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REVIEW

New updates on transcranial magnetic stimulation in chronic pain

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Purpose of review
Chronic pain is the most prevalent symptomatic disease worldwide. Nonpharmacological interventions, such as noninvasive neuromodulation (NIN), have gained scientific evidence to support their use as an add-on strategy to pharmacological pain management. The most studied NIN technique is repetitive transcranial magnetic stimulation (rTMS). This review aims to identify the current indications for rTMS in the treatment of chronic pain and its new perspectives.

Recent findings
High-frequency rTMS delivered to the primary motor cortex (M1) is currently a treatment strategy with the most literature support for decreased pain intensity and alleviation of associated symptoms in peripheral neuropathic pain, fibromyalgia and migraine. It has been shown that stimulation sessions are well tolerated and tolerable, and the effects of daily stimulation sessions can be prolonged by spaced maintenance stimulation sessions. Despite its efficacy, some individuals will not respond to rTMS targeted to M1. Lines of research are currently being developed to improve rTMS efficacy either by exploring new therapeutic targets, using novel stimulation parameters or more comprehensively profiling patients who are likely to respond to this treatment modality.

Summary
Noninvasive brain stimulation for chronic TMS pain is a well tolerated and reasonable add-on treatment approach for pain syndromes such as neuropathic pain, migraine and fibromyalgia. Strategies to improve its efficacy are an active field of research.

Keywords
chronic pain, migraine, neuropathic pain, noninvasive neuromodulation, transcranial magnetic stimulation

INTRODUCTION

Chronic pain refers to pain lasting longer than 3 months, being present for most of the days [1]. It affects around 18% of the general population [2]. Management of chronic pain is a major health and societal challenge. It is associated with very high costs related to absenteeism, excessive health related expenses and the highest number of years lived with disability among all other healthcare conditions. Beyond the obvious suffering related to its sensory symptoms, chronic pain is comorbid with negative mood, behavioural and cognitive symptoms [3–6]. Chronic pains can be classified into three mechanistic groups: nociceptive pain (persistent inflammation leads to plastic peripheral and central changes leading to pain, e.g. osteoarthritis, cancer); neuropathic pain (pain associated with lesions or diseases to the somatosensory system, e.g. diabetic neuropathy, stroke); and nociplastic pain (pain in the absence of detectable, major somatic or nervous tissue injuries, but in which the pain system is abnormally activated, e.g. fibromyalgia, primary headaches [7,8]). These mechanisms frequently occur concomitantly, giving rise to mixed pain syndromes [9].

Despite current advances in pain management, approximately 40% of patients with neuropathic pain [10], 30% of those with low-back pain [11]

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KEY POINTS

- Repetitive transcranial magnetic stimulation can induce analgesic effects and plastic changes outlasting the stimulation sessions,
- High-frequency repetitive transcranial magnetic stimulation delivered to the primary motor cortex has currently shown to decrease pain intensity and associated symptoms in peripheral neuropathic pain, fibromyalgia and migraine.
- New lines of research are being developed to try to improve rTMS effectiveness in clinical practice, such as the exploration of new targets, new stimulation patterns and a deeper understanding of responder profiles.

and 5% of chronic migraineurs remain symptomatic [11–13]. Treatment of chronic pain is traditionally centred around pharmacological approaches. However, recent studies have revealed that the actual efficacy of several compounds is much lower than originally thought, and in some instances, may even be contraindicated [14,15]. Not to mention that some prescriptions used for pain control have been shown to cause several personal and societal adverse events, such as the opioids crisis.

Nonpharmacological treatments have been used to relieve symptoms other than pain intensity, such as altered cognition, mood, sleep, fatigue and exaggerated catastrophizing in some pain syndromes including fibromyalgia [16]. Indeed, nonpharmacological treatments have gained traction in the management of chronic pain and other brain disorders such as major depression. It has been shown that several such strategies may modify and restore abnormal brain connectivity associated with pain-related symptoms [17▪▪]. One of these approaches is neuromodulation.

Neuromodulation includes several different techniques that influence the central nervous system activity, usually by electric stimulation, to restore abnormal neuronal patterns of connectivity as means to improve symptoms [18,19]. The use of implanted electrodes connected to pacemakers has been used for decades in the control of symptoms of Parkinson disease (e.g. deep brain stimulation) or in cases of neuropathic pain (e.g. spinal cord stimulation) [20]. In the last years, noninvasive neuromodulation (NIN) techniques entered the potential treatment armamentarium against chronic pain. NIN encompasses several techniques used to stimulate the central nervous system noninvasively. The most common one is transcranial magnetic stimulation (TMS). TMS is based on the principle of electromagnetic induction: a very localized and precise electrical current is induced in the brain by a fast-oscillating magnetic field produced by a coil placed on the scalp. By choosing the exact cortical target wherein the coil will be placed, TMS can influence brain activity of cortical area underneath the coil, and its interconnected network constituents. During a TMS session, the patient sits comfortably in an armchair and the TMS coil is placed on their scalp. The electrical current flows through the coil. It creates an electromagnetic field of about 1.9 tesla, which then produces an induced electric current inside the brain parenchyma, at a certain distance from the coil (1.0–5.0 cm) [21]. Single-pulse TMS has been used in neurophysiology for years to obtain motor evoked responses by stimulating the primary motor cortex and then probe the functional integrity of the corticospinal pathways. Different from single pulse TMS, it was later shown that repetitive pulses of TMS (i.e. rTMS) can induce long-term neuroplastic effects. rTMS was first employed to treat major depression and it has been FDA approved to treat pharmaco-resistant major depression for more than a decade [22]. In 1999, rTMS was initially shown to relieve pain when applied to the precentral gyrus of patients with refractory neuropathic pain [23]. Differently from single-pulse TMS, rTMS delivered to M1 can induce long-term effects and change pain perception in healthy volunteers [24] and chronic pain patients [25] that outlast the treatment session. Interestingly, the analgesic effects of M1 rTMS seem to be rather diffuse, rather than restricted to the body area related to its respective cortical representation within M1 [17▪▪,25,26].

In the last 15 years, rTMS has been tested as a treatment for fibromyalgia [26] and neuropathic pain [27]. It has been demonstrated that daily stimulation sessions of rTMS can induce pain intensity improvement and relief of several associated symptoms during the stimulation period. However, one important point when proposing the use of rTMS in clinical practice is to demonstrate that its effects can be maintained in time, so that maintenance stimulation sessions several days apart can sediment or maintain the beneficial effects of the initial series of sessions (induction sessions). In 2011, Mhalla *et al.* [25] demonstrated in fibromyalgia patients that maintenance sessions of rTMS performed initially weekly, but then fortnightly and monthly could maintain the effects of daily induction sessions. They also found that not only was pain intensity improved, but mood and catastrophizing were also impacted [25]. These clinical improvements were paralleled to restoration of abnormal neurophysiological measurements detected before treatment,

indicating that pain improvement after rTMS correlated with improvement of abnormally low inhibitory GABAergic capacity in the M1.

Since the early reports on the effects of M1 stimulation by Tsubokawa *et al.* [28], reiterated by recent randomized trials [29▪▪], chronic surgically implanted M1 stimulation has been shown to benefit some patients with neuropathic pain. It was only very recently that long-term treatment by rTMS has been shown to benefit patients with peripheral neuropathic pain. In the largest multicentre trial to date, Attal *et al.* [17▪▪] compared M1 with dorsolateral prefrontal cortex (DLPFC) and sham sessions. They found that 10 Hz daily stimulation sessions improved pain intensity in the primary motor cortex group only, and the effects could be maintained in time for 25 weeks by spaced sessions of stimulation. A recent guideline also indicated that M1 high-frequency rTMS could be useful in the preventive treatment of migraine [30▪]. These findings, when added to previous ones, granted the indication of M1 to treat peripheral neuropathic pain in recent treatment recommendations and societal guidelines [31–33].

So far, the most significant results were obtained following M1 stimulation. The second most studied cortical target in rTMS studies in chronic pain was the DLPFC. Despite its beneficial effects in major depression, and possibly in depressed patients presenting with comorbid pain, DLPFC rTMS had a very weak effect in chronic pain. It was similar to placebo in peripheral and central neuropathic pain [17▪▪], and in migraine patients, it performed worse than sham stimulation, which suggests its use could even affect the placebo response [17▪▪,34].

Although the exact mechanisms of action of M1 rTMS in pain relief remain unclear, some insights have been gained from previous basic research. In healthy volunteers, M1 rTMS increased thermal pain thresholds. These effects were blocked by naloxone and ketamine, which suggests they depend on the availability of mu-opioid receptors and on glutamate's effects on N-methyl-d-aspartate receptor [35–37]. These findings were later replicated in animal experimental pain models [38] and in pain patients who had undergone surgically implanted motor cortex stimulation for pain control [29▪▪]. Interestingly, improvement in pain-associated symptoms such as mood, catastrophizing and fatigue present in fibromyalgia occurred concurrent to a significant change in cortical excitability, which was restored towards baseline as the treatment progressed [25,27]. Cortical excitability refers to a large number of neurophysiology responses based on evoked potentials triggered by pulses of TMS. Some cortical excitability responses include motor-evoked potentials obtained after M1 stimulation, among which is short interval intracortical inhibition (SICI). SICI is a motor response to two pulses of TMS delivered to the primary motor cortex in an inter-pulse interval of a few milliseconds [17▪▪,39]. It partially depends on GABAergic interneuronal activity in layer III of the precentral gyrus [40,41] and has been found to be defective in both neuropathic pain and fibromyalgia [25,27]. In addition, SICI deficits correlated with some clinical features of fibromyalgia such as mood and catastrophizing symptoms. Upon M1 rTMS treatment, fibromyalgia and neuropathic pain patients showed SICI normalization and were highly correlated with symptom improvement [25]. RTMS also changes oscillatory frequency in local beta band oscillations [42], increases the connectivity between M1 and related areas, increases global cortical connectivity measures [43,44] and provides long-term modifications in motor output [45] by induction neuroplasticity outlasting the stimulation period [43].

In summary, high frequency (10–20 Hz) rTMS is progressively accepted as an option to treat some pain syndromes such as fibromyalgia and peripheral neuropathic pain when induction sessions of 5–10 daily sessions followed by maintenance sessions spaced in time. In most studies, rTMS was used as an 'add-on' pharmacological treatment [32]. Central neuropathic pain (e.g. pain associated with lesions affecting the central nervous system) is globally more refractory to treatment [15] and the effects of rTMS have been less impressive.

Other pain conditions have been studied with a potential benefit, yet uncertain benefit of M1 rTMS, such as musculoskeletal pain and complex regional pain syndrome (CRPS) of type I [31,46]. rTMS paradigms targeting more than one brain area has recently been used to treat episodic migraine [47]. This protocol reduced the number and intensity of migraine attacks compared with placebo treatment. In a recent systematic review and meta-analysis about NIN for acute and preventive migraine treatment, HF-rTMS over M1 was effective, with small to medium side effects [30▪].

SAFETY

The most common adverse effects of rTMS are headache or migraine, pain at the site of stimulation, increase in bodily pain or paresthesia, fatigue, sleep disorders, nausea, dizziness, anxiety/irritability/cognitive complaints and muscle sensations during stimulation [17▪▪]. However, in a recent trial, these adverse events were not different between M1-rTMS (53% of participants had adverse event) and sham-rTMS (47.9%). Furthermore, no serious treatment-related adverse effects were observed, confirming the safety

and tolerability of this technique [17▪▪]. Serious adverse events such as seizures are rare. The latest guideline on safety and recommendations for TMS use in healthy individuals and patient populations shows that the risk of rTMS in inducing a seizure is definitely low even in populations of patients taking drugs that act on of the central nervous system, at least with the use of stimulation parameters and focal coils for which large data sets are available [48]. One seizure was reported in pain studies in patients to date, and in the protocol, suprathreshold stimulations were used over M1, which is an approach no longer applied. Instead, only stimulation intensities below motor thresholds are currently recommended. The patient in question had a single seizure and even after a long follow-up never developed epilepsy, having several normal EEGs on follow-up and never presenting seizures [46]. Current safety screens exist to ascertain rTMS studies are performed according to best research and clinical safety evidence [48].

rTMS of the M1 over a 3-month period did not modify cognitive functions in chronic pain patients [49]. Recently, repetitive sessions of deep-TMS (see below) targeted to the posterior superior insula (PSI) or the anterior cingulate cortex (ACC) did not cause any cognitive decline, even in patients with CNS structural lesions such as stroke and neuropathic pain [49,50].

NEW PERSPECTIVES

Despite these advances, a significant proportion of patients (up to 50%) may remain symptomatic despite M1 stimulation delivered by invasive electrodes [29▪▪] or by rTMS [17▪▪]. Alternatively, new NIN strategies have been developed to improve efficacy.

(1) New targets: In recent years, targets beyond the somatosensory and prefrontal areas were tested to treat chronic pain. With the aid of special electromagnetic coils to deliver deeper pulses of stimulation, deep cortical areas such as the leg area representation of M1 [51], the posterior insula and anterior cingulate cortices (ACCs) were stimulated in double-blind controlled trials. The insula is deeply involved in the central integration of the sensory-discriminative aspect of pain processing. Neuroimaging studies have shown that insula is highly engaged in acute and chronic pain functional neuroimaging studies [52]. Deep brain stimulation of the posterior insula led to antinociceptive effects dependent on endogenous opioids and cannabinoids in experimental models of peripheral neuropathic pain in rats [53,54]. The first noninvasive method to stimulate the human posterior insula noninvasively was based on neuronavigation and proposed the use of a special cooled TMS coil designed for deep TMS [55]. Posterior insular direct stimulation in patients [56], and noninvasive TMS in healthy volunteers [57] and in central neuropathic pain patients [58] increased thermal pain thresholds. Despite having no significant effects in central neuropathic pain, rTMS of the posterior insula led to significant pain relief in a pilot cross over study in patients with neuropathic pain of peripheral origin whose pain was refractory to usual treatment [59▪].

(2) Patterned delivery of TMS: The theta burst stimulation (TBS) is a modality of patterned repeated TMS, which makes it possible to induce long-lasting effects using a lower stimulation intensity and a shorter time of stimulation compared to standard TMS protocols [60]. The terminology 'theta burst' relates to envelopes of three to five pulses delivered at 50 Hz (gamma range bursts), repeated five times per second (theta frequency), and it can be delivered in continuous (cTBS) or intermittent (iTBS) modes. This stimulation can very quickly produce an LTP-like (long-term potentiation) or LTD-like (long-term depression) effect in experimental models. Coupling of low (theta) with high (gamma) frequencies has been found in several brain networks such as those implicated in memory consolidation in the hippocampus, and it is believed to be a strategy the brain employs to integrate long-range information traveling in low-frequencies to local high-frequency information processing [61,62]. Irrespective of its mechanisms of action, TBS protocols are significantly shorter than traditional rTMS one, lasting less than 3 min in some instances. There was much enthusiasm, when TBS shown to be as effective as traditional rTMS to treat major depression, received FDA approval for this indication. Shorter stimulation time has a major impact in patient compliance to treatment and to costs.
Studies with healthy volunteers showed that application of a TBS protocol was an effective approach in establishing long-term M1 neuroplasticity [63], as it increased heat pain thresholds after rTMS and TBS on left DLPFC [64], and prolonged cTBS had stronger analgesic effects than the classic high-frequency protocol [65]. Both protocols had similar responses demonstrating the clinical potential of TBS in a short period of stimulation compared with conventional rTMS sessions lasting 20–30 min. However, a recent study reported that iTBS did not

outperform traditional 20-Hz rTMS for neuropathic pain [66].

There is not yet, however, an effective method to identify which patients would respond to M1 stimulation, and which patients would benefit from treatments targeted at other brain areas. It has been suggested that certain causes of neuropathic pain would preferentially respond to implanted M1 stimulation such as complex regional pain syndrome, phantom limb pain and facial pain, while benefits in central neuropathic pain syndromes would be less clear [29▪▪]. It was reported that neither cause of peripheral neuropathic pain nor the pain body region targeted impacted treatment response, even when all treatment sessions were directed to the hand representation of M1 [17▪▪]. Recently, Cunha *et al.* [67] reported that PSI rTMS in peripheral neuropathic pain depended on the pain phenotype, rather than on the subregion targeted by neuro-navigation rTMS. Using a symptom-based classification derived from the neuropathic pain symptom inventory [68▪], they reported that patients with evoked pain were less likely to respond to treatment than those with other neuropathic pain clusters such as deep pain-predominant pain.

CONCLUSION

Noninvasive brain stimulation for chronic pain by TMS is gaining guidelines and treatment recommendations. Like several neuromodulation techniques used in neurology and psychiatry, its use is slowly evolving from frequently overinflated effects derived from small sample pilot studies to more realistic, real-life information derived from larger multicentre trials. High-frequency M1 rTMS is currently the treatment strategy that shows the most promising results, with a good adverse event profile and potential to improve the overall efficacy of multimodal approaches to chronic pain syndromes such as fibromyalgia, peripheral neuropathic pain and some types of migraine. Efforts to delineate the exact responder profile to rTMS and strategies to improve its efficacy are the current challenges ahead, along with a more accurate estimation of cost-effectiveness of these approaches in clinical practice.

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Conflicts of interest

There are no conflicts of interest.

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This study described the profile of potential responders to pharmacological treatment for peripheral neuropathic pain using a symptom-based classification derived from the neuropathic pain symptom inventory.