EXPERT REVIEWS

Use of repetitive transcranial magnetic stimulation in pain relief

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Repetitive transcranial magnetic stimulation (rTMS) of the cerebral cortex is a noninvasive strategy that could have the potential to relieve severe chronic pain, at least partially and transiently. The most studied target of stimulation is the precentral (motor) cortex, but other targets, such as the dorsolateral prefrontal cortex or the parietal cortex, could be of interest. Analgesic effects have been produced by rTMS in patients with neuropathic pain, fibromyalgia or visceral pain. Therapeutic applications of rTMS in pain syndromes are limited by the short duration of the induced effects, but prolonged pain relief can be obtained by performing rTMS sessions every day for several weeks. In patients who respond to rTMS but relapse, surgical implantation of epidural cortical electrodes and a pulse generator can be proposed to make clinical effects more permanent. The rate of improvement produced by rTMS may be predictive for the outcome of the implanted procedure. The place of rTMS as a therapeutic tool in the management of chronic pain remains to be determined.

KEYWORDS: chronic pain • epidural cortical stimulation • fibromyalgia • motor cortex • neuromodulation • neuropathic pain • prefrontal cortex • repetitive transcranial magnetic stimulation • transcranial direct current stimulation • visceral pain

Chronic motor cortex stimulation (MCS) with surgically implanted epidural electrodes was first performed in the early 1990s and was found to produce significant analgesic effects in patients suffering from chronic, drug-resistant, central pain [1]. Since this first report, numerous studies confirmed the beneficial effects of epidural MCS in the treatment of chronic neuropathic pain of either peripheral or central origin (reviewed in [2]). In the late 1990s, the technique of repetitive transcranial magnetic stimulation (rTMS) was introduced in this field of research [3]. The basic principle of TMS is as follows: a magnetic pulse is delivered by a stimulating coil applied on the scalp, and then the magnetic field is able to pass through the skull bone without being affected and to induce an electrical field into the brain that is sufficient to activate cortical neuron fibers. The application of repetitive trains of TMS can produce sustained changes in cortical excitability and regional brain activities.

At present, approximately 20 studies (case reports and open or controlled trials) have assessed the efficacy of rTMS in more than 300 patients with drug-resistant chronic pain (post-stroke pain, complex regional pain syndrome, visceral pain, fibromyalgia, trigeminal neuralgia, phantom limb pain or pain related to lesion of the spinal cord, brachial plexus or nerve trunks). This article will review the current knowledge about the use of rTMS for the treatment of chronic pain. First, the MEDLINE database was searched for relevant papers from 1995 to 2007 using the terms 'transcranial' AND 'magnetic' AND 'stimulation' AND 'pain'. This approach identified 191 references. Reviews and editorials were excluded. Only studies of patients with chronic pain were considered and distinguished from studies of healthy volunteers with experimental pain. All study designs were included even if the importance given to open-label studies has to be toned down as to inherent bias of such type of studies in the field of pain. In total, 23 studies were retained for analysis (TABLE 1).

Frequency of stimulation

First, in 1995, Migita *et al.* applied repeated TMS pulses at 0.2 Hz in two patients with central pain, using a nonfocal, circular coil that was

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Table 1. Effects of transcranial cortical stimulation in patients with chronic pain.

Study	Pain origin (n)	Target of stimulation	Frequency of stimulation	Intensity of stimulation	Number and duration of trains	Pain relief	Comparison with placebo condition	Responders to active rTMS and effect duration	Ref.
Primary motor cortex stimulation, rTMS and figure-of-eight coil									
Lefaucheur *et al.* (2001)	Thalamic (6) or brainstem (6) stroke, brachial plexus lesion (6)	M1	80% RMT	10 Hz/0.5 Hz	10 Hz/0.5 Hz rTMS: 20 trains of 5 s/1 train of 20 min (1000/600 pulses)	10 Hz/0.5 Hz/sham rTMS: 20%/4%/7%	p = 0.001 vs sham coil (10 Hz-rTMS)	7 r (39%), duration ND	[6]
Lefaucheur *et al.* (2001)	Thalamic stroke (7), trigeminal nerve lesion (7)	M1	80% RMT	10 Hz	20 trains of 5 s (1000 pulses)	10 Hz rTMS: 31% (sham: 11% pain increase)	p = 0.01 vs sham coil	8 r (57%), ~1 week	[23]
Lefaucheur *et al.* (2004)	Thalamic (12) or brainstem (12) stroke, trigeminal nerve (12), brachial plexus (12) or spinal cord (12) lesion	M1	80% RMT	10 Hz	20 trains of 5 s (1000 pulses)	10 Hz rTMS: 23% (sham: 8%)	p = 0.0002 vs sham coil	22 r (37%), duration ND	[14]
Lefaucheur *et al.* (2004)	Brachial plexus lesion (1)	M1	80% RMT	10 Hz	20 trains of 5 s (1000 pulses), 16 sessions for 16 months	10 Hz rTMS: 40% (sham: 15%)	p < 0.05 vs sham coil	~1 week	[26]
Pleger *et al.* (2004)	Complex regional pain syndrome (10)	M1	110% RMT	10 Hz	10 trains of 1.2 s (120 pulses)	10 Hz rTMS: 21% (sham: pain increase)	p = 0.02 vs angled coil	7 r (70%), >90 min	[45]
Khedr *et al.* (2005)	Stroke (24), trigeminal nerve lesion (24)	M1	80% RMT	20 Hz	10 trains of 10 s (2000 pulses), 5 sessions (1 week)	20 Hz rTMS: 45% (sham: 5%)	p < 0.001 vs angled coil	22 r (79%), ≥2 weeks after the last session	[24]
André-Obadia *et al.* (2006)	Thalamic (8) or brainstem (2) stroke, trigeminal nerve (1), brachial plexus (1), nerve trunk (1), or spinal cord (1) lesion	M1	90% RMT	20 Hz/1 Hz	20 Hz/1 Hz rTMS: 20 trains of 4 s/1 train of 26 min (1600 pulses)	20 Hz/1 Hz/sham rTMS: 11%/2% increase/8%	p > 0.05 vs angled coil (20 Hz rTMS)	5 r (36%)/1 r (7%)/4 r (29%), ~1 week	[7]
Irlbacher *et al.* (2006)	Thalamic (3) or brainstem (7) stroke, spinal cord lesion (3), phantom limb pain (14)	M1	95% RMT	5 Hz/1 Hz	Unknown (500 pulses), 5 sessions (1 week)	5 Hz/1 Hz/sham rTMS: 5%/6%/10%	p = 0.06 (5 Hz rTMS)/0.08 (1 Hz rTMS) vs sham coil	2 r (7%) whatever the type of rTMS, duration ND	[9]

DLPFC: Dorsolateral prefrontal cortex; M1: Primary motor cortex; ND: Not determined; PMC: Premotor cortex; PPC: Posterior parietal cortex; r: Responders; RMT: Resting motor threshold; rTMS: Repetitive transcranial magnetic stimulation; S1: Primary sensory cortex; S2: Secondary sensory cortex; SMA: Supplementary motor area; SO: Stimulator output; tDCS: Transcranial direct current stimulation.

Table 1. Effects of transcranial cortical stimulation in patients with chronic pain (cont.).

Study	Pain origin (n)	Target of stimulation	Frequency of stimulation	Intensity of stimulation	Number and duration of trains	Pain relief	Comparison with placebo condition	Responders to active rTMS and effect duration	Ref.
Primary motor cortex stimulation, rTMS and figure-of-eight coil (cont.)									
Johnson *et al.* (2006)	Back pain (17)	M1	95% RMT	20 Hz	12.5 trains of 2 s (500 pulses)	20 Hz rTMS: 28% (sham: 1%)	$p < 0.001$ vs angled coil		[37]
Lefaucheur *et al.* (2006)	Thalamic (5) or brainstem (4) stroke, trigeminal nerve (14), brachial plexus (4), nerve trunk (4), or spinal cord (5) lesion	M1	90% RMT	10 Hz	20 trains of 10 s (2000 pulses)	10 Hz rTMS (painful zone area/adjacent zone, no sham): 15%/32%		7 r (19%)/20 r (56%), ~1 week	[15]
Lefaucheur *et al.* (2006)	Thalamic (8) or brainstem (2) stroke, brachial plexus (4) nerve trunk (4), or spinal cord (4) lesion	M1	90% RMT	10 Hz/1 Hz	10 Hz/1 Hz rTMS: 20 trains of 6 s/1 train of 20 min (1200 pulses)	10 Hz/1 Hz/sham rTMS: 32%/11%/10%, $p = 0.002$ vs sham coil (10 Hz rTMS)		12 r (55%)/3 r (14%)/3 r (14%), duration ND	[27]
Defrin *et al.* (2007)	Spinal cord lesion (11)	M1	115% RMT	5 Hz	10 trains of 10 s (500 pulses), 10 sessions (2 weeks)	5 Hz rTMS: 27% (sham: 37%) at the end of the treatment	$p > 0.05$ vs sham coil	5 Hz rTMS: 30% (sham: 10%) in the follow-up period (2–6 weeks after the last session)	[36]
Passard *et al.* (2007)	Fibromyalgia (30)	M1	80% RMT	10 Hz	25 trains of 8 s (2000 pulses), 10 sessions (2 weeks)	10 Hz rTMS: 30% (sham: 3%)	$p < 0.01$ vs sham coil	≥2 weeks after the last session	[25]
Lefaucheur *et al.* (2008)	Thalamic stroke (13), trigeminal nerve (13), brachial plexus (10) or spinal cord (10) lesion	M1	90% RMT	10 Hz/1 Hz	10 Hz/1 Hz rTMS: 20 trains of 6 s/1 train of 20 min (1200 pulses)	10 Hz/1 Hz/sham rTMS: 24%/5%/10%	$p = 0.002$ vs sham coil (10 Hz rTMS)	20 r (43%)/4 r (9%)/9 r (20%), duration ND	[38]
Lefaucheur *et al.* (unpublished data)	Thalamic or cortical stroke (10), brachial plexus (10), nerve trunk (6), or spinal cord (6) lesion	M1	90% RMT	10 Hz	20 trains of 10 s (2000 pulses)	10 Hz rTMS: 26% (sham: 10%)	$p = 0.009$ vs sham coil	11 r (34%), duration ND	

DLPFC: Dorsolateral prefrontal cortex; M1: Primary motor cortex; ND: Not determined; PMC: Premotor cortex; PPC: Posterior parietal cortex; r: Responders; RMT: Resting motor threshold; rTMS: Repetitive transcranial magnetic stimulation; S1: Primary sensory cortex; S2: Secondary sensory cortex; SMA: Supplementary motor area; SO: Stimulator output; tDCS: Transcranial direct current stimulation.

Table 1. Effects of transcranial cortical stimulation in patients with chronic pain (cont.).

Study	Pain origin (n)	Target of stimulation	Frequency of stimulation	Intensity of stimulation	Number and duration of trains	Pain relief	Comparison with placebo condition	Responders to active rTMS and effect duration	Ref.
Primary motor cortex stimulation, rTMS and various types of coil									
Migita *et al.* (1995)	Cerebral palsy + thalamotomy (1), putamen hemorrhage (1)	M1	80% SO	0.2 Hz (circular coil)	1 train of 16.7 min (200 pulses)	0.2 Hz rTMS: 30% and 0% (no sham)		1 r (50%), 1 h	[4]
Canavero *et al.* (2002)	Stroke (5), spinal cord lesion (4)	M1	100% SO	0.2 Hz (figure-of-eight, double-cone coils)	1 train of 16.7 min (200 pulses)	0.2 Hz rTMS: unknown, not done vs angled coil		5 r (56%), 16 h	[5]
Rollnik *et al.* (2002)	Spinal cord lesion (2), osteomyelitis (1), peripheral nerve lesion (6), CRPS (2), phantom limb (1)	M1	80% RMT	20 Hz (circular, double-cone coils)	20 trains of 2 s (800 pulses)	20 Hz rTMS: 4% (sham: 2%)	$p > 0.05$ vs angled coil	6 r (50%), 6 days	[13]
Various cortical targets, rTMS and figure of-8-coil									
Reid *et al.* (2001)	Teeth removal (1)	Left DLPFC	100% RMT	20 Hz	30 trains of 2 s (1200 pulses), 14 sessions (3 weeks)	20 Hz rTMS: 42% (no sham)		≥4 weeks	[16]
Töpper *et al.* (2003)	Root avulsion (2)	PPC	110% RMT	10 Hz /1 Hz	10 Hz/1 Hz rTMS: 20 trains of 2 s (400 pulses)/1 train of 12 min (720 pulses), 15 sessions (3 weeks)	10 Hz/1 Hz rTMS (no sham): 24–61%/ 48–88%		2–15 min	[20]
Fregni *et al.* (2005)	Pain due to chronic pancreatitis (5)	Left/right S2	90% RMT	20 Hz/1 Hz	Unknown (1600 pulses)	20 Hz rTMS-left S2/1 Hz rTMS-right S2: pain increase/62%	$p = 0.037$ vs sham coil (1 Hz-rTMS)	Duration ND	[21]
Hirayama *et al.* (2006), Saitoh *et al.* (2006)	Thalamic (7) or brainstem (5) stroke, trigeminal nerve (3), brachial plexus (2), or spinal cord (3) lesion	M1/S1/PMC/ SMA	90% RMT	5 Hz	10 trains of 10 s (500 pulses)	5 Hz rTMS, best cortical target (M1): 28%	$p < 0.01$ vs angled coil	10 r (50%), ~3 days	[22,43]
Sampson *et al.* (2006)	Fibromyalgia (4)	Right DLPFC	110% RMT	1 Hz	2 trains of 800 s (1600 pulses), 20 sessions (4 weeks)	1 Hz rTMS: 82% (no sham)		4 r (100%), 15–27 weeks	[17]

DLPFC: Dorsolateral prefrontal cortex; M1: Primary motor cortex; ND: Not determined; PMC: Premotor cortex; PPC: Posterior parietal cortex; r: Responders; RMT: Resting motor threshold; rTMS: Repetitive transcranial magnetic stimulation; S1: Primary sensory cortex; S2: Secondary sensory cortex; SMA: Supplementary motor area; SO: Stimulator output; tDCS: Transcranial direct current stimulation.

Table 1. Effects of transcranial cortical stimulation in patients with chronic pain (cont.).

Study	Pain origin (n)	Target of stimulation	Frequency of stimulation	Intensity of stimulation	Number and duration of trains	Pain relief	Comparison with placebo condition	Responders to active rTMS and effect duration	Ref.
Various cortical targets and tDCS									
Fregni *et al.* (2006)	Spinal cord lesion (17)	M1		2mA, anodal (11) or sham (6)	20 min, 5 sessions	Anodal M1 tDCS: 58%	p = 0.004 vs sham tDCS	7 r (64%), ≥2 weeks	[35]
Fregni *et al.* (2006)	Fibromyalgia (22)	M1/left DLPFC		2mA, anodal M1 (11), DLPFC (11), or sham M1 (11)	20 min, 5 sessions	Anodal M1 tDCS: 58%	p = 0.01 vs sham tDCS (DLPFC: no significant effect)	≥3 weeks	[51]

DLPFC: Dorsolateral prefrontal cortex; M1: Primary motor cortex; ND: Mot determined; PMC: Premotor cortex; PPC: Posterior parietal cortex; r: Responders; RMT: resting motor threshold; rTMS: Repetitive transcranial magnetic stimulation; S1: Primary sensory cortex; S2: Secondary sensory cortex; SMA: Supplementary motor area; SO: Stimulator output; tDCS: Transcranial direct current stimulation.

centered over the motor cortex, contralateral to the painful side [4]. The first patient experienced 30% pain relief for 1 h, while TMS was ineffective for the second patient. TMS effects paralleled the therapeutic outcome of subsequent chronic epidural MCS. Later, Canavero *et al.* also applied repeated TMS pulses at 0.2 Hz in a series of patients with chronic pain secondary to stroke or spinal cord lesion, using a figure-of-eight coil for arm area stimulation or a double-cone coil for leg area stimulation [5]. Of the nine patients enrolled in this study, one was relieved for allodynia, and four patients for both spontaneous pain and allodynia. Pain relief lasted 16 h in one case.

The frequency of stimulation applied in these two studies was very low (0.2 Hz) compared with the frequencies used in chronic epidural MCS (20–55 Hz) [2]. In a controlled trial, we demonstrated that motor cortex rTMS engendered pain relief when administered at 10 Hz, but not at 0.5 Hz [6]. Later, it was shown that rTMS provided more analgesia at 20 Hz than at 1 Hz [7]. A third study found that 10 Hz rTMS was more efficacious than 5 Hz rTMS, while 1 Hz rTMS did not produce significant effects [8]. Therefore, the use of too low a frequency of stimulation (1–5 Hz) may explain the lack of efficacy of motor cortex rTMS to induce significant analgesic effects in some studies [9]. Stimulus frequency governs synaptic changes that are induced by rTMS: in general, high-frequency stimulation (>5 Hz) is excitatory [10], while low-frequency stimulation (≤1 Hz) causes inhibition [11]. However, opposite effects can be observed depending on the nature of the rTMS targets and recruited circuits. The variability of cortical excitability between individuals may also explain differences in synaptic changes induced by rTMS.

Site of stimulation

The efficacy of epidural MCS was found to be homotopic [2]. This means that epidural electrodes have to be implanted over the motor cortical area corresponding to the painful zone [12]. The efficacy of rTMS also depends on a precise targeting, since nonfocal high-frequency rTMS (using circular or double-cone coil) failed to produce significant analgesia [13]. However, rTMS targeting differs from epidural MCS targeting. In a series of 60 patients with chronic neuropathic pain of various origins and locations, we found that facial pain improved better than hand pain when the hand motor area was stimulated [14]. In another study, rTMS was found to be more effective when the stimulation was adjacent to the cortical representation of the painful zone rather than within the painful zone itself [15]. Differences in current flow geometry or current densities may explain targeting differences between rTMS and epidural cortical stimulation.

A few studies assessed the value of cortical targets other than the primary motor cortex. There are reports of patients with neuropathic pain or fibromyalgia associated with depression in whom dorsolateral prefrontal cortex stimulation (at high frequency over the left hemisphere or low frequency over the right hemisphere), initially performed to treat depression, also produced analgesic effects [16,17]. A drastic reduction of the total morphine intake

required to control postoperative pain for the first 2 days after gastric bypass surgery was obtained in a series of patients who received left prefrontal rTMS [18]. Finally, rTMS applied over the right dorsolateral prefrontal cortex was shown to increase the tolerance of healthy volunteers to experimental cold-induced pain [19].

Parietal targets have also been assessed. Two patients with chronic pain secondary to root avulsion benefited from rTMS over the posterior parietal cortex, regardless of the frequency of stimulation [20]. Significant analgesic effects have been obtained with 20 Hz rTMS delivered over the secondary somatosensory cortex in patients with chronic visceral pain secondary to pancreatitis [21]. By contrast, negative results have been reported in chronic neuropathic pain of various origins following high-frequency rTMS centered over the primary somatosensory cortex or the premotor cortex [22].

Because chronic pain has a multifaceted aspect, cortical stimulation may provide analgesic effects by acting through various circuits and at different sites. Thus, there are a variety of potentially efficacious targets depending on pain causes and clinical presentation.

Delay & duration of action

Following a single session of motor cortex rTMS, we found that the maximal analgesic effect was delayed for 2–4 days and that pain level could remain significantly reduced for approximately 1 week [23]. This observation was later confirmed in single cases [13] and controlled series [7]. This time course is in keeping with what is observed for chronic epidural MCS: clinical changes are delayed by several days after switching the stimulator 'on' or 'off', or after modifying the parameters of stimulation. Expression of secondary messengers and time-consuming processes of synaptic plasticity in cortical circuitry may explain why the effects are delayed and occur beyond the time of stimulation.

Regarding the duration of action, analgesic effects resulting from single rTMS sessions are too short lived to be compatible with a durable control of chronic pain. By contrast, repeated rTMS sessions on consecutive days are able to produce cumulative effects lasting beyond the time of stimulation [24,25]. This can be of value in clinical practice to control intractable pain for a limited period; for example, to help rTMS responders in waiting for the surgical implantation of epidural electrodes [26]. It is not clear yet whether a technique of noninvasive cortical stimulation might induce long-lasting significant clinical effects sufficient to be applied for chronic treatment. Conversely, pain control can be surely maintained over time by means of chronic stimulation using epidural electrodes and an implanted pulse generator.

Mechanisms of action

The hypotheses made on the mechanisms of action of cortical stimulation, using either rTMS or epidural electrodes, reflect the multifaceted aspect of pain and the variety of CNS structures involved in pain processing.

First, MCS could act on intracortical motor circuitry, as suggested by rTMS-induced changes in cortical excitability parameters measured in the motor cortex corresponding to the painful side [27]. Active 10 Hz rTMS was found to restore intracortical inhibition in parallel with pain relief. Motor cortex inhibition is associated with the existence of 20-Hz cortical oscillations that are abolished in the presence of chronic or provoked pain [28,29]. By restoring such oscillatory activity within the primary motor cortex, MCS could restore defective inhibitory mechanisms.

However, MCS effects on chronic pain also likely depend on the recruitment of fibers, which are located within the motor cortex but project to remote structures. Various structures are functionally connected with the motor cortex and involved in pain and sensory processing. PET demonstrated that implanted MCS led to regional cerebral blood flow changes in the thalamus, anterior insula and upper brainstem [30]. All these structures could mediate the concomitant effects of MCS on spontaneous pain and innocuous thermal sensory perception. For instance, MCS could reduce pain-related hyperactivity in thalamic relays or interfere with abnormal thalamo-thalamic or thalamocortical oscillations, via corticothalamic projections and connections between thalamic nuclei. Increases in cerebral blood flow in the upper brainstem and modulation of nociceptive spinal reflexes (RIII) by switching on MCS support the role of descending controls triggered by the motor corticothalamic output [31,32]. The location of such descending controls in the brainstem or spinal cord is further supported by the low rate of efficacy of motor cortex rTMS [14] or implanted MCS [33,34] in patients with brainstem stroke or a spinal cord lesion. However, recent studies showed that patients with spinal cord injury might benefit from a series of transcranial direct current stimulation (tDCS) or rTMS treatments [35,36].

By acting on descending controls, MCS could act on the sensoridiscriminative aspects of pain. Consistent with this hypothesis, it was shown that rTMS applied at a high frequency over the motor cortex improved sensory discrimination in association with pain relief [37,38]. Similar results have been observed in patients with neuropathic pain when epidural MCS is switched 'on' [39]. Motor cortex rTMS was also found to act on sensoridiscriminative aspects of acute pain provoked by the application of laser stimuli in a territory of pre-existing chronic pain (according to the preferential changes in the N2 component of the laser-evoked potentials) [Lefaucheur JP, Jarry G, Drouot X, Ménard-Lefaucheur I, Keravel Y, Nguyen JP. Motor cortex rTMS reduces acute provoked pain induced by laser stimulation in patients with chronic neuropathic pain. Submitted]. These effects appeared to be specific for thermo–nociceptive signals that are conveyed by the spinothalamic tract. This precludes a mechanism of pain relief due to the reinforcement of the lemniscal 'gate control' over the nociceptive system, in contrast to the action of implanted spinal cord stimulation [40].

Beside sensoridiscriminative effects, neuroimaging studies showed that epidural MCS induced potent functional changes in structures that play a role in the motivational–affective

aspect of pain, such as the cingulate, prefrontal and orbitofrontal cortical areas [30]. In particular, the beneficial effects of motor cortex rTMS on capsaicin-induced acute pain was found to be associated with a significant regional cerebral blood flow increase in the caudal part of the anterior cingulate cortex, concomitant with a decrease in the medial prefrontal cortex [41]. Cortical regions involved in cognitive and emotional adaptation to nociceptive sensation have been assessed as rTMS targets in experimental pain studies. For instance, paired TMS pulses applied over a medial frontal cortical area that could be strongly connected to the anterior cingulate cortex were able to reduce laser-induced pain perception in normal subjects [42]. Finally, as mentioned previously, several studies reported beneficial effects of dorsolateral prefrontal rTMS in various types of chronic or acute pain, unrelated to mood changes [16–19].

Predictive factors for surgical implantation of epidural cortical electrodes

We reported the case of a patient with chronic pain, who was a good responder to repeated rTMS sessions and later experienced a durable pain relief under chronic MCS with surgically implanted electrodes [26]. This case, as others [4,5,7,43], suggested that rTMS could predict the outcome of subsequent chronic epidural stimulation. Actually, we observed that a positive response to rTMS (pain score decrease by >30–40% following verum minus sham rTMS) was always associated with a good outcome at long-term follow-up. By contrast, the absence of response to motor cortex rTMS sessions did not indicate the result of the implanted procedure, particularly for patients with trunk or lower limb pain. Therefore, rTMS could be used to confirm the indication of epidural MCS implantation, but not to exclude a patient from chronic cortical neuromodulation.

Various clinical criteria, including the origin and site of pain, could differentiate rTMS responders from nonresponders [8,14,43]. More particularly, the absence of severe sensory or motor loss in the painful zone was considered as a favorable condition for chronic MCS [39,44]. However, the influence of clinical variables on the outcome of motor cortex rTMS or epidural MCS remains to be further investigated in larger, controlled series.

Expert commentary

The mechanisms at the origin of the analgesic effects of MCS are probably multiple, depending on pain presentation (spontaneous or provoked pain symptoms) and on the presence or type of sensory or motor deficits. The main interest of rTMS is to provide a noninvasive tool to determine whether the stimulation of the motor cortex or other cortical areas is able to modulate pain perception in individuals or in a series of patients with chronic pain.

On average, high-frequency motor cortex rTMS reduces pain scores by 20–45% following active stimulation and by less than 10% following sham stimulation. Regarding individual results, 35–60% of patients have been considered as good responders to rTMS (>30% pain relief following active rTMS) in most of the published series. Two studies reported even higher percentages of responders (70–80%) [24,45]. By contrast, negative results have rarely been reported. On the whole, they could be attributed to too low a frequency of stimulation or too limited a number of pulses [9,13]. To increase the total number of pulses per session and to repeat the sessions for several days or weeks should enhance and prolong rTMS-induced analgesia [24,25]. Finally, the influence of stimulus intensity remains unknown, but stimulations performed above motor threshold were not associated with a better efficacy [36]. All these observations underline the clinical impact of technical features. To summarize our opinion, we think that rTMS can provide significant analgesics effects, but their short duration is a potent limit for the application of this technique in routine therapeutic practice. Therefore, the place of rTMS as a neuromodulation therapy for chronic pain is still debated in guidelines [46]. Regarding the mechanisms of action, the stimulation of the motor cortex could attenuate pain perception by modifying neural activities in some networks involved in pain processing. However, the exact nature of the involved pathways remains hypothetical.

Five-year view

The technique of stimulation will certainly be optimized in the future. First, the targeting procedure should improve by using image-guided navigation, especially if the target is determined on functional brain imaging or located outside the motor cortex [22]. Second, conditioning rTMS with a previous stimulation (priming stimulation) could increase the rate and duration of rTMS-induced pain relief [47]. θ-burst stimulation and tDCS are two potent ways of conditioning rTMS. θ bursts are brief trains of stimuli with inner low intensity and high frequency (50 Hz) that are delivered at a θ range (5 Hz) [48]. The technique of tDCS consists of weak anodal or cathodal constant direct currents that are applied onto the scalp and cross the skull to induce prolonged changes in brain excitability [49,50]. In a series of patients with chronic pain due to spinal cord lesion or fibromyalgia, repeated daily sessions of anodal tDCS used alone as an alternative technique to rTMS were found to decrease pain scores by 58%; which is a better result than in most rTMS studies [35,51]. Pain relief was maximal at the end of the week of stimulation and was still significant 2–3 weeks later. In the future, various methodological and technical improvements will probably open new perspectives for the application of noninvasive transcranial cortical stimulation as an alternative method to surgically implanted MCS in the treatment of chronic pain. Future investigation should also include the study of the inter-individual variability of the analgesic effects provided by transcranial or epidural MCS and the characterization of significant predictors of efficacy.

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Key issues

- Motor cortex repetitive transcranial magnetic stimulation (rTMS) applied focally (figure-of-eight coil) at a high rate (5–20 Hz) for at least 1000 pulses relieves neuropathic pain significantly compared with sham stimulation.
- Motor cortex rTMS applied nonfocally (circular coil) or at a low rate (0.2–1 Hz) is less able to produce significant analgesic effects compared with sham stimulation.
- Following a single rTMS session, analgesic effects are optimal a few days later and last for less than 1 week.
- Repeated daily rTMS sessions increase and prolong the effects of a single rTMS session.
- Active motor cortex rTMS reduces pain scores by 25–30% (versus <10% following sham-rTMS).
- Motor cortex rTMS is more efficacious when applied to an area adjacent to the cortical representation of the painful zone.
- The mechanisms of action of rTMS in patients with chronic pain could include the restoration of defective intracortical GABAergic inhibitory processes and the normalization of neuronal activity in thermal sensory relays.
- A positive response to high-frequency rTMS could predict a positive outcome of subsequent chronic motor cortex stimulation using surgically implanted epidural electrodes.

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