

## Transcranial magnetic stimulation as a new tool to control pain perception

Emanuela Onesti, Maria Cristina Gori, Vittorio Frasca, Maurizio Inghilleri

Emanuela Onesti, Maria Cristina Gori, Vittorio Frasca, Maurizio Inghilleri, Department of Neurology and Psychiatry, University of Rome "Sapienza", 00185 Rome, Italy

**Author contributions:** Onesti E and Inghilleri M designed the research; Onesti E and Inghilleri M performed the research; Onesti E, Gori MC, Frasca V and Inghilleri M analyzed the data; Onesti E, Gori MC, Frasca V and Inghilleri M wrote the paper.

**Conflict-of-interest statement:** Authors declare no conflict of interest for this article.

**Open-Access:** This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

**Correspondence to:** Maurizio Inghilleri, Professor, Department of Neurology and Psychiatry, University of Rome "Sapienza", Viale dell'Università 30, 00185 Rome, Italy. [maurizio.inghilleri@uniroma1.it](mailto:maurizio.inghilleri@uniroma1.it)  
Telephone: +39-06-49914120  
Fax: +39-06-49914120

Received: June 27, 2015

Peer-review started: June 30, 2015

First decision: September 17, 2015

Revised: November 26, 2015

Accepted: December 13, 2015

Article in press: December 15, 2015

Published online: March 27, 2016

### Abstract

Treatment for chronic pain is frequently unsuccessful or characterized by side-effects. The high-frequency repetitive transcranial magnetic stimulation (HF-rTMS) has been suggested in the management of refractory chronic pain. Various studies have shown that HF-

rTMS sessions of long-duration applied at primary motor cortex induce pain relief through mechanisms of plastic changes. Efficacy of rTMS mostly depends on stimulation parameters, but this aspect requires better characterization. A rationale to target other cortical areas exists. Current data are promising, but a careful analysis of stimulation settings and maintenance treatment design are needed.

**Key words:** Transcranial magnetic stimulation; Repetitive transcranial magnetic stimulation; Neuropathic pain; Non-neuropathic pain; Chronic pain; Neuromodulation

© **The Author(s) 2016.** Published by Baishideng Publishing Group Inc. All rights reserved.

**Core tip:** The high-frequency repetitive transcranial magnetic stimulation (HF-rTMS) is emerging as a possible approach for pain relief. The HF-rTMS delivered to motor cortex modulates brain network implicated in pain processes, facilitating descending pain inhibitory mechanisms. Current data are promising, but a careful analysis of stimulation settings and maintenance treatment design are necessary.

Onesti E, Gori MC, Frasca V, Inghilleri M. Transcranial magnetic stimulation as a new tool to control pain perception. *World J Anesthesiol* 2016; 5(1): 15-27 Available from: URL: <http://www.wjgnet.com/2218-6182/full/v5/i1/15.htm> DOI: <http://dx.doi.org/10.5313/wja.v5.i1.15>

### INTRODUCTION

Chronic pain can be neuropathic, non-neuropathic, mixed, or without demonstrated origin<sup>[1]</sup>. Whilst acute pain is nociceptive secondary to chemical, mechanical and thermal stimulation of A-delta and C receptors, chronic neuropathic pain (NP) can persist after the initial injury because the nervous system is malfunctioning,

becoming the origin of the pain. Examples of NP are trigeminal neuralgia, postherpetic neuralgia, phantom limb pain, monoradiculopathies, complex regional pain syndromes and peripheral neuropathies. The prevalence of NP ranges from 7% to 8%<sup>[2-4]</sup>. The mechanisms involved in NP are complex and engage both peripheral and central pathophysiologic events. Several NP research studies point to different causal mechanisms including neurogenic inflammation, abnormal ectopic activity in nociceptive nerves, and impaired inhibitory modulation, defining the so-called peripheral and central sensitization<sup>[5]</sup>. Available treatments provide mainly symptomatic relief, including nonpharmacological, pharmacological, and interventional therapies<sup>[6,7]</sup>. Unfortunately, the management of NP is not easy because the response to most drugs is not univocal<sup>[8,9]</sup>. According to recent guidelines, less than 50% of the patients with chronic NP reach symptomatic benefits with drugs<sup>[6,10,11]</sup>.

In this setting, neurostimulation is a promising procedure in the treatment of pain<sup>[6,12]</sup>. The techniques suggested are: Transcutaneous electrical nerve stimulation, nerve root stimulation, spinal cord stimulation, deep brain stimulation, transcranial direct current stimulation (tDCS), epidural motor cortex stimulation, and repetitive transcranial magnetic stimulation (rTMS)<sup>[6]</sup>.

Specifically, TMS was first introduced in the late 1980s<sup>[13]</sup>. Initially, rTMS of the motor cortex was used to select patients for chronic stimulation by implanted electrodes<sup>[14]</sup>. It is a noninvasive method of stimulating cortical motor neurons through the scalp and skull capable of inducing electrical currents and depolarizing neurons in focal brain areas with the use of rapidly changing electromagnetic fields generated by a coil placed over the scalp<sup>[15-17]</sup>. Since then, several studies used rTMS as an investigational tool and a potential treatment for a variety of neurological and psychiatric disorders. Studies showed that rTMS provided at least partial and transient relief of chronic NP. When applied repetitively, trains of rTMS can modify cortical activity beyond the duration of the stimulation<sup>[18]</sup>. Three main aspects influence the effect of rTMS: Frequency, intensity, and duration of stimulation. In general, bursts of high-frequency stimulation ( $\geq 5$  Hz) lead to a facilitation of activity in the targeted brain region, whereas continuous low-frequency stimulation (about 1 Hz) provides a suppression in activity of the targeted brain region.

The rTMS produces analgesic effects activating fibres in the motor cortex and projecting to distant areas involved in pain processing<sup>[19,20]</sup>. In 2007, the EFNS produced the first guidelines on neurostimulation therapy for NP<sup>[6]</sup>. In recent years, new randomized controlled trials have published in various NP conditions. Therefore, we aimed to review all available evidence for TMS in neuropathic and non-NP, focusing the methods. A narrative synthesis was used to report the results.

## TMS AND CHRONIC PAIN TREATMENT

A search of literature on the analgesic effect of rTMS in chronic pain published from 1991 to May 2015 was performed using PubMed and the Cochrane Library. Keywords included chronic pain and neurostimulation, chronic pain and transcranial magnetic stimulation, NP and neurostimulation, NP and transcranial magnetic stimulation. The present review included controlled studies with at least 10 subjects enrolled to ensure the quality of the studies. Moreover, we excluded observational studies, and only papers in English were included. To minimize possible bias, the study selection-process was carried out independently by two authors (EO, MI).

We identified 38 controlled studies, including sham stimulations, in patients with NP (spinal cord lesions, central post-stroke pain-CPSP-, trigeminal nerve lesions, peripheral nerve lesions, phantom pain, fibromyalgia and complex regional pain syndrome type II -CRPSII-) or non-NP (migraine, CRPS type I, low back pain, visceral and postoperative pain). Table 1 summarizes these studies. The analysis included 983 patients. Among them, 31 studies showed significant pain reduction with the high-frequency rTMS (HF-rTM) of the motor cortex (Table 1).

Unfortunately, the studies currently available have been performed on groups of patients with different kinds of NP. Evidence at medium follow-up allowing solid conclusions to be drawn is insufficient and conflicting, while evidence at long follow-up is restricted. Future studies on a large number of patients with pain due to specific diseases and the evaluation of maintenance treatment cycles should provide more certain and reproducible data.

### Efficacy of rTMS in NP

Efficacy of rTMS mostly depends on stimulation parameters. When rTMS is applied in the primary motor cortex at low-frequency it is unsuccessful<sup>[21-23]</sup>, while repeated sessions of long-duration (at least 1000 pulses) stimulations at high-frequency (5-20 Hz) applied over repeated sessions induce pain relief<sup>[1,24-27]</sup>. rTMS seems most effective when stimulation is focal (*i.e.*, figure-of-eight rather than circular coil)<sup>[6]</sup>. The effect starts a few days later; its duration is less than a week after a single session, 2-3 wk after consecutive sessions of rTMS<sup>[28-30]</sup>. This last aspect is the keystone for the clinical benefit<sup>[31,32]</sup>. However, this feature requires better characterization<sup>[6]</sup>. The TMS parameters vary in the studies, and it is complex to establish the best stimulation parameters to use<sup>[12]</sup>. The role of coil orientation, time of train of stimulation, inter-train interval, and number of trains, is also to definite<sup>[12]</sup>.

Moreover, 22 of the 32 studies had small sample sizes, with less than 30 enrolled patients, and only 16 of 32 studies recruited homogeneous populations of patients (CRPS, spinal cord injury, diabetic polyneuropathy, poststroke pain and fibromyalgia), reducing

**Table 1 Summary of the studies evaluating the effects of repetitive transcranial magnetic stimulation on chronic neuropathic pain and non-neuropathic pain**

Ref.	Painful syndrome	Study design	Number of patients	Coil	Site stimulation	Frequency, intensity, <i>n</i> sessions	Outcomes	Efficacy
NP								
Lefaucheur <i>et al</i> <sup>[26]</sup>	Intractable neurogenic pain	Double-blind, controlled, crossover	18 (12 central NP; 6 peripheral NP)	F8	Hand M1	0.5-10 Hz 80% RMT 1	Pain intensity	Analgesic effect (only for 10 Hz)
Lefaucheur <i>et al</i> <sup>[116]</sup>	Pain due to thalamic stroke or trigeminal neuropathy	Double-blind, controlled, crossover	14 (7 central NP; 7 peripheral NP)	F8	Hand M1	10 Hz 80% RMT 1	VAS	Decrease in VAS
Rollnik <i>et al</i> <sup>[41]</sup>	Chronic refractory NP	Double-blind, controlled, crossover	12 (2 central NP; 7 peripheral NP; 2 CRPS; 1 osteomyelitis)	Double coin - Circular coin	M1	20 Hz 80% RMT 1	VAS	No effect
Lefaucheur <i>et al</i> <sup>[27]</sup>	Pain do to thalamic stroke, brainstem stroke, spinal cord lesion, brachial plexus lesion, or trigeminal nerve lesion	Double-blind, controlled, crossover	60 (36 central NP; 24 peripheral NP)	F8	Hand M1	10 Hz 80% RMT 1	VAS, thermal sensory thresholds	Analgesic effect mainly in trigeminal nerve lesions
Khedr <i>et al</i> <sup>[25]</sup>	Trigeminal neuralgia and post-stroke pain syndrome	Double-blind, controlled	48 (24 central NP; 24 trigeminal NP)	F8	Hand M1	20 Hz 80% RMT 5	VAS and the LANSS scale	Analgesic effect
André-Obadia <i>et al</i> <sup>[22]</sup>	Chronic refractory NP	Double-blind, controlled, crossover	14 (11 central NP; 3 peripheral NP)	F8	Hand M1	1-20 Hz 90% RMT 1	VAS	Analgesic effect (only for 20 Hz)
Hirayama <i>et al</i> <sup>[104]</sup>	Intractable deafferentation pain	Double-blind, controlled, crossover	20 (14 central NP; 6 peripheral NP)	F8	M1	5 Hz 90% RMT 1	VAS and SF-MPQ	Analgesic effect
Irlbacher <i>et al</i> <sup>[117]</sup>	Chronic NP	Double-blind, controlled	27 (13 central NP; 14 phantom p)	F8	M1	1-5 Hz 95% RMT 5	VAS	No effect
Lefaucheur <i>et al</i> <sup>[15]</sup>	Unilateral hand pain of various neurologic origins	Double-blind, controlled, crossover	22 (14 central NP; 8 peripheral NP)	F8	Hand M1	10 Hz 90% RMT 1	Motor threshold at rest, MEP amplitude, CSP, ICI	ICI increase
Lefaucheur <i>et al</i> <sup>[118]</sup>	Chronic NP	Double-blind, controlled, crossover	36	F8	Face M1	10 Hz 80% RMT 1	VAS	Analgesic effect with the stimulation applied on area adjacent to the cortical representation of the painful zone
Defrin <i>et al</i> <sup>[35]</sup>	Spinal cord injury	Double-blind, controlled	12	F8	Vertex	5 Hz 115% RMT 10	VAS, MPQ, pain threshold	Increased heat pain threshold
Passard <i>et al</i> <sup>[20]</sup>	Fibromyalgia	Double-blind, controlled	30	F8	M1	10 Hz 80% RMT 10	VAS, MPQ, quality of life (Brief Pain Inventory and the Fibromyalgia Impact Questionnaire)	Decrease in VAS and better quality of life
Saitoh <i>et al</i> <sup>[115]</sup>	Intractable deafferentation pain	Double-blind, controlled, crossover	13 (9 central NP; 4 peripheral NP)	F8	M1	1-5-10 Hz 90% RMT 1	VAS	Decrease in VAS (only for 5-10 Hz)
André-Obadia <i>et al</i> <sup>[119]</sup>	Chronic NP	Double-blind, randomized, controlled, crossover	28	F8	M1	20 Hz 90% RMT 1	Pain relief, quality of life and rescue drug intake	Analgesic effect

Onesti E *et al.* Transcranial magnetic stimulation for chronic pain

Lefaucheur <i>et al</i> <sup>[120]</sup>	Chronic refractory NP	Double-blind, controlled, crossover	46 (23 central NP; 23 peripheral NP)	F8	Hand M1	10 Hz 90% RMT 1	Thresholds for thermal and mechanical sensations	Thermal perception improvement
Carretero <i>et al</i> <sup>[121]</sup>	Fibromyalgia	Randomized, single-blinded	28	Butterfly coil	DLPFC	1 Hz 110% RMT 20	FibroFatigue, Likert pain, HDRS, CBI	No effect
Kang <i>et al</i> <sup>[36]</sup>	Spinal cord injury	Double-blind, controlled, crossover	11	F8	M1	10 Hz 80% RMT 5	NRS, BPI	No effect
Picarelli <i>et al</i> <sup>[33]</sup>	CRPS type 1	Double-blind, controlled	23	F8	M1	10 Hz 90% RMT 10	VAS, MPQ, the SF-36, HDRS	Analgesic effect and improved quality of life
Ahmed <i>et al</i> <sup>[108]</sup>	Phantom pain	Double-blind, controlled	27	F8	DLPFC	20 Hz 80% RMT 5	VAS, LANSS scale	Decrease in VAS and LANSS scale
Mhalla <i>et al</i> <sup>[38]</sup>	Fibromyalgia	Double-blind, controlled	40	F8	M1	10 Hz 80% RMT	Pain intensity over the last 24 h, BPI, quality of life, mood and anxiety, parameters of motor cortical excitability	Analgesic effect
Short <i>et al</i> <sup>[63]</sup>	Fibromyalgia	Double-blind, controlled	20	F8	M1	14 10 Hz 120% RMT	BPI, HDRS, Fibromyalgia Impact Questionnaire	Improvement of daily pain, number of tender points, HDRS and FIQ scores
Lefaucheur <i>et al</i> <sup>[122]</sup>	Chronic refractory NP	Controlled, crossover	14 (3 localized in the face, 4 upper limb, 3 lower limb, 4 hemibody)	F8	M1	10 10 Hz 90% RMT 3	VAS	Analgesic effect
Hosomi <i>et al</i> <sup>[109]</sup>	NP	Double-blind, controlled, crossover	64	F8	M1	50 Hz 90% RMT 10	VAS, SF-MPQ, PGIC, and BDI	Analgesic effect
Onesti <i>et al</i> <sup>[28]</sup>	Diabetic neuropathy	Double-blind, controlled, crossover	23	H-coil	Vertex	20 Hz 100% RMT 5	VAS, area and threshold of RIII nociceptive flexion reflex	Decrease in VAS and RIII area
Jetté <i>et al</i> <sup>[34]</sup>	Spinal cord injury	Randomized, controlled, crossover	16	F8	M1	10 Hz 90%-110% RMT 3	RIII reflex VAS, motor mapping parameters	Decrease in VAS
Boyer <i>et al</i> <sup>[30]</sup>	Fibromyalgia	Double-blind, randomized, controlled	38	F8	M1	10 Hz 90% RMT 14	FIQ, SF-36, brain metabolism	Improvement of quality of life
Dall'Agnol <i>et al</i> <sup>[123]</sup>	Myofascial pain syndrome	Double-blind, randomized, controlled	24	F8	M1	10 Hz 80% RMT 10	Pain quantitative sensory testing, conditioned pain modulation, TMS parameters, BDNF	Analgesic effect mediated by mechanisms enhancing the corticospinal inhibitory system and BDNF
Yilmaz <i>et al</i> <sup>[40]</sup>	Spinal cord injury	Double-blind, randomized, controlled	17	F8	Vertex	10 Hz 110% RMT 10	VAS	No effect

Hodaj <i>et al</i> <sup>[124]</sup>	Chronic refractory facial pain	Open-label study	55  (19 cluster headache; 21 trigeminal neuropathic pain; 15 atypical facial pain)	F8	Face M1	10 Hz 80% RMT 12	VAS, CGIC scale	Analgesic effect
Khedr <i>et al</i> <sup>[125]</sup>	Malignant NP	Randomized, controlled	34	F8	Hand M1	20 Hz 80% RMT 10	VDS, VAS, LANSS, HDRS	Analgesic effect
Lindholm <i>et al</i> <sup>[126]</sup>	Neuropathic orofacial pain	Randomized, controlled, cross-over	16	-	S1/M1, right SII	-	NRS, BPI	Analgesic effect (only for SII)
Brighina <i>et al</i> <sup>[46]</sup>	Migraine	Double-blind, randomized, controlled	11	F8	DLPFC	10 Hz 90% RMT 12	Frequency of attacks, Headache index	Significant reduction of outcome measures
Pleger <i>et al</i> <sup>[48]</sup>	CRPS	Double-blind, controlled, crossover	10	F8	M1	10 Hz 110% RMT 1	VAS	Analgesic effect
Borckardt <i>et al</i> <sup>[127]</sup>	Postoperative pain	Double-blind, controlled	20	F8	Left PFC	10 Hz 100% RMT 1	VAS for mood, opioid pump use	Reduction in opioid use
Johnson <i>et al</i> <sup>[49]</sup>	Low back pain	Double-blind, controlled, crossover	17	F8	M1	20 Hz 95% RMT 1	Detection and pain thresholds for cold and heat sensations	Increased heat pain threshold and lowered cold detection
Fregni <i>et al</i> <sup>[50]</sup>	Pancreatitis	Double-blind, controlled	17	F8	SII	1 Hz 70% RMT 10 -	VAS, BDI	Analgesic effect
Conforto <i>et al</i> <sup>[47]</sup>	Migraine	Randomized, double-blind, parallel-group	18	-	DLPFC	-	Number of headache days	No effect
Melchior <i>et al</i> <sup>[51]</sup>	Irritable bowel syndrome	Double-blind, controlled, crossover	21	F8	M1	20 Hz 80% RMT 5	Pressure pain threshold, changes in maximum tolerated rectal volume, rectal compliance and average pain intensity	Maximum tolerated rectal volume and analgesic effects
Avery <i>et al</i> <sup>[52]</sup>	Chronic widespread pain	Double-blind, randomized, controlled	19	-	DLPFC	- 15	BIRS	No effect

NP: Neuropathic pain; BPI: Brief pain inventory; FIQ: Fibromyalgia impact questionnaire; F8: Figure of 8 coil; H: Hersed; HDRS: Hamilton depression rating scale; ICI: Intracortical inhibition; LANSS: Leeds assessment of neuropathic symptoms and signs; MPQ: McGill pain questionnaire; PFC: Prefrontal cortex; RIII: Nociceptive flexion reflex; SF-36: 36-item short-form health survey; SICI: Short intracortical inhibition; SII: Somatosensory cortex; VAS: Visual analog scale; MEP: Motor evoked potential; NRS: Numeric rating scale; PGIC: Patient global impression of change scale; BDNF: Brain-derived neurotrophic factor; VDS: Verbal descriptor scale; CGIC: Clinical global impression of change; DLPFC: Dorsolateral prefrontal cortex; BIRS: Gracely box intensity scale.

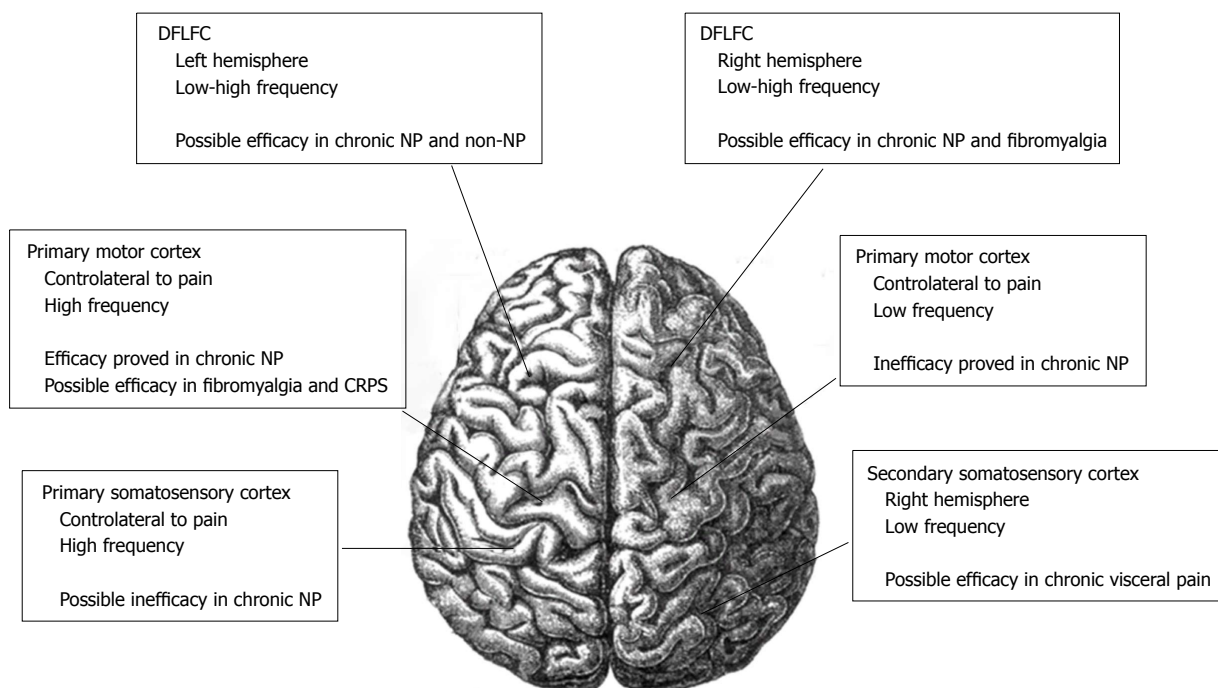
assurance about which states are more responsive to TMS<sup>[1,28-30,33-41]</sup>. Another unsolved question concerns which site in the motor cortex gives the most effective pain relief. Stimulation is commonly delivered to the contralateral motor cortex to painful area<sup>[1,42]</sup>.

Also the left DLPFC could have a function in nociceptive control, while the left prefrontal cortex has been used in rTMS studies in patients with fibromyalgia<sup>[39,43]</sup> (Figure 1).

Also tDCS, a technique that elicits constant weak electric currents through the scalp through two electrodes, is able to modulate excitability in cortical

tissue. Moreover, it is important to specify that tDCS does not induce action potentials in axons, but it cause polarization of neurons changing their average level of discharge. Several studies examined the tDCS applied to the motor cortex as a possible treatment of chronic pain, but a recent meta-analysis does not suggest a significant analgesic effect of this technique<sup>[23]</sup>.

The mechanisms underlying the effect of rTMS in pain are not clearly identified, but probably involve neuronal plasticity<sup>[44,45]</sup>. Therefore it is suggested that maintenance therapy for longer intervals should prolong long-lasting effects. Unfortunately, only one study to



**Figure 1 Analgesic efficacy of repetitive transcranial magnetic stimulation according to the cortical target.** DLPFC: Dorsolateral prefrontal cortex; NP: Neuropathic pain; CRPS: Complex regional pain syndrome.

date evaluated long-term rTMS maintenance therapy<sup>[38]</sup>.

### Efficacy of rTMS in non-NP

In the past ten years, the rTMS have been also evaluated in different non-NP conditions<sup>[1]</sup> (Table 1).

Regarding application for migraine, active HF-rTMS delivered over the left DLPFC gave promising results but, in the absence of large controlled studies, no recommendation can be suggested<sup>[1,46,47]</sup>. Also regarding to the treatment of chronic visceral pain, low back pain and CRPS type I with rTMS, literature is still limited, and no conclusion can be definitely drawn<sup>[48-52]</sup>. Future research in this field should specifically investigate in a large number of patients the most appropriate cortical target, and the frequency of stimulation<sup>[1]</sup>. Moreover, a specific analysis regarding to the possible effect of rTMS on other clinical aspects of these syndromes, such as affective-emotional and cognitive components is needed.

## PHYSIOLOGICAL BASIS OF rTMS

### Practical aspects of rTMS

In 1985 Barker *et al.*<sup>[13]</sup> proposed the first magnetic stimulator for the transcranial stimulation of the human brain, giving the prerequisite for subsequent clinical use of TMS. A stimulating coil produces a brief magnetic field when an electrical pulse generator creates a discharge current of several thousand amperes. When the coil is placed on the skull of a subject, it induces an electrical field able to depolarize nerve cells and to stimulate neural networks<sup>[1]</sup>. The stimulus waveform can be monophasic or biphasic<sup>[53]</sup>. The rTMS using monophasic pulses activates an homogeneous population of

neurons, while biphasic pulses tend to generate a more complex pattern of neural activation, producing local changes but also effects at distance from the stimulus site<sup>[1,54]</sup>.

### Site of stimulation

The first task for pain modulation is to locate primary motor cortex (M1), checking visually the muscle twitch inducing by TMS pulses<sup>[12]</sup>. Commonly in clinical settings, the intensity of the TMS should be not able to induce a motor response<sup>[12]</sup>. Specifically, TMS applied in short trains at high frequency and suprathreshold intensity over the M1 elicits a progressive increase in motor evoked potential (MEP) amplitude, demonstrating the phenomenon of MEP amplitude facilitation, through intracortical mechanisms similar to short-term synaptic plasticity<sup>[55-59]</sup>.

However, a rationale for targeting other cortical areas exists. The DLPFC could have a role in nociceptive control<sup>[43]</sup>. In healthy subjects with pain induced by a capsaicin injection into their hand, the stimulation of the left DLPFC produced a significant pain relief. No improvement was noted when the right DLPFC was stimulated<sup>[60]</sup>. The effect may be related to the release of endogenous opioids by the left DLPFC<sup>[61]</sup>. Also rTMS of the cerebellum has been considered for the possible lowering in pain thresholds<sup>[62]</sup>. Moreover, The left prefrontal cortex has been used in rTMS fibromyalgia studies, but only a small analgesic effect has been noted<sup>[63]</sup>.

### Intensity of stimulation

The intensity of the stimulation is classically regulated for each patient to obtain the minimal intensity of

stimulation applied to M1 that evokes a motor response. It is measured according to the RMT, the lowest stimulation intensity able to generate a MEP small (50 mV) amplitude in 5 of 10 TMS pulses. In the clinical setting, stimulation intensity is frequently subthreshold (80%-90% of RMT)<sup>[64]</sup>. When the RMT is identified, rTMS is performed in bursts of stimuli ("trains") with a definite frequency<sup>[12]</sup>.

### Frequency of stimulation

rTMS can be carried out at low (1 Hz) or high frequencies (5 Hz). When performed at high frequencies, rTMS pulses are delivered in trains divided by specific intertrain intervals. Typically, low-frequency rTMS is considered to have inhibitory properties, whereas HF-rTMS is considered to have excitatory properties<sup>[64]</sup>. HF-rTMS consists specifically of intermittent bursts of TMS pulses able to induce a long-term potentiation of synaptic activity, which may clarify why rTMS effects can overcome the period of stimulation<sup>[64]</sup>.

### Number of sessions and total number of pulses per session

A central question is whether the analgesic effect of rTMS can be prolonged by maintenance sessions performed periodically. To date, 24 of 39 studies have performed repetitive sessions of rTMS to enhance analgesic effects of a single session of stimulation, but maintenance protocol was only tested in one study<sup>[38]</sup>. Usually, the number of sessions applied range from 5 sessions to 30 sessions. The majority of studies have involved a total of 10 sessions. Based on more recent studies, a general trend indicates a greater number of sessions (> 10) associated with more persisting improvement in pain perception (Table 1).

The total number of pulses in each rTMS session seems related to the analgesic effect, but it is not clear whether a minimum number of pulses is required to obtain the clinical outcome. Usually this value ranges between 1000 to 2000<sup>[1]</sup>. Moreover an important safety parameter as the intertrain interval (the time in between trains of pulsed energy when no stimulation is occurring) is usually about 10 s<sup>[1]</sup>.

### Coil

Coil design and orientation are important. The "figure-of-eight" coil is able to induce a focal magnetic field stimulating only superficial cortical regions of the brain<sup>[12]</sup>. Other novel models are the Tilted double-coil and the Heschl (H)-coil, which drop at a depth of about 6 cm<sup>[12]</sup>. Specifically, the H-coil lets deep brain stimulation without significantly increasing induced fields in superficial cortical regions, therefore preventing the risk of adverse effects<sup>[65,66]</sup>. rTMS with the H-coil has already proved effective as an acute treatment for major depressive disorder, bipolar depression, schizophrenia and post-traumatic stress disorder<sup>[65,67-69]</sup>. Furthermore, there are ongoing studies of its use to

treat a very wide range of neurological, psychiatric and medical conditions, including NP<sup>[28]</sup>.

### Placebo rTMS

Placebo effects need to be better reported<sup>[25]</sup>. Theoretically, ideal placebo rTMS should be characterized by the same subjective somatic scalp sensation and the acoustic artifacts compared to active coil, and no physiological effect on the targeted cortical region<sup>[70]</sup>. In the early research, placebo was considered a coil placed in a different area from zone stimulated in the active condition, or a coil oriented with an angle of 45-90 grades on the scalp instead of tangentially<sup>[1]</sup>. These solutions are not the most reliable, because the stimulation site could be perceived by the subject, or the sham location could cause unexpected effects<sup>[1,71]</sup>. In the last decades, sham coils have been projected and commercialized in order to block the magnetic field provided, and to produce auditory artifacts and scalp sensation equivalent to that of a real coil<sup>[72,73]</sup>. Although this stimulation ideally seems a perfect placebo, the cutaneous sensation remains different in about half of the cases, especially when the stimulation intensity is high<sup>[72,74]</sup>.

## CONSIDERATIONS ABOUT MECHANISMS OF ACTION OF rTMS

Although the TMS acts on the superficial cortex, the generated action potentials propagate influencing distant neural networks<sup>[12]</sup>. The M1 contains pyramidal cells that give rise to numerous excitatory corticospinal projections. Most of These projections are oriented perpendicularly to the brain surface. rTMS applied on the M1 modulate the cortical excitability producing changes in the following physiological parameters: MT, MEP, silent period, intracortical facilitation, and intracortical inhibition<sup>[75]</sup>. In chronic pain, the involvement of M1 projections to pain-modulating structures has been demonstrated<sup>[23]</sup>. Moreover, a rationale for targeting other cortical areas exists. The DLPFC is a cortical target used in studies on major depression, and it is considered to have a function also in nociceptive control<sup>[43,61,76]</sup>. HF-rTMS on the right DLPFC has shown analgesic effects similar to M1 stimulation<sup>[46,77]</sup>. Furthermore, left DLPFC stimulation should induce an improvement of pain perception in a model of acute pain<sup>[43,78]</sup>. The left prefrontal cortex has been used in rTMS studies in patients with fibromyalgia, but it has shown a minor analgesic effect<sup>[63]</sup>.

rTMS seems to modulate cortical plasticity, referred to as the functional reorganization of the inter neuron connections and neuronal properties. Inhibition of the gamma-aminobutyric acid (GABA) pathways produces cortical excitation, rather than a direct enhancement of motor cortex excitability<sup>[79-82]</sup>. On the other hand, low-frequency rTMS could increase the inhibitory corticospinal control, perhaps through GABA-B

transmission, prolonging the CSP duration<sup>[1,83-86]</sup>. The changes in synaptic plasticity brought by rTMS are explained by long term potentiation (LTP) and long term depression (LTD)<sup>[44]</sup>. LTP is induced by high frequency stimulation and LTD by low frequency stimulation. The LTP is mediated by the post-synaptic N-methyl-D-aspartate (NMDA) receptors, that lead to calcium flux into the post-synaptic neuron when activated<sup>[45]</sup>. Calcium activates enzymatic changes in pre- and post-synaptic neurons, increasing the synaptic activity. It also induces the expression of alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors on the postsynaptic neuron, increasing the cells sensitivity to glutamate<sup>[87]</sup>. Furthermore, LTD is characterized by depression of the synaptic transmission, depending on the modulation of NMDA receptors with the reduction of calcium influx, and the internalization of AMPA<sup>[87]</sup>.

The long lasting effect of rTMS (late-LTP) is thought to be exercised by gene induction and protein synthesis<sup>[87]</sup>. Gene expression has resulted in increased synthesis of c-fos mRNA in the thalamus and parietal cortex, and BDNF mRNA in the hippocampus and parietal cortex<sup>[88-90]</sup>. Considerable evidence from HF-rTMS studies suggests that short-term synaptic plasticity happens at cortical rather than spinal level<sup>[91-94]</sup>. When rTMS is delivered in human subjects, the amplitude of the MEP and the duration of the CSP increases during the train<sup>[55,75,95-100]</sup>. The MEP facilitation also persists after the train ends, and it is probably due to the recruitment of cortical excitatory interneurons<sup>[55,75,92,94,99]</sup>. It is influenced by the number of stimuli in the train, being greater with longer (20, 40 and 60-stimuli), suggesting mechanisms of short-term synaptic enhancement<sup>[59,101]</sup>.

rTMS has also been found to modulate the activity of brain neurotransmitters, reducing dopamine in the frontal cortex and increasing its levels in the striatum<sup>[102]</sup>. Moreover, serotonin levels increased in the hippocampus<sup>[102]</sup>. All these aspects may explain why different rTMS protocols are effective or not, depending on various parameters of stimulation. Further, age, and genetic features could influence the clinical effect of rTMS, with heterogeneous therapeutic responses<sup>[1,103]</sup>.

## LIMITATIONS OF rTMS IN PAIN TREATMENT

The results of studies exploring the effects of rTMS on pain are positive but still inconsistent, because of small samples of patients, differences in the TMS methodologies, heterogeneous populations of patients and lack of maintenance protocols. In a Cochrane Review of 2013, a short-term effect on pain of HF-rTMS applied to M1 was confirmed<sup>[23]</sup>. Moreover, a detailed study to determine which are the best stimulation parameters, is targeted. Studies on image-guided navigation to perform rTMS of M1 in pain patients have provided evidence that the analgesic effect of rTMS links with the integrity of the thalamocortical tract<sup>[1,104,105]</sup>.

Unfortunately, objective indicators of perceived pain, including MEP and RIII, were considered in only two studies neurophysiological<sup>[15,28]</sup>. New extended studies should improve knowledge in this field of research.

Further rigorously designed studies, particularly of longer courses of stimulation applied on large population of patients, are required to address the issue. Future evidence may significantly confirm the current results. The main question is whether the clinical effect could indeed improve the management of patients with chronic pain in daily clinical practice.

## FUTURE RESEARCH DIRECTIONS

The conclusions of our analysis, related to the actual literature data on rTMS for chronic pain, match with those suggested in previous reviews and meta-analyses<sup>[1,6,17,23-25,32,106]</sup>. rTMS has become a promising therapeutic tool for a variety of neurological and psychiatric diseases<sup>[107]</sup>. Different types of NP respond to rTMS, and this is producing a fast growth in researchers interested in rTMS for clinical purposes<sup>[6,26,108-110]</sup>. Unfortunately at the current time in the lack of large studies, only careful recommendations of rTMS can be suggested<sup>[1,6]</sup>. The efficacy of a single HF-rTMS session persists for some days, and it could extend with the repetition of sessions<sup>[1]</sup>. Moreover, the best stimulation settings may be yet to determined.

Studies including neurophysiological evaluation of the effects of the cortex TMS in other brain regions through the use of imaging and electrophysiologic techniques (such as electroencephalography, magnetoencephalography, MRI navigated TMS) could add value at the understanding of the mechanism of action of this technique<sup>[111]</sup>. New TMS machines have allowed the administration of pulses more focally and at higher frequencies. Moreover, frameless stereotactic systems, have been developed, permitting the identification of specific location in the desired brain target and the precise and comparable placing of the coil during different TMS sessions<sup>[112-114]</sup>.

In future, therapeutic studies need to define the correct utilization of rTMS in the clinical practice for chronic pain, above all if the long-term effect exists. Moreover, studies of rTMS in other diseases associated with chronic pain, such as osteoarthritis, bladder pain syndrome and post-stroke pain, could be of interest. Finally, if rTMS becomes a proven method for the treatment of chronic pain, the development of a home-based rTMS system will be necessary<sup>[115]</sup>.

Active research in pain is still taking place and has the potential to provide useful data (31 open studies on TMS and pain on <https://clinicaltrials.gov>). Based on this new research, novel therapeutic guidelines may be established in future. Apart from its potential clinical role, rTMS is a valuable probe of brain function that can be used to investigate the neural circuitry. This additional knowledge might help in the development of new treatments. rTMS is non-invasive and can be



applied to any patient with drug-resistant NP who could be aspirant for the insertion of a cortical stimulator. In addition, further studies using maintenance sessions of rTMS and evaluating the multiple features of chronic pain are needed to give a more solid basis for its clinical applications.

## ACKNOWLEDGMENTS

The authors thank Ms Mali Sion Evans for English language editing.

## REFERENCES

- 1 **Lefaucheur JP**, André-Obadia N, Antal A, Ayache SS, Baeken C, Benninger DH, Cantello RM, Cincotta M, de Carvalho M, De Ridder D, Devanne H, Di Lazzaro V, Filipović SR, Hummel FC, Jääskeläinen SK, Kimiskidis VK, Koch G, Langguth B, Nyffeler T, Oliviero A, Padberg F, Poulet E, Rossi S, Rossini PM, Rothwell JC, Schönfeldt-Lecuona C, Siebner HR, Slotema CW, Stagg CJ, Valls-Sole J, Ziemann U, Paulus W, Garcia-Larrea L. Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS). *Clin Neurophysiol* 2014; **125**: 2150-2206 [PMID: 25034472 DOI: 10.1016/j.clinph.2014.05.021]
- 2 **Treede RD**, Jensen TS, Campbell JN, Cruccu G, Dostrovsky JO, Griffin JW, Hansson P, Hughes R, Nurmikko T, Serra J. Neuropathic pain: redefinition and a grading system for clinical and research purposes. *Neurology* 2008; **70**: 1630-1635 [PMID: 18003941 DOI: 10.1212/01.wnl.0000282763.29778.59]
- 3 **Bouhassira D**, Lantéri-Minet M, Attal N, Laurent B, Touboul C. Prevalence of chronic pain with neuropathic characteristics in the general population. *Pain* 2008; **136**: 380-387 [PMID: 17888574 DOI: 10.1016/j.pain.2007.08.013]
- 4 **Torrance N**, Smith BH, Bennett MI, Lee AJ. The epidemiology of chronic pain of predominantly neuropathic origin. Results from a general population survey. *J Pain* 2006; **7**: 281-289 [PMID: 16618472 DOI: 10.1016/j.jpain.2005.11.008]
- 5 **Truini A**, Cruccu G. Pathophysiological mechanisms of neuropathic pain. *Neurol Sci* 2006; **27** Suppl 2: S179-S182 [PMID: 16688626 DOI: 10.1007/s10072-006-0597-8]
- 6 **Cruccu G**, Aziz TZ, Garcia-Larrea L, Hansson P, Jensen TS, Lefaucheur JP, Simpson BA, Taylor RS. EFNS guidelines on neurostimulation therapy for neuropathic pain. *Eur J Neurol* 2007; **14**: 952-970 [PMID: 17718686 DOI: 10.1111/j.1468-1331.2007.01916.x]
- 7 **Attal N**, Cruccu G, Baron R, Haanpää M, Hansson P, Jensen TS, Nurmikko T. EFNS guidelines on the pharmacological treatment of neuropathic pain: 2010 revision. *Eur J Neurol* 2010; **17**: 1113-1e88 [PMID: 20402746 DOI: 10.1111/j.1468-1331.2010.02999.x]
- 8 **Attal N**, Lanteri-Minet M, Laurent B, Fermanian J, Bouhassira D. The specific disease burden of neuropathic pain: results of a French nationwide survey. *Pain* 2011; **152**: 2836-2843 [PMID: 22019149 DOI: 10.1016/j.pain.2011.09.014]
- 9 **Torrance N**, Ferguson JA, Afolabi E, Bennett MI, Serpell MG, Dunn KM, Smith BH. Neuropathic pain in the community: more under-treated than refractory? *Pain* 2013; **154**: 690-699 [PMID: 23485369 DOI: 10.1016/j.pain.2012.12.022]
- 10 **Attal N**, Cruccu G, Haanpää M, Hansson P, Jensen TS, Nurmikko T, Sampaio C, Sindrup S, Wiffen P; EFNS Task Force. EFNS guidelines on pharmacological treatment of neuropathic pain. *Eur J Neurol* 2006; **13**: 1153-1169 [PMID: 17038030 DOI: 10.1111/j.1468-1331.2006.01511.x]
- 11 **Finnerup NB**, Otto M, McQuay HJ, Jensen TS, Sindrup SH. Algorithm for neuropathic pain treatment: an evidence based proposal. *Pain* 2005; **118**: 289-305 [PMID: 16213659 DOI: 10.1016/j.pain.2005.08.013]
- 12 **Treister R**, Lang M, Klein MM, Oaklander AL. Non-invasive Transcranial Magnetic Stimulation (TMS) of the Motor Cortex for Neuropathic Pain-At the Tipping Point? *Ramban Maimonides Med J* 2013; **4**: e0023 [PMID: 24228166 DOI: 10.5041/RMMJ.10130]
- 13 **Barker AT**, Jalinous R, Freeston IL. Non-invasive magnetic stimulation of human motor cortex. *Lancet* 1985; **1**: 1106-1107 [PMID: 2860322 DOI: 10.1016/S0140-6736(85)92413-4]
- 14 **Tsubokawa T**, Katayama Y, Yamamoto T, Hirayama T, Koyama S. Chronic motor cortex stimulation for the treatment of central pain. *Acta Neurochir Suppl* (Wien) 1991; **52**: 137-139 [PMID: 1792954 DOI: 10.1007/978-3-7091-9160-6\_37]
- 15 **Lefaucheur JP**, Drouot X, Ménard-Lefaucheur I, Keravel Y, Nguyen JP. Motor cortex rTMS restores defective intracortical inhibition in chronic neuropathic pain. *Neurology* 2006; **67**: 1568-1574 [PMID: 17101886 DOI: 10.1212/01.wnl.0000242731.10074.3c]
- 16 **Fregni F**, Boggio PS, Valle AC, Rocha RR, Duarte J, Ferreira MJ, Wagner T, Fecteau S, Rigonatti SP, Riberto M, Freedman SD, Pascual-Leone A. A sham-controlled trial of a 5-day course of repetitive transcranial magnetic stimulation of the unaffected hemisphere in stroke patients. *Stroke* 2006; **37**: 2115-2122 [PMID: 16809569 DOI: 10.1161/01.STR.0000231390.58967.6b]
- 17 **Leo RJ**, Latif T. Repetitive transcranial magnetic stimulation (rTMS) in experimentally induced and chronic neuropathic pain: a review. *J Pain* 2007; **8**: 453-459 [PMID: 17434804 DOI: 10.1016/j.jpain.2007.01.009]
- 18 **Rothwell JC**, Thompson PD, Day BL, Boyd S, Marsden CD. Stimulation of the human motor cortex through the scalp. *Exp Physiol* 1991; **76**: 159-200 [PMID: 2059424 DOI: 10.1113/expphysiol.1991.sp003485]
- 19 **Lefaucheur JP**. The use of repetitive transcranial magnetic stimulation (rTMS) in chronic neuropathic pain. *Neurophysiol Clin* 2006; **36**: 117-124 [PMID: 17046606 DOI: 10.1016/j.neucli.2006.08.002]
- 20 **Gilhus NE**, Barnes MR, Brainin M. European Handbook of Neurological Management. John Wiley & Sons, 2011
- 21 **Lefaucheur JP**, Antal A, Ahdab R, Ciampi de Andrade D, Fregni F, Khedr EM, Nitsche M, Paulus W. The use of repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS) to relieve pain. *Brain Stimul* 2008; **1**: 337-344 [PMID: 20633392 DOI: 10.1016/j.brs.2008.07.003]
- 22 **André-Obadia N**, Peyron R, Mertens P, Mauguière F, Laurent B, Garcia-Larrea L. Transcranial magnetic stimulation for pain control. Double-blind study of different frequencies against placebo, and correlation with motor cortex stimulation efficacy. *Clin Neurophysiol* 2006; **117**: 1536-1544 [PMID: 16753335 DOI: 10.1016/j.clinph.2006.03.025]
- 23 **O'Connell NE**, Wand BM, Marston L, Spencer S, Desouza LH. Non-invasive brain stimulation techniques for chronic pain. *Cochrane Database Syst Rev* 2014; **4**: CD008208 [PMID: 24729198 DOI: 10.1002/14651858.CD008208.pub3]
- 24 **Leung A**, Donohue M, Xu R, Lee R, Lefaucheur JP, Khedr EM, Saitoh Y, André-Obadia N, Rollnik J, Wallace M, Chen R. rTMS for suppressing neuropathic pain: a meta-analysis. *J Pain* 2009; **10**: 1205-1216 [PMID: 19464959 DOI: 10.1016/j.jpain.2009.03.010]
- 25 **Khedr EM**, Kotb H, Kamel NF, Ahmed MA, Sadek R, Rothwell JC. Longlasting antalgic effects of daily sessions of repetitive transcranial magnetic stimulation in central and peripheral neuropathic pain. *J Neurol Neurosurg Psychiatry* 2005; **76**: 833-838 [PMID: 15897507 DOI: 10.1136/jnnp.2004.055806]
- 26 **Lefaucheur JP**, Drouot X, Keravel Y, Nguyen JP. Pain relief induced by repetitive transcranial magnetic stimulation of precentral cortex. *Neuroreport* 2001; **12**: 2963-2965 [PMID: 11588611 DOI: 10.1097/00001756-200109170-00041]
- 27 **Lefaucheur JP**, Drouot X, Menard-Lefaucheur I, Zerah F, Bendib B, Cesaro P, Keravel Y, Nguyen JP. Neurogenic pain relief by repetitive transcranial magnetic cortical stimulation depends on the origin and the site of pain. *J Neurol Neurosurg Psychiatry* 2004; **75**: 612-616 [PMID: 15026508 DOI: 10.1136/jnnp.2003.022236]
- 28 **Onesti E**, Gabriele M, Cambieri C, Ceccanti M, Raccach R, Di Stefano G, Biasiotta A, Truini A, Zangen A, Inghilleri M. H-coil repetitive transcranial magnetic stimulation for pain relief in patients with diabetic neuropathy. *Eur J Pain* 2013; **17**: 1347-1356 [PMID: 23629867 DOI: 10.1002/j.1532-2149.2013.00320.x]

- 29 **Passard A**, Attal N, Benadhira R, Brasseur L, Saba G, Sichere P, Perrot S, Januel D, Bouhassira D. Effects of unilateral repetitive transcranial magnetic stimulation of the motor cortex on chronic widespread pain in fibromyalgia. *Brain* 2007; **130**: 2661-2670 [PMID: 17872930 DOI: 10.1093/brain/awm189]
- 30 **Boyer L**, Dousset A, Roussel P, Dossetto N, Cammilleri S, Piano V, Khalfa S, Mundler O, Donnet A, Guedj E. rTMS in fibromyalgia: a randomized trial evaluating QoL and its brain metabolic substrate. *Neurology* 2014; **82**: 1231-1238 [PMID: 24670891 DOI: 10.1212/WNL.000000000000280]
- 31 **Wassermann EM**, Lisanby SH. Therapeutic application of repetitive transcranial magnetic stimulation: a review. *Clin Neurophysiol* 2001; **112**: 1367-1377 [PMID: 11459676 DOI: 10.1016/S1388-2457(01)00585-5]
- 32 **Galhardoni R**, Correia GS, Araujo H, Yeng LT, Fernandes DT, Kaziyama HH, Marcolin MA, Bouhassira D, Teixeira MJ, de Andrade DC. Repetitive transcranial magnetic stimulation in chronic pain: a review of the literature. *Arch Phys Med Rehabil* 2015; **96**: S156-S172 [PMID: 25437106 DOI: 10.1016/j.apmr.2014.11.010]
- 33 **Picarelli H**, Teixeira MJ, de Andrade DC, Myczkowski ML, Luvisotto TB, Yeng LT, Fonoff ET, Pridmore S, Marcolin MA. Repetitive transcranial magnetic stimulation is efficacious as an add-on to pharmacological therapy in complex regional pain syndrome (CRPS) type I. *J Pain* 2010; **11**: 1203-1210 [PMID: 20430702 DOI: 10.1016/j.jpain.2010.02.006]
- 34 **Jetté F**, Côté I, Meziane HB, Mercier C. Effect of single-session repetitive transcranial magnetic stimulation applied over the hand versus leg motor area on pain after spinal cord injury. *Neurorehabil Neural Repair* 2013; **27**: 636-643 [PMID: 23579183 DOI: 10.1177/1545968313484810]
- 35 **Defrin R**, Grunhaus L, Zamir D, Zeilig G. The effect of a series of repetitive transcranial magnetic stimulations of the motor cortex on central pain after spinal cord injury. *Arch Phys Med Rehabil* 2007; **88**: 1574-1580 [PMID: 18047871 DOI: 10.1016/j.apmr.2007.07.025]
- 36 **Kang BS**, Shin HI, Bang MS. Effect of repetitive transcranial magnetic stimulation over the hand motor cortical area on central pain after spinal cord injury. *Arch Phys Med Rehabil* 2009; **90**: 1766-1771 [PMID: 19801069 DOI: 10.1016/j.apmr.2009.04.008]
- 37 **Matsumura Y**, Hirayama T, Yamamoto T. Comparison between pharmacologic evaluation and repetitive transcranial magnetic stimulation-induced analgesia in poststroke pain patients. *Neuromodulation* 2013; **16**: 349-354; discussion 354 [PMID: 23311356 DOI: 10.1111/ner.12019]
- 38 **Mhalla A**, Baudic S, Ciampi de Andrade D, Gautron M, Perrot S, Teixeira MJ, Attal N, Bouhassira D. Long-term maintenance of the analgesic effects of transcranial magnetic stimulation in fibromyalgia. *Pain* 2011; **152**: 1478-1485 [PMID: 21397400 DOI: 10.1016/j.pain.2011.01.034]
- 39 **Lee SJ**, Kim DY, Chun MH, Kim YG. The effect of repetitive transcranial magnetic stimulation on fibromyalgia: a randomized sham-controlled trial with 1-mo follow-up. *Am J Phys Med Rehabil* 2012; **91**: 1077-1085 [PMID: 23159954 DOI: 10.1097/PHM.0b013e3182745a04]
- 40 **Yilmaz B**, Kesikburun S, Yaşar E, Tan AK. The effect of repetitive transcranial magnetic stimulation on refractory neuropathic pain in spinal cord injury. *J Spinal Cord Med* 2014; **37**: 397-400 [PMID: 24621025 DOI: 10.1179/2045772313Y.0000000172]
- 41 **Rollnik JD**, Wüstefeld S, Däuper J, Karst M, Fink M, Kossev A, Dengler R. Repetitive transcranial magnetic stimulation for the treatment of chronic pain - a pilot study. *Eur Neurol* 2002; **48**: 6-10 [PMID: 12138303 DOI: 10.1159/000064950]
- 42 **Nizard J**, Lefaucheur JP, Helbert M, de Chauvigny E, Nguyen JP. Non-invasive stimulation therapies for the treatment of refractory pain. *Discov Med* 2012; **14**: 21-31 [PMID: 22846200]
- 43 **Fierro B**, De Tommaso M, Giglia F, Giglia G, Palermo A, Brighina F. Repetitive transcranial magnetic stimulation (rTMS) of the dorsolateral prefrontal cortex (DLPFC) during capsaicin-induced pain: modulatory effects on motor cortex excitability. *Exp Brain Res* 2010; **203**: 31-38 [PMID: 20232062 DOI: 10.1007/s00221-010-2206-6]
- 44 **Hallett M**. Transcranial magnetic stimulation: a primer. *Neuron* 2007; **55**: 187-199 [PMID: 17640522 DOI: 10.1016/j.neuron.2007.06.026]
- 45 **Cooke SF**, Bliss TV. Plasticity in the human central nervous system. *Brain* 2006; **129**: 1659-1673 [PMID: 16672292 DOI: 10.1093/brain/awl082]
- 46 **Brighina F**, Piazza A, Vitello G, Aloisio A, Palermo A, Daniele O, Fierro B. rTMS of the prefrontal cortex in the treatment of chronic migraine: a pilot study. *J Neurol Sci* 2004; **227**: 67-71 [PMID: 15546593 DOI: 10.1016/j.jns.2004.08.008]
- 47 **Conforto AB**, Amaro E, Gonçalves AL, Mercante JP, Guendler VZ, Ferreira JR, Kirschner CC, Peres MF. Randomized, proof-of-principle clinical trial of active transcranial magnetic stimulation in chronic migraine. *Cephalalgia* 2014; **34**: 464-472 [PMID: 24326236 DOI: 10.1177/0333102413515340]
- 48 **Pleger B**, Janssen F, Schwenkreis P, Völker B, Maier C, Tegenthoff M. Repetitive transcranial magnetic stimulation of the motor cortex attenuates pain perception in complex regional pain syndrome type I. *Neurosci Lett* 2004; **356**: 87-90 [PMID: 14746870 DOI: 10.1016/j.neulet.2003.11.037]
- 49 **Johnson S**, Summers J, Pridmore S. Changes to somatosensory detection and pain thresholds following high frequency repetitive TMS of the motor cortex in individuals suffering from chronic pain. *Pain* 2006; **123**: 187-192 [PMID: 16616419 DOI: 10.1016/j.pain.2006.02.030]
- 50 **Fregni F**, Potvin K, Dasilva D, Wang X, Lenkinski RE, Freedman SD, Pascual-Leone A. Clinical effects and brain metabolic correlates in non-invasive cortical neuromodulation for visceral pain. *Eur J Pain* 2011; **15**: 53-60 [PMID: 20822942 DOI: 10.1016/j.ejpain.2010.08.002]
- 51 **Melchior C**, Gourcerol G, Chastan N, Verin E, Menard JF, Ducrotte P, Leroi AM. Effect of transcranial magnetic stimulation on rectal sensitivity in irritable bowel syndrome: a randomized, placebo-controlled pilot study. *Colorectal Dis* 2014; **16**: O104-O111 [PMID: 24119239 DOI: 10.1111/codi.12450]
- 52 **Avery DH**, Zarkowski P, Krashin D, Rho WK, Wajdik C, Joesch JM, Haynor DR, Buchwald D, Roy-Byrne P. Transcranial magnetic stimulation in the treatment of chronic widespread pain: a randomized controlled study. *J ECT* 2015; **31**: 57-66 [PMID: 24755729 DOI: 10.1097/YCT.000000000000125]
- 53 **Sommer M**, Alfaro A, Rummel M, Speck S, Lang N, Tings T, Paulus W. Half sine, monophasic and biphasic transcranial magnetic stimulation of the human motor cortex. *Clin Neurophysiol* 2006; **117**: 838-844 [PMID: 16495145 DOI: 10.1016/j.clinph.2005.10.029]
- 54 **Arai N**, Okabe S, Furubayashi T, Terao Y, Yuasa K, Ugawa Y. Comparison between short train, monophasic and biphasic repetitive transcranial magnetic stimulation (rTMS) of the human motor cortex. *Clin Neurophysiol* 2005; **116**: 605-613 [PMID: 15721074 DOI: 10.1016/j.clinph.2004.09.020]
- 55 **Di Lazzaro V**, Oliviero A, Berardelli A, Mazzone P, Insola A, Pilato F, Saturno E, Dileone M, Tonali PA, Rothwell JC. Direct demonstration of the effects of repetitive transcranial magnetic stimulation on the excitability of the human motor cortex. *Exp Brain Res* 2002; **144**: 549-553 [PMID: 12037639 DOI: 10.1007/s00221-002-1106-9]
- 56 **Berardelli A**, Inghilleri M, Cruccu G, Manfredi M. Descending volley after electrical and magnetic transcranial stimulation in man. *Neurosci Lett* 1990; **112**: 54-58 [PMID: 2385364 DOI: 10.1016/0304-3940(90)90321-Y]
- 57 **Di Lazzaro V**, Oliviero A, Pilato F, Saturno E, Dileone M, Mazzone P, Insola A, Tonali PA, Rothwell JC. The physiological basis of transcranial motor cortex stimulation in conscious humans. *Clin Neurophysiol* 2004; **115**: 255-266 [PMID: 14744565 DOI: 10.1016/j.clinph.2003.10.009]
- 58 **Inghilleri M**, Berardelli A, Cruccu G, Priori A, Manfredi M. Corticospinal potentials after transcranial stimulation in humans. *J Neurol Neurosurg Psychiatry* 1989; **52**: 970-974 [PMID: 2552023 DOI: 10.1136/jnnp.52.8.970]

- 59 **Gilio F**, Conte A, Vanacore N, Frasca V, Inghilleri M, Berardelli A. Excitatory and inhibitory after-effects after repetitive magnetic transcranial stimulation (rTMS) in normal subjects. *Exp Brain Res* 2007; **176**: 588-593 [PMID: 16900360 DOI: 10.1007/s00221-006-0638-9]
- 60 **Brighina F**, De Tommaso M, Giglia F, Scalia S, Cosentino G, Puma A, Panetta M, Giglia G, Ferro B. Modulation of pain perception by transcranial magnetic stimulation of left prefrontal cortex. *J Headache Pain* 2011; **12**: 185-191 [PMID: 21350791 DOI: 10.1007/s10194-011-0322-8]
- 61 **Taylor JJ**, Borckardt JJ, George MS. Endogenous opioids mediate left dorsolateral prefrontal cortex rTMS-induced analgesia. *Pain* 2012; **153**: 1219-1225 [PMID: 22444187 DOI: 10.1016/j.pain.2012.02.030]
- 62 **Zunhammer M**, Busch V, Griesbach F, Landgrebe M, Hajak G, Langguth B. rTMS over the cerebellum modulates temperature detection and pain thresholds through peripheral mechanisms. *Brain Stimul* 2011; **4**: 210-217.e1 [PMID: 22032736 DOI: 10.1016/j.brs.2010.11.002]
- 63 **Short EB**, Borckardt JJ, Anderson BS, Frohman H, Beam W, Reeves ST, George MS. Ten sessions of adjunctive left prefrontal rTMS significantly reduces fibromyalgia pain: a randomized, controlled pilot study. *Pain* 2011; **152**: 2477-2484 [PMID: 21764215 DOI: 10.1016/j.pain.2011.05.033]
- 64 **Pascual-Leone A**, Tormos JM, Keenan J, Tarazona F, Cañete C, Catalá MD. Study and modulation of human cortical excitability with transcranial magnetic stimulation. *J Clin Neurophysiol* 1998; **15**: 333-343 [PMID: 9736467 DOI: 10.1097/00004691-199807000-00005]
- 65 **Zangen A**, Roth Y, Voller B, Hallett M. Transcranial magnetic stimulation of deep brain regions: evidence for efficacy of the H-coil. *Clin Neurophysiol* 2005; **116**: 775-779 [PMID: 15792886 DOI: 10.1016/j.clinph.2004.11.008]
- 66 **Roth Y**, Amir A, Levkovitz Y, Zangen A. Three-dimensional distribution of the electric field induced in the brain by transcranial magnetic stimulation using figure-8 and deep H-coils. *J Clin Neurophysiol* 2007; **24**: 31-38 [PMID: 17277575 DOI: 10.1097/WNP.0b013e31802fa393]
- 67 **Kranz G**, Shamim EA, Lin PT, Kranz GS, Hallett M. Transcranial magnetic brain stimulation modulates blepharospasm: a randomized controlled study. *Neurology* 2010; **75**: 1465-1471 [PMID: 20956792 DOI: 10.1212/WNL.0b013e3181f8814d]
- 68 **Harel EV**, Zangen A, Roth Y, Reti I, Braw Y, Levkovitz Y. H-coil repetitive transcranial magnetic stimulation for the treatment of bipolar depression: an add-on, safety and feasibility study. *World J Biol Psychiatry* 2011; **12**: 119-126 [PMID: 20854181 DOI: 10.3109/15622975.2010.510893]
- 69 **Harel EV**, Rabany L, Deutsch L, Bloch Y, Zangen A, Levkovitz Y. H-coil repetitive transcranial magnetic stimulation for treatment resistant major depressive disorder: An 18-week continuation safety and feasibility study. *World J Biol Psychiatry* 2014; **15**: 298-306 [PMID: 22313023 DOI: 10.3109/15622975.2011.639802]
- 70 **Loo CK**, Taylor JL, Gandevia SC, McDermont BN, Mitchell PB, Sachdev PS. Transcranial magnetic stimulation (TMS) in controlled treatment studies: are some "sham" forms active? *Biol Psychiatry* 2000; **47**: 325-331 [PMID: 10686267 DOI: 10.1016/S0006-3223(99)00285-1]
- 71 **Lisanby SH**, Gutman D, Lubner B, Schroeder C, Sackeim HA. Sham TMS: intracerebral measurement of the induced electrical field and the induction of motor-evoked potentials. *Biol Psychiatry* 2001; **49**: 460-463 [PMID: 11274658 DOI: 10.1016/S0006-3223(00)01110-0]
- 72 **Rossi S**, Ferro M, Cincotta M, Ulivelli M, Bartalini S, Miniussi C, Giovannelli F, Passero S. A real electro-magnetic placebo (REMP) device for sham transcranial magnetic stimulation (TMS). *Clin Neurophysiol* 2007; **118**: 709-716 [PMID: 17188568 DOI: 10.1016/j.clinph.2006.11.005]
- 73 **Mennemeier M**, Triggs W, Chelette K, Woods A, Kimbrell T, Dornhoffer J. Sham Transcranial Magnetic Stimulation Using Electrical Stimulation of the Scalp. *Brain Stimul* 2009; **2**: 168-173 [PMID: 20160893 DOI: 10.1016/j.brs.2009.02.002]
- 74 **Arana AB**, Borckardt JJ, Ricci R, Anderson B, Li X, Linder KJ, Long J, Sackeim HA, George MS. Focal electrical stimulation as a sham control for repetitive transcranial magnetic stimulation: Does it truly mimic the cutaneous sensation and pain of active prefrontal repetitive transcranial magnetic stimulation? *Brain Stimul* 2008; **1**: 44-51 [PMID: 19424459 DOI: 10.1016/j.brs.2007.08.006]
- 75 **Pascual-Leone A**, Valls-Solé J, Wassermann EM, Hallett M. Responses to rapid-rate transcranial magnetic stimulation of the human motor cortex. *Brain* 1994; **117** (Pt4): 847-858 [PMID: 7922470 DOI: 10.1093/brain/117.4.847]
- 76 **Rumi DO**, Gattaz WF, Rigonatti SP, Rosa MA, Fregni F, Rosa MO, Mansur C, Myczkowski ML, Moreno RA, Marcolin MA. Transcranial magnetic stimulation accelerates the antidepressant effect of amitriptyline in severe depression: a double-blind placebo-controlled study. *Biol Psychiatry* 2005; **57**: 162-166 [PMID: 15652875 DOI: 10.1016/j.biopsych.2004.10.029]
- 77 **de Andrade DC**, Mhalla A, Adam F, Texeira MJ, Bouhassira D. Neuropharmacological basis of rTMS-induced analgesia: the role of endogenous opioids. *Pain* 2011; **152**: 320-326 [PMID: 21146300 DOI: 10.1016/j.pain.2010.10.032]
- 78 **Lorenz J**, Minoshima S, Casey KL. Keeping pain out of mind: the role of the dorsolateral prefrontal cortex in pain modulation. *Brain* 2003; **126**: 1079-1091 [PMID: 12690048 DOI: 10.1093/brain/awg102]
- 79 **Ziemann U**, Tergau F, Wischer S, Hildebrandt J, Paulus W. Pharmacological control of facilitatory I-wave interaction in the human motor cortex. A paired transcranial magnetic stimulation study. *Electroencephalogr Clin Neurophysiol* 1998; **109**: 321-330 [PMID: 9751295 DOI: 10.1016/S0924-980X(98)00023-X]
- 80 **Wu T**, Sommer M, Tergau F, Paulus W. Lasting influence of repetitive transcranial magnetic stimulation on intracortical excitability in human subjects. *Neurosci Lett* 2000; **287**: 37-40 [PMID: 10841985 DOI: 10.1016/S0304-3940(00)01132-0]
- 81 **Di Lazzaro V**, Oliviero A, Saturno E, Pilato F, Insola A, Mazzone P, Profice P, Tonali P, Rothwell JC. The effect on corticospinal volleys of reversing the direction of current induced in the motor cortex by transcranial magnetic stimulation. *Exp Brain Res* 2001; **138**: 268-273 [PMID: 11417469 DOI: 10.1007/s002210100722]
- 82 **Ziemann U**. TMS induced plasticity in human cortex. *Rev Neurosci* 2004; **15**: 253-266 [PMID: 15526550 DOI: 10.1515/REVNEURO.2004.15.4.253]
- 83 **Cincotta M**, Borgheresi A, Gambetti C, Balestrieri F, Rossi L, Zaccara G, Ulivelli M, Rossi S, Civardi C, Cantello R. Suprathreshold 0.3 Hz repetitive TMS prolongs the cortical silent period: potential implications for therapeutic trials in epilepsy. *Clin Neurophysiol* 2003; **114**: 1827-1833 [PMID: 14499744 DOI: 10.1016/S1388-2457(03)00181-0]
- 84 **Daskalakis ZJ**, Möller B, Christensen BK, Fitzgerald PB, Gunraj C, Chen R. The effects of repetitive transcranial magnetic stimulation on cortical inhibition in healthy human subjects. *Exp Brain Res* 2006; **174**: 403-412 [PMID: 16683138 DOI: 10.1007/s00221-006-0472-0]
- 85 **Murase N**, Rothwell JC, Kaji R, Urushihara R, Nakamura K, Murayama N, Igasaki T, Sakata-Igasaki M, Mima T, Ikeda A, Shibasaki H. Subthreshold low-frequency repetitive transcranial magnetic stimulation over the premotor cortex modulates writer's cramp. *Brain* 2005; **128**: 104-115 [PMID: 15483042 DOI: 10.1093/brain/awh315]
- 86 **Filipović SR**, Rothwell JC, Bhatia K. Slow (1 Hz) repetitive transcranial magnetic stimulation (rTMS) induces a sustained change in cortical excitability in patients with Parkinson's disease. *Clin Neurophysiol* 2010; **121**: 1129-1137 [PMID: 20350836 DOI: 10.1016/j.clinph.2010.01.031]
- 87 **Malenka RC**, Bear MF. LTP and LTD: an embarrassment of riches. *Neuron* 2004; **44**: 5-21 [PMID: 15450156 DOI: 10.1016/j.neuron.2004.09.012]
- 88 **Ji RR**, Schlaepfer TE, Aizenman CD, Epstein CM, Qiu D, Huang JC, Rupp F. Repetitive transcranial magnetic stimulation activates specific regions in rat brain. *Proc Natl Acad Sci USA* 1998; **95**: 15635-15640 [PMID: 9861022 DOI: 10.1073/pnas.95.26.15635]

- 89 **Hausmann A**, Weis C, Marksteiner J, Hinterhuber H, Humpel C. Chronic repetitive transcranial magnetic stimulation enhances c-fos in the parietal cortex and hippocampus. *Brain Res Mol Brain Res* 2000; **76**: 355-362 [PMID: 10762712 DOI: 10.1016/S0169-328X(00)00024-3]
- 90 **Müller MB**, Toschi N, Kresse AE, Post A, Keck ME. Long-term repetitive transcranial magnetic stimulation increases the expression of brain-derived neurotrophic factor and cholecystokinin mRNA, but not neuropeptide tyrosine mRNA in specific areas of rat brain. *Neuropsychopharmacology* 2000; **23**: 205-215 [PMID: 10882847 DOI: 10.1016/S0893-133X(00)00099-3]
- 91 **Rothwell J**, Burke D, Hicks R, Stephen J, Woodforth I, Crawford M. Transcranial electrical stimulation of the motor cortex in man: further evidence for the site of activation. *J Physiol* 1994; **481** (Pt1): 243-250 [PMID: 7853247 DOI: 10.1113/jphysiol.1994.sp020435]
- 92 **Berardelli A**, Inghilleri M, Rothwell JC, Romeo S, Currà A, Gilio F, Modugno N, Manfredi M. Facilitation of muscle evoked responses after repetitive cortical stimulation in man. *Exp Brain Res* 1998; **122**: 79-84 [PMID: 9772114 DOI: 10.1007/s002210050493]
- 93 **Di Lazzaro V**, Oliviero A, Tonali PA, Marra C, Daniele A, Profice P, Saturno E, Pilato F, Masullo C, Rothwell JC. Noninvasive in vivo assessment of cholinergic cortical circuits in AD using transcranial magnetic stimulation. *Neurology* 2002; **59**: 392-397 [PMID: 12177373 DOI: 10.1212/WNL.59.3.392]
- 94 **Inghilleri M**, Conte A, Frasca V, Gilio F, Lorenzano C, Berardelli A. Synaptic potentiation induced by rTMS: effect of lidocaine infusion. *Exp Brain Res* 2005; **163**: 114-117 [PMID: 15940502 DOI: 10.1007/s00221-005-2225-x]
- 95 **Jennum P**, Winkel H, Fuglsang-Frederiksen A. Repetitive magnetic stimulation and motor evoked potentials. *Electroencephalogr Clin Neurophysiol* 1995; **97**: 96-101 [PMID: 7537209 DOI: 10.1016/0924-980X(94)00293-G]
- 96 **Berardelli A**, Inghilleri M, Gilio F, Romeo S, Pedace F, Currà A, Manfredi M. Effects of repetitive cortical stimulation on the silent period evoked by magnetic stimulation. *Exp Brain Res* 1999; **125**: 82-86 [PMID: 10100980 DOI: 10.1007/s002210050661]
- 97 **Chen R**. Studies of human motor physiology with transcranial magnetic stimulation. *Muscle Nerve Suppl* 2000; **9**: S26-S32 [PMID: 11135281 DOI: 10.1002/1097-4598]
- 98 **Romeo S**, Gilio F, Pedace F, Ozkaynak S, Inghilleri M, Manfredi M, Berardelli A. Changes in the cortical silent period after repetitive magnetic stimulation of cortical motor areas. *Exp Brain Res* 2000; **135**: 504-510 [PMID: 11156314 DOI: 10.1007/s002210000541]
- 99 **Modugno N**, Nakamura Y, MacKinnon CD, Filipovic SR, Bestmann S, Berardelli A, Rothwell JC. Motor cortex excitability following short trains of repetitive magnetic stimuli. *Exp Brain Res* 2001; **140**: 453-459 [PMID: 11685398 DOI: 10.1007/s002210100843]
- 100 **Lorenzano C**, Gilio F, Inghilleri M, Conte A, Fofi L, Manfredi M, Berardelli A. Spread of electrical activity at cortical level after repetitive magnetic stimulation in normal subjects. *Exp Brain Res* 2002; **147**: 186-192 [PMID: 12410333 DOI: 10.1007/s00221-002-1237-z]
- 101 **Inghilleri M**, Conte A, Frasca V, Curra' A, Gilio F, Manfredi M, Berardelli A. Antiepileptic drugs and cortical excitability: a study with repetitive transcranial stimulation. *Exp Brain Res* 2004; **154**: 488-493 [PMID: 14579005 DOI: 10.1007/s00221-003-1685-0]
- 102 **Ben-Shachar D**, Belmaker RH, Grisaru N, Klein E. Transcranial magnetic stimulation induces alterations in brain monoamines. *J Neural Transm* (Vienna) 1997; **104**: 191-197 [PMID: 9203081 DOI: 10.1007/BF01273180]
- 103 **Hoogendam JM**, Ramakers GM, Di Lazzaro V. Physiology of repetitive transcranial magnetic stimulation of the human brain. *Brain Stimul* 2010; **3**: 95-118 [PMID: 20633438 DOI: 10.1016/j.brs.2009.10.005]
- 104 **Hirayama A**, Saitoh Y, Kishima H, Shimokawa T, Oshino S, Hirata M, Kato A, Yoshimine T. Reduction of intractable deafferentation pain by navigation-guided repetitive transcranial magnetic stimulation of the primary motor cortex. *Pain* 2006; **122**: 22-27 [PMID: 16495011 DOI: 10.1016/j.pain.2005.12.001]
- 105 **Goto T**, Saitoh Y, Hashimoto N, Hirata M, Kishima H, Oshino S, Tani N, Hosomi K, Kakigi R, Yoshimine T. Diffusion tensor fiber tracking in patients with central post-stroke pain; correlation with efficacy of repetitive transcranial magnetic stimulation. *Pain* 2008; **140**: 509-518 [PMID: 19004554 DOI: 10.1016/j.pain.2008.10.009]
- 106 **Lefaucheur JP**. Use of repetitive transcranial magnetic stimulation in pain relief. *Expert Rev Neurother* 2008; **8**: 799-808 [PMID: 18457536 DOI: 10.1586/14737175.8.5.799]
- 107 **Wasserman EM**, Epstein CM, Ziemann U, Walsh V, Paus T, Lisanby SH. *The Oxford Handbook of Transcranial Stimulation*. Oxford: Oxford University Press, 2008
- 108 **Ahmed MA**, Mohamed SA, Sayed D. Long-term antalgic effects of repetitive transcranial magnetic stimulation of motor cortex and serum beta-endorphin in patients with phantom pain. *Neurol Res* 2011; **33**: 953-958 [PMID: 22080997 DOI: 10.1179/1743132811Y.00000000045]
- 109 **Hosomi K**, Shimokawa T, Ikoma K, Nakamura Y, Sugiyama K, Ugawa Y, Uozumi T, Yamamoto T, Saitoh Y. Daily repetitive transcranial magnetic stimulation of primary motor cortex for neuropathic pain: a randomized, multicenter, double-blind, crossover, sham-controlled trial. *Pain* 2013; **154**: 1065-1072 [PMID: 23623156 DOI: 10.1016/j.pain.2013.03.016]
- 110 **Ceccanti M**, Inghilleri M, Attilia ML, Raccach R, Fiore M, Zangen A, Ceccanti M. Deep TMS on alcoholics: effects on cortisolemia and dopamine pathway modulation. A pilot study. *Can J Physiol Pharmacol* 2015; **93**: 283-290 [PMID: 25730614 DOI: 10.1139/cjpp-2014-0188]
- 111 **Kakigi R**, Inui K, Tamura Y. Electrophysiological studies on human pain perception. *Clin Neurophysiol* 2005; **116**: 743-763 [PMID: 15792883 DOI: 10.1016/j.clinph.2004.11.016]
- 112 **Cincotta M**, Giovannelli F, Borgheresi A, Balestrieri F, Toscani L, Zaccara G, Carducci F, Viggiano MP, Rossi S. Optically tracked neuronavigation increases the stability of hand-held focal coil positioning: evidence from "transcranial" magnetic stimulation-induced electrical field measurements. *Brain Stimul* 2010; **3**: 119-123 [PMID: 20633439 DOI: 10.1016/j.brs.2010.01.001]
- 113 **Ahdab R**, Ayache SS, Brugières P, Goujon C, Lefaucheur JP. Comparison of "standard" and "navigated" procedures of TMS coil positioning over motor, premotor and prefrontal targets in patients with chronic pain and depression. *Neurophysiol Clin* 2010; **40**: 27-36 [PMID: 20230933 DOI: 10.1016/j.neucli.2010.01.001]
- 114 **Bashir S**, Edwards D, Pascual-Leone A. Neuronavigation increases the physiologic and behavioral effects of low-frequency rTMS of primary motor cortex in healthy subjects. *Brain Topogr* 2011; **24**: 54-64 [PMID: 21076861 DOI: 10.1007/s10548-010-0165-7]
- 115 **Saitoh Y**. Validation and the future of stimulation therapy of the primary motor cortex. *Neurol Med Chir* (Tokyo) 2012; **52**: 451-456 [PMID: 22850491 DOI: 10.2176/nmc.52.451]
- 116 **Lefaucheur JP**, Drouot X, Nguyen JP. Interventional neurophysiology for pain control: duration of pain relief following repetitive transcranial magnetic stimulation of the motor cortex. *Neurophysiol Clin* 2001; **31**: 247-252 [PMID: 11601430 DOI: 10.1016/S0987-7053(01)00260-X]
- 117 **Irlbacher K**, Kuhnert J, Rörich S, Meyer BU, Brandt SA. [Central and peripheral deafferent pain: therapy with repetitive transcranial magnetic stimulation]. *Nervenarzt* 2006; **77**: 1196, 1198-1203 [PMID: 16955313 DOI: 10.1007/s00115-006-2148-1]
- 118 **Lefaucheur JP**, Hatem S, Nineb A, Ménard-Lefaucheur I, Wendling S, Keravel Y, Nguyen JP. Somatotopic organization of the analgesic effects of motor cortex rTMS in neuropathic pain. *Neurology* 2006; **67**: 1998-2004 [PMID: 17159107 DOI: 10.1212/01.wnl.0000247138.85330.88]
- 119 **André-Obadia N**, Mertens P, Gueguen A, Peyron R, Garcia-Larrea L. Pain relief by rTMS: differential effect of current flow but no specific action on pain subtypes. *Neurology* 2008; **71**: 833-840 [PMID: 18779511 DOI: 10.1212/01.wnl.0000325481.61471.f0]
- 120 **Lefaucheur JP**, Drouot X, Ménard-Lefaucheur I, Keravel Y, Nguyen JP. Motor cortex rTMS in chronic neuropathic pain: pain relief is associated with thermal sensory perception improvement. *J Neurol Neurosurg Psychiatry* 2008; **79**: 1044-1049 [PMID:

- 18223016 DOI: 10.1136/jnnp.2007.135327]
- 121 **Carretero B**, Martin MJ, Juan A, Pradana ML, Martín B, Carral M, Jimeno T, Pareja A, Montoya P, Aguirre I, Salva J, Roca M, Gili M, Garcia-Toro M. Low-frequency transcranial magnetic stimulation in patients with fibromyalgia and major depression. *Pain Med* 2009; **10**: 748-753 [PMID: 19460131 DOI: 10.1111/j.1526-4637.2009.00625.x]
- 122 **Lefaucheur JP**, Ayache SS, Sorel M, Farhat WH, Zouari HG, Ciampi de Andrade D, Ahdab R, Ménard-Lefaucheur I, Brugières P, Goujon C. Analgesic effects of repetitive transcranial magnetic stimulation of the motor cortex in neuropathic pain: influence of theta burst stimulation priming. *Eur J Pain* 2012; **16**: 1403-1413 [PMID: 22508405 DOI: 10.1002/j.1532-2149.2012.00150.x]
- 123 **Dall'Agnol L**, Medeiros LF, Torres IL, Deitos A, Brietzke A, Laste G, de Souza A, Vieira JL, Fregni F, Caumo W. Repetitive transcranial magnetic stimulation increases the corticospinal inhibition and the brain-derived neurotrophic factor in chronic myofascial pain syndrome: an explanatory double-blinded, randomized, sham-controlled trial. *J Pain* 2014; **15**: 845-855 [PMID: 24865417 DOI: 10.1016/j.jpain.2014.05.001]
- 124 **Hodaj H**, Alibeu JP, Payen JF, Lefaucheur JP. Treatment of Chronic Facial Pain Including Cluster Headache by Repetitive Transcranial Magnetic Stimulation of the Motor Cortex With Maintenance Sessions: A Naturalistic Study. *Brain Stimul* 2015; **8**: 801-807 [PMID: 25979838 DOI: 10.1016/j.brs.2015.01.416]
- 125 **Khedr EM**, Kotb HI, Mostafa MG, Mohamad MF, Amr SA, Ahmed MA, Karim AA, Kamal SM. Repetitive transcranial magnetic stimulation in neuropathic pain secondary to malignancy: a randomized clinical trial. *Eur J Pain* 2015; **19**: 519-527 [PMID: 25142867 DOI: 10.1002/ejp.576]
- 126 **Lindholm P**, Lamusuo S, Taiminen T, Pesonen U, Lahti A, Virtanen A, Forssell H, Hietala J, Hagelberg N, Pertovaara A, Parkkola R, Jääskeläinen S. Right secondary somatosensory cortex-a promising novel target for the treatment of drug-resistant neuropathic orofacial pain with repetitive transcranial magnetic stimulation. *Pain* 2015; **156**: 1276-1283 [PMID: 25830924 DOI: 10.1097/j.pain.0000000000000175]
- 127 **Borckardt JJ**, Weinstein M, Reeves ST, Kozel FA, Nahas Z, Smith AR, Byrne TK, Morgan K, George MS. Postoperative left prefrontal repetitive transcranial magnetic stimulation reduces patient-controlled analgesia use. *Anesthesiology* 2006; **105**: 557-562 [PMID: 16931989 DOI: 10.1097/00000542-200609000-00020]

**P- Reviewer:** Khashayar P, Saade NE

**S- Editor:** Song XX **L- Editor:** A **E- Editor:** Jiao XK





Published by **Baishideng Publishing Group Inc**

8226 Regency Drive, Pleasanton, CA 94588, USA

Telephone: +1-925-223-8242

Fax: +1-925-223-8243

E-mail: [bpgoffice@wjgnet.com](mailto:bpgoffice@wjgnet.com)

Help Desk: <http://www.wjgnet.com/esps/helpdesk.aspx>

<http://www.wjgnet.com>

