on [36].

3.2. Use of rTMS in Non-neuropathic Pain Conditions

A few studies assessed the analgesic effects of rTMS in non-neuropathic pan conditions. Fregni et al. [37] first showed the analgesic effects of 1Hz rTMS over the right S2 in a series of patients with visceral pain due to pancreatitis. They found a mean reduction of 62% on the Visual Analogue Scale (VAS) right after the end of the stimulation, which was a very impressive result in this clinical condition. Passard et al. [6] assessed the effect of 10 daily consecutive sessions of 10 Hz rTMS over M1 in patients with fibromyalgia. They found a persisting analgesic effect and a sustained improvement in quality of life up to 30 days after the period of stimulation. Johnson et al. [38] evaluated the effect of a single session of 20 Hz rTMS over M1 in low back pain patients. They found a mean VAS reduction of 28%, correlated with a decrease in cold perception and thermal evoked pain in the contralateral hand.

This finding is in accordance with data obtained in healthy volunteers [39] but it is the inverse of what was found in neuropathic pain patients, who usually present an improvement in thermal discrimination when they do respond to EMCS [36] and rTMS [35]. Finally, Borckardt et al. [40] showed in 20 patients undergoing gastric bypass surgery that 10 Hz rTMS over the left prefrontal cortex significantly reduced morphine consumption by 40% to control postoperative pain. The main effect occurred during the first 24 hours after the intervention, but was still significant 48 hours later. This study suggests the utility of rTMS as an opioid-sparing tool in the postoperative period to treat primary acute nociceptive pain.

3.3. Summary

On the whole, the sham-controlled rTMS studies in chronic pain showed that:

1) A single session of rTMS over M1 at a high-frequency range (usually 10 or 20 Hz) with more than 1000 pulses is able to reduce pain level (usually scored on VAS).
2) Pain score reduction is significant in about 40–55% of patients, with a mean reduction of about 30% (although greater pain score reductions have been reported). The decrease in VAS score is usually below 10% following sham rTMS.
3) The analgesic effect of a single session lasts less than a week, being maximal two to four days after the stimulation [5, 22, 32, 40].
4) Cumulative effects can be produced by consecutive daily sessions of rTMS. Long-term effects may be observed up to 15 days after the last day of stimulation [22] and may differentially affect the various aspects of pain [6].

4. Conclusions and Perspectives

NICS techniques are promising tools in the arsenal against refractory chronic pain. These techniques could be used to select patients for EMCS therapy with implanted electrodes and also to treat some pain syndromes, in particular non-neuropathic ones, taking into account the long-lasting effects of consecutive daily rTMS sessions. The best parameters of stimulation, including the definition of the optimal stimulation site, remain to be clearly determined in the various conditions of cortical stimulation therapy for pain. In addition, it is not known how the various aspects of pain, i.e. sensory-discriminatory, cognitive-motivational and emotional-affective components can be modulated by cortical stimulation. In the next future, new perspectives to treat pain patients by NICS will be made possible by the development of novel paradigms, techniques (including tDCS), or priming strategies (such as pharmacologic modulation combined with NICS).

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