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Modified Non-invasive Brain Stimulation in Fibromyalgia

Rozisky JR[1], Mendonca ME[2], Castillo Saavedra L[1] and Fregni F[1,2]*

[1]Spaulding Neuromodulation Center, Spaulding Rehabilitation Hospital, Harvard Medical School, Boston MA, USA
[2]Departamento de Neurociência e Comportamento (NEC), Institute of Psychology, University of São Paulo (USP), São Paulo, Brazil

Abstract

Objective: A recent review showed that rTMS and tDCS are associated with initial efficacy for the treatment of chronic pain in fibromyalgia (FM). Based on these initial positive findings, there has been an interest in testing modified methods of rTMS and tDCS for the treatment of FM. Our aim was to review efficacy of modified rTMS and tDCS in recent studies published after this initial review.

Methods: We screened electronic databases including Medline/Pubmed, Cochrane Controlled Trials Register, Embase, Google Scholar and Scopus Elsevier, entering keywords "fibromyalgia" with "HD-tDCS", "HD-direct current stimulation", "low-intensity rTMS", "low-intensity magnetic stimulation", "multi coil rTMS", and "multi coil magnetic stimulation".

Results: We found 4 studies using the following methods: (1) HD-tDCS, (2) low-intensity rTMS and (1) multi-coil rTMS in the treatment of pain in FM. They were double-blinded and sham-controlled trials. These studies used different parameters of stimulation such as number and duration of sessions, and cortical target area (low-intensity rTMS: twice-daily 40 min for seven days in the auditory cortex vs. eight consecutive weekly 20-min sessions over the entire cortex; Multi-coil rTMS: 20 daily 20 min session in the prefontal cortex; HD-tDCS: single, 20-min sessions for both cathodal and anodal stimulation of M1). These studies showed a significant improvement in pain in FM patients and also quality of life as indexed by Fibromyalgia Inventory Questionnaire in some of them. For the studies with multiple sessions, there was a long-lasting effect that varied between multi-coil rTMS and low-intensity rTMS. No serious adverse events were reported.

Conclusion: These results show that the modified NIBS techniques HD-tDCS, low-intensity rTMS and multi-coil rTMS can have a significant effect on pain symptoms in FM. It is not clear whether these methods are more efficacious or safer than standard TMS and tDCS. Development of modified rTMS and tDCS is discussed.

Keywords: Fibromyalgia; HD-tDCS; Low intensity rTMS; Multi coil rTMS; Pain

Introduction

Fibromyalgia (FM) is one of the most difficult chronic pain syndromes to treat, affecting 3% to 5% of the world population [1,2]. It is characterized by musculoskeletal pain and muscle tenderness, accompanied by depression, sleep disorders, fatigue [3], cognitive and mood disturbances, and decreased physical function [4], which leads to a decreased quality of life. Although FM is well studied, little is known about its etiology. Recently, some studies have indicated that FM is a "dysfunctional pain syndrome", given the structural and neurochemical changes found in central pain pathways affecting pain modulatory systems [5-7]. Mhalla et al. [8] showed that FM is associated with impairment of intracortical modulation, which supports the hypothesis that FM is associated with changes in cortical excitability.

Considering these central pain-processing changes in FM and given the effects of non-invasive brain stimulation (NIBS) on plasticity, particularly transcranial direct current stimulation (tDCS) [9-12] and repetitive transcranial magnetic stimulation (rTMS) [13-18], some studies have tested the effects of these techniques on chronic pain in FM [13,19-26]. Indeed, not only the effects of rTMS and tDCS on neuroplasticity, but also their effects on neuropathic pain have supported their testing in FM. The first study to test such hypothesis assessed the effects of rTMS on FM in four female subjects [19]. This study showed that low-frequency rTMS applied to the right dorsal lateral prefrontal cortex (DLPFC) reduced pain average after twenty daily sessions. After this initial study, there was further interest in testing tDCS for FM. Fregni et al. [13] tested the initial effects of tDCS in 32 female subjects. They showed that anodal tDCS over primary motor cortex (M1) induced greater pain improvement after 3 weeks. After these two studies, seven more studies have been performed through 2012.

Marlow et al. [27] reviewed the results of these studies published by 2011 and they showed a significant efficacy of both tDCS and rTMS for treating pain related to FM and improving quality of life measurements. In this review nine clinical trials were included: five used rTMS in different cortical regions (DLPFC and M1) with different frequencies (low or high), and fours studies used anodal tDCS over the M1 or DLPFC. They showed that 80% of rTMS studies that measured pain reported significant decreases, while 100% of tDCS studies reported the same result. They also showed that the most common side effects were transient headaches for active rTMS, and discomfort in the stimulation site for sham and active tDCS.

Based on these initial results, there has been an interest in investigating enhanced, safer or simpler protocols of tDCS and rTMS. Therefore, the aim of this new review is to summarize the initial efficacy and safety of modified methods of rTMS and tDCS to relieve pain related to FM, considering studies published after the review from Marlow et al. [27]. We summarized main clinical results as well as clinical characteristics, study design, sample size, exclusion criteria, intervention, main results and adverse events.

***Corresponding author:** Felipe Fregni, Spaulding Neuromodulation Center, Spaulding Rehabilitation Hospital, Harvard Medical School, 79/96 13th Street, Charlestown MA, USA, Tel: +1 617 9526156; E-mail: felipe.fregni@ppcr.hms.harvard.edu

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Methodology

Strategies for the literature search

The search of scientific literature was made through the following electronic databases: Medline/Pubmed, Cochrane Controlled Trials Register, Embase, Google Scholar and Scopus Elsevier, and the keywords used were "fibromyalgia" with "transcranial stimulation". After this initial search and the initial results, we found the following techniques and included them in our search methods: "HD-tDCS", "HD-direct current stimulation", "low-intensity rTMS", "low-intensity magnetic stimulation", "multi coil TMS", and "multi coil magnetic stimulation".

Inclusion criteria

Studies had to meet the following criteria: (1) published in English, (2) conducted in human subjects, (3) original research, (4) published after 2011 and using a modified method of rTMS and tDCS for FM pain treatment purposes, and with a prospective design (experimental and observational trials were considered), (5) patients with fibromyalgia syndrome only and (6) outcome measures with pain intensity changes.

Data extraction

Data extraction was adopted from the Cochrane Handbook of Systematic Reviews for Intervention Studies; which comprises country of origin, level of evidence and study design, study population, inclusion and exclusion criteria, intervention (multi-coil TMS or low-intensity rTMS, and HD-tDCS), session description, total number of sessions, follow-up time, totals number of patients per group (active/ sham, including proportions completing study), FM symptom measures, significant results, and side effects. The study outcome was level of pain measured by the Visual Analogue Scale (VAS) and the Brief Pain Inventory (BPI).

Results

Study selection

Our initial search strategy yielded forty articles. According to our inclusion criteria only 3 citations were included. The main reasons for exclusion were: review articles, articles not assessing FM, and articles published before Marlow's review and standard tDCS and rTMS. The full-text of these articles were reviewed and included in this review. Additionally, manual screening of the references section of these studies identified 1 additional reference.

Level of evidence and study design

All the studies were double-blinded (both the patients and the investigator were blinded for the intervention and for the outcomes assessment, expect for the individual applying the intervention), sham controlled trials. Two were conducted in the United States, one in Spain and one in Canada. Two studies applied the American College of Rheumatology criteria for FM diagnosis, and two had a formal diagnosis of FM made by a rheumatologist, who analyzed the following patients' characteristics: FM was chosen as a type of diffuse musculoskeletal pain disorder, duration greater than 6 months at the time of enrollment, pain intensity of at least 3 on a visual numerical scale (VNS), pain refractory to common analgesics and muscle relaxants.

Study sample, quality and intervention

The FM sample included 18 subjects for HD-tDCS, 71 for low-intensities TMS (54 vs. 17) and 16 for multi-coil TMS (total n = 105). Most of them were female subjects. All of them used concomitant therapy/medication in association with tDCS or TMS, with stable doses before and throughout the trial.

Outcome measures, FM symptoms improvement

The studies assessed as main outcomes changes in pain levels using the Brief Pain Inventory (BPI) questionnaire, pain thresholds measured at 18 tender points using an algometer, and VNS of pain scale. As secondary outcomes, they assessed changes in the Fibromyalgia Impact Questionnaire (FIQ), Beck Depression Inventory (BDI-II), blood serotonin levels, VNS for anxiety, Semmes-Weinstein monofilaments (SWMs) for pain and mechanical detection thresholds, and diffuse noxious inhibitory controls (DNICs).

In terms of pain reduction as indexed by VAS (or NRS) three studies found a greater improvement of pain. The Multi-coil study showed a reduction in the pain numeric rating scale of 43% over the last 24 hours of stimulation compared to baseline ratings, which was maintained for 4 weeks after the last treatment session. Stimulation with HD-tDCS elicited a significant pain improvement across cathodal and anodal interventions immediately and 30 min after a single session (there was a decrease of 26% and 27% in VAS after anodal and cathodal HD-tDCS 30 minutes after the stimulation was turned off, respectively). While the low-intensity rTMS study performed by Thomas et al. [28] found a trend for statistical significance (p=0.06) in VAS changes, Maestu et al. [29] found a significant decrease in perceived pain indexed by VAS in addition to an increase in pain threshold at FM tender points after the last session of treatment.

For the BPI scores, the multi-coil rTMS study found significant analgesic effects after treatment, with the most pronounced effect with a specific coil configuration ("E", 56%).

When assessing FIQ, one study found significant global improvement in the ability to perform daily activities and sleep quality [29], while another study [32] found only an effect of time on this measurement.

One of these studies assessed the effects on the treatment on pain threshold (SWMs for pain thresholds, PPTs, or DNICs), and found a significant increase in mechanical detection thresholds in both the left (p=0.003) and right (p=0.004) hands after a single session of HD-tDCS. No significant changes were detected for any of the other measurements [30].

No changes in BDI, blood serotonin levels, and in the VNS for anxiety were found in these studies.

Adverse events

No serious adverse events were observed in any of the four studies. In the HD-tDCS study, they reported mild-to-moderate tingling or itching sensation during both active and sham stimulation, which typically faded out after a few minutes. In the multi-coil TMS, the adverse events with relatively high incidences (more than 10% of patients, sham vs. real) included scalp pain (11 vs. 2%), headache (78 vs. 75%), lightheadedness (22 vs. 2%), back pain (11 vs. 8%), neck pain (0 vs. 13%, $p < 0.001$), otalgia (11 vs. 4%, ns), nausea (11 vs. 19%, ns), hot flashes (22 vs. 0%), and pruritus (22 vs. 7%). Some of these adverse events (lightheadedness, hot flashes, and scalp pain) occurred with a highest frequency in the 4-coil, 1 Hz sham rTMS group. In both low-intensity TMS studies no adverse effects were reported.

Discussion

NIBS as a therapeutic approach for pain management has been

Author, year, country	Title	Diagnosis	Study design	Sample size	Exclusion Criteria	Intervention	Results/ comments	Adverse Events
Maestu et al, [29] / Spain	Reduction of pain thresholds in fibromyalgia after very low-intensity magnetic stimulation: a double-blinded, randomized placebo-controlled clinical trial	American Association of Rheumatology	Double-blind, randomized clinical trial	67	Current pregnancy, other medical condition diagnosed than FM, use of pacemaker or metal implants	LOW INTENSITY TMS: Using a General Stimulation with an EEG cap with 33 coils, 8 Hz, low intensity (545 μA). Stimulation sessions occurred once per week for eight consecutive weeks.	Significant increase in pain threshold after 8 weeks was observed for the stimulation group comparing the entire period (p=0.01). Significant improvement in the ability to perform daily activities (p=0.03) and sleep quality (p=0.04), and a decrease in perceived pain (p=0.02) were also observed when compared to sham, after 6 weeks of treatment.	No adverse events found
Tzabazis et al, [32] / United States	Shaped magnetic field pulses by multi-coil repetitive transcranial magnetic stimulation (rTMS) differentially modulate anterior cingulate cortex responses and pain in volunteers and fibromyalgia patients	American College of Rheumatology	Two different designs: Cross-over and parallel clinical trial	16 healthy volunteers and 16 FM patients	Exclusion for FM patients: seizure disorder, metal implants on or in the brain, spinal cord, ear, eye or heart, current use of potentially proconvulsant medications, medication of oral amitriptyline > 100 mg/ day, non-scheduled (PRN) analgesics, anticonvulsant or antidepressant medications, use of opioid analgesics during study participation, severe depression or suicidality, other significant psychiatric disorder, and previous experience with TMS	MULTI COIL TMS in 3 different configurations, using 1 and 10Hz. The coil configurations (A, B and C) were generated using mathematical modeling of the composite field generated by simultaneous activation of 4 coils. For FM patients, configuration B was used, as it had a better result for the volunteer protocol. Configurations differentiated by rotation and direction of the current. The configuration E using two coils was also used for FM patients	Two multi-coil configurations at 10 Hz showed a progressive analgesic effect developed over the 20 sessions (4 weeks) of treatment. I was observed a 43% reduction in NRS pain over last 24 hours compared to the pre-treatment baseline ratings, which was maintained for at least 4 weeks after the end of treatment.	No severe adverse events found. Other adverse events (sham vs. active) included scalp pain (11 vs. 2%, p = 0.03), headache (78 vs. 75%, ns), lightheadedness (22 vs. 2%, p < 0.001), back pain (11 vs. 8%, ns), neck pain (0 vs. 13%, p < 0.001), otalgia (11 vs. 4%, ns), nausea (11 vs. 19%, ns), hot flashes (22 vs. 0%, p < 0.001), and pruritus (22 vs. 7%, ns)

Villamar et al, [30] / United States	Focal Modulation of the Primary Motor Cortex in Fibromyalgia Using 4x1-Ring High-Definition Transcranial Direct Current Stimulation (HD-tDCS): Immediate and Delayed Analgesic Effects of Cathodal and Anodal Stimulation	Diagnosis of FM made by a rheumatologist	Double-blind, randomized clinical trial	18	Current pregnancy, presence of metallic implants in the head, history of substance abuse within the past 6 months, use of carbamazepine within the past 6 months, severe depression, as defined by a baseline score in the Beck Depression Inventory-II (BDI-II), any history of epilepsy, stroke, moderate-to-severe traumatic brain injury, severe migraines, or brain surgery. Intensity of 2mA for 20 minutes, single session	HD-tDCS: 4x1 Multichannel Stimulation Adaptor connected to a conventional tDCS device. Electrode positioning was: the center electrode (anode or cathode) over C3 (left M1); four return electrodes (cathode or anode, respectively) were placed in a radius of approximately 7.5 cm from the center electrode (Cz, F3, T7, and P3)	Both anodal and cathodal stimulation conditions led to significant reduction in overall perceived pain as compared to sham immediately and 30 min after a single session (there was a decrease in VAS of 26% and 27% after anodal and cathodal HD-tDCS as compared to baseline after 30 minutes stimulation was turned off). Active anodal stimulation induced a significant bilateral increase in mechanical detection thresholds	Mild-to-moderate tingling or itching sensation, with no severe adverse events
Thomas et al, [28] / Canada	A randomized, double-blind, placebo-controlled clinical trial using a low-frequency magnetic field in the treatment of musculoskeletal chronic pain	Diagnosis of FM made by a specialist	Double-blind, randomized clinical trial	17	Current pregnant, malignancies or other potentially rapidly progressive cause of pain, any medical condition that would preclude the participation, deemed to be incompetent to provide informed consent, deemed to be unable to understand the nature of the study or be able to report pain severity without requiring a proxy.	LOW INTENSITY TMS: Using pulsed electromagnetic field through a portable device fitted to their head during twice-daily 40 min treatments over seven days, 400 μT, 1000 Hz or less, 800 mT/sec.	After seven days of twice-daily 40 min treatment it was noticed in FM patients an approached statistical significance (p=0.06) comared to sham in pain level measured by VAS.	No adverse events found

Table 1: Detailed interventions for each study.

studied thoroughly in several chronic pain conditions. The rationale for the use of this approach lies mainly on the ability of NIBS to modulate intrinsic brain activity and excitability that can then modify the underlying alterations in neural networks in charge of pain perception and processing. The main port of entry for NIBS in pain treatment is the M1, which is not an intrinsic part of the pain matrix but it is believed to play a critical role in pain modulation by exerting an inhibitory tone on thalamus and other cortical areas. Therefore, using NIBS to modulate the activity of this and other areas is able to strengthen its inhibitory control, that is believed to be otherwise decreased in FM [7,30].

The results described in this review showed that the modified NIBS techniques, high-definition tDCS, low-intensity rTMS and multi-coil TMS, can be effective to improve pain in FM patients. However, it is not clear whether these methods are safer or more efficacious than standard TMS and tDCS. We discuss initially each technique separately and then these results on the context of the clinical development of rTMS and tDCS for treatment of FM symptoms.

The HD-tDCS crossover study reported that a single 20-min session of active tDCS using a 4x1 ring montage over the left M1 led to a significant decrease in pain scores immediately after (with cathodal stimulation) and 30 min after stimulation (with both anodal and cathodal stimulations). In addition, anodal stimulation also induced a significant bilateral increase in pain mechanical thresholds.

HD-tDCS is a novel noninvasive brain stimulation approach developed recently with the goal to increase the accuracy of current delivery to the stimulated brain area. In contrast to conventional montages of tDCS, which use big electrodes placed over the scalp area correspondent to the targeted cortical area, HD-tDCS uses an array of smaller electrodes in a 4x1-ring configuration, in which a center ring electrode (anode or cathode) placed over the center of the same scalp region is surrounded by four return electrodes, which help circumscribe the area of stimulation. This technique combines the well-recognized advantages of tDCS (safety, cost and ease of use) with an increased focality and, consequently, more accuracy of the brain stimulation. Similar to conventional tDCS, this technique can be effectively and safely blinded by using sham stimulation, which consists of a program that delivers active stimulation for 30 seconds and is then automatically turned off. This allows researchers to simulate the initial sensation of

tDCS on subjects so that it can't be easily identified from the active procedure [30].

Similar to conventional anodal tDCS over M1, which has an effective and lasting impact on pain in FM patients [13,20,26], the 4x1 HD-tDCS also showed that a single 20-min session has important analgesic effects after both cathodal and anodal stimulation over M1, with the peak effect observed at 30 minutes after anodal stimulation. These findings support the hypothesis that modulatory effects of tDCS on pain-central pathways are dependent on modulation of M1 activity. In addition, no adverse effects other than a mild-to-moderate tingling or itching sensation were reported. However, the authors mentioned important limitations of this study that need to be considered: 1) there is a variability in the pain score reported by the patients, which could lead to less powerful results from measurements; and 2) 66% of the patients were taking 1 or more psychoactive drugs at the beginning of the study, and because of the small sample (n=18) and the heterogeneity of medication, it was not possible to conduct subgroup analyses based on the dosages of these drugs. Furthermore, no changes in quality of life, depression scores and analgesic drug intake were reported after the single-session of treatment.

Thus, future studies using prolonged protocols and different study designs should be conducted to demonstrate the efficacy of HD-tDCS in the improvement of pain-symptoms and quality of life in FM. In fact, considering the long-lasting after-effects reported by Kuo et al. [31], multiple HD-tDCS sessions may be critical to define optimized HD-tDCS protocols. Up to this date, no meta-analytic study regarding the effect size of a single tDCS session in a chronic pain disorder has been published. Therefore, it is difficult to conclude whether HD-tDCS is optimal to improve pain symptoms given the lack of studies using multiple sessions.

In regards to the studies using low-intensity rTMS, one study found significant changes in pain scores ($p<0.05$) while the other study only reached a trend for significance ($p=0.06$). Thomas et al. [28] observed that FM patients who underwent two daily sessions of 40 min, for seven consecutive days (with an observational period of 3 weeks), with a magnetic field intensity of 400 μT delivered through a headset, had a pain improvement indexed by VAS that approached statistical significance ($p=0.06$). In this study, the sham condition consisted of a pair of headsets with similar physical appearance as the active ones, but they did not deliver any form of treatment. In contrast to this first result, Maestu et al. [29] used magnetic fields applied in 20-min, weekly sessions, for eight consecutive weeks, using a 545 μA intensity, and a 43 nT magnetic field, delivered using a EEG cap with 33 coils. They observed that after the sixth week, patients showed an improvement in self-reported chronic pain, sleep quality, and an increase in the ability to perform daily activities. However, no significant improvement was found for fatigue, anxiety, depression, and severity of headaches or levels of serotonin in blood. For this study, the sham procedure consisted of devices with similar appearance to the active ones, but modified so that they could not provide any active treatment.

Although the general approach for these studies using low-intensity TMS seems to be similar, the following differences between both studies were observed: 1) the first study [28] was performed using two daily sessions of 40 min for seven consecutive days, and the low-intensity of magnetic field was in the order of μT, while in the second study [29], magnetic fields were applied once per week for 20 min for eight consecutive weeks, and intensity was considered as very-low, in the order of nT; 2) in the second study the stimulation coils were distributed across the scalp using an EEG cap, while in the first study a more focal source was used (headset), and thus, the field was less homogeneous. Thomas et al. [28] reported that the no-significant difference observed in the first study was most likely due to the headsets not fitting each individual correctly, which might have led to discomfort, and thus, to interferences in the magnetic field delivered. However, participants in this study described no headset discomforts.

It is important to compare the novel low-intensity TMS studies to those using standard repetitive rTMS in FM patients. Passard et al. [20] showed that unilateral rTMS of the left M1 using 2 sets of 5 consecutive daily sessions, improved pain scores, depression, ability to walking and sleep, and quality of life indexed by FIQ. Also, Mhalla et al. [26] showed that rTMS of the left M1 during 5 consecutive daily sessions with a maintenance period of 21 weeks decreased pain and improved FIQ. The adverse events reported in these studies included headaches, dizziness, nausea and tinnitus [20,26]. However, in contrast to these studies, no adverse events were reported in the low-intensity rTMS, showing thus a potential main advantage upon the previous studies as this technique is a well-tolerated. Furthermore, the other important advantage is the possibility of developing a portable device that may provide a cost advantage over standard rTMS.

In addition to low-intensity TMS, another novel TMS technique that has been tested for chronic pain treatment is the multi-coil rTMS. This novel multi-coil rTMS is able to stimulate deeper brain structures. Tzabazis et al. [32] tested the hypothesis that multi-coil rTMS of the dorsal anterior cingulate cortex (dACC), an important area in central pain pathway, can be safe, efficacious and more tolerable than traditional single-coil rTMS in the treatment of chronic pain related to FM. They performed 2 different experiments: 1) to verify the efficacy in an acute-pain induced model, using an experimental pain model, different coil configurations were tested in a placebo-controlled crossover design in healthy subjects. They used PET computed tomography scans to evaluate changes in brain activity, and recorded the differences in pain between active and sham groups. 2) FM patients received 20 sessions of multi-coil rTMS during 30 minutes, over 4 weeks and the effects on pain scales were recorded. After testing 3 coil configurations, they observed an important analgesic effect after a single 30-minute session with one of 3 tested rTMS coil configurations in evoked experimental tonic pain. While in FM patients, 20 sessions of multi-coil rTMS produced a significant improvement in chronic pain, no effect was observed in depressive symptoms (to assess the original figures of coil configurations, please see [32]). Considering that this is the only study reporting the effects with multi-coil rTMS, the mechanism underling the analgesic effects with this different montage remain to be clarified. The authors cited that a possible explanation for this analgesic effect could be due the ability of the shaped magnetic field pulses to differentially target neuronal structures that are more critical in the central pain circuitry, which cannot be done using a single-coil TMS.

There is indeed a debate regarding the optimal neural target for the treatment of FM. Mhalla et al. [26] found that in 10 rTMS sessions of high frequency over the left prefrontal cortex leads to reduction in pain scores and this effect remains for two weeks. Fregni et al. [13] on the other hand, showed pain improvement with tDCS over M1, but no effects after stimulation over the DLPFC. Thus it is unclear which is the best neural target for stimulation; making it difficult to compare results from the multi-coil study.

Conclusion

This review showed important results of modified NIBS techniques

for the treatment of pain-symptoms in FM patient. First of all, we found an analgesic effect associated with these novel techniques, but no effect on quality of life in some of these studies. Although the study using HD-tDCS showed promising results, it only assessed a single session of stimulation; studies using prolonged protocols are needed in order to assess the efficacy of HD-tDCS in the improvement of pain-symptoms related to FM. In the two low-intensity TMS studies, just one study [29] found a significant improvement in pain associated with FM. However, given that both studies were performed with different parameters and designs, and given also the trends of the study with non-significant findings, results also encourage further testing. Additionally, both studies reported no adverse events in contrast to HD-tDCS and multi coil TMS studies, showing that low-intensity TMS is a well-tolerated NIBS technique. The multi-coil rTMS study also showed a significant improvement in chronic pain after 20 sessions of stimulation in FM.

It is unclear from these studies whether novel methods of rTMS and tDCS add benefits compared to the traditional methods. Initial results are encouraging but they do not seem to show additional benefit as compared to results of traditional methods; although low intensity rTMS seems to be associated with less adverse effects which could be an important advantage. Future development needs to consider head to head clinical trials comparing standard rTMS and tDCS with modified methods as to test whether there are any advantages.

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