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

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

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**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 need.

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

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**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 decending pain inhibitory mechainsms. Current data are promising, but a careful analysis of stimulation settings and maintenance treatment design are necessary.

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**INTRODUCTION**

Chronic pain can be neuropathic, non-neuropathic, mixed, or without demonstrated origin[1]. 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%[2-4]. 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[5]. Available treatments provide mainly symptomatic relief, including nonpharmacological, pharmacological, and interventional therapies[6,7]. Unfortunately, the management of NP is not easy because the response to most drugs is not univocal[8,9]. According to recent guidelines, less than 50% of the patients with chronic NP reach symptomatic benefits with drugs[6,10,11].

In this setting, neurostimulation is a promising procedure in the treatment of pain[6,12]. 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)[6].

Specifically, TMS was first introduced in the late 1980s[13]. Initially, rTMS of the motor cortex was used to select patients for chronic stimulation by implanted electrodes[14]. 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[15-17]. 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[18]. Three main aspects influence the effect of rTMS: frequency, intensity, and duration of stimulation. In general, bursts of high-frequency stimulation (≥ 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[19,20]. In 2007, the EFNS produced the first guidelines on neurostimulation therapy for NP[6]. In recent years, new randomized controlled trials (RCTs) 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 HF-rTMS 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 maintainance 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[21-23], while repeated sessions of long-duration (at least 1000 pulses) stimulations at high-frequency (5–20 Hz) applied over repeated sessions induce pain relief[1,24-27]. RTMS seems most effective when stimulation is focal (*i.e.*, figure-of-eight rather than circular coil)[6]. 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[28-30]. This last aspect is the keystone for the clinical benefit[31,32]. However, this feature requires better characterization[6]. The TMS parameters vary in the studies, and it is complex to establish the best stimulation parameters to use[12]. The role of coil orientation, time of train of stimulation, inter-train interval, and number of trains, is also to definite[12].

Moreover, 22 of the 32 studies had small sample sizes, with less than 30 enroled patients, and only 16 of 32 studies recruited homogeneous populations of patients (CRPS, spinal cord injury, diabetic polyneuropathy, poststroke pain and fybromialgia), reducing assurance about which states are more responsive to TMS[1,28-30,33-41]. 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[1,42].

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 fibromialgia[39,43] (Figure 1).

Also tDCS, a technique that elicits constant weak electric currents through the scalp throught 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[23].

The mechanisms underlying the effect of rTMS in pain are not clearly identified, but probably involve neuronal plasticity[44,45]. Therefore it is suggested that maintenance therapy for longer intervals should prolong long-lasting effects. Unfortunately, only one study to date evaluated long-term rTMS maintenance therapy[38].

***Efficacy of rTMS in non-NP***

In the past ten years, the rTMS have been also evaluated in different non-NP conditions[1].(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[1,46,47]. 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 [48-52]. Future research in this field should specifically investigate in a large number of patients the most appropriate cortical target, and the frequency of stimulation[1]. 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 proposed the first magnetic stimulator for the transcranial stimulation of the human brain, giving the prerequisite for subsequent clinical use of TMS[13]. 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[1]. The stimulus waveform can be monophasic or biphasic[53]. 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[1,54].

***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[12]. Commonly in clinical settings, the intensity of the TMS should be not able to induce a motor response[12]. 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[55-59].

However, a rationale for targeting other cortical areas exists. The DLPFC could have a role in nociceptive control[43]. 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[60]. The effect may be related to the release of endogenous opioids by the left DLPFC[61]. Also rTMS of the cerebellum has been considered for the possible lowering in pain thresholds[62]. Moreover, The left prefrontal cortex has been used in rTMS fibromyalgia studies, but only a small analgesic effect has been noted[63].

***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)[64]. When the RMT is identified, rTMS is performed in bursts of stimuli (“trains”) with a definite frequency[12].

***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[64]. HF-rTMS consists specifically of intermittent bursts of TMS pulses able to induce a long-term potentiation of synaptic activiy, which may clarify why rTMS effects can overcome the period of stimulation[64].

***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[38]. 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[1]. 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[1].

***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[12]. Other novel models are the Tilted double-coil and the Hesed (H)-coil, which drop at a depth of about 6 cm[12]. Specifically, the H-coil lets deep brain stimulation without significantly increasing induced fields in superficial cortical regions, therefore preventing the risk of adverse effects[65,66]. rTMS with theH-coil has already proved effective as an acute treatment for major depressive disorder, bipolar depression, schizophrenia and post-traumatic stress disorder[65,67-69]. Furthermore, there are ongoing studies of its use to treat a very wide range of neurological, psychiatric and medical conditions, including NP[28].

***Placebo rTMS***

Placebo effects need to be better reported[25]. Theorically, 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[70]. 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[1]. 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[1,71]. 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[72,73]. 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[72,74].

**CONSIDERATIONS ABOUT MECHANISMS OF ACTION OF rTMS**

Although the TMS acts on the superficial cortex, the generated action potentials propagate influencing distant neural networks[12]. 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 applycated on the M1 modulate the cortical excitability producing changes in the following physiological parameters: MT, MEP, silent period, intracortical facilitation, and intracortical inhibition[75]. In chronic pain, the involvement of M1 projections to pain-modulating structures has been demonstrated[23]. 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[43,61,76]. HF-rTMS on the right DLPFC has shown analgesic effects similar to M1 stimulation[46,77]. Furthermore, left DLPFC stimulation should induce an improvement of pain perception in a model of acute pain[43,78]. The left prefrontal cortex has been used in rTMS studies in patients with fibromyalgia, but it has shown a minor analgesic effect[63].

rTMS seems to modulate cortical plasticity, referred to as the functional reorganization of the inter neuron connections and neuronal properties. Inhibition of the gamma-amminobutyric acid (GABA) pathways produces cortical excitation, rather than a direct enhancement of motor cortex excitability[79-82]. On the other hand, low-frequency rTMS could increase the inhibitory corticospinal control, perhaps through GABA-B transmission, prolonging the CSP duration[1,83-86]. The changes in synaptic plasticity brought by rTMS are explained by long term potentiation (LTP) and long term depression (LTD)[44]. 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 [45]. 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[87]. 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[87].

The long lasting effect of rTMS (late-LTP) is thought to be exercised by gene induction and protein synthesis[87]. 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[88-90]. Considerable evidence from HF-rTMS studies suggests that short-term synaptic plasticity happens at cortical rather than spinal level[91-94]. When rTMS is delivered in human subjects, the amplitude of the MEP and the duration of the CSP increases during the train[55,75,95-100]. The MEP facilitation also persists after the train ends, and it is probably due to the recruitment of cortical excitatory interneurons[55,75,92,94,99]. 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[59,101].

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[102]. Moreover, serotonin levels increased in the hippocampus[102]. 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[1,103].

**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[23]. 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[1,104,105]. Unfortunately, objective indicators of perceived pain, including MEP and RIII, were considered in only two studies neurophysiological[15,28]. 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[1,6,17,23-25,32,106]. rTMS has become a promising therapeutic tool for a variety of neurological and psychiatric diseases[107]. Different types of NP respond to rTMS, and this is producing a fast growth in researchers interested in rTMS for clinical purposes [6,26,108-110]. Unfortunately at the current time in the lack of large studies, only careful recommendations of rTMS can be suggested[1,6]. The efficacy of a single HF-rTMS session persists for some days, and it could extend with the repetition of sessions[1]. 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[111]. 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[112-114].

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[115].

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.

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**Figure 1 Analgesic efficacy of repetitive transcranial magnetic stimulation according to the cortical target.**

**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, n sessions** | **Outcomes** | **Efficacy** |
| **NP** |  |  |  |  |  |  |  |  |
| Lefaucheur *et al*[26] | Intractable neurogenic pain | Double-blind, controlled, crossover | 18 (12 central NP; 6 peripheral NP) | F8 | Hand M1 | 0.5 Hz – 10 Hz80% RMT1 | Pain intensity | Analgesic effect (only for 10 Hz) |
| Lefaucheur *et al*[116] | Pain due to thalamic stroke or trigeminal neuropathy | Double-blind, controlled, crossover | 14 (7 central NP; 7 peripheral NP) | F8 | Hand M1 | 10 Hz80% RMT1 | VAS | Decrease in VAS |
| Rollnik *et al*[41] | Chronic refractory NP | Double-blind, controlled, crossover | 12 (2 central NP; 7 peripheral NP; 2 CRPS; 1 osteomyelitis) | Double coin – Circular coin | M1 | 20 Hz80% RMT1 | VAS | No effect |
| Lefaucheur *et al*[27] | 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 Hz80% RMT1 | VAS, thermal sensory thresholds | Analgesic effect mainly in trigeminal nerve lesions |
| Khedr *et al*[25] | Trigeminal neuralgia and post-stroke pain syndrome | Double-blind, controlled | 48 (24 central NP; 24 trigeminal NP) | F8 | Hand M1 | 20 Hz80% RMT5 | VAS and the LANSS scale | Analgesic effect |
| Andrè-Obadia *et al*[22] | Chronic refractory NP | Double-blind, controlled, crossover | 14(11 central NP; 3 peripheral NP)  | F8 | Hand M1 | 1-20 Hz90% RMT1 | VAS | Analgesic effect (only for 20 Hz) |
| Hirayama *et al*[104] | Intractable deafferentation pain | Double-blind, controlled, crossover | 20(14 central NP; 6 peripheral NP) | F8 | M1 | 5 Hz90% RMT1 | VAS and SF-MPQ | Analgesic effect |
| Irlbarcher *et al*[117] | Chronic NP | Double-blind, controlled | 27(13 central NP; 14 phantom p) | F8 | M1 | 1-5 Hz95% RMT5 | VAS | No effect |
| Lefaucheur *et al*[15]  | Unilateral hand pain of various neurologic origins | Double-blind, controlled, crossover | 22(14 central NP; 8 peripheral NP) | F8 | Hand M1 | 10 Hz90% RMT1 | Motor threshold at rest, MEP amplitude, CSP, ICI  | ICI increase |
| Lefaucheur *et al*[118] | Chronic NP | Double-blind, controlled, crossover | 36 | F8 | Face M1 | 10 Hz80% RMT1 | VAS | Analgesic effect with the stimulation applied on area adjacent to the cortical representation of the painful zone |
| Defrin *et al*[35] | Spinal cord injury | Double-blind, controlled | 12 | F8 | Vertex | 5 Hz115% RMT10 | VAS, MPQ, pain threshold | Increased heat pain threshold  |
| Passard *et al*[29] | Fibromyalgia | Double-blind, controlled | 30 | F8 | M1 | 10 Hz80% RMT10 | VAS, MPQ, quality of life (Brief Pain Inventory and the Fibromyalgia Impact Questionnaire) | Decrease in VAS and better quality of life |
| Saitoh *et al*[115] | Intractable deafferentationpain | Double-blind, controlled, crossover | 13(9 central NP; 4 peripheral NP) | F8 | M1 | 1-5-10 Hz90% RMT1 | VAS | Decrease in VAS (only for 5-10 Hz) |
| Andrè-Obadia *et al*[119] | Chronic NP | Double-blind, randomized, controlled, crossover | 28 | F8 | M1 | 20 Hz90% RMT1 | Pain relief, quality of life and rescue drug intake | Analgesic effect |
| Lefaucheur *et al*[120] | Chronic refractory NP | Double-blind, controlled, crossover | 46(23 central NP; 23 peripheral NP) | F8 | Hand M1 | 10 Hz90% RMT1 | Thresholds for thermal and mechanical sensations | Thermal perception improvement |
| Carretero *et al*[121] | Fibromyalgia | Randomized, single-blinded | 28 | Butterfly coil | DLPFC | 1 Hz110% RMT20 | FibroFatigue, Likert pain, HDRS, CBI | No effect |
| Kang *et al*[36] | Spinal cord injury | Double-blind, controlled, crossover | 11 | F8 | M1 | 10 Hz80% RMT5 | NRS, BPI | No effect |
| Picarelli *et al*[33] | CRPS type 1 | Double-blind, controlled | 23 | F8 | M1 | 10 Hz90% RMT10 | VAS, MPQ, the SF-36, HDRS | Analgesic effect and improved quality of life |
| Ahmed *et al*[108] | Phantom pain | Double-blind, controlled | 27 | F8 | DLPFC | 20 Hz80% RMT5 | VAS, LANSS scale | Decrease in VAS and LANSS scale |
| Mhalla *et al*[38] | Fibromyalgia | Double-blind, controlled | 40 | F8 | M1 | 10 Hz80% RMT14 | Pain intensity over the last 24 hours, BPI, quality of life, mood and anxiety, parameters of motor cortical excitability | Analgesic effect |
| Short *et al*[63] | Fibromyalgia | Double-blind, controlled | 20 | F8 | M1 | 10 Hz120% RMT10 | BPI, HDRS, Fibromyalgia Impact Questionnaire. | Improvement of daily pain, number of tender points, HDRS and FIQ scores |
| Lefaucheur *et al*[122] | Chronic refractory NP  | Controlled, crossover | 14 (3 localized in theface, 4 upper limb, 3 lower limb, 4 hemibody) | F8 | M1 | 10 Hz90% RMT3 | VAS | Analgesic effect |
| Hosomi *et al*[109] | NP | Double-blind, controlled, crossover | 64 | F8 | M1 | 50 Hz90% RMT10 | VAS, SF-MPQ, PGIC, and BDI | Analgesic effect |
| Onesti *et al*[28] | Diabetic neuropathy | Double-blind, controlled, crossover | 23 | H-coil | Vertex | 20 Hz100% RMT5 | VAS, area and threshold of RIII nociceptiveflexion reflex (RIII reflex | Decrease in VAS and RIII area |
| Jettè *et al*[34] | Spinal cord injury | Randomized, controlled, crossover | 16 | F8 | M1 | 10 Hz90-110% RMT3 | VAS, motor mapping parameters | Decrease in VAS |
| Boyer *et al*[30] | Fibromyalgia | Double-blind, randomized, controlled | 38 | F8 | M1 | 10 Hz90% RMT14 | FIQ, SF-36, brain metabolism | Improvement of quality of life |
| Dall’Agnol *et al*[123] | Myofascial pain syndrome | Double-blind, randomized, controlled | 24 | F8 | M1 | 10 Hz80% RMT10 | Pain quantitative sensory testing, conditioned pain modulation, TMS parameters, BDNF | Analgesic effect mediated by mechanisms enhancing the corticospinal inhibitory system and BDNF |
| Yilmaz *et al*[40] | Spinal cord injury | Double-blind, randomized, controlled | 17 | F8 | Vertex | 10 Hz110% RMT10 | VAS | No effect |
| Hodaj *et al*[124] | Chronic refractory facial pain | Open-label study | 55(19 cluster headache; 21 trigeminal neuropathic pain;15 atypical facial pain) | F8 | Face M1 | 10 Hz80% RMT12 | VAS, CGI-C scale | Analgesic effect |
| Khedr *et al*[125] | Malignant NP | Randomized, controlled | 34 | F8 | Hand M1 | 20 Hz80% RMT10 | VDS, VAS, LANSS, HDRS | Analgesic effect |
| Lindholm *et al*[126] | Neuropathic orofacial pain | Randomized, controlled, cross-over  | 16 | - | S1/M1, right SII | - | NRS, BPI | Analgesic effect (only for SII) |
| **Non-NP** |  |  |  |  |  |  |  |  |
| Brighina *et al*[46] | Migraine | Double-blind, randomized, controlled | 11 | F8 | DLPFC | 10 Hz90% RMT12 | Frequency of attacks, Headache index | Significant reduction of outcome measures |
| Pleger *et al*[48] | CRPS | Double-blind, controlled, crossover | 10 | F8 | M1 | 10 Hz110% RMT1 | VAS | Analgesic effect |
| Borckardt *et al*[127] | Postoperative pain | Double-blind, controlled | 20 | F8 | Left PFC | 10 Hz100% RMT1 | VAS for mood, opioid pump use | Reduction in opioid use |
| Johnson *et al*[49] | Low back pain | Double-blind, controlled, crossover | 17 | F8 | M1 | 20 Hz95% RMT1 | Detection and pain thresholds for cold and heat sensations | Increased heat pain threshold and lowered cold detection |
| Fregni *et al*[50] | Pancreatitis | Double-blind, controlled | 17 | F8 | SII | 1 Hz70% RMT10 | VAS, BDI | Analgesic effect |
| Conforto *et al*[47] | Migraine | Randomized, double-blind, parallel-group | 18 | - | DLPFC | - | Number of headache days | No effect |
| Melchior *et al*[51] | Irritable bowel syndrome | Double-blind, controlled, crossover | 21 | F8 | M1 | 20 Hz80% RMT5 | Pressure pain threshold, changes in maximum tolerated rectal volume, rectal compliance and average pain intensity | Maximun tolerated rectal volume and analgesic effects |
| Avery *et al*[52] | 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: Hesed; 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; CGI-C: Global impression of change scale; DLPFC: Dorsolateral prefrontal cortex; BIRS: Gracely box intensity scale.