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Non-invasive brain stimulation techniques for chronic pain

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[Intervention Review]

Non-invasive brain stimulation techniques for chronic pain

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ABSTRACT

Background

This is an updated version of the original Cochrane Review published in 2010, Issue 9, and last updated in 2014, Issue 4. Non-invasive brain stimulation techniques aim to induce an electrical stimulation of the brain in an attempt to reduce chronic pain by directly altering brain activity. They include repetitive transcranial magnetic stimulation (rTMS), cranial electrotherapy stimulation (CES), transcranial direct current stimulation (tDCS), transcranial random noise stimulation (tRNS) and reduced impedance non-invasive cortical electrostimulation (RINCE).

Objectives

To evaluate the efficacy of non-invasive cortical stimulation techniques in the treatment of chronic pain.

Search methods

For this update we searched CENTRAL, MEDLINE, Embase, CINAHL, PsycINFO, LILACS and clinical trials registers from July 2013 to October 2017.

Selection criteria

Randomised and quasi-randomised studies of rTMS, CES, tDCS, RINCE and tRNS if they employed a sham stimulation control group, recruited patients over the age of 18 years with pain of three months' duration or more, and measured pain as an outcome. Outcomes of interest were pain intensity measured using visual analogue scales or numerical rating scales, disability, quality of life and adverse events.

Data collection and analysis

Two review authors independently extracted and verified data. Where possible we entered data into meta-analyses, excluding studies judged as high risk of bias. We used the GRADE system to assess the quality of evidence for core comparisons, and created three 'Summary of findings' tables.

Main results

We included an additional 38 trials (involving 1225 randomised participants) in this update, making a total of 94 trials in the review (involving 2983 randomised participants). This update included a total of 42 rTMS studies, 11 CES, 36 tDCS, two RINCE and two tRNS. One study evaluated both rTMS and tDCS. We judged only four studies as low risk of bias across all key criteria. Using the GRADE criteria we judged the quality of evidence for each outcome, and for all comparisons as low or very low; in large part this was due to issues of blinding and of precision.

rTMS

Meta-analysis of rTMS studies versus sham for pain intensity at short-term follow-up (0 to < 1 week postintervention), (27 studies, involving 655 participants), demonstrated a small effect with heterogeneity (standardised mean difference (SMD) -0.22, 95% confidence interval (CI) -0.29 to -0.16, low-quality evidence). This equates to a 7% (95% CI 5% to 9%) reduction in pain, or a 0.40 (95% CI 0.53 to 0.32) point reduction on a 0 to 10 pain intensity scale, which does not meet the minimum clinically important difference threshold of 15% or greater. Pre-specified subgroup analyses did not find a difference between low-frequency stimulation (low-quality evidence) and rTMS applied to the prefrontal cortex compared to sham for reducing pain intensity at short-term follow-up (very low-quality evidence). High-frequency stimulation of the motor cortex in single-dose studies was associated with a small short-term reduction in pain intensity at short-term follow-up (low-quality evidence, pooled n = 249, SMD -0.38 95% CI -0.49 to -0.27). This equates to a 12% (95% CI 9% to 16%) reduction in pain, or a 0.77 (95% CI 0.55 to 0.99) point change on a 0 to 10 pain intensity scale, which does not achieve the minimum clinically important difference threshold of 15% or greater. The results from multiple-dose studies were heterogeneous and there was no evidence of an effect in this subgroup (very low-quality evidence). We did not find evidence that rTMS improved disability. Meta-analysis of studies of rTMS versus sham for quality of life (measured using the Fibromyalgia Impact Questionnaire (FIQ) at short-term follow-up demonstrated a positive effect (MD -10.80 95% CI -15.04 to -6.55, low-quality evidence).

CES

For CES (five studies, 270 participants) we found no evidence of a difference between active stimulation and sham (SMD -0.24, 95% CI -0.48 to 0.01, low-quality evidence) for pain intensity. We found no evidence relating to the effectiveness of CES on disability. One study (36 participants) of CES versus sham for quality of life (measured using the FIQ) at short-term follow-up demonstrated a positive effect (MD -25.05 95% CI -37.82 to -12.28, very low-quality evidence).

tDCS

Analysis of tDCS studies (27 studies, 747 participants) showed heterogeneity and a difference between active and sham stimulation (SMD -0.43 95% CI -0.63 to -0.22, very low-quality evidence) for pain intensity. This equates to a reduction of 0.82 (95% CI 0.42 to 1.2) points, or a percentage change of 17% (95% CI 9% to 25%) of the control group outcome. This point estimate meets our threshold for a minimum clinically important difference, though the lower confidence interval is substantially below that threshold. We found evidence of small study bias in the tDCS analyses. We did not find evidence that tDCS improved disability. Meta-analysis of studies of tDCS versus sham for quality of life (measured using different scales across studies) at short-term follow-up demonstrated a positive effect (SMD 0.66 95% CI 0.21 to 1.11, low-quality evidence).

Adverse events

All forms of non-invasive brain stimulation and sham stimulation appear to be frequently associated with minor or transient side effects and there were two reported incidences of seizure, both related to the active rTMS intervention in the included studies. However many studies did not adequately report adverse events.

Authors' conclusions

There is very low-quality evidence that single doses of high-frequency rTMS of the motor cortex and tDCS may have short-term effects on chronic pain and quality of life but multiple sources of bias exist that may have influenced the observed effects. We did not find evidence that low-frequency rTMS, rTMS applied to the dorsolateral prefrontal cortex and CES are effective for reducing pain intensity in chronic pain. The broad conclusions of this review have not changed substantially for this update. There remains a need for substantially larger, rigorously designed studies, particularly of longer courses of stimulation. Future evidence may substantially impact upon the presented results.

PLAIN LANGUAGE SUMMARY

Stimulating the brain without surgery in the management of chronic pain in adults

Bottom line

There is a lack of high-quality evidence to support or refute the effectiveness of non-invasive brain stimulation techniques for chronic pain.

Background

Electrical stimulation of the brain has been used to address a variety of painful conditions. Various devices are available that can electrically stimulate the brain without the need for surgery or any invasive treatment. There are five main treatment types: repetitive transcranial magnetic stimulation (rTMS) in which the brain is stimulated by a coil applied to the scalp, cranial electrotherapy stimulation (CES) in which electrodes are clipped to the ears or applied to the scalp, transcranial direct current stimulation (tDCS), reduced impedance non-invasive cortical electrostimulation (RINCE) and transcranial random noise stimulation (tRNS) in which electrodes are applied to the scalp. These have been used to try to reduce pain by aiming to alter the activity of the brain. How effective they are is uncertain.

Study characteristics

This review update included 94 randomised controlled studies: 42 of rTMS, 11 of CES, 36 of tDCS two of RINCE, two of tRNS and one study which evaluated both tDCS and rTMS.

Key findings

rTMS applied to the motor cortex may lead to small, short-term reductions in pain but these effects are not likely to be clinically important. tDCS may reduce pain when compared with sham but for rTMS and tDCS our estimates of benefit are likely to be exaggerated by the small number of participants in each of the studies and limitations in the way the studies were conducted. Low- or very low-quality evidence suggests that low-frequency rTMS and rTMS that is applied to prefrontal areas of the brain are not effective. Low-quality evidence does not suggest that CES is an effective treatment for chronic pain. For all forms of stimulation the evidence is not conclusive and there is substantial uncertainty about the possible benefits and harms of the treatment. Of the studies that clearly reported side effects, short-lived and minor side effects such as headache, nausea and skin irritation were usually reported both with real and sham stimulation. Two cases of seizure were reported following real rTMS. Our conclusions for rTMS, CES, tDCS, and RINCE have not changed substantially in this update.

Quality of the evidence

We rated the quality of the evidence from studies using four levels: very low, low, moderate, or high. Very low-quality evidence means that we are very uncertain about the results. High-quality evidence means that we are very confident in the results. We considered all of the evidence to be of low or very low quality, mainly because of bias in the studies that can lead to unreliable results and the small size of the studies, which makes them imprecise.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

rTMS compared with sham for chronic pain

Patient or population: adults with chronic pain
Settings: laboratory/ clinic
Intervention: active rTMS
Comparison: sham rTMS

Outcomes	Effect size	Relative and absolute effect (average % improvement (reduction) in pain (95% CIs) in relation to post-treatment score from sham group)* *Where 95%CIs do not cross the line of no effect.	No of participants (studies)	Quality of the evidence (GRADE)
Pain intensity (0 to < 1 week postintervention) measured using visual analogue scales or numerical rating scales	SMD -0.22 (-0.29 to -0.16)	This equates to a 7% (95% CI 5% to 9%) reduction in pain intensity, or a 0.40 (95% CI 0.53 to 0.32) point reduction on a 0 to 10 pain intensity scale	655 (27)	⊕⊕◯◯ **low**[1]
Disability (0 to < 1 week postintervention) measured using self-reported disability/pain interference scales	SMD -0.29, 95% CI -0.87 to 0.29	-	119 (5)	⊕◯◯◯ **very low**[2]
Quality of life (0 to < 1 week postintervention) measured using Fibromyalgia Impact Questionnaire	MD -10.80, 95% CI -15.04 to -6.55	-	105 (4)	⊕⊕◯◯ **low**[3]

CI: confidence interval; **MD**: mean difference; **rTMS**: repetitive transcranial magnetic stimulation; **SMD**: standardised mean difference

GRADE Working Group grades of evidence
High quality: we are very confident that the true effect lies close to that of the estimate of the effect;
Moderate quality: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of effect, but there is a possibility that it is substantially different;
Low quality: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect;
Very low quality: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect

[1]Downgraded once for study limitations due to high or unclear risk of bias and once for inconsistency due to heterogeneity.
[2]Downgraded once for study limitations due to high or unclear risk of bias, once for inconsistency due to heterogeneity and once for imprecision due to low participant numbers.
[3]Downgraded once for study limitations due to high or unclear risk of bias and once for imprecision due to low participant numbers.

BACKGROUND

This is an updated version of the original Cochrane Review published in 2010, Issue 9, on non-invasive brain stimulation techniques for chronic pain (O'Connell 2010) and updated in 2014 (O'Connell 2014).

Description of the condition

Chronic pain is a common problem. When defined as pain of greater than three months' duration, prevalence studies indicate that up to half the adult population suffer from chronic pain, and 10% to 20% experience clinically significant chronic pain (Smith 2008; Van Hecke 2013). In Europe, 19% of adults experience chronic pain of moderate to severe intensity with serious negative implications for their social and working lives and many of these receive inadequate pain management (Breivik 2006; Van Hecke 2013). Chronic pain is a heterogeneous phenomenon that results from a wide variety of pathologies including chronic somatic tissue degeneration such as in arthritis, peripheral nerve injury and central nervous system injury, as well as a range of chronic pain syndromes such as fibromyalgia and complex regional pain syndrome. It is likely that different mechanisms of pain production underpin these different types of chronic pain (Ossipov 2006).

Description of the intervention

Electrical brain stimulation techniques have been used to address a variety of pathological pain conditions including fibromyalgia, chronic poststroke pain and complex regional pain syndrome (Cruccu 2017; Fregni 2007; Gilula 2007), and clinical studies of both invasive and non-invasive techniques have produced preliminary data showing reductions in pain (Fregni 2007; Lefaucheur 2008b). Various types of brain stimulation, both invasive and non-invasive, are currently in clinical use for the treatment of chronic pain (Cruccu 2017). Non-invasive stimulation techniques require no surgical procedure and are therefore easier and safer to apply than invasive procedures.

Repetitive transcranial magnetic stimulation (rTMS) involves stimulation of the cerebral cortex (the outer layer of the brain) by a stimulating coil applied to the scalp. Electric currents are induced in the neurons (brain cells) directly using rapidly changing magnetic fields (Fregni 2007). Trains of these stimuli are applied to the target region of the cortex to induce alterations in brain activity both locally and in remote brain regions (Leo 2007). A recent meta-analysis suggested that rTMS may be more effective in the treatment of neuropathic pain conditions (pain arising as a result of a lesion or a disease of the somatosensory nervous system, as in diabetes, traumatic nerve injury, stroke, multiple sclerosis, epilepsy, spinal cord injury and cancer) with a central compared to a peripheral nervous system origin (Leung 2009).

Transcranial direct current stimulation (tDCS), transcranial random noise stimulation (tRNS) and cranial electrotherapy stimulation (CES) involve the safe and painless application of low-intensity (commonly $\leq$ 2 mA) electrical current to the cerebral cortex of the brain (Fregni 2007; Gilula 2007; Hargrove 2012a). tDCS has been developed as a clinical tool for the modulation of brain activity in recent years and uses relatively large electrodes that are applied to the scalp over the targeted brain area to deliver a weak constant current (Lefaucheur 2008a). Clinical studies have concluded that tDCS was more effective than sham stimulation at reducing pain in both fibromyalgia and spinal cord injury-related pain (Fregni 2006a; Fregni 2006b). tRNS is similar to tDCS but the stimulating current is varied randomly. It has been found to increase cortical excitability (Paulus 2011). CES was initially developed in the USSR as a treatment for anxiety and depression in the 1950s and its use later spread to Europe and the USA, where it began to be considered and used as a treatment for pain (Kirsch 2000). The electrical current in CES is commonly pulsed and is applied via clip electrodes that are attached to the patient's earlobes. A Cochrane Review of non-invasive treatments for headaches identified limited evidence that CES is superior to placebo in reducing pain intensity after six to 10 weeks of treatment (Bronfort 2004). Reduced impedance non-invasive cortical electrostimulation (RINCE) similarly applies an electrical current via scalp electrodes but utilises specific stimulation frequencies, which are hypothesised to reduce electrical impedance from the tissues of the skin and skull, allowing deeper cortical penetration and modulation of lower-frequency cortical activity (Hargrove 2012a).

How the intervention might work

Brain stimulation techniques primarily seek to modulate activity in brain regions by directly altering the level of brain activity. The aim of brain stimulation in the management of pain is to reduce pain by altering activity in the areas of the brain that are involved in pain processing.

Both tDCS and rTMS have been shown to modulate brain activity specific to the site of application and the stimulation parameters. As a general rule, low-frequency rTMS ($\leq$ 1 Hz) results in lowered cortical excitability at the site of stimulation, whereas high-frequency stimulation ($\geq$ 5 Hz) results in raised cortical excitability (Lefaucheur 2008a; Pascual-Leone 1999). Similarly, anodal tDCS, wherein the anode electrode is placed over the cortical target, results in a raised level of excitability at the target, whereas cathodal stimulation decreases local cortical excitability (Nitsche 2008). It is suggested that the observed alterations in cortical excitability (readiness for activity) following rTMS and tDCS that last beyond the time of stimulation are the result of long-term synaptic changes (Lefaucheur 2008a). Both RINCE and tRNS are applied in a similar way to tDCS, though the current is delivered differently to enhance, in theory, signal transmission to neural networks. Modulation of activity in brain networks is also proposed

as the mechanism of action of CES therapy and it is suggested that the therapeutic effects are primarily achieved by direct action upon the hypothalamus, limbic system and/or the reticular activating system (Gilula 2007).

Imaging studies in humans suggest that motor cortex stimulation may reduce pain by modulating activity in networks of brain areas involved in pain processing, such as the thalamus, and by facilitating descending pain inhibitory mechanisms (Garcia-Larrea 1997; Garcia-Larrea 1999; Peyron 2007).

Sham credibility issues for non-invasive brain stimulation studies

An issue regarding the credibility of sham conditions specifically for rTMS studies is whether the sham condition that is employed controls for the auditory (clicking sounds of various frequencies) and sensory stimulation that occurs during active stimulation (Lisanby 2001; Loo 2000). Various types of sham have been proposed including angling the coil away from the scalp (thus preserving the auditory cues but not the sensation of stimulation), using coils that mimic the auditory cues combined with gentle scalp electrical stimulation to mask the sensation and simple inert coils that reproduce neither the sound nor the sensation of active stimulation. Failure to control for such cues may impact negatively on participant blinding, particularly in cross-over design studies. Lisanby 2001 and Loo 2000 suggest that an ideal sham condition for rTMS should:

- not stimulate the cortex;
- be the same as active stimulation in visual terms and in terms of its position on the scalp; and
- not differ from active stimulation in terms of the acoustic and afferent sensory sensations that it elicits.

Strategies have been developed to try to meet these criteria (Borckardt 2008; Rossi 2007; Sommer 2006). There is evidence that simply angling the coil away from the scalp at an angle of less than 90° may still result in brain stimulation and not be truly inert (Lisanby 2001). This strategy is also easily detected by the recipient of stimulation. In these ways this type of sham might obscure or exaggerate a real clinical effect of active stimulation.

In studies of tDCS the sham condition commonly involves the delivery of a short initial period (30 seconds to one minute) of identical stimulation to the active condition, at which point the stimulation is ceased without the participant's knowledge. There is evidence that this achieves effective blinding of tDCS at stimulation intensities of 1 mA in naive participants (Ambrus 2012; Gandiga 2006), but at a stimulation intensity of 2 mA tDCS both participant and assessor blinding has been shown to be inadequate, since participants can distinguish the active condition more than would be expected by chance and a proportion of those receiving active stimulation develop a temporary but visible redness over the electrode sites (O'Connell 2012). At 1.5 mA there are detectable differences in the experience of tDCS that might compromise blinding (Kessler 2013), though a formal investigation of the adequacy of blinding at this intensity has not been published to date.

Why it is important to do this review

This approach to pain treatment is relatively novel. It is important to assess the existing literature robustly to ascertain the current level of supporting evidence and to inform future research and potential clinical use. Published reviews have addressed this area and concluded that non-invasive brain stimulation can exert a significant effect on chronic pain, but they have restricted their findings to specific cortical regions, types of painful condition or types of stimulation and did not carry out a thorough assessment of study quality or risk of bias (Lefaucheur 2008b; Leung 2009; Lima 2008).

OBJECTIVES

To evaluate the efficacy of non-invasive cortical stimulation techniques in the treatment of chronic pain.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised controlled trials (RCTs) and quasi-randomised trials (e.g. by order of entry or date of birth) that utilised a sham control group. We included parallel and cross-over study designs. We included studies regardless of language.

Types of participants

We included studies involving male or female participants over the age of 18 years with any chronic pain syndrome (with a duration of more than three months). It was not anticipated that any studies were likely to exist in a younger population. Migraine and other headache studies were not included due to the episodic nature of these conditions.

Types of interventions

We included studies investigating the therapeutic use of non-invasive forms of brain stimulation (tDCS, rTMS, CES, RINCE or tRNS). We did not include studies of electroconvulsive therapy (ECT), as its mechanism of action (the artificial induction

of an epileptic seizure (Stevens 1996)) differs substantially from the other forms of brain stimulation. We also excluded invasive forms of brain stimulation involving the use of electrodes implanted within the brain, and indirect forms of stimulation, such as caloric vestibular stimulation and occipital nerve stimulation. In order to meet our second objective of considering the influence of varying stimulation parameters, we included studies regardless of the number of stimulation sessions delivered, including single-dose studies.

Types of outcome measures

Primary outcomes

The primary outcome measure was change in pain intensity using validated measures of pain intensity such as visual analogue scales (VAS), verbal rating scales (VRS) or numerical rating scales (NRS).

Secondary outcomes

Secondary outcomes that we extracted when available were self-reported disability data, quality-of-life measures and the incidence/nature of adverse events.

Search methods for identification of studies

Electronic searches

For the OVID MEDLINE search, we ran the subject search with the Cochrane Highly Sensitive Search Strategy for identifying randomised trials in MEDLINE: sensitivity maximising version (2008 revision) as referenced in Chapter 6 and detailed in box 6.4c of the *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.0.1 (Lefebvre 2011). We have slightly adapted this filter to include the term 'sham' in the title or abstract. The search strategies for this update are presented in Appendix 1 and included a combination of controlled vocabulary (MeSH) and free-text terms. We based all database searches on this strategy but appropriately revised them to suit each database.

Electronic databases

Previous updates searched all databases from their inception to July 2013. To identify studies for inclusion in this update we searched the following electronic databases from July 2013 to September 2016 to identify additional published articles and performed a further search update in October 2017:

- the Cochrane Central Register of Controlled Trials (CENTRAL; 2017, Issue 10);
- MEDLINE & MEDLINE in Process via OVID to 11 October 2017;
- Embase via OVID to 11 October 2017;
- PsycINFO via OVID to 11 October 2017;
- CINAHL via EBSCO to 11 October 2017;
- LILACS via Birme to 11 October 2017;

For full details of the search parameters including for this update see Appendix 1 and Appendix 2.

Searching other resources

Reference lists

We searched reference lists of all eligible trials, key textbooks and previous systematic reviews to identify additional relevant articles.

Unpublished data

For this update we searched ClinialTrials.gov (clinicaltrials.gov) and the World Health Organization International Clinical Trials Registry Platform (www.who.int/ictrp/en/) to October 2017 to identify research in progress and unpublished research.

Language

The search attempted to identify all relevant studies irrespective of language. We assessed non-English papers and, if necessary, translated them with the assistance of a native speaker.
We sent a final list of included articles to two experts in the field of therapeutic brain stimulation with a request that they review the list for possible omissions.

Data collection and analysis

Selection of studies

Two review authors (NOC and BW) independently checked the search results and the reference lists of included eligible studies. Initially two review authors (NOC and BW) read the titles or abstracts (or both) of identified studies. Where it was clear from the study title or abstract that the study was not relevant or did not meet the selection criteria we excluded it. If it was unclear then we assessed the full paper, as well as all studies that appeared to meet the selection criteria. Disagreement was resolved through discussion between the two review authors. Where resolution was not achieved a third review author (LDS) considered the paper(s) in question.

Data extraction and management

Two review authors (NOC and BW) extracted data independently using a standardised form that was piloted by both authors independently on three randomised controlled trials of transcutaneous electrical nerve stimulation prior to the searches. We resolved discrepancies by consensus. The form included the following.

- 'Risk of bias' assessment results
- Country of origin
- Study design
- Study population - condition; pain type; duration of symptoms; age range; gender split; prior management
- Sample size - active and control groups
- Intervention - stimulation site, parameters and dosage (including number and duration of trains of stimuli and number of pulses for rTMS studies)
- Type of sham
- Credibility of sham (for rTMS studies - see below)
- Outcomes - mean postintervention pain scores for the active and sham treatment groups at all follow-up points
- Results - short, intermediate and long-term follow-up
- Adverse effects
- Conflict of interest disclosure

Assessment of risk of bias in included studies

We assessed risk of bias using the Cochrane 'Risk of bias' assessment tool outlined in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.0.1 (Higgins 2011a). The criteria assessed for parallel study designs (using low/high/unclear judgements) were: adequate sequence generation; adequate allocation concealment; adequate blinding of assessors; adequate blinding of participants; adequate assessment of incomplete outcome data; whether free of suggestion of selective outcome reporting; and whether free of other bias.

The criteria assessed for cross-over study designs (using low/high/unclear judgements) were: adequate sequence generation; whether data were clearly free from carry-over effects; adequate blinding of assessors; adequate blinding of participants; whether free of the suggestion of selective outcome reporting; and whether free of other bias.

As with the previous update, in compliance with new author guidelines from Cochrane Pain, Palliative and Supportive Care and the recommendations of Moore 2010 we added two criteria, 'study size' and 'study duration', to our 'Risk of bias' assessment using the thresholds for judgement suggested by Moore 2010:

- **size** (we rated studies with fewer than 50 participants per arm as being at high risk of bias, those with between 50 and 199 participants per arm at unclear risk of bias, and 200 or more participants per arm at low risk of bias);
- **duration** (we rated studies with follow-up of less than two weeks as being at high risk of bias, two to seven weeks at unclear risk of bias and eight weeks or longer at low risk of bias).

Two review authors (NOC and BW) independently checked risk of bias. Disagreement between review authors was resolved through discussion between the two review authors. Where resolution was not achieved a third review author (LDS) considered the paper(s) in question.

Assessment of sham credibility

We rated the type of sham used in studies of rTMS for credibility: as optimal (the sham controls for the auditory and sensory characteristics of stimulation and is visually indistinguishable from real stimulation (Lisanby 2001; Loo 2000)) and suboptimal (fails to account for either the auditory and sensory characteristics of stimulation, or is visually distinguishable from the active stimulation, or fails on more than one of these criteria). We made a judgement of 'unclear' where studies did not adequately describe the sham condition.

In light of empirical evidence that tDCS may be inadequately blinded at intensities of 2 mA (O'Connell 2012), and of detectable differences in the experience of tDCS at 1.5 mA (Kessler 2013), for this update we assessed studies that used these stimulation intensities to be at unclear risk of bias for participant and assessor blinding. We chose 'unclear' instead of 'high' risk of bias as the available evidence demonstrates the potential for inadequate blinding rather than providing clear evidence that individual studies were effectively unblinded. We applied this rule to all newly identified studies and retrospectively to studies identified in the first version of this review.

Two independent review authors (NOC and BW) performed rating of sham credibility. We resolved disagreement between review authors through consensus. Where resolution was not achieved a third review author (LDS) considered the paper(s) in question. Where sham credibility was assessed as unclear or suboptimal we made a judgement of 'unclear' for the criterion 'adequate blinding of participants' in the 'Risk of bias' assessment.

Measures of treatment effect

We used standardised mean difference (SMD) to express the size of treatment effect on pain intensity measured with a VAS or NRS. In order to aid interpretation of the pooled effect size we back-transformed the SMD to a 0 to 10 pain intensity rating scale on the basis of the mean standard deviation from trials using a 0 to 10 point VAS. We considered the likely clinical importance of the pooled effect size using the criteria proposed in the IMMPACT consensus statement (Dworkin 2008). Specifically, we judged a decrease in pain of less than 15% as no important change, of 15% or more as a minimally important change, of 30% or more as a moderately important change and of 50% or more as a substantially important change.

Unit of analysis issues

We entered cross-over trials into a meta-analysis where it was clear that these data were free of carry-over effects. We combined the results of cross-over studies with parallel studies using the generic inverse-variance method as suggested in the *Cochrane Handbook for Systematic Reviews of Interventions*, section 16.4.6.2 (Higgins 2011b). We imputed the post-treatment between-condition correlation coefficient from an included cross-over study that presented individual participant data and used this to calculate the standard error of the standardised mean difference (SE (SMD)). Where data from the same cross-over trials were entered more than once into the same meta-analysis we corrected the number of participants by dividing by the number of times data from that trial were entered in the meta-analysis. We calculated the SMD (SE) for parallel studies in Review Manager 5 (RevMan 5) (RevMan 2014). For each study we entered the SMD (SE) into the meta-analysis using the generic inverse-variance method.

Dealing with missing data

Where insufficient data were presented in the study report to enter a study into the meta-analysis, we contacted the study authors to request access to the missing data.

Assessment of heterogeneity

We conducted separate meta-analysis for each type of brain stimulation. We assessed heterogeneity using the Chi^2 test to investigate its statistical significance and the I^2 statistic (Higgins 2003) to estimate the amount. We planned to investigate the influence of altered chronic pain condition or stimulation parameters through pre-planned subgroup analyses (see Subgroup analysis and investigation of heterogeneity).

Assessment of reporting biases

We planned to consider the possible influence of publication/small study biases on review findings. The influence of small study biases were, in part, addressed by the risk of bias criterion 'study size'. We planned to use funnel plots to visually explore the likelihood of reporting biases when at least 10 studies were included in a meta-analysis and included studies differed in size. For continuous outcomes, we planned to use Egger's test to detect possible small study bias and, for dichotomised outcomes, we planned to test for the possible influence of publication bias on each outcome by estimating the number of participants in studies with zero effect required to change the number needed to treat for an additional beneficial outcome (NNTB) to an unacceptably high level (defined as a NNTB of 10).

Data synthesis

We performed pooling of results where adequate data supported this using RevMan 5 software (RevMan 2014), with a random-effects model. Where an analysis included parallel and cross-over trials we used the generic inverse variance method (see Unit of analysis issues). We conducted separate meta-analyses for different forms of stimulation intervention (i.e. rTMS, tDCS, CES, RINCE and tRNS) and for short-term (0 to < 1 week postintervention), mid-term (≥ 1 to 6 weeks postintervention) and long-term (≥ 6 weeks postintervention) outcomes where adequate data were identified.

Where more than one data point was available for short-term outcomes, we used the first poststimulation measure, and where multiple treatments were given we took the first outcome at the end of the treatment period. For medium-term outcomes where more than one data point was available, we used the measure that fell closest to the mid-point of this time period. We excluded studies from the meta-analysis that we rated at high risk of bias on any criteria, excluding the criteria 'study size' and 'study duration'.

Two review authors (NOC, BW) independently rated the quality of the outcomes. We used the GRADE system to rank the quality of the evidence, and the guidelines provided in Chapter 12.2 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Schünemann 2011). The GRADE approach uses five considerations (study limitations, consistency of effect, imprecision, indirectness and publication bias) to assess the quality of the body of evidence for each outcome. The GRADE system uses the following criteria for assigning grade of evidence.

- High: we are very confident that the true effect lies close to that of the estimate of the effect.
- Moderate: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of effect, but there is a possibility that it is substantially different.
- Low: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
- Very low: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

The GRADE system uses the following criteria for assigning a quality level to a body of evidence (Chapter 12, Schünemann 2011).

- High: randomised trials; or double-upgraded observational studies
- Moderate: downgraded randomised trials; or upgraded observational studies
- Low: double-downgraded randomised trials; or observational studies
- Very low: triple-downgraded randomised trials; or downgraded observational studies; or case series/case reports

Factors that may decrease the quality level of a body of evidence are:

- limitations in the design and implementation of available studies suggesting high likelihood of bias;

- indirectness of evidence (indirect population, intervention, control, outcomes);
- unexplained heterogeneity or inconsistency of results (including problems with subgroup analyses);
- imprecision of results (wide confidence intervals);
- high probability of publication bias.

To ensure consistency of GRADE judgements we applied the following criteria to each domain equally for all key comparisons of the primary outcome.

- Limitations of studies: downgrade once if less than 75% of included studies are at low risk of bias across all key 'Risk of bias' criteria.
- Inconsistency: downgrade once if heterogeneity is significant ($p<0.05$) and the I^2 value is more than 40%.
- Indirectness: downgrade once if more than 50% of the participants were outside the target group.
- Imprecision: downgrade once if there were fewer than 400 participants for continuous data and fewer than 300 events for dichotomous data (Guyatt 2011).
- Publication bias: downgrade where there is direct evidence of publication bias.

We considered single studies to be both inconsistent and imprecise, unless more than 400 participants were randomised.

'Summary of findings' table

We included three 'Summary of findings' tables to present the main findings in a transparent and simple tabular format for the three main forms of non-invasive brain stimulation techniques (rTMS, tDCS, CES) compared to sham. In particular, we included key information concerning the quality of evidence, the magnitude of effect of the interventions examined and the sum of available data on the outcomes pain, disability and quality of life at short-term follow-up (see Summary of findings for the main comparison; Summary of findings 3; Summary of findings 2).

Subgroup analysis and investigation of heterogeneity

Where heterogeneity ($P < 0.1$) was present we explored subgroup analyses. Pre-planned comparisons included site of stimulation, frequency of rTMS stimulation (low $\leq$ 1 Hz, high $\geq$ 5 Hz), multiple-dose versus single-dose studies and the type of painful condition (central neuropathic versus peripheral neuropathic versus non-neuropathic pain versus facial pain) for each stimulation type. Central neuropathic pain included pain due to identifiable pathology of the central nervous system (e.g. stroke, spinal cord injury), peripheral neuropathic pain included injury to the nerve root or peripheral nerves, facial pain included trigeminal neuralgia and other idiopathic chronic facial pains, and non-neuropathic pain included all chronic pain conditions without a clear neuropathic cause (e.g. chronic low back pain, fibromyalgia, complex regional pain syndrome type I).

Sensitivity analysis

When sufficient data were available, we conducted sensitivity analyses on the following study factors: risk of bias, sham credibility (for rTMS studies) and cross-over versus parallel-group designs.

RESULTS

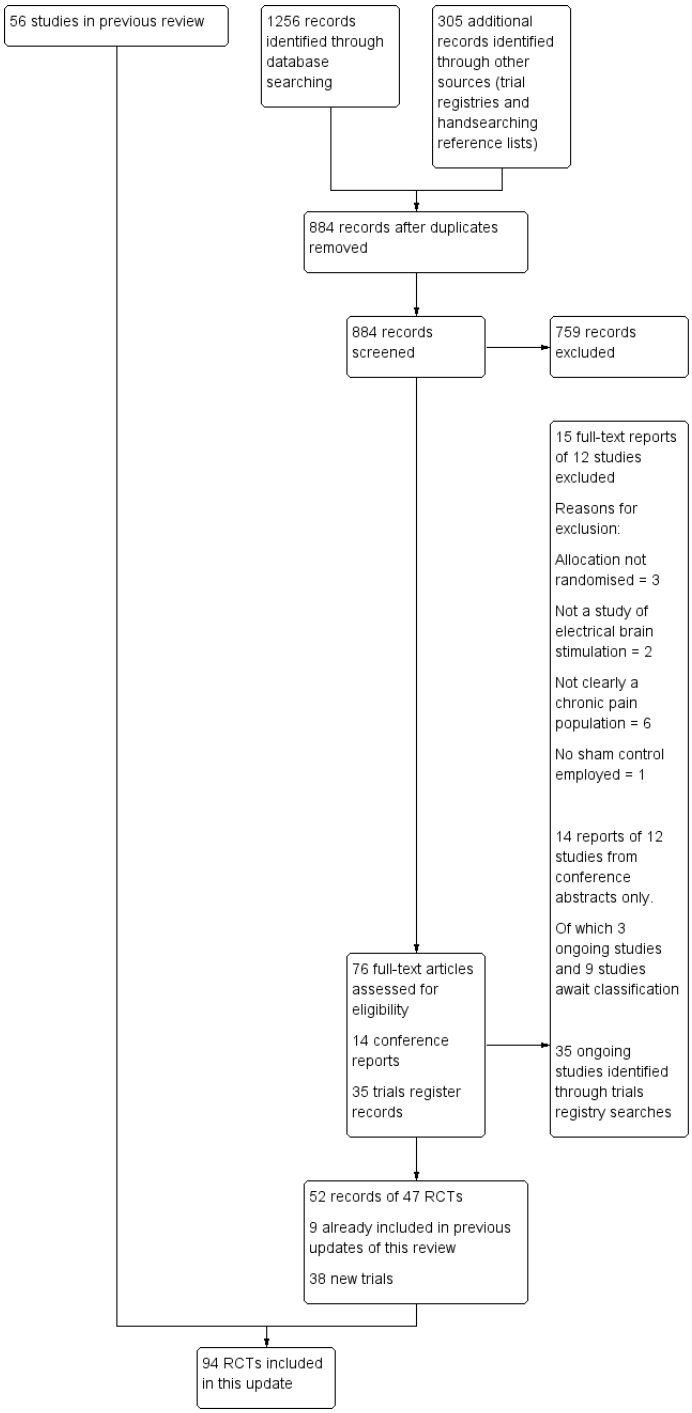
Description of studies

See: Characteristics of included studies; Characteristics of excluded studies.

Results of the search

For a full description of our screening process, see the study flow diagram (Figure 1). For a summary of the search results for this update see Appendix 2 and Appendix 3. See Appendix 4; Appendix 5; Appendix 6; Appendix 7 and Appendix 8 for full details of the search results and strategies from earlier versions of this review.

Figure 1. Study flow diagram



This 2017 update is based on a September 2016 search and a further search update in October 2017. For this update, the searches of the databases (see Electronic searches) retrieved 1256 records. Handsearching reference lists of included articles identified one additional RCT that met the inclusion criteria. Our searches of the trials registers identified 305 records. We therefore had a total of 1561 records. Once duplicates had been removed from the main searches and nonrelevant records were removed from the trials registry search results we had a total of 884 records. We excluded 759 records based on titles and abstracts leaving 76 full-text papers, 14 conference reports and 35 trials register records. We obtained the full text of the remaining 76 records. We excluded 12 studies from 15 records, see Characteristics of excluded studies). Fourteen records were conference abstract reports relating to 12 RCTs. Of these we added nine records to Studies awaiting classification and classified three as Ongoing studies. Of the remaining 52 records (47 RCTs), nine RCTs had been included in previous versions of this update.

We included 38 new studies in this review. Of these, 12 studies (355 participants) investigated only rTMS (Boyer 2014; Dall'Agnol 2014; de Oliveira 2014; Jetté 2013; Malavera 2013; Medeiros 2016; Nardone 2017; Nurmikko 2016; Tekin 2014; Umezaki 2016; Yagci 2014; Yilmaz 2014), 22 studies (772 participants) investigated tDCS (Ahn 2017; Ayache 2016; Bae 2014; Brietzke 2016; Chang 2017; Donnell 2015; Fagerlund 2015; Hagenacker 2014; Harvey 2017; Hazime 2017; Jales Junior 2015; Khedr 2017; Kim 2013; Lagueux 2017; Luedtke 2015; Mendonca 2016; Ngernyam 2015; Oliveira 2015; Sakrajai 2014; Souto 2014; Thibaut 2017; Volz 2016) one study (36 participants) investigated tDCS and rTMS (Attal 2016), two studies (16 participants) investigated tRNS (Curatolo 2017; Palm 2016) and one study investigated RINCE (Deering 2017, 46 participants). Overall this updated review included 94 studies (2983 participants), with 42 trials of rTMS (1101 participants), 36 trials of tDCS (1073 participants), 11 studies of CES (572 participants), one study (36 participants) of both rTMS and tDCS, two studies of RINCE (137 participants) and two studies of tRNS (36 participants). We identified 13 conference abstract reports of 11 studies that were not related to full published studies (Ansari 2013; Fricová 2013; Deering 2017; Hwang 2015; Mattoo 2017; Moreno-Duarte 2013a; Muniswamy 2016; Mylius 2013; Parhizgar 2011; Tanwar 2016; Williams 2014). We contacted the authors of these abstracts to try to ascertain whether they were unique studies or duplicates and to acquire full study reports. Of these, two authors confirmed that the studies were ongoing or had been submitted for publication (Ansari 2013; Muniswamy 2016) and they were subsequently included in Ongoing studies. The authors of one abstract (Deering 2017) shared a full unpublished study report and the study was included in this review. Where we were unable to obtain this information we placed these records in Studies awaiting classification.

One report previously placed in Studies awaiting classification was identified as a full paper and included in this review (Yagci 2014). We identified 35 new ongoing studies in total (see Characteristics of ongoing studies). We contacted the authors by email for any relevant data but no data were available for inclusion. Three studies, classified as ongoing after previous searches, had been published and were included in the review (Boyer 2014 NCT00697398; Luedtke 2015 ISRCTN89874874, Thibaut 2017 NCT01599767), one was terminated without results (NCT01608321). The remaining studies identified as ongoing in the last update of this review remain unpublished to our knowledge (NCT00815932; NCT00947622; NCT01112774; NCT01220323; NCT01402960; NCT01404052; NCT01575002; NCT01746355; NCT01747070).

Included studies

See Characteristics of included studies.

Country of origin and language of publication

All but one of the studies (Irlbacher 2006, written in German) were written in English. Studies were undertaken in Brazil, Canada, Colombia, Egypt, Europe (Austria, France, Germany, Italy, Spain, Norway, Russia and the UK), Israel, Japan, South Korea, Thailand, Australia and the USA. Most studies were based in a laboratory or outpatient pain clinic setting.

Type of stimulation, application and use

In total 43 studies investigated rTMS (Ahmed 2011; André-Obadia 2006; André-Obadia 2008; André-Obadia 2011; Avery 2013; Borckardt 2009; Boyer 2014, Carretero 2009; Dall'Agnol 2014; Defrin 2007; de Oliveira 2014; Fregni 2005; Fregni 2011; Hirayama 2006; Hosomi 2013; Irlbacher 2006; Jetté 2013, Kang 2009; Khedr 2005; Lee 2012; Lefaucheur 2001a; Lefaucheur 2001b; Lefaucheur 2004; Lefaucheur 2006; Lefaucheur 2008; Malavera 2013; Medeiros 2016; Mhalla 2011; Nardone 2017; Nurmikko 2016; Onesti 2013; Passard 2007; Picarelli 2010; Pleger 2004; Rollnik 2002; Saitoh 2007; Short 2011; Tekin 2014; Tzabazis 2013; Umezaki 2016; Yagci 2014; Yilmaz 2014). Eleven studies investigated CES (Capel 2003; Cork 2004; Gabis 2003; Gabis 2009; Katsnelson 2004; Lichtbroun 2001; Rintala 2010; Tan 2000; Tan 2006; Tan 2011; Taylor 2013), 36 studies investigated tDCS (Ahn 2017; Antal 2010; Ayache 2016; Bae 2014; Boggio 2009; Brietzke 2016; Chang 2017; Donnell 2015; Fagerlund 2015; Fenton 2009; Fregni 2006a; Fregni 2006b; Hagenacker 2014; Harvey 2017; Hazime 2017; Jales Junior 2015; Jensen 2013; Khedr 2017; Kim 2013; Lagueux 2017; Luedtke 2015; Mendonca 2011; Mendonca 2016; Mori 2010; Ngernyam

2015; Oliveira 2015; Portilla 2013; Riberto 2011; Sakrajai 2014; Soler 2010; Souto 2014; Thibaut 2017; Valle 2009; Villamar 2013; Volz 2016; Wrigley 2014), two studies investigated RINCE (Deering 2017; Hargrove 2012a) two studies investigated tRNS (Curatolo 2017; Palm 2016) and one both rTMS and tDCS (Attal 2016).

Study designs

There was a mixture of parallel and cross-over study designs. For rTMS there were 22 parallel studies (Ahmed 2011; Avery 2013; Boyer 2014; Carretero 2009; Dall'Agnol 2014; Defrin 2007; de Oliveira 2014; Fregni 2011; Khedr 2005; Lee 2012; Malavera 2013; Medeiros 2016; Mhalla 2011; Nardone 2017 Passard 2007; Picarelli 2010; Short 2011; Tekin 2014; Tzabazis 2013; Umezaki 2016; Yagci 2014; Yilmaz 2014), and 20 cross-over studies (André-Obadia 2006; André-Obadia 2008; André-Obadia 2011; Borckardt 2009; Fregni 2005; Hirayama 2006; Hosomi 2013; Irlbacher 2006; Jetté 2013; Kang 2009; Lefaucheur 2001a; Lefaucheur 2001b; Lefaucheur 2004; Lefaucheur 2006; Lefaucheur 2008; Nurmikko 2016; Onesti 2013; Pleger 2004; Rollnik 2002; Saitoh 2007). For CES there were eight parallel studies (Gabis 2003; Gabis 2009; Katsnelson 2004; Lichtbroun 2001; Rintala 2010; Tan 2006; Tan 2011; Taylor 2013), and three cross-over studies (Capel 2003; Cork 2004; Tan 2000), of which we considered two as parallel studies, with only the opening phase of the study considered in this review because subsequent phases were unblinded (Capel 2003; Cork 2004). For tDCS there were 26 parallel studies (Ahn 2017; Bae 2014; Brietzke 2016; Chang 2017; Donnell 2015; Fagerlund 2015; Fregni 2006a; Fregni 2006b; Harvey 2017; Hazime 2017; Jales Junior 2015; Khedr 2017; Lagueux 2017; Kim 2013; Luedtke 2015; Mendonca 2011; Mendonca 2016; Mori 2010; Oliveira 2015; Riberto 2011; Sakrajai 2014; Soler 2010; Souto 2014; Thibaut 2017; Valle 2009; Volz 2016), and 10 cross-over studies (Antal 2010; Ayache 2016; Boggio 2009; Fenton 2009; Hagenacker 2014; Jensen 2013; Ngernyam 2015; Portilla 2013; Villamar 2013; Wrigley 2014), of which we considered one as a parallel study with only the opening phase of the study considered in this review due to excessive attrition after the first phase (Antal 2010). One study of tRNS (Palm 2016) used a cross-over design and one a parallel design (Curatolo 2017) and both RINCE studies used a parallel design (Deering 2017; Hargrove 2012a). The one study of both rTMS and tDCS employed a parallel design (Attal 2016).

Study participants

The included studies were published between 2000 and 2017. In rTMS studies sample sizes at the study outset ranged from four to 70 participants. In CES studies sample size ranged from 19 to 105 participants, in tDCS studies sample size ranged from three to 135 participants, the two RINCE studies recruited 91 and 46 participants and the two studies of tRNS included 16 and 20 participants.

Studies included a variety of chronic pain conditions. Ten rTMS studies included participants with neuropathic pain of mixed origin; of these, seven included a mix of participants with central, peripheral and facial neuropathic pain (André-Obadia 2006; André-Obadia 2008; André-Obadia 2011; Hirayama 2006; Hosomi 2013, Lefaucheur 2004; Lefaucheur 2008), three included a mix of participants with central and peripheral neuropathic pain (Lefaucheur 2006; Nurmikko 2016; Saitoh 2007), of which two studies included one or more participants with phantom limb pain (Nurmikko 2016; Saitoh 2007). One study included a mix of participants with central neuropathic pain and phantom limb pain (Irlbacher 2006). One study included a mix of participants with central and facial neuropathic pain (Lefaucheur 2001a), six rTMS studies included only participants with central neuropathic pain (Defrin 2007; de Oliveira 2014; Jetté 2013; Kang 2009; Nardone 2017, Yilmaz 2014), one included only participants with peripheral neuropathic pain (Borckardt 2009), and one study included participants with burning mouth syndrome (Umezaki 2016). Sixteen studies included non-neuropathic chronic pain including fibromyalgia (Boyer 2014; Carretero 2009; Lee 2012; Mhalla 2011; Passard 2007; Short 2011; Tekin 2014; Tzabazis 2013; Yagci 2014), chronic widespread pain (Avery 2013), chronic pancreatitis pain (Fregni 2005; Fregni 2011), chronic myofascial pain (Dall'Agnol 2014; Medeiros 2016) and complex regional pain syndrome type I (CRPSI) (Picarelli 2010; Pleger 2004). Two studies included only phantom limb pain (Ahmed 2011; Malavera 2013). Finally one study included a mix of peripheral neuropathic and non-neuropathic chronic pain (Rollnik 2002), including one participant with phantom limb pain and one with osteomyelitis. The majority (21) of rTMS studies specified chronic pain that was refractory to current medical management (André-Obadia 2006; André-Obadia 2008, André-Obadia 2011; Defrin 2007; Hirayama 2006; Hosomi 2013; Kang 2009; Khedr 2005; Lefaucheur 2001a; Lefaucheur 2001b; Lefaucheur 2004; Lefaucheur 2006; Lefaucheur 2008; Nardone 2017; Nurmikko 2016; Onesti 2013; Picarelli 2010; Rollnik 2002; Saitoh 2007; Yagci 2014; Yilmaz 2014). This inclusion criterion was varyingly described as intractable, resistant to medical intervention or resistant to drug management.

Of the studies investigating CES, one study included participants with pain related to osteoarthritis of the hip and knee (Katsnelson 2004), and two studied chronic back and neck pain (Gabis 2003; Gabis 2009). Of these, the later study also included participants with chronic headache but these data were not considered in this review. Three studies included participants with fibromyalgia (Cork 2004; Lichtbroun 2001; Taylor 2013), and three studies included participants with chronic pain following spinal cord injury (Capel 2003; Tan 2006; Tan 2011), although only one of these reports specified that the pain was neuropathic (Tan 2011). One study included participants with a mixture of "neuromuscular

pain" excluding fibromyalgia, of which back pain was reportedly the most prevalent complaint (Tan 2000), although further details were not reported. One study included participants with chronic pain related to Parkinson's disease (Rintala 2010).

Of the studies of tDCS one study included participants with a mixture of central, peripheral and facial neuropathic pain (Boggio 2009), two studies included participants with neuropathic pain secondary to multiple sclerosis (Ayache 2016; Mori 2010), five included participants with central neuropathic pain following spinal cord injury (Fregni 2006a; Ngernyam 2015; Soler 2010; Thibaut 2017; Wrigley 2014), one with central poststroke pain (Bae 2014), one with neuropathic or non-neuropathic pain following spinal cord injury (Jensen 2013), one with trigeminal neuralgia (Hagenacker 2014) and one with painful diabetic polyneuropathy (Kim 2013). Twenty studies included non-neuropathic pain, specifically chronic pelvic pain (Fenton 2009), osteoarthritis (OA) of the knee (Ahn 2017; Chang 2017), fibromyalgia (Fagerlund 2015; Fregni 2006b; Jales Junior 2015; Khedr 2017; Mendonca 2011; Mendonca 2016; Riberto 2011; Villamar 2013), temporomandibular joint pain (Donnell 2015; Oliveira 2015), hepatitis C-related chronic pain (Brietzke 2016), human T-lymphotropic virus 1 (HTLV-1) and viral hepatitis-related chronic back or leg pain (Souto 2014), chronic nonspecific low back pain (Hazime 2017; Luedtke 2015), inflammatory bowel disease-related pain (Volz 2016) or a mixed pain group (Antal 2010; Harvey 2017). One study included participants with neuropathic pain following burn injury (Portilla 2013) and one included participants with CRPS1 (Lagueux 2017). Four studies of tDCS specified recruiting participants with pain that was refractory to medical management (Antal 2010; Boggio 2009; Fenton 2009; Fregni 2006a). The studies relating to RINCE included participants with fibromyalgia (Deering 2017; Hargrove 2012a). The studies of tRNS included participants with multiple sclerosis-related neuropathic pain (Palm 2016) and fibromyalgia (Curatolo 2017). The study of both tDCS and rTMS included participants with lumbar radicular pain (Attal 2016).

Most studies included both male and female participants except Fenton 2009 (chronic pelvic pain), Dall'Agnol 2014, Medeiros 2016 (chronic myofascial pain), Donnell 2015 (temporomandibular disorder), Curatolo 2017; Fregni 2006b; Jales Junior 2015; Lee 2012; Mhalla 2011; Riberto 2011; Valle 2009; Yagci 2014 (fibromyalgia) which recruited women only and Yilmaz 2014 (post-spinal cord injury pain), which recruited only men. Three studies did not present data on gender distribution (Capel 2003; Fregni 2005; Katsnelson 2004).

Outcomes

Primary outcomes

All included studies assessed pain using self-reported pain visual analogue scales (VAS) or numerical rating scales (NRS). There was variation in the precise measure of pain (for example, current pain intensity, average pain intensity over 24 hours) and in the anchors used particularly for the upper limit of the scale (e.g. "worst pain imaginable", "unbearable pain", "most intense pain sensation"). Several studies did not specify the anchors used.

All studies assessed pain at the short-term (< 1 week post-treatment) follow-up stage. Thirty-seven studies reported medium-term outcome data (1 to 6 weeks post-treatment) (Ahmed 2011; Ahn 2017 André-Obadia 2008; Antal 2010; Ayache 2016; Bae 2014; Borckardt 2009; Carretero 2009; Defrin 2007; de Oliveira 2014; Fagerlund 2015; Fenton 2009; Fregni 2006a; Fregni 2006b; Fregni 2011; Gabis 2009; Kang 2009; Khedr 2005; Khedr 2017; Kim 2013; Lee 2012; Lefaucheur 2001a; Luedtke 2015; Mendonca 2016; Mori 2010; Nardone 2017; Nurmikko 2016; Passard 2007; Picarelli 2010; Short 2011; Soler 2010; Thibaut 2017; Tzabazis 2013; Valle 2009; Volz 2016; Wrigley 2014; Yagci 2014). Eight studies collected outcome data at long-term (> 6 weeks post-treatment) follow-up (Avery 2013; Hazime 2017; Kang 2009; Luedtke 2015; Mendonca 2016; Passard 2007; Thibaut 2017; Yagci 2014).

Secondary outcomes

We considered secondary outcomes that distinctly measured self-reported disability (that capture the extent of disability or functional limitation experienced, usually in relation to the pain) or quality of life (a multidimensional construct that includes domains related to physical, emotional and social functioning).

Sixteen studies used measures of disability (Ahn 2017; Attal 2016; Avery 2013; Chang 2017; Cork 2004; Hazime 2017; Kang 2009; Lagueux 2017; Luedtke 2015; Mhalla 2011; Passard 2007; Short 2011; Soler 2010; Tan 2000; Tan 2006; Umezaki 2016), and 27 studies collected measures of quality of life (Avery 2013; Boyer 2014; Curatolo 2017; de Oliveira 2014; Fregni 2006b; Jales Junior 2015; Lagueux 2017; Lee 2012; Lichtbroun 2001; Mendonca 2016; Mhalla 2011; Mori 2010; Oliveira 2015; Passard 2007; Picarelli 2010; Riberto 2011;Sakrajai 2014; Short 2011; Tan 2011; Taylor 2013; Tekin 2014; Thibaut 2017; Tzabazis 2013; Valle 2009; Villamar 2013; Volz 2016; Yagci 2014).

Twenty-four studies did not report any information regarding adverse events (Ahmed 2011; André-Obadia 2011; Bae 2014; Borckardt 2009; Brietzke 2016; Cork 2004; Curatolo 2017; Defrin 2007; Gabis 2009; Harvey 2017; Jales Junior 2015; Jensen 2013; Kang 2009; Katsnelson 2004; Khedr 2005; Lefaucheur 2006; Lefaucheur 2008; Lichtbroun 2001; Pleger 2004; Riberto 2011; Tan 2000; Tan 2006; Tekin 2014; Yilmaz 2014). Reporting of adverse events in the remaining studies varied substantially in terms of detail.

Studies of rTMS

See Table 1 for a summary of stimulation characteristics utilised in rTMS studies.

Stimulation location

The parameters for rTMS application varied significantly between studies, including by site of stimulation, stimulation parameters and the number of stimulation sessions. The majority of rTMS studies targeted the primary motor cortex (M1) (Ahmed 2011; André-Obadia 2006; André-Obadia 2008; André-Obadia 2011; Attal 2016; Boyer 2014; Dall'Agnol 2014; Defrin 2007; Hirayama 2006; Hosomi 2013; Irlbacher 2006; Jetté 2013; Kang 2009; Khedr 2005; Lee 2012, Lefaucheur 2001a; Lefaucheur 2001b; Lefaucheur 2004; Lefaucheur 2006; Lefaucheur 2008; Malavera 2013; Medeiros 2016; Mhalla 2011; Nurmikko 2016; Onesti 2013; Passard 2007; Picarelli 2010; Pleger 2004; Rollnik 2002; Saitoh 2007; Tekin 2014;). Of these, one study specified stimulation of the right hemisphere (Kang 2009), five studies specified the left hemisphere (Boyer 2014; Dall'Agnol 2014; Medeiros 2016; Mhalla 2011; Yagci 2014), and four studies specified stimulation over the midline (Defrin 2007; Pleger 2004; Tekin 2014; Yilmaz 2014). One study used a novel H-coil to stimulate the motor cortex of the leg representation situated deep in the central sulcus (Onesti 2013), and the remainder stimulated over the contralateral cortex to the side of dominant pain. One of these studies also investigated stimulation of the supplementary motor area (SMA), pre-motor area (PMA) and primary somatosensory cortex (S1) (Hirayama 2006). Seven studies stimulated the dorsolateral prefrontal cortex (DLPFC) or prefrontal cortex (PFC), with five studies stimulating the left hemisphere (Borckardt 2009; de Oliveira 2014; Nardone 2017; Short 2011; Umezaki 2016), and two studies the right (Carretero 2009; Lee 2012). One study investigated stimulation of the left and right secondary somatosensory cortex (SII) as separate treatment conditions (Fregni 2005), and another investigated stimulation to the right SII area (Fregni 2011). One study used a four-coil configuration to target the anterior cingulate cortex (Tzabazis 2013).

Stimulation parameters

Frequency

Twelve studies investigated low-frequency (< 5 Hz) rTMS (André-Obadia 2006; Carretero 2009; Fregni 2005; Fregni 2011; Irlbacher 2006; Lee 2012; Lefaucheur 2001b; Lefaucheur 2006; Lefaucheur 2008; Saitoh 2007; Tzabazis 2013; Yagci 2014). Of these, one study used a frequency of 0.5 Hz in one treatment condition (Lefaucheur 2001b), and the rest used a frequency of 1 Hz. Thirty-nine studies investigated high-frequency (≥ 5 Hz) rTMS (Ahmed 2011; André-Obadia 2006; André-Obadia 2008; André-Obadia 2011; Attal 2016; Avery 2013; Borckardt 2009; Boyer 2014; Dall'Agnol 2014; Defrin 2007; de Oliveira 2014; Fregni 2005; Hirayama 2006; Hosomi 2013; Irlbacher 2006; Jetté 2013; Kang 2009; Khedr 2005; Lee 2012; Lefaucheur 2001a; Lefaucheur 2001b; Lefaucheur 2004; Lefaucheur 2006; Lefaucheur 2008; Malavera 2013; Medeiros 2016; Mhalla 2011; Nardone 2017; Nurmikko 2016; Onesti 2013; Passard 2007; Picarelli 2010; Pleger 2004; Rollnik 2002; Saitoh 2007; Short 2011; Tekin 2014; Umezaki 2016; Yilmaz 2014). While the study by Tzabazis 2013 did apply high-frequency stimulation to some participants, the allocation of the high-frequency groups was not randomised in that study (confirmed through correspondence with authors) and so those data will not be considered further in this review as they do not meet our inclusion criteria.

Other parameters

We observed wide variation between studies for various stimulation parameters. The overall number of rTMS pulses delivered varied from 120 to 4000. Defrin 2007 reported a total number of pulses of 500 although the reported stimulation parameters of 500 trains, delivered at a frequency of 5 Hz for 10 seconds would imply 25,000 pulses. Thirteen studies specified a posteroanterior or parasagittal orientation of the stimulating coil (André-Obadia 2006; Attal 2016; Boyer 2014; Lefaucheur 2001b; Lefaucheur 2004; Lefaucheur 2006; Lefaucheur 2008; Nardone 2017; Nurmikko 2016; Passard 2007; Picarelli 2010; Short 2011; Yilmaz 2014), seven studies specified a coil orientation 45º to the midline (Ahmed 2011; Dall'Agnol 2014; Jetté 2013; Kang 2009; Malavera 2013; Medeiros 2016; Tekin 2014), one study compared a posteroanterior coil orientation with a medial-lateral coil orientation (André-Obadia 2008), one used an H-coil (Onesti 2013), one used a four-coil configuration (Tzabazis 2013), and the remaining studies did not specify the orientation of the coil. Within studies that reported the information, the duration and number of trains and the inter-train intervals varied. Two studies did not report this information (Fregni 2005; Fregni 2011).

Type of sham

rTMS studies employed a variety of sham controls. In 13 studies the stimulating coil was angled away from the scalp to prevent significant cortical stimulation (Ahmed 2011; André-Obadia 2006; André-Obadia 2008; Carretero 2009; Hirayama 2006; Kang 2009; Khedr 2005; Lee 2012; Pleger 2004; Rollnik 2002; Saitoh 2007; Yagci 2014; Yilmaz 2014), of which two studies also simultaneously electrically stimulated the skin of the scalp in both the active and sham stimulation conditions in order to mask the sensations elicited by active rTMS and thus preserve participants' blinding (Hirayama 2006; Saitoh 2007). One study (Nurmikko 2016) applied active stimulation at the same parameters as for the active stimulation condition, but applied to the occipital fissure, which is a site at which stimulation is not hypothesised to induce analgesia. The remaining studies utilised sham

coils. Of these, 13 studies specified that the sham coil made similar or identical sounds to those elicited during active stimulation (André-Obadia 2011; Borckardt 2009; Boyer 2014; Defrin 2007; de Oliveira 2014; Irlbacher 2006; Malavera 2013; Mhalla 2011; Nardone 2017; Passard 2007; Picarelli 2010; Tekin 2014; Tzabazis 2013), and eight specified that the sham coil made similar sounds, looked the same and elicited similar scalp sensations as the real coil (Attal 2016; Avery 2013; Fregni 2011; Hosomi 2013; Jetté 2013; Onesti 2013; Short 2011; Umezaki 2016). Eight studies did not specify whether the sham coil controlled for the auditory characteristics of active stimulation (Dall'Agnol 2014; Fregni 2005; Lefaucheur 2001a; Lefaucheur 2001b; Lefaucheur 2004; Lefaucheur 2006; Lefaucheur 2008; Medeiros 2016).

Studies of CES

See Table 2 for a summary of stimulation characteristics utilised in CES studies.

Stimulation device, parameters and electrode location

Seven studies of CES used the 'Alpha-stim' CES device (Electromedical Products International, Inc, Mineral Wells, Texas, USA). This device uses two ear clip electrodes that attach to each of the participant's ears (Cork 2004; Lichtbroun 2001; Rintala 2010; Tan 2000; Tan 2006; Tan 2011; Taylor 2013), and these studies utilised stimulation intensities of 100 μA with a frequency of 0.5 Hz. One study (Capel 2003) used a device manufactured by Carex (Hemel Hempstead, UK) that also used earpiece electrodes and delivered a stimulus intensity of 12 μA.

Two studies used the 'Pulsatilla 1000' device (Pulse Mazor Instruments, Rehavol, Israel) (Gabis 2003; Gabis 2009). The electrode array for this device involved an electrode attached to each of the participant's mastoid processes and one attached to the forehead; current is passed to the mastoid electrodes. One study used the 'Nexalin' device (Kalaco Scientific Inc, Scottsdale, AZ, USA) (Katsnelson 2004). With this device current is applied to a forehead electrode and returned via electrodes placed behind the participant's ears. These three studies utilised significantly higher current intensities than those using ear clip electrodes with intensities of 4 mA (Gabis 2003; Gabis 2009), and 11 to 15 mA (Katsnelson 2004).

All CES studies gave multiple treatment sessions for each treatment group with variation between the number of treatments delivered.

Type of sham

Eight studies utilised inert sham units (Capel 2003; Cork 2004; Lichtbroun 2001; Rintala 2010; Tan 2000; Tan 2006; Tan 2011; Taylor 2013). These units were visually indistinguishable from the active devices. Stimulation at the intensities used is subsensation and as such it should not have been possible for participants to distinguish between the active and sham conditions.

Two studies utilised an "active placebo" treatment unit (Gabis 2003; Gabis 2009). This sham device was visually indistinguishable and delivered a current of much lower intensity ($\leq$ 0.75 mA) than the active stimulator to evoke a similar sensation to ensure participant blinding. Similarly, Katsnelson 2004 utilised a visually indistinguishable sham device that delivered brief pulses of current of less than 1 mA. The placebo conditions used in these three studies delivered current at much greater intensities than those used in the active stimulation conditions of the other CES studies.

Studies of tDCS

See Table 3 for a summary of stimulation characteristics utilised in tDCS studies.

Stimulation parameters and electrode location

Four studies of tDCS stimulated the dorsolateral prefrontal cortex in one treatment group (Ayache 2016; Fregni 2006b; Kim 2013; Valle 2009). Thirty-four studies stimulated the motor cortex (Ahn 2017; Antal 2010; Bae 2014; Boggio 2009; Brietzke 2016; Chang 2017; Donnell 2015; Fagerlund 2015; Fenton 2009; Fregni 2006a; Fregni 2006b; Hagenacker 2014; Harvey 2017; Hazime 2017; Jales Junior 2015; Jensen 2013; Khedr 2017; Kim 2013; Lagueux 2017; Luedtke 2015; Mendonca 2016; Mori 2010; Ngernyam 2015; Oliveira 2015; Portilla 2013; Riberto 2011; Sakrajai 2014; Soler 2010; Souto 2014; Thibaut 2017; Valle 2009; Villamar 2013; Volz 2016; Wrigley 2014). Of these, 23 stimulated the cortex contralateral to the side of worst pain (Ahn 2017; Bae 2014; Boggio 2009; Chang 2017; Donnell 2015; Fregni 2006a; Fregni 2006b; Hagenacker 2014; Harvey 2017; Hazime 2017; Khedr 2017; Lagueux 2017; Mori 2010; Ngernyam 2015; Oliveira 2015; Portilla 2013; Riberto 2011; Sakrajai 2014; Soler 2010; Thibaut 2017; Villamar 2013; Volz 2016; Wrigley 2014), of which six studies stimulated the opposite hemisphere to the dominant hand where pain did not have a unilateral dominance (Fregni 2006a; Fregni 2006b; Jensen 2013; Riberto 2011; Soler 2010; Wrigley 2014). Seven studies stimulated the left hemisphere for all participants (Antal 2010; Brietzke 2016; Jales Junior 2015; Mendonca 2016; Souto 2014; Valle 2009; Villamar 2013). One study of chronic pelvic pain stimulated the opposite hemisphere to the dominant hand in all participants (Fenton 2009). One study specifically investigated the use of tDCS in conjunction with transcutaneous electrical nerve stimulation (TENS) therapy (Boggio 2009). We extracted data comparing active tDCS and sham TENS with sham tDCS and sham TENS for the purposes of this review. One study applied anodal or cathodal stimulation to the left motor cortex or to the right supraorbital area (Mendonca 2011).

Eighteen studies delivered a current intensity of 2 mA for 20 minutes once a day for five days (Ahn 2017; Antal 2010; Brietzke 2016; Donnell 2015; Fagerlund 2015; Fregni 2006a; Fregni 2006b; Harvey 2017; Kim 2013; Luedtke 2015; Mendonca 2016; Mori

2010; Sakrajai 2014; Souto 2014; Thibaut 2017; Valle 2009; Volz 2016; Wrigley 2014). Across the remaining studies, dose, in terms of the number and frequency of stimulation sessions, varied considerably, from a single 20-minute session to up to 10 weeks of stimulation with either one or multiple sessions of stimulation in a week. In one study (Hagenacker 2014) tDCS was self-administered by participants, daily for 14 days. Six studies (Antal 2010; Chang 2017; Fenton 2009; Hagenacker 2014; Jales Junior 2015; Sakrajai 2014) delivered stimulation at a current intensity of 1 mA.

All studies of tDCS utilised a sham condition whereby active stimulation was ceased after 30 seconds without the participants' knowledge.

Excluded studies

See Characteristics of excluded studies.

In previous versions of this review we excluded 20 studies after consideration of the full study report. Of these, two were not studies of brain stimulation (Carraro 2010; Frentzel 1989), two did not assess self-reported pain as an outcome (Belci 2004; Johnson 2006), seven were not restricted to participants with chronic pain or clearly in a chronic pain population (Avery 2007; Choi 2012a; Choi 2012b; Evtiukhin 1998; Katz 1991; Longobardi 1989; Pujol 1998), two were single case studies (Silva 2007; Zaghi 2009), one study presented duplicate data from a study already accepted for inclusion (Roizenblatt 2007, duplicate data from Fregni 2006b), one did not employ a sham control (Evtiukhin 1998), one was not a randomised controlled trial (O'Connell 2013), one reported uncontrolled long-term follow-up data from an included study (Hargrove 2012b), one employed an intervention that was not designed to alter cortical activity directly through electrical stimulation (Nelson 2010), and one included some participants who did not meet our criterion of chronic pain (Bolognini 2013). A final study was screened by a Russian translator and excluded on the basis that it did not employ a sham control for tDCS (Sichinava 2012).

In this update we excluded a further 14 reports of 12 studies. Three of these studies did not randomly allocate participants to groups (Cummiford 2016; Lindholm 2015; Yoon 2014). Six were not clearly in a chronic population (Bolognini 2015; Choi 2014; Khedr 2005; Ma 2015; Morin 2017; Schabrun 2014), two were not studies of electrical brain stimulation (Maestu 2013; Smania 2005), one did not employ a sham control (Seada 2013).

Studies awaiting classification

In this update we have 18 studies registered as awaiting classification. Of these 16 have been published as conference abstracts but we have not been able to obtain a full study report. We were unable to source the original study report for the remaining two. For further details see Characteristics of studies awaiting classification.

Ongoing studies

In this update we have identified 48 ongoing studies. These studies all investigate the effect of either tDCS or rTMS for chronic pain. For further details see Characteristics of ongoing studies.

Risk of bias in included studies

Risk of bias varied across studies for all of the assessment criteria. For summaries of 'Risk of bias' assessment across studies see Figure 2 and Figure 3.

Figure 2. Methodological quality summary: review authors' judgements about each methodological quality item for each included study

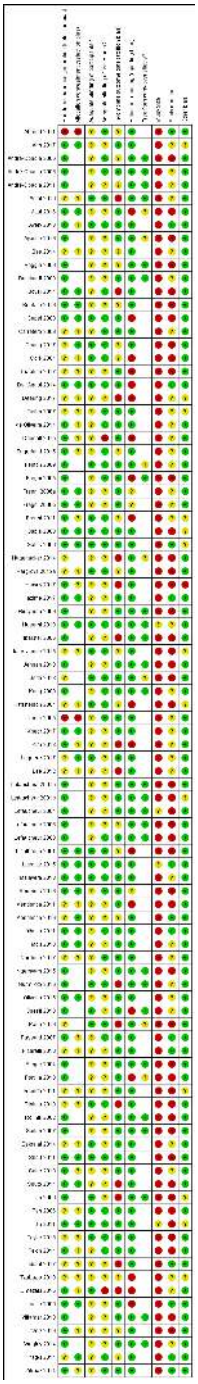
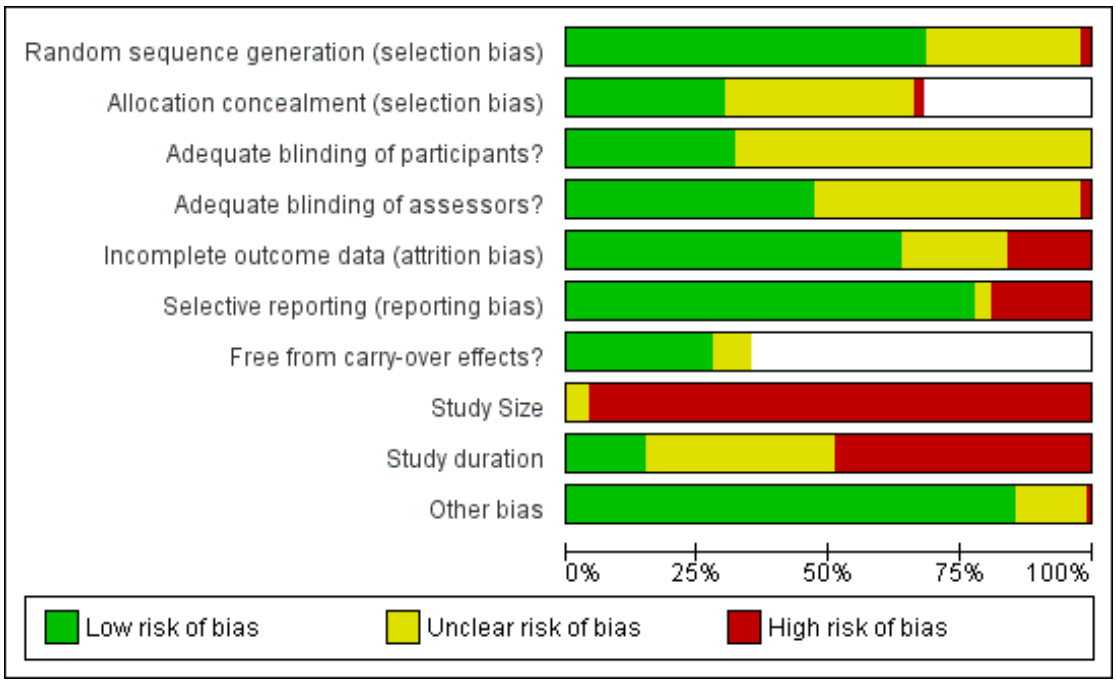


Figure 3. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies



Sequence generation

For the criterion 'adequate sequence generation' we awarded cross-over trials a judgement of 'low risk of bias' where the study report mentioned that the order of treatment conditions was randomised. Since this criterion has a greater potential to introduce bias in parallel designs we only awarded a judgement of 'low risk of bias' where the method of randomisation was specified and adequate.

We judged 28 trials as having an unclear risk of bias (Antal 2010; Bae 2014; Carretero 2009; Chang 2017; Cork 2004; Curatolo 2017; Deering 2017; Defrin 2007; Hagenacker 2014; Hargrove 2012a; Jales Junior 2015; Jetté 2013; Katsnelson 2004; Lagueux 2017; Lee 2012; Mendonca 2011; Mendonca 2016; Nardone 2017; Palm 2016; Picarelli 2010; Riberto 2011; Rintala 2010; Sakrajai 2014; Tan 2006; Taylor 2013; Thibaut 2017; Tzabazis 2013; Yagci 2014), as they did not specify the method of randomisation used or the description was not clear. We judged two studies as having a high risk of bias for this criterion (Ahmed 2011; Khedr 2005), as the reports suggested that participants were allocated depending on the day of the week on which they were recruited, which we did not judge as being genuinely random. We judged the remaining 64 studies as having a low risk of bias for this domain.

Allocation concealment

We only considered allocation concealment for parallel designs or cross-over trials from which only data from the first cross-over phase of the study was included (i.e. we considered them as parallel-group studies). Thirty-four studies did not clearly report concealment of allocation and we judged them as unclear (Antal 2010; Avery 2013; Bae 2014; Carretero 2009; Cork 2004; Curatolo 2017; de Oliveira 2014; Deering 2017; Defrin 2007; Donnell 2015; Fagerlund 2015; Fregni 2011; Hargrove 2012a; Harvey 2017; Jales Junior 2015; Katsnelson 2004; Kim 2013; Lee 2012; Mendonca 2011; Nardone 2017; Passard 2007; Picarelli 2010; Riberto 2011; Rintala 2010; Sakrajai 2014; Soler 2010; Tan 2006; Taylor 2013; Tekin 2014; Thibaut 2017; Tzabazis 2013; Umezaki 2016; Volz 2016; Yilmaz 2014), and we judged two studies as having a high risk of bias for this criterion since the method of randomisation employed would not have supported conceal-

ment of allocation (Ahmed 2011; Khedr 2005). We judged 28 studies as having a low risk of bias for this domain.

Blinding

Blinding of participants

All studies attempted to blind participants. However, due to the difficulties involved in producing a robust sham control in rTMS studies (see Assessment of risk of bias in included studies) we made an assessment of sham credibility. Where the coil was angled or angled and elevated away from the scalp, this is potentially distinguishable both visually and by the sensory effects of stimulation. Two studies simultaneously electrically stimulated the scalp during rTMS stimulation to mask the differences in sensation between conditions (Hirayama 2006; Saitoh 2007). However, by angling the coil away from the scalp, participants may have been able to visually distinguish between the conditions. Where sham coils were utilised they usually did not control for the sensory aspects of stimulation. We assessed most rTMS studies as having suboptimal sham control conditions and we therefore assessed them as having an 'unclear' risk of bias.

One study with a sham of this type presented a formal assessment of blinding that demonstrated blinding success (Malavera 2013) and was rated at low risk. Seven rTMS studies included in this update utilised sham coils that are visually indistinguishable, emit the same noise during stimulation and elicit similar scalp sensations (Avery 2013; Dall'Agnol 2014; Fregni 2011; Jetté 2013; Onesti 2013; Short 2011; Umezaki 2016). One study (Nurmikko 2016) applied active stimulation to a site of the brain not hypothesised to elicit analgesia as its sham condition. While there may be a risk of this stimulation having an effect we considered that this sham could be expected to be indistinguishable from real stimulation. These studies met the criteria for an optimal sham condition and as such we judged them at low risk of bias for participant blinding.

Similarly with tDCS studies, due to evidence that blinding of participants to the stimulation condition may be compromised at intensities of 1.5 mA and above, we judged the majority of tDCS studies at unclear risk of bias on this criterion (Ahn 2017; Attal 2016; Ayache 2016; Bae 2014; Boggio 2009; Brietzke 2016; Donnell 2015; Fagerlund 2015; Fregni 2006a; Fregni 2006b; Harvey 2017; Hazime 2017; Jensen 2013; Khedr 2017; Kim 2013; Mendonca 2011; Mendonca 2016; Mori 2010; Ngernyam 2015; Oliveira 2015; Portilla 2013; Riberto 2011; Soler 2010; Souto 2014; Thibaut 2017; Valle 2009; Villamar 2013; Volz 2016; Wrigley 2014) unless there was evidence of blinding success (Lagueux 2017; Luedtke 2015). We judged one study Hagenacker 2014 at unclear risk of bias as the method of blinding was not described.

We assessed all studies of CES and RINCE and the single study of tRNS as having a low risk of bias for this criterion.

Overall, we judged 27 studies at low risk of bias, and 57 studies at unclear risk of bias.

Blinding of assessors

While many studies used self-reported pain outcomes we considered that the complex nature of the intervention, and the level of interaction this entails between participants and assessors, suggested that a lack of blinding of the researchers engaged in the collection of outcomes might potentially introduce bias. This is particularly the case when a VAS is used to measure pain intensity as this requires the assessor to measure the distance from the zero anchor point to the mark made by the participant. As such, where blinding of assessors was not clearly stated we made a judgement of 'unclear' for this criterion. We rated studies of tDCS that applied stimulation intensity of 2 mA and where no formal assessment of blinding success was presented as at unclear risk of bias, since there is evidence that assessor blinding may be compromised at the stimulation intensities used (O'Connell 2012).

We judged 48 studies to be at unclear risk of bias (Ahn 2017; André-Obadia 2011; Attal 2016; Ayache 2016; Bae 2014; Boggio 2009; Borckardt 2009; Brietzke 2016; Curatolo 2017; Deering 2017; Fregni 2006a; Fregni 2006b; Hagenacker 2014; Harvey 2017; Hazime 2017; Hirayama 2006; Irlbacher 2006; Jensen 2013; Khedr 2017; Kim 2013; Lagueux 2017;Lee 2012; Lefaucheur 2001a; Lefaucheur 2001b; Lefaucheur 2004; Lefaucheur 2006; Mendonca 2011; Mendonca 2016; Mori 2010; Ngernyam 2015; Oliveira 2015; Onesti 2013; Picarelli 2010; Pleger 2004; Portilla 2013; Riberto 2011; Rollnik 2002; Saitoh 2007; Sakrajai 2014; Soler 2010; Souto 2014; Tan 2000; Thibaut 2017; Tzabazis 2013; Valle 2009; Villamar 2013; Volz 2016; Wrigley 2014), two studies (Donnell 2015; Umezaki 2016) at high risk of bias, as they clearly reported that assessors were not blinded, and we rated the remaining studies at low risk of bias.

Incomplete outcome data

We assessed 19 studies as having an unclear risk of bias for this criterion (Ahmed 2011; André-Obadia 2006; André-Obadia 2011; Bae 2014; Brietzke 2016; Boggio 2009; Chang 2017; Cork 2004; Fagerlund 2015; Fregni 2011; Hargrove 2012a; Jales Junior 2015; Katsnelson 2004; Lefaucheur 2006; Lichtbroun 2001; Mendonca 2016; Tzabazis 2013; Volz 2016; Yagci 2014). Of these, Ahmed 2011; Bae 2014; Cork 2004; Fregni 2011; Jales Junior 2015; Katsnelson 2004; Lefaucheur 2006; Lichtbroun 2001; Tzabazis 2013 and Volz 2016 did not report the level of dropout from their studies. Tzabazis 2013 reported recruiting 16 participants in the full study report (Tzabazis 2013), but an earlier abstract report of the same study reported the recruitment of 45 participants. In the study of André-Obadia 2006, two participants (17% of the study cohort) did not complete the study and this was not clearly accounted for in the data analysis. This was also the case for

Boggio 2009, where two participants (25% of the cohort) failed to complete the study. Brietzke 2016 and Mendonca 2016 reported dropout of more than10% and used the last observation carried forward (LOCF) approach for imputation. Chang 2017 and Yagci 2014 reported dropout of more than 10% and conducted an available case analysis. Fagerlund 2015 had a high noncompletion rate for some outcomes and did not clearly report how many participants were analysed for each outcome.

We assessed fifteen studies as having a high risk of bias for this criterion (Antal 2010; Boyer 2014; Deering 2017; Hagenacker 2014; Harvey 2017; Irlbacher 2006; Kim 2013; Lee 2012; Nurmikko 2016; Palm 2016; Rintala 2010; Souto 2014; Tan 2000; Thibaut 2017; Umezaki 2016). In the Antal 2010 study, of 23 participants recruited only 12 completed the full cross over. Boyer 2014 reported dropout of more than 20% and, while an intention-to-treat approach was reported the details of this and any imputation of missing data were not reported. Deering 2017 excluded eight out of 15 participants randomised to the sham condition on the basis that "an unexpected signal source was discovered in EEG traces". Harvey 2017 reported a 25% dropout rate in the active stimulation arm only and those participants appear to have been excluded from the analysis. In the study by Irlbacher 2006, only 13 of the initial 27 participants completed all of the treatment conditions. Kim 2013 reported a 15% dropout rate and excluded those participants from the analysis. Nurmikko 2016 reported a 33% dropout rate with a per-protocol analysis. Palm 2016 reported 13% dropout and excluded those participants from the analysis. Souto 2014 reported 20% dropout and used the LOCF method to impute missing data. In the studies of Hagenacker 2014; Lee 2012 and Rintala 2010, attrition exceeded 30% of the randomised cohort. In the study by Tan 2000, 17 participants did not complete the study (61% of the cohort) and this was not clearly accounted for in the analysis. Thibaut 2017 reported a 57% dropout rate. Umezaki 2016 reported dropout of more than 20% and conducted a per-protocol analysis.

Selective reporting

We assessed studies as having a high risk of bias for this criterion where the study report did not produce adequate data to assess the effect size for all groups/conditions at all follow-up time points, and these data were not made available upon request. We assessed 18 studies as having a high risk of bias for this criterion (Attal 2016; Capel 2003; Cork 2004; Curatolo 2017; Dall'Agnol 2014; Deering 2017; Donnell 2015; Fregni 2005; Fregni 2011; Katsnelson 2004; Kim 2013; Lichtbroun 2001; Mendonca 2011; Onesti 2013; Portilla 2013; Tzabazis 2013; Umezaki 2016; Valle 2009). We judged three studies as being at unclear risk of bias (Fregni 2006a; Fregni 2006b; Medeiros 2016). In the reports of Fregni 2006a and Fregni 2006b data were not presented in a format that could be easily interpreted. On request data were available from these two studies for the primary outcome at baseline and short-term follow-up but not for other follow-up points. Medeiros 2016 reported pain VAS scores but not the results of pain diaries that were described in the methods. We assessed the remaining 73 studies as having a low risk of bias for this criterion. For this update, we first made requests for data (by email where possible). If any data are made available in time for future updates then we will revise judgements on this criterion accordingly.

Carry-over effects in cross-over trials

We judged seven studies (Attal 2016; Ayache 2016; Fenton 2009; Hagenacker 2014; Jetté 2013; Palm 2016; Portilla 2013) as unclear on this criterion as no formal investigation of carry-over effects was discussed in the study report. In one cross-over study baseline differences between the sham and the 10 Hz stimulation condition were notable (Saitoh 2007). A paired t-test did not show a difference ($P > 0.1$) and we judged this study as having a low risk of bias for carry-over effects. We rated 25 cross-over studies at low risk of bias and the remaining 52 studies were not assessed due to their parallel design.

A number of studies were judged at unclear risk of bias as information regarding between group baseline comparability was not presented.

Study size

We rated four studies at unclear risk of bias (Hosomi 2013; Lefaucheur 2004; Luedtke 2015; Tan 2011), with all remaining studies rated at high risk of bias on this criterion.

Study duration

We rated 14 studies at low risk of bias on this criterion (Ahmed 2011; Avery 2013; Dall'Agnol 2014; Gabis 2009; Hazime 2017; Luedtke 2015; Mendonca 2016; Mhalla 2011; Passard 2007; Picarelli 2010; Thibaut 2017; Valle 2009; Yagci 2014; Yilmaz 2014), 34 studies at unclear risk of bias (Ahn 2017; André-Obadia 2008; André-Obadia 2011; Antal 2010; Bae 2014; Borckardt 2009; Carretero 2009; Deering 2017; Defrin 2007; de Oliveira 2014; Donnell 2015; Fagerlund 2015; Fenton 2009; Fregni 2006a; Fregni 2006b; Fregni 2011; Hosomi 2013; Kang 2009; Khedr 2005; Khedr 2017; Kim 2013; Lagueux 2017; Lee 2012; Malavera 2013; Mori 2010; Nardone 2017; Nurmikko 2016; Oliveira 2015; Onesti 2013; Sakrajai 2014; Soler 2010; Tzabazis 2013; Umezaki 2016; Wrigley 2014), and the remaining studies at high risk of bias (André-Obadia 2006; Attal 2016; Ayache 2016; Boggio 2009; Boyer 2014; Brietzke 2016; Capel 2003; Chang 2017; Cork 2004; Curatolo 2017; Fregni 2005; Gabis 2003; Hagenacker 2014; Hargrove 2012a; Harvey 2017; Hirayama 2006; Irlbacher 2006; Jales Junior 2015; Jensen 2013; Jetté 2013; Katsnelson 2004; Lefaucheur 2001a; Lefaucheur 2001b; Lefaucheur 2004; Lefaucheur 2006; Lefaucheur 2008; Lichtbroun 2001; Medeiros 2016; Mendonca 2011; Ngernyam 2015; Palm

2016; Pleger 2004; Portilla 2013; Riberto 2011; Rintala 2010; Rollnik 2002; Saitoh 2007; Short 2011; Souto 2014; Tan 2000; Tan 2006; Tan 2011; Taylor 2013; Tekin 2014; Villamar 2013; Volz 2016).

Other potential sources of bias

Overall, we judged 13 studies at unclear risk of bias and one study at high risk of bias on this criterion. Five studies (Deering 2017; Fregni 2011; Jales Junior 2015; Katsnelson 2004; Tzabazis 2013) were judged at unclear risk of bias as they did not adequately report baseline values for the groups to allow assessment of baseline comparability. One of those studies (Deering 2017) was rated as unclear on the criteria as no formal baseline comparisons were presented and around half of those randomised to the sham group were excluded from the baseline score. We judged four studies (Ahn 2017; Defrin 2007; Riberto 2011; Tan 2011) at unclear risk of bias as baseline differences were apparent for pain-related measures. We rated Harvey 2017 at high risk of bias on the basis of a greater than 3-point difference between the active and sham groups in baseline pain levels on a 0 to 10 scale.

One study of CES also applied electrical stimulation to the painful body area as part of the treatment, which may have affected the final outcomes (Tan 2000). Two studies of CES used an "active placebo condition" that delivered a level of cortical stimulation that was greater than that used in the active arm of other CES studies (Gabis 2003; Gabis 2009). It is possible that delivering cortical stimulation in the sham group might mask differences between the sham and active condition. Also such a large difference in current intensity compared with other studies of CES might be a source of heterogeneity. We judged these three studies as 'unclear' on this criterion. We rated one study (Lefaucheur 2001b) at unclear risk of bias as the outcome of a planned statistical analysis was not reported. We judged 80 studies at low risk of bias for this criterion.

Effects of interventions

See: **Summary of findings for the main comparison** Repetitive transcranial magnetic stimulation (rTMS) compared with sham for chronic pain; **Summary of findings 2** Cranial electrotherapy stimulation (CES) compared with sham for chronic pain; **Summary of findings 3** Transcranial direct current stimulation (tDCS) compared with sham for chronic pain

For a summary of all core findings, see Summary of findings for the main comparison; Summary of findings 2; Summary of findings 3.

Primary outcome: pain intensity

Repetitive transcranial magnetic stimulation (rTMS): short-term (0 to < 1 week postintervention)

The primary meta-analysis (Analysis 1.1) pooled data from all rTMS studies with low or unclear risk of bias (excluding the risk of bias criteria 'study size' and 'study duration') where data were available (27 studies, n = 655), including cross-over and parallel designs, using the generic inverse variance method (André-Obadia 2006; André-Obadia 2008; André-Obadia 2011; Avery 2013; Borckardt 2009; Carretero 2009; Defrin 2007; de Oliveira 2014; Hirayama 2006; Hosomi 2013; Jetté 2013; Kang 2009; Lefaucheur 2001a; Lefaucheur 2001b; Lefaucheur 2004; Lefaucheur 2006; Lefaucheur 2008; Medeiros 2016; Mhalla 2011; Nardone 2017; Passard 2007; Pleger 2004; Rollnik 2002; Saitoh 2007; Short 2011; Tekin 2014; Yagci 2014). We excluded the studies by Ahmed 2011; Boyer 2014; Dall'Agnol 2014; Khedr 2005; Irlbacher 2006; Lee 2012; Nurmikko 2016 and Umezaki 2016 as we classified them as having a high risk of bias on at least one criterion. We were unable to include data from six studies (Fregni 2005; Fregni 2011; Onesti 2013; Picarelli 2010; Tzabazis 2013; Umezaki 2016, combined n = 107) as the necessary data were not available in the study report or upon request by the submission date of this update. We could not include the data from Yilmaz 2014 as outcomes were only reported as a median (interquartile range). We imputed the correlation coefficient used to calculate the standard error (SE) (standardised mean difference (SMD)) for cross-over studies (0.764) from data extracted from André-Obadia 2008 (as outlined in Unit of analysis issues) and we entered the SMD (SE) for each study into a generic inverse variance meta-analysis. We divided the number of participants in each cross-over study by the number of comparisons made by that study included in the meta-analysis. For parallel studies we calculated the standard error of the mean (SEM) from the 95% confidence intervals (CIs) of the standardised mean difference (SMD) and entered both the SMD and the SEM into the meta-analysis. We then entered this into the meta-analysis with the SMD using the generic inverse variance method.

The pooled SMD for this comparison was -0.22 (95% CI -0.29 to -0.16, P < 0.001). We back-transformed the SMD to a mean difference using the mean standard deviation of the post-treatment sham group scores of the studies included in this analysis (1.86). We then used this to estimate the real percentage change on a 0 to 10 pain intensity scale of active stimulation compared with the mean poststimulation score from the sham groups of the included studies (5.94). This equates to a 7% (95% CI 5% to 9%) reduction in pain, or a 0.40 (95% CI 0.53 to 0.32) point reduction on a 0 to 10 pain intensity scale, which does not meet the minimum clinically important difference threshold of 15% or more. Using GRADE we rated the quality of evidence for this comparison as low, downgraded once on the basis of study limitations due to risk of bias and once on the basis of inconsistency due to heterogeneity (see Summary of findings for the main comparison). We observed substantial heterogeneity (I^2 = 70%, P < 0.001) and investigated this using pre-planned subgroup analyses. Categorising studies by high (≥ 5 Hz) or low (< 5 Hz) frequency, rTMS demonstrated

a difference between subgroups (P < 0.001) and reduced heterogeneity in the low-frequency group (n = 106, I^2 = 0%). In this group there was no evidence of an effect of low-frequency rTMS for pain intensity (SMD 0.13, 95% CI -0.03 to 0.28, P = 0.11). While high-frequency stimulation demonstrated an effect (n = 560, SMD -0.30, 95% CI -0.37 to -0.23, P < 0.001), we observed substantial heterogeneity in this analysis (P < 0.001, I^2 = 68%). Separating studies that delivered a single treatment per condition from those that delivered multiple treatment sessions did not reduce heterogeneity substantially in multiple-dose studies (n = 357, I^2 = 80%, P < 0.001) or single-dose studies (n = 319, I^2 = 57%, P < 0.001) (Analysis 1.2).

There were insufficient data to support the subgroup analysis by the type of painful condition as planned. However, when the analysis was restricted to studies including only well-defined neuropathic pain populations (Analysis 1.3), there was little impact on heterogeneity (I^2 = 69%, P < 0.001). In the subgroup of non-neuropathic pain studies overall heterogeneity remained high (I^2 = 77%, P < 0.001) (Analysis 1.4). Responder data were available from one study not judged at high risk of bias (Malavera 2013 n = 54, Analysis 1.14; Analysis 1.25). This demonstrated an effect in favour of active stimulation for 30% reduction in pain (risk ratio (RR) 2.11, 95% CI 1.17 to 3.80, P = 0.01).

rTMS motor cortex

Restricting the analysis to studies of high-frequency stimulation of the motor cortex (Analysis 1.5) (21 studies, n = 505) the pooled SMD was -0.37 (-0.51 to 0.22, P < 0.001) though heterogeneity was high (I^2 = 67%, P < 0.001). Using GRADE we rated the quality of evidence for this comparison as low, downgraded once on the basis of study limitations due to risk of bias and once on the basis of inconsistency due to heterogeneity (see Summary of findings for the main comparison).

Further restricting the analysis to single-dose studies of high-frequency stimulation of the motor cortex (n = 249) reduced heterogeneity (I^2 = 23%, P = 0.19) (Analysis 1.5). The pooled SMD was -0.38 (95% CI -0.49 to -0.27, P < 0.001). We back-transformed the SMD to a mean difference using the mean standard deviation of the post-treatment sham group scores of the studies included in this analysis (2.04). We then used this to estimate the real percentage change on a 0 to 10 pain intensity scale of active stimulation compared with the mean poststimulation score from the sham groups of the included studies (6.2). This equated to a reduction of 0.77 (95% CI 0.55 to 0.99) points, or a percentage change of 12% (95% CI 9% to 16%) of the control group outcome. This estimate does not reach the pre-established criteria for a minimal clinically important difference (≥ 15%). Of the included studies in this subgroup, nine did not clearly report blinding of assessors and we awarded them a judgement of 'unclear' risk of bias for this criterion (André-Obadia 2011; Hirayama 2006; Lefaucheur 2001a; Lefaucheur 2001b; Lefaucheur 2004; Lefaucheur 2006; Pleger 2004; Rollnik 2002; Saitoh 2007). A sensitivity analysis removing these studies reduced heterogeneity to I^2 = 0% although only three studies were preserved in the analysis (André-Obadia 2006; André-Obadia 2008; Lefaucheur 2008). There remained a difference between sham and active stimulation although the SMD reduced to -0.29 (95% CI -0.49 to -0.13). This equates to a percentage change of 9% (95% CI 4% to 14%) in comparison with sham stimulation. For multiple-dose studies of high-frequency motor cortex stimulation heterogeneity was high (n = 256, I^2 = 82%, P < 0.001), and the pooled effect was not significant (SMD -0.34, 95% CI -0.73 to 0.05, P = 0.09).

When the analysis was restricted to studies of single-dose, high-frequency motor cortex stimulation in well-defined neuropathic pain populations (excluding data from Pleger 2004 and Rollnik 2002), there was little effect on the pooled estimate (SMD -0.41, 95% CI -0.52 to -0.29) or heterogeneity (I^2 = 23%, P = 0.20). When we applied the same process to multiple-dose studies of high-frequency motor cortex stimulation (excluding data from Medeiros 2016; Mhalla 2011; Passard 2007; Tekin 2014 and Yagci 2014 we found no pooled effect (SMD 0.12, 95% CI -0.16 to 0.40) and heterogeneity remained high.

Sensitivity analysis

To assess whether the imputation of standard errors for cross-over studies was robust we repeated the analysis with the correlation coefficient reduced to 0.66 and increased to 0.86. This had no marked effect on the overall analysis (Analysis 1.6; Analysis 1.7). We applied the same process to the subgroup analysis of single-dose studies of high-frequency motor cortex stimulation (Analysis 1.8; Analysis 1.9). This had a negligible impact on the effect size or the statistical significance for this subgroup.

To assess the impact of excluding the studies at high risk of bias we performed the analysis with data from these studies included (Analysis 1.10). While this produced a modest increase in the SMD it increased heterogeneity from 68% to 72%. Inclusion of high risk of bias studies to the multiple-dose studies of high-frequency motor cortex stimulation subgroup increased heterogeneity (I^2 = 85%, P < 0.001), though the analysis demonstrated an effect (SMD -0.53, 95% CI -0.91 to -0.15, P = 0.006) (Analysis 1.11). Inclusion of the Irlbacher 2006 study in the single-dose studies of high-frequency motor cortex stimulation subgroup caused a slight decrease in the pooled effect size (SMD -0.35, 95% CI -0.46 to -0.24) with no impact on heterogeneity.

Small study effects

We investigated small study effects using Egger's test. The results are not suggestive of a significant influence of small study effects.

rTMS prefrontal cortex

Restricting the analysis to studies that stimulated the prefrontal cortex (PFC) included six studies (n = 103) (Avery 2013; Borckardt 2009; Carretero 2009; de Oliveira 2014; Nardone 2017; Short 2011) (Analysis 1.12). We excluded the study by Lee 2012 due to its high risk of bias. There was no clear pooled effect (P = 0.11) with substantial heterogeneity (I^2 = 79%, P < 0.001). Restricting the analysis to high-frequency studies (Avery 2013; Borckardt 2009; Nardone 2017; Short 2011), the results were unchanged (P = 0.12, I^2 = 83%, P < 0.001).

Sensitivity analysis

To assess the impact of excluding the study of Lee 2012, we performed the analysis with data from this study included (Analysis 1.13). The overall effect remained non-significant (P = 0.08) with high heterogeneity (I^2 = 75%, P < 0.001).

rTMS: medium-term (≥ 1 to < 6 weeks postintervention)

Eleven studies provided data on medium-term pain outcomes (Avery 2013; Carretero 2009; de Oliveira 2014; Hosomi 2013; Lefaucheur 2001a; Kang 2009; Malavera 2013; Nardone 2017; Passard 2007; Short 2011; Yagci 2014). We excluded the studies by Ahmed 2011; Khedr 2005; Lee 2012 and Nurmikko 2016 as we classified them as having a high risk of bias. The analysis included 293 participants (Analysis 1.16). Overall heterogeneity was high (I^2 = 77%, P < 0.001) and no clear evidence of effect was observed (SMD -0.28, 95% CI -0.61 to 0.05, P = 0.09). Using GRADE we rated the quality of evidence for this comparison as very low, downgraded once on the basis of study limitations due to risk of bias, once on the basis of inconsistency due to heterogeneity and once for imprecision due to low participant numbers. Restricting the analysis to studies of prefrontal cortex stimulation (Avery 2013; Carretero 2009; de Oliveira 2014; Nardone 2017; Short 2011) demonstrated no clear effect (SMD -1.08, 95% CI -2.49 to 0.32, P = 0.13, I^2 = 88%, P < 0.001, Analysis 1.19). Studies of motor cortex stimulation also demonstrated no effect (SMD -0.22, 95% CI -0.46 to 0.02, P = 0.08) although heterogeneity was high (I^2 = 59%, P < 0.02) and remained high when only high-frequency stimulation studies were included (SMD -0.23 (-0.49 to 0.03, P = 0.08, I^2 = 66%, P = 0.01) (Analysis 1.18). We performed sensitivity analysis to assess the impact of excluding the studies by Ahmed 2011; Khedr 2005; Lee 2012 and Nurmikko 2016 on the basis of risk of bias (Analysis 1.17). Including these studies did not substantially alter heterogeneity (I^2 = 80%, P < 0.01) though the effect reached significance overall (SMD -0.50, 95% CI -0.80 to -0.20, P = 0.001).

rTMS: long-term (≥ 6 weeks postintervention)

Four studies provided data for long-term pain relief (Avery 2013; Kang 2009; Passard 2007; Yilmaz 2014) (Analysis 1.20). The analysis included 75 participants. There was no heterogeneity (I^2 = 0%, P = 0.99). The analysis demonstrated no effect (SMD -0.14, 95% CI -0.44 to 0.17, P = 0.39). Using GRADE we rated the quality of evidence for this comparison as low, downgraded once on the basis of study limitations due to risk of bias and once for imprecision due to low participant numbers. Sensitivity analysis to assess the impact of excluding the study of Ahmed 2011 due to its high risk of bias continued to demonstrate no evidence of effect, though heterogeneity was introduced (Analysis 1.21, I^2 = 57%, P = 0.05).

Cranial electrotherapy stimulation (CES): short-term (0 to < 1 week postintervention)

Six studies provided data for this analysis (Gabis 2003; Gabis 2009; Tan 2006; Tan 2011; Taylor 2013) (Analysis 2.1, n = 270). We excluded the study by Rintala 2010 due to high risk of attrition bias. All studies utilised a parallel-group design and so we used a standard inverse variance meta-analysis using SMD. Four studies did not provide the necessary data to enter into the analysis (Capel 2003; Cork 2004; Katsnelson 2004; Lichtbroun 2001, combined n = 228) and we classified two studies as being at high risk of bias on criteria other than 'free of selective outcome reporting' (Katsnelson 2004; Tan 2000). The studies by Gabis 2003 and Gabis 2009 differed substantially from the other included studies on the location of electrodes and the intensity of the current provided. Despite this, there was no heterogeneity (I^2 = 0%). No individual study in this analysis demonstrated superiority of active stimulation over sham and the results of the meta-analysis do not demonstrate a clear effect (SMD -0.24, 95% CI -0.48 to 0.01, P = 0.06). Using GRADE we rated the quality of evidence for this comparison as low, downgraded once on the basis of study limitations due to risk of bias and once for imprecision due to low participant numbers (see Summary of findings 2). Sensitivity analysis, including the study by Rintala 2010, did not meaningfully affect the results (SMD -0.21, 95% CI -0.45 to 0.02, P = 0.07).

CES: medium-term (≥ 1 to 6 weeks postintervention) and long-term (≥ 6 weeks postintervention)

There were insufficient data to perform a meta-analysis for medium- or long-term pain outcomes for CES.

Transcranial direct current stimulation (tDCS): short-term (0 to < 1 week postintervention)

Adequate data were available from 27 studies (Ahn 2017; Antal 2010; Ayache 2016; Bae 2014; Boggio 2009; Brietzke 2016; Chang 2017; Fagerlund 2015; Fenton 2009; Fregni 2006a; Fregni 2006b; Hazime 2017; Jales Junior 2015; Jensen 2013; Khedr 2017; Lagueux 2017; Luedtke 2015; Mendonca 2016; Mori 2010; Ngernyam 2015; Oliveira 2015; Riberto 2011; Sakrajai 2014;

Soler 2010; Villamar 2013; Volz 2016; Wrigley 2014) for this analysis (n = 747). We were unable to include data from Donnell 2015; Mendonca 2011; and Valle 2009 (combined n = 95) as the necessary data were not reported in the study report or available upon request to the study authors. We analysed data using the generic inverse variance method. We imputed the correlation coefficient (0.635) used to calculate the SE (SMD) for cross-over studies from data extracted from Boggio 2009 (see Unit of analysis issues). One study compared two distinct active stimulation conditions to one sham condition (Fregni 2006b). We considered that combining the treatment conditions would be inappropriate, as each involved stimulation of different locations and combination would hinder subgroup analysis. Instead we included both comparisons separately with the number of participants in the sham control group divided by the number of comparisons. We excluded data from Harvey 2017 as there was a baseline imbalance greater than 3 out of 10 in pain scores. We only included first-stage data from the study of Antal 2010 (n = 12) due to the unsustainable level of attrition following this stage.

The overall meta-analysis demonstrated an effect of active stimulation (SMD -0.43, 95% CI -0.63 to -0.22, P < 0.001) (Analysis 3.1), but heterogeneity was high (I^2 = 60%, P < 0.001). We back-transformed the SMD to a mean difference using the mean standard deviation of the post-treatment sham group scores of the studies included in this analysis (1.91). We then used this to estimate the real percentage change on a 0 to 10 pain intensity scale of active stimulation compared with the mean post-stimulation score from the sham groups of the included studies (4.77). This equates to a reduction of 0.82 (95% CI 0.42 to 1.2) points, or a percentage change of 17% (95% CI 9% to 25%) of the control group outcome, which meets our threshold for a clinically important difference, though the lower confidence interval is substantially below that threshold. Using GRADE we rated the quality of evidence for this comparison as very low, downgraded once on the basis of study limitations due to risk of bias, once for inconsistency due to heterogeneity and once for evidence of possible publication bias (see Summary of findings 3).

Subgrouping studies by multiple or single dose decreased heterogeneity in the single-dose subgroup (I^2 = 0%, P = 0.70) but did not reduce heterogeneity in the multiple-dose subgroup (I^2 = 64%, P < 0.001). Inclusion of studies at high risk of bias (Analysis 3.4; Antal 2010; Hagenacker 2014; Kim 2013; Souto 2014; Thibaut 2017) slightly increased the effect size (SMD -0.48, 95% CI -0.67 to -0.29, P < 0.001, I^2 = 60%, P < 0.001). Analysis restricted to comparisons of active motor cortex stimulation (single- and multiple-dose studies) (n = 655, Analysis 3.5) did not reduce heterogeneity substantially (I^2 = 58%, P < 0.001) and demonstrated an effect (SMD -0.47, 95% CI -0.67 to -0.28, P < 0.001).

There were insufficient data to support the planned subgroup analysis by the type of painful condition as planned. However, a modified subgroup analysis by neuropathic or non-neuropathic pain conditions (Analysis 3.8) demonstrated no subgroup difference (P = 0.41) though heterogeneity was reduced in the neuropathic pain group (I^2 = 40%, P = 0.10).

Responder data were only available from a small number of studies, all that were considered at high risk of bias. As such we did not conduct a formal meta-analysis but the data can be seen in Analysis 3.9; Analysis 3.10; Analysis 3.12 and Analysis 3.13.

To assess whether the imputation of standard errors for cross-over studies was robust we repeated the analyses with the imputed correlation coefficient reduced and increased by a value of 0.1 (Analysis 3.2; Analysis 3.3; Analysis 3.6; Analysis 3.7). This had no meaningful impact upon the results.

Small study effects

We investigated small study effects using Egger's test. Funnel plot asymmetry was apparent and Egger's test indicated small study effects for the overall comparisons (Figure 4, P = 0.019) and the subgroups of motor cortex stimulation studies (Figure 5, P = 0.002).

Figure 4. Funnel plot of comparison 3. Transcranial direct current stimulation (tDCS), outcome 3.1. Pain: short-term follow-up

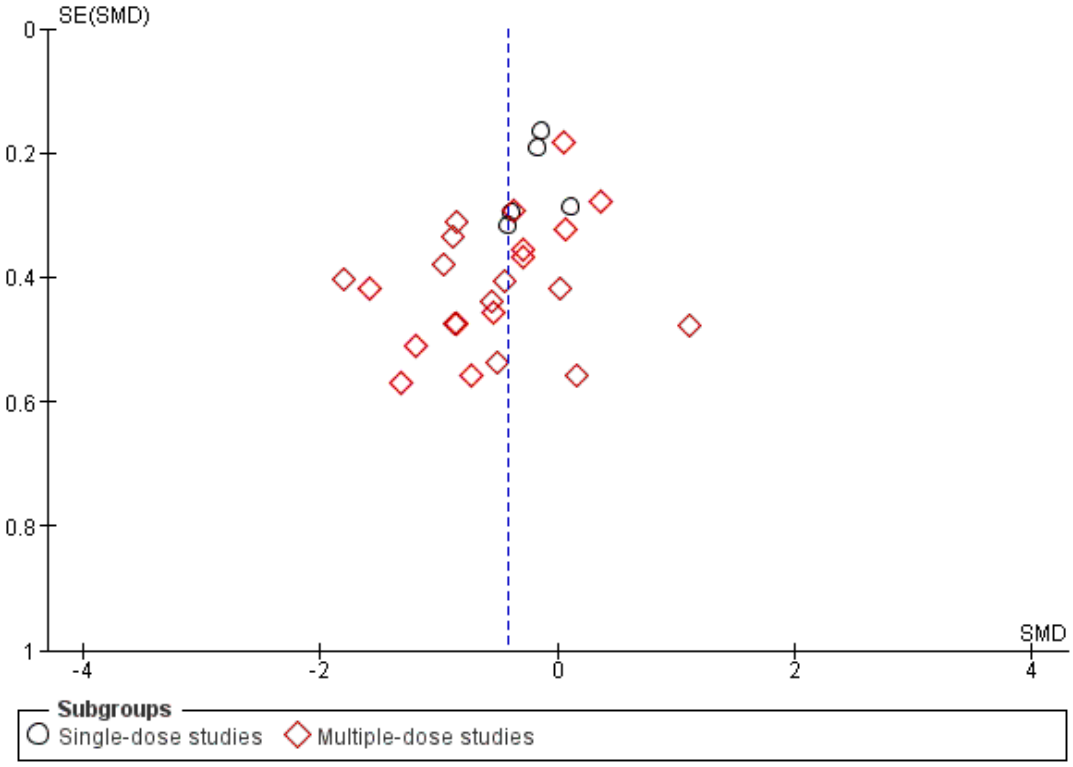
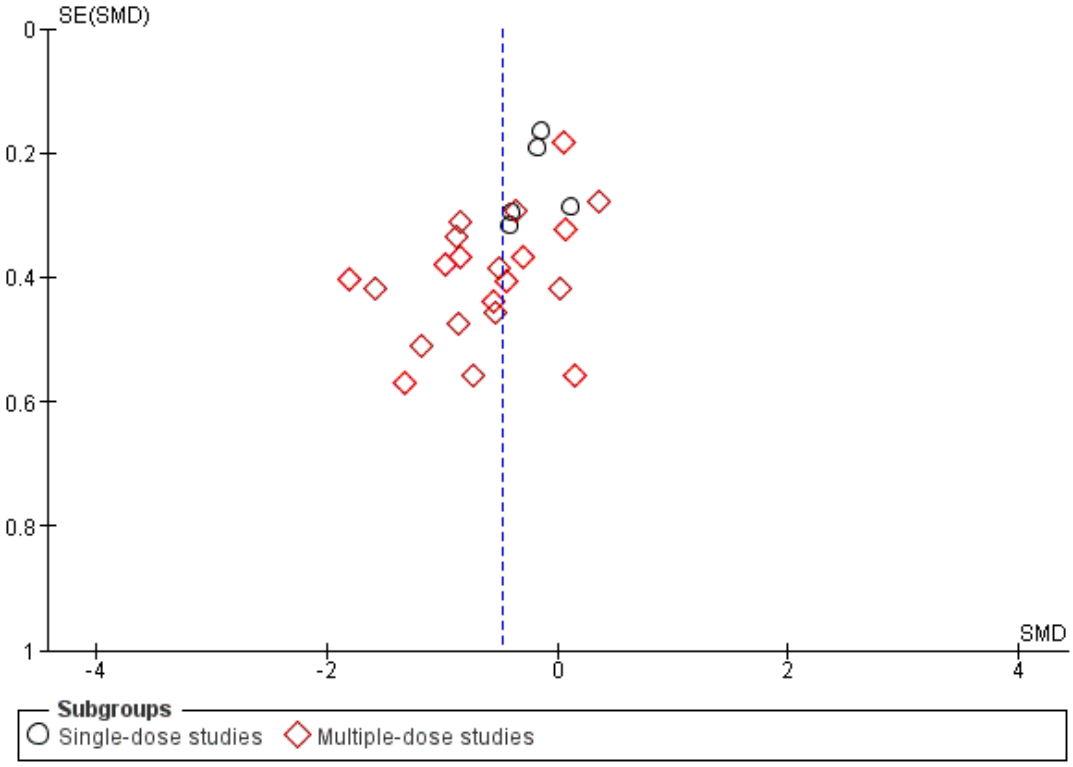


Figure 5. Funnel plot of comparison 3. Transcranial direct current stimulation (tDCS), outcome 3.5. Pain: short-term follow-up, subgroup analysis: motor cortex studies only



tDCS: medium-term (1 to < 6 weeks post-treatment)

Fourteen studies provided adequate data for this analysis (Ahn 2017; Ayache 2016 ; Bae 2014; Fagerlund 2015; Fenton 2009; Khedr 2017; Lagueux 2017; Luedtke 2015; Mendonca 2016; Mori 2010; Sakrajai 2014; Soler 2010, Volz 2016; Wrigley 2014, pooled n = 443) (Analysis 3.11). There was heterogeneity (I^2 = 60%, P = 0.003) and the pooled results demonstrated an effect of tDCS (SMD -0.43, 95% CI -0.72 to -0.13, P = 0.004). Using GRADE we rated the quality of evidence for this comparison as very low, downgraded once on the basis of study limitations due to risk of bias, once for inconsistency and once for evidence of publication bias.

Small study effects

We investigated small study effects using Egger's test. Funnel plot asymmetry was apparent and Egger's test indicated small study effects (P = 0.013).

tDCS: long-term (> 6 weeks post-treatment)

Three studies provide data for this analysis (Hazime 2017; Luedtke 2015; Mendonca 2016, pooled n = 137). There was no heterogeneity (I^2 = 36%, P = 0.21) and no effect of tDCS was observed (SMD -0.01, 95% CI -0.43 to 0.41, P = 0.97) (Analysis 3.15). Using GRADE we rated the quality of evidence for this comparison as low, downgraded once on the basis of study limitations due to risk of bias and once for imprecision due to low participant numbers.

Reduced impedance non-invasive cortical electrostimulation (RINCE): short-term (0 to < 1 week postintervention)

The one study not at high risk of bias that investigated RINCE demonstrated a positive effect on pain intensity (n = 77, mean difference (0 to 10 pain scale) -1.41, 95% CI -2.48 to -0.34, P < 0.01) (Analysis 4.1; Hargrove 2012a). Using GRADE we rated the quality of evidence as very low, downgraded once on the basis of study limitations due to risk of bias, once for inconsistency (single study) and once for imprecision due to low participant

numbers. Sensitivity analysis including the study at high risk of bias (Deering 2017) did not increase heterogeneity (pooled n = 115, SMD -0.59, 95% CI -0.99 to -0.18, P = 0.004).

Transcranial random noise stimulation (tRNS): short-term (0 to < 1 week postintervention)

One study at high risk of bias Palm 2016 offered data for tRNS. This study did not report a difference between active and sham stimulation (Analysis 5.1). Using GRADE we rated the quality of evidence as very low, downgraded once on the basis of study limitations due to risk of bias, once for inconsistency (single study) and once for imprecision due to low participant numbers. Curatolo 2017 did not report outcome data in a numeric format at any postintervention time point but the authors reported a statistically significant difference in favour of tRNS. It was not possible to extract an estimate of effect size from this high-risk-of-bias study.

tRNS: medium-term (≥1 to 6 weeks postintervention) and long-term (≥ 6 weeks postintervention)

No data were available for medium- or long-term pain outcomes for tRNS.

Secondary outcome: disability

rTMS: short-term (0 to < 1 week postintervention) disability

Five studies provided data on disability at short-term follow-up (Avery 2013; Kang 2009; Mhalla 2011; Passard 2007; Short 2011). Pooling of these studies (Analysis 1.22; n = 119) demonstrated no effect (SMD -0.29, 95% CI -0.87 to 0.29, P = 0.33) with substantial heterogeneity (I^2 = 71%, P = 0.007). All of these studies delivered multiple doses of high-frequency stimulation. Using GRADE we rated the quality of evidence for this comparison as very low, downgraded once on the basis of study limitations due to risk of bias, once on the basis of inconsistency due to heterogeneity and once for imprecision due to low participant numbers (see Summary of findings for the main comparison). Two studies stimulated the DLPFC (Avery 2013; Short 2011) and three stimulated the motor cortex (Kang 2009; Mhalla 2011; Passard 2007). Subgrouping studies by stimulation site had no impact on heterogeneity. Sensitivity analysis including studies at high risk of bias (Umezaki 2016, n = 20) increased heterogeneity but did not substantially change the outcome (pooled n = 139, SMD -0.36, 95% CI -0.72 to 0.12, P = 0.16, I^2 = 59%, P = 0.02).

rTMS:medium-term (1 to < 6 weeks postintervention) disability

Four studies provided data on disability at medium-term follow-up (Avery 2013; Kang 2009; Mhalla 2011; Passard 2007). Pooling of these studies (Analysis 1.24; n = 99) demonstrated no effect (SMD -0.37, 95% CI -1.07 to 0.33, P = 0.3) with heterogeneity (I^2 = 78%, P = 0.004). Using GRADE we rated the quality of evidence for this comparison as very low, downgraded once on the basis of study limitations due to risk of bias, once on the basis of inconsistency due to heterogeneity and once for imprecision due to low participant numbers (see Summary of findings for the main comparison).

All studies delivered multiple sessions of high-frequency stimulation. Of these, one study stimulated the DLPFC (Avery 2013) and the remaining studies stimulated the motor cortex (Kang 2009; Mhalla 2011; Passard 2007). Removing the study of Avery 2013 did not decrease heterogeneity (I^2 = 85%, P = 0.001). Sensitivity analysis including studies at high risk of bias (Umezaki 2016, n = 20) increased heterogeneity but did not substantially change the outcome (pooled n = 119, SMD -0.42, 95% CI -1.01 to 0.17, P = 0.17, I^2 = 72%, P < 0.001).

rTMS: long-term (≥ 6 weeks postintervention) disability

Three studies provided data on disability at long-term follow-up (Avery 2013; Kang 2009; Passard 2007). Pooling of these studies demonstrated no effect (pooled n = 63, SMD -0.23, 95% CI -0.62 to 0.16, P = 0.24) without heterogeneity (I^2 = 15%, P = 0.31) (Analysis 1.26). Using GRADE we rated the quality of evidence for this comparison as low, downgraded once on the basis of study limitations due to risk of bias and once for imprecision due to low participant numbers. Sensitivity analysis including studies at high risk of bias (Umezaki 2016, n = 20) did not substantially change the outcome (pooled n = 83, SMD -0.41, 95% CI -0.87 to 0.05, P = 0.08, I^2 = 39%, P = 0.18).

tDCS: short-term (0 to < 1 week postintervention) disability

Four studies (Ahn 2017; Chang 2017; Luedtke 2015; Soler 2010) provided data on disability in the short term. While Ayache 2016 reported disability, this was a cross-over study and we were unable to source a representative correlation coefficient for this outcome in order to calculate the standard error (SMD) for cross-over studies. No effect was seen (pooled n = 212, SMD -0.01, 95% -0.28 to 0.26, P = 0.84) and there was no heterogeneity (I^2 = 0%, P = 0.59, Analysis 3.16). Using GRADE we rated the quality of evidence for this comparison as low, downgraded once on the basis of study limitations due to risk of bias and once for imprecision due to low participant numbers (see Summary of findings 3).

tDCS: medium-term (1 to < 6 weeks post-treatment) disability

One study (Luedtke 2015) provided data on disability in the medium term. This study demonstrated no effect of tDCS (RMDQ mean difference 0.00 (95% CI -0.38 to 0.38).

Secondary outcome: quality of life

rTMS: short-term (0 to < 1 week postintervention) quality of life

Four studies provided data on quality of life at short-term follow-up (Mhalla 2011; Passard 2007; Short 2011; Yagci 2014). We were unable to include data from Tzabazis 2013, as the size of the treatment groups was not clear from the study report. All studies used the Fibromyalgia Impact Questionnaire (FIQ) so we were able to use the mean difference as the measure of effect. Pooling data from these studies (Analysis 1.28; n = 105) demonstrated an effect in favour of active stimulation (mean difference (MD) -10.80, 95% CI -15.04 to -6.55, P < 0.001) with no heterogeneity (I^2 = 0%, P = 0.96). Using GRADE we rated the quality of evidence for this comparison as low, downgraded once on the basis of study limitations due to risk of bias and once for imprecision due to low participant numbers (see Summary of findings for the main comparison). Tekin 2014 measured quality of life using the World Health Organization Quality of Life (WH-QoL) scale but only reported data from individual subdomains. They reported a statistically significant difference in favour of active stimulation for the physical subdomain but not the psychological, social, environmental or national domains.

rTMS: medium-term (1 to < 6 weeks postintervention) quality of life

The same four studies provided data on quality of life at medium-term follow-up (Mhalla 2011; Passard 2007; Short 2011; Yagci 2014). All studies used the FIQ so we were able to use the mean difference as the measure of effect. Pooling data from these studies (Analysis 1.29; n = 105) demonstrated an effect (MD -11.49, 95% CI -16.73 to -6.25, P < 0.001) with no heterogeneity (I^2 = 0%, P = 0.82). Using GRADE we rated the quality of evidence for this comparison as low, downgraded once on the basis of study limitations due to risk of bias and once for imprecision due to low participant numbers. Sensitivity analysis including studies at high risk of bias (Boyer 2014) did not meaningfully alter the result (pooled n = 143, MD -8.93, 95% CI -13.49 to -4.37, P < 0.001, I^2 = 15%, P = 0.32).

rTMS: long-term (≥ 6 weeks postintervention) quality of life

Data were available from two studies (Passard 2007, Yagci 2014, pooled n = 51) for quality of life at long-term follow-up. The analysis demonstrated an effect in favour of active stimulation (FIQ total score: MD -6.78, 95% CI -13.43 to -0.14, I^2 = 0%, P = 0.56) (Analysis 1.31). Using GRADE we rated the quality of evidence for this comparison as low, downgraded once on the basis of study limitations due to risk of bias and once for imprecision due to low participant numbers. Sensitivity analysis including studies at high risk of bias (Boyer 2014) did not meaningfully alter the result (pooled n = 89, MD -8.58, 95% CI -13.84 to -3.33, P < 0.001, I^2 = 0%, P = 0.58).

CES: short-term (0 to < 1 week postintervention) quality of life

Two studies provided quality of life data for this analysis (Tan 2011; Taylor 2013). One study used the physical component score of the SF-12 and the other used the FIQ. However, one study demonstrated a baseline imbalance of the SF-12 that exceeded in size any pre-poststimulation change (Tan 2011), therefore we considered it inappropriate to enter this into a meta-analysis. The study by Taylor 2013 (n = 36) demonstrated a positive effect on this outcome (MD -25.05,95%CI -37.82, -12.28, Analysis 2.2). Using GRADE we rated the quality of evidence for this comparison as very low, downgraded once on the basis of study limitations due to risk of bias, once for inconsistency (single study) and once for imprecision due to low participant numbers (see Summary of findings 2).

tDCS: short-term (0 to < 1 week postintervention) quality of life

Four studies provided adequate data for this analysis (Jales Junior 2015; Mori 2010; Riberto 2011; Volz 2016; pooled n = 82). Of these, Jales Junior 2015 used the FIQ, Mori 2010 used the Multiple Sclerosis Quality of Life 54 scale (MS-QoL-54), Riberto 2011 used the SF-36 (total score) and Volz 2016 used the Inflammatory Bowel Disease Questionnaire Quality of Life scale. The pooled effect was in favour of active stimulation (SMD 0.66, 95% CI 0.21 to 1.11, P = 0.004) with no heterogeneity (I^2 = 0%, P = 0.62) (Analysis 3.18). Using GRADE we rated the quality of evidence for this comparison as low, downgraded once on the basis of study limitations due to risk of bias and once for imprecision due to low participant numbers. Lagueux 2017, Mendonca 2016 and Oliveira 2015 reported quality of life using the or SF-36 and WH-QoL scales but did not report composite scores that we could enter into the meta-analysis. All three studies reported no statistically significant differences across the different quality-of-life domains. We excluded Thibaut 2017 from the analysis due to high risk of bias. They measured quality of life using the Patient Health Questionnaire (PHQ-9) but reported no significant difference between groups.

tDCS: medium-term (1 to < 6 weeks post-treatment) quality of life

At medium-term follow-up Fagerlund 2015; Mori 2010 and Volz 2016 (pooled n = 87) provided data and demonstrated no clear effect of tDCS on quality of life (SMD 0.34, 95% CI -0.09 to 0.76, P = 0.12, I^2 = 0%, P = 0.54, Analysis 3.19). Using GRADE

we rated the quality of evidence for this comparison as low, downgraded once on the basis of study limitations due to risk of bias and once for imprecision due to low participant numbers.

RINCE: short-term (0 to < 1 week postintervention) quality of life

One study of RINCE therapy (Hargrove 2012a, n = 77) demonstrated no effect on quality of life (FIQ, MD -6.50, 95% CI -15.21 to 2.21, Analysis 4.3). Using GRADE we rated the quality of evidence as very low, downgraded once on the basis of study limitations due to risk of bias, once for inconsistency (single study) and once for imprecision due to low participant numbers. Sensitivity analysis including studies at risk of bias (the addition of Deering 2017, n = 38) did not alter the outcome (SMD -0.45, 95% CI -0.91 to 0.02, P = 0.06, I^2 = 10%, P = 0.33).

Secondary outcome: adverse events

rTMS

Minor

Thirty-one of 42 studies of rTMS reported on adverse events. Of these, 10 studies reported none (André-Obadia 2006; André-Obadia 2008; Boyer 2014; Fregni 2005; Hirayama 2006; Lefaucheur 2001a; Lefaucheur 2001b; Lefaucheur 2004; Onesti 2013; Saitoh 2007). Attal 2016 reported similar proportions of side effects between stimulation conditions with no serious events. Avery 2013 reported a range of reported sensations including headache, pain at the stimulation site, muscle aches/fatigue, dizziness and insomnia, though there were no clear differences in the frequency of these events between the two groups. Carretero 2009 reported neck pain or headache symptoms in six out of 14 participants in the active stimulation group compared with two out of 12 in the sham group. One participant in the active stimulation group reported worsening depression and four participants in the sham group reported symptoms of nausea and tiredness. Dall'Agnol 2014 reported that they did not observe moderate or severe adverse effects but did not report any details on the incidence of mild effects. de Oliveira 2014 reported mild headaches in three participants (27.3%) receiving active rTMS and in one participant receiving sham rTMS. In the study by Fregni 2011, the incidence of headache and neck pain was higher in the active stimulation group than in the sham group. Forty-one participants reported headache after active stimulation compared to 19 after sham and 18 participants reported neck pain after active stimulation compared with three after sham. Hosomi 2013 reported no difference between real and sham rTMS for minor adverse events. Jetté 2013 reported that seven participants receiving rTMS reported mild discomfort related to scalp pressure and facial twitching. Malavera 2013 reported no serious adverse effects but reports of headache, neck pain and sleepiness without differences between groups, while Medeiros 2016 simply reported that they did not observe serious or moderate side effects from the treatment, with no further detail. Mhalla 2011 reported that nine participants (five following active stimulation and four following sham stimulation) reported transient headache, and one participant reported transient dizziness after active stimulation. Nardone 2017 reported that two participants undergoing active rTMS reported uncomfortable twitching of facial muscles during stimulation but that rTMS was tolerated well. Nurmikko 2016 reported that rTMS was well tolerated. Minor adverse effects observed during active stimulation included headache (25%), sleepiness (38%), transient increase in pain (31%) and dizziness (15%). Passard 2007 reported incidence of headaches (four out of 15 participants in the active group versus five out of 15 in the sham group), feelings of nausea (one participant in the active group), tinnitus (two participants in the sham group) and dizziness (one participant in the sham group). Picarelli 2010 found six reports of headache following active stimulation and four following sham stimulation, and two reports of neck pain following active stimulation with four reports following sham stimulation. Rollnik 2002 reported that one participant experienced headache, but it is unclear in the report whether this was following active or sham stimulation. Short 2011 reported that there were few side effects.Following four-coil rTMS, Tzabazis 2013 reported no serious adverse events. The incidence of scalp pain, headache, lightheadedness, back pain, otalgia, hot flashes and pruritis was more commonly reported following sham stimulation than active stimulation. Neck pain (14% of participants following active stimulation versus no participants following sham) and nausea (19% of participants following active stimulation versus 11% following sham) were more common with active stimulation. Umezaki 2016 reported headaches in seven (58%) participants in the active stimulation and five (62%) in the sham stimulation group that were mild and resolved in one to two days. Yagci 2014 reported that three (23%) participants in the active group and one (8%) in the sham group reported adverse events. They only described those in the active group, which were two cases of transient headache and one of "daily tinnitus".

Major

Both Lee 2012 and Picarelli 2010 reported one incidence of seizure following high-frequency active stimulation. The seizures occurred after the 6th and 7th session of active stimulation respectively. Nurmikko 2016 reported that one participant experienced a permanent reduction of hearing during an active stimulation phase. Investigations ruled out cochlear damage leading the study authors to conclude that an association with rTMS was unlikely.

CES

Four out of 11 studies of CES reported the incidence of adverse events (Capel 2003; Gabis 2003; Rintala 2010; Tan 2011). In these studies no serious adverse events were reported. Rintala 2010 reported that in the active stimulation group participants reported incidences of pulsing, tingling and tickling in the ears (three participants), tender ears (one participant) and a pins and needles feeling near the bladder (one participant). In the sham group they reported drowsiness (one participant), warm ears (one participant) and headache after one session (one participant). Tan 2011 reported only mild adverse events with a total of 41 reports in the active stimulation group and 56 in the sham group. Of note, sensations of ear pulse/sting/itch/electric sensations or ear clip tightness seemed more common in active group than the sham group (12 versus six incidents). Through correspondence with the authors of Taylor 2013, we confirmed that there were no adverse events reported.

tDCS

Thirty out of 36 studies of tDCS reported the incidence of adverse events with varying degrees of detail. Of these, five studies reported none (Fregni 2006a; Hagenacker 2014; Mendonca 2011; Mori 2010; Portilla 2013). Attal 2016 reported similar proportions of side effects between stimulation conditions with no serious events. Most studies reported similar rates of mild and transient effects. Ahn 2017 reported six incidents of pain at the stimulation site; two in the sham group and four in the active group. One participant in the active group reported change in visual perception. Thirteen participants reported tingling, itching or burning sensations at the stimulation site. The severity of these symptoms was rated as low. Tingling was more common during active stimulation. Antal 2010 recorded reports of tingling, moderate fatigue, tiredness, headache and sleep disturbances, though there were no large differences in the frequency of these between the active and sham stimulation groups. Ayache 2016 reported that headache occurred in three participants after active stimulation and one after sham but that otherwise rates were similar between active and sham stimulation and there was no difference in discomfort rates. Boggio 2009 reported that one participant experienced headache with active stimulation. Chang 2017 reported two adverse reactions to tDCS, one participant reported a headache after active stimulation and one participant reported a single incident of painful sensation under the electrode that resolved on cessation of stimulation. Donnell 2015 reported only mild adverse events with higher rates of skin redness in the active group (16.6% in active group versus 3.3% in the sham group) but similar rates for all others. Fagerlund 2015 found no difference in adverse events between active and sham stimulation except for acute mood change, which was higher in the sham group. However trouble concentrating was higher after active stimulation (18% of total sessions after active stimulation versus 5% of sessions after sham), as was scalp pain (18% of sessions versus 9%) and headache (18% of sessions versus 12%).The study by Fenton 2009 reported three cases of headache, two of neck ache, one of scalp pain and five of a burning sensation over the scalp in the active stimulation group versus one case of headache in the sham stimulation group. Fregni 2006b reported one case of sleepiness and one of headache in response to active stimulation of the DLPFC, three cases of sleepiness and three of headache with active stimulation of M1 and one case of sleepiness and two of headache in response to sham stimulation. Hazime 2017 reported the incidence of a variety of adverse effects but did not separate them into active and sham stimulation groups. These included headache, neck pain, scalp pain, back pain, tingling, itching, redness, burning sensations, sleepiness, trouble concentrating and largely reported as mild or moderate in severity. Khedr 2017 reported that all participants tolerated stimulation well with three cases of itching and redness seen in the active stimulation group. Kim 2013 reported that all participants tolerated tDCS well without "significant adverse events". Headache was reported in three participants, all in an active stimulation group, and skin itching was reported by three participants, one in each active stimulation group and one in the sham group. Lagueux 2017 reported that three participants in the active stimulation group and two in the sham group reported minor transient headaches. One participant reported skin redness and itching after active stimulation. Two participants in the active group and one in the sham group reported feelings of tiredness. Four participants in the active stimulation group are reported to have declared "being indisposed" by a stinging/ burning sensation under the electrodes. Luedtke 2015 briefly reported that the stimulation was tolerated well with minimal transitory side effects but gave no further detail. Mendonca 2016 reported just that all adverse events were mild and did not differ between groups, with no further detail. Ngernyam 2015 reported that all participants tolerated stimulation well, seven (of 20) in the active group experienced erythematous skin rash at the cathode placement site. Oliveira 2015 also did not formally report all events but reported that one of the participants suffered burns due to an electrode being placed on a skin site with acne, the skin healed but left a small scar. Similarly Sakrajai 2014 reported no adverse events in either group except transient skin redness in 13% of the active group. Soler 2010 recorded three reports of headache, all following active stimulation. Souto 2014 recorded adverse events in nine out of 10 participants in the sham group and all 10 participants in the active group. Thibaut 2017 reported that all participants tolerated stimulation well and that the majority reported mild to moderate itching and tingling during both active and sham stimulations. These were all mild and transient. Villamar 2013 reported that the vast majority of participants reported a mild to moderate tingling or itching sensation during both active and sham stimulation that faded over a few minutes but no other adverse effects. Valle 2009 reported "minor and uncommon" side effects, such as skin redness and tingling, which were equally distributed between active and sham stimulation. Volz 2016 reported no differences in side effects

between stimulation groups except that skin redness was more common in the active group. Wrigley 2014 reported only "mild to moderate" side effects with no difference between active and sham over the 24-hour poststimulation period. These included sleepiness (70% of participants following active, 60% following sham), fatigue, inertia (60% of participants following active, 30% following sham), lightheadedness (20% of participants during active and sham treatment) and headache (10% of participants during active and sham treatment).

Four studies monitored for possible effects on cognitive function using the Mini Mental State Examination questionnaire (Boggio 2009; Fregni 2006a; Fregni 2006b; Valle 2009) and three of these also used a battery of cognitive tests including the digit-span memory test and the Stroop word-colour test (Boggio 2009; Fregni 2006a; Fregni 2006b) and simple reaction time tasks (Fregni 2006a). No studies demonstrated any negative influence of stimulation on these outcomes. No studies of tDCS reported severe or lasting side effects. Bae 2014; Brietzke 2016; Harvey 2017; Jales Junior 2015; Jensen 2013 and Riberto 2011 did not consider adverse events in their study reports.

tRNS

Curatolo 2017 did not report on adverse events. Palm 2016 reported similar rates of adverse events between the active and sham groups with no suggestion of higher rates of any in the active group. Phosphenes were reported by one participant after sham treatment but none after active treatment. Six participants reported insomnia after sham treatment compared to five after tRNS, nausea occurred in four participants after sham treatment and in two after tRNS. Severe headache was reported by one participant after sham treatment but no participants reported severe headache after active stimulation.

RINCE

Hargrove 2012a reported a low incidence of side effects from RINCE including short-lived headache (two participants in the active group, one in the sham group), eye movement/flutter during stimulation (one active, one sham), restlessness (one active and none sham) and nausea (one active and none sham). Deering 2017 reported an average of two adverse events per participant, of which 47% were reported to be mild and 50% moderate in severity. Thirty-seven per cent of adverse events were reported to be related to study treatments. The authors reported that compared to sham, RINCE may be associated with small increases in the risk of mild to moderate headaches, nausea, dizziness/vertigo, and localised skin reactions, possibly due to the electrode gel. All events were short lived and resolved without further intervention. The study by Attal 2016 delivered both rTMS and tDCS. They reported that the proportion of participants displaying side effects was low and similar between active rTMS or tDCS and sham stimulations. Three (out of 35) participants withdrew from the study because of side effects, after the second day of stimulation in the second treatment block.

ADDITIONAL SUMMARY OF FINDINGS *[Explanation]*

CES compared with sham for chronic pain

Patient or population: adults with chronic pain
Settings: laboratory/ clinic
Intervention: active CES
Comparison: sham CES

Outcomes	Effect size	Relative effect (average % improvement (reduction) in pain (95%CIs) in relation to post-treatment score from sham group)* *Where 95%CIs do not cross the line of no effect.	No of participants (studies)	Quality of the evidence (GRADE)
Pain intensity (0 to < 1 week postintervention) measured using visual analogue scales or numerical rating scales	SMD -0.24 (-0.48 to 0.01)	-	270 (5)	⊕⊕◯◯ **low**[1]
Disability (0 to < 1 week postintervention) measured using self-reported disability/pain interference scales	No data available	No data available	No data available	No data available
Quality of life (0 to < 1 week postintervention) measured using Fibromyalgia Impact Questionnaire	MD -25.05 (-37.82 to -12.28)	-	36 (1)	⊕◯◯◯ **very low**[2]

CI: confidence interval; **CES**: cranial electrotherapy stimulation; **MD**: mean difference; **SMD**: standardised mean difference

GRADE Working Group grades of evidence
High quality: we are very confident that the true effect lies close to that of the estimate of the effect;
Moderate quality: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of effect, but there is a possibility that it is substantially different;
Low quality: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect;
Very low quality: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect

[1]Downgraded once for study limitations due to high or unclear risk of bias and once for imprecision due to low participant numbers.

[2]Downgraded once for study limitations due to high or unclear risk of bias, once for inconsistency (single study) and once for imprecision due to low participant numbers.

tDCS compared with sham for chronic pain

Patient or population: adults with chronic pain
Settings: laboratory/ clinic
Intervention: active tDCS
Comparison: sham tDCS

Outcomes	Effect size	Relative effect (average % improvement (reduction) in pain (95% CIs) in relation to post-treatment score from sham group)* *Where 95%CIs do not cross the line of no effect.	No of participants (studies)	Quality of the evidence (GRADE)
Pain intensity (0 to < 1 week postintervention) measured using visual analogue scales or numerical rating scales	SMD -0.43 (-0.63 to -0.22)	This equates to a 17% (95% CI 9% to 25%) reduction in pain intensity or a 0.82 (95% CI 0.42 to 1.2) point reduction on a 0 to 10 pain intensity scale	747 (27)	⊕◯◯◯ **very low**[1]
Disability (0 to < 1 week postintervention) measured using self-reported disability/pain interference scales	SMD -0.01, (95% CI -0.28 to 0.26)	-	212 (4)	⊕⊕◯◯ **low**[2]
Quality of life (0 to < 1 week postintervention) measured using different scales across studies	SMD 0.66, 95% CI 0.21 to 1.11	-	82 (4)	⊕⊕◯◯ **low**[2]

CI: confidence interval; **MD**: mean difference; **SMD**: standardised mean difference; **tDCS**: transcranial direct current stimulation

GRADE Working Group grades of evidence
High quality: we are very confident that the true effect lies close to that of the estimate of the effect;
Moderate quality: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of effect, but there is a possibility that it is substantially different;
Low quality: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect;
Very low quality: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect

[1]Downgraded once for study limitations due to high or unclear risk of bias, once for inconsistency due to heterogeneity and once for evidence of possible publication bias.
[2]Downgraded once for study limitations due to high or unclear risk of bias and once for imprecision due to low participant numbers.

DISCUSSION

Summary of main results

This update has included a substantial number of new studies. Despite this our findings have not altered substantially from the previous version of this review.

Repetitive transcranial magnetic stimulation (rTMS) for chronic pain

Meta-analysis of all rTMS studies in chronic pain demonstrated substantial heterogeneity. Predetermined subgroup analysis suggests a short-term effect of single-dose, high-frequency rTMS applied to the motor cortex on chronic pain. This effect is small and does not conclusively exceed the threshold of minimal clinical importance. The evidence from multiple-dose studies of rTMS demonstrates conflicting results with substantial heterogeneity both overall and when the analysis is confined to high-frequency motor cortex studies. Low-frequency rTMS does not appear to be effective. rTMS applied to the prefrontal cortex does not appear to be effective. That the majority of studies in this analysis are at unclear risk of bias, particularly for participant blinding, suggests that the observed effect sizes might be exaggerated. While there is substantial unexplained heterogeneity the available evidence does not strongly suggest an effect of rTMS in the medium term. The limited evidence at long-term follow-up consistently suggests no effect of rTMS. The evidence for all comparisons or rTMS is considered to be of low to very low quality.

Cranial electrotherapy stimulation (CES) for chronic pain

The evidence from trials where it is possible to extract data is not clearly suggestive of a beneficial effect of CES on chronic pain. While there are substantial differences within the trials in terms of the populations studied and the stimulation parameters used, there is no measurable heterogeneity and no trial shows a clear benefit of active CES over sham stimulation. The evidence for all comparisons or CES is considered to be of low to very low quality.

Transcranial direct current stimulation (tDCS) for chronic pain

Meta-analysis of all tDCS studies in chronic pain demonstrated heterogeneity but did demonstrate an effect versus sham interventions. Predetermined subgroup analyses did not reduce heterogeneity. This effect may be exaggerated by study biases and small study effects. The evidence available at the medium term also demonstrates an effect but with substantial heterogeneity. Evidence from long follow-up does not suggest an effect of tDCS. We consider the evidence for all comparisons for tDCS to be of low to very low quality.

Reduced impedance non-invasive cortical electrostimulation (RINCE) stimulation for chronic pain

We analysed one small trial suggesting a positive effect of RINCE over sham for chronic pain. This trial is at unclear risk of bias due to possible attrition bias. As such, further high-quality research is needed to confirm this exploratory finding.

Transcranial random noise stimulation (tRNS) for chronic pain

We identified two small studies of tRNS, both at high risk of bias. We are unable to draw any conclusions about the effectiveness or lack of effectiveness of tRNS for chronic pain.

Secondary outcome measures

The available evidence does not suggest an effect of rTMS or tDCS on disability levels at any follow-up point. There is insufficient evidence from which to draw conclusions regarding CES for disability.

Limited, low-quality to very low-quality evidence suggests that rTMS and tDCS may have positive effects on quality of life. Given the limited amount of data available to inform these analyses, the risks of bias in the evidence base and the small effects observed in pain for both rTMS and tDCS we would recommend that this finding should be interpreted with caution. Limited evidence suggest that RINCE has no effect on quality of life.

rTMS, CES, tDCS, RINCE, tRNS and sham stimulation are associated with transient adverse effects such as headache, scalp irritation and dizziness, but reporting of adverse effects was inconsistent and did not allow for a detailed analysis. There were two incidences of seizure following active rTMS, which occurred in separate studies. For all forms of stimulation, adverse events reporting is inconsistent across studies.

Overall completeness and applicability of evidence

For rTMS we were unable to include pain intensity data from six full published studies (Fregni 2005; Fregni 2011, Onesti 2013; Picarelli 2010; Tzabazis 2013; Umezaki 2016, combined n = 107). In addition, we identified 11 studies of rTMS published in abstract format for which we have not been able to acquire full study reports. A conservative estimate of the combined number of participants that those studies might add is 438, assuming that some reports refer to the same study.

We were unable to extract the relevant data from four studies of CES (Capel 2003; Cork 2004; Katsnelson 2004; Lichtbroun 2001). This may have impacted upon the results of our meta-analysis although one of those studies would have been excluded

from the meta-analysis as we judged it as being at risk of bias on criteria other than selective outcome reporting (Katsnelson 2004). We were also unable to extract the relevant data from three studies of tDCS (Donnell 2015; Mendonca 2011; Valle 2009), and these data were not made available upon request to the study authors. These data would have contributed a further 95 participants to our analysis and may have altered our conclusions. In addition, we identified five studies of tDCS (Acler 2012; Albu 2011; Knotkova 2011; Moreno-Duarte 2013a; Mylius 2013) published in abstract format that appear clearly relevant for which we have not been able to acquire full study reports.

For both rTMS and tDCS there are a number of ongoing studies identified through the trials registry searches. Of note, eight trials were registered prior to 2012, seven of which are of tDCS and have not yet been published to our knowledge. Given our finding of small study effects in tDCS studies this gives cause for concern regarding the risk of potential publication bias and this is reflected in our GRADE judgements. We hope that future updates of this review will include the aforementioned data.

Quality of the evidence

Using the GRADE criteria we judged the quality of evidence for all comparisons as low or very low, meaning that our confidence in the effect estimate is limited or we have very little confidence in the effect estimate and the true effect is likely to be substantially different from the estimated effect. In large part this is due to issues of blinding and of precision. The majority of studies of rTMS were at unclear risk of bias. The predominant reason for this was the use of suboptimal sham controls that were unable to control for all possible sensory cues associated with active stimulation. A number of studies did not clearly report blinding of assessors and sensitivity analysis excluding those studies reduced both heterogeneity and the pooled effect size. It could be reasonably argued that the presence of a subgroup of single-dose studies of high-frequency stimulation specific to the motor cortex that does demonstrate superiority over sham with acceptable levels of heterogeneity is evidence for a specific clinical effect of rTMS. It should be considered, however, that high-frequency rTMS is associated with more intense sensory and auditory cues that might plausibly elicit a larger placebo response, and many of the included studies were unable to control conclusively for these factors. Furthermore, the pooled effect size for the high-frequency studies of motor cortex rTMS does not meet our predetermined threshold for clinical significance. This estimate is based solely on studies that delivered a single dose of rTMS. It is feasible that a single dose may be insufficient to induce clinically meaningful improvement. These single-dose studies included in the analysis are best characterised as proof of principle studies, which sought to test whether rTMS could modulate pain, rather than full-scale clinical studies with the aim of demonstrating clinical utility. The combined evidence from studies of high-frequency rTMS to the motor cortex that delivered multiple doses, so better reflecting the likely clinical delivery of rTMS (excluding studies judged as being at high risk of bias), demonstrate no effect, but with substantial heterogeneity.

There are multiple sources of potential heterogeneity within the rTMS literature, relating to stimulation parameters, dose and population. We have explored, through pre-planned subgroup analyses the influence of cortical target, stimulation frequency and dose at the crude level of single versus multiple dose. However we did not plan to formally explore the influence of all of the potential sources of variation in terms of stimulation parameters. As an example it is possible that some studies delivered suboptimal stimulation in terms of the numbers of pulses delivered, which ranged in our review from 120 to more than 2000 per treatment session. In addition, for studies of motor cortex stimulation there was variation in the somatotopic target of stimulation and this may be an important factor. While some studies used imaging-based neuro-navigation techniques to more precisely locate targeted brain regions most did not. There were not adequate data to meaningfully explore the influence of using neuro-navigation on outcomes. There is evidence that approaches to identifying prefrontal targets that do not use neuronavigation are inaccurate (Ahdab 2010; Herwig 2001). Should neuro-navigation be found to be crucial to effectiveness it would have implications for the costs and availability of this intervention.

Similarly, we judged no study of tDCS as having a low risk of bias on all criteria. While there is evidence that the sham control used in tDCS does achieve effective blinding of participants at stimulation intensities of 1 mA (Gandiga 2006), evidence has emerged since the first version of this review that indicates that at 1.5 mA the sensory profile of stimulation differs between active and sham stimulation (Kessler 2013), and at 2 mA participant and assessor blinding may be compromised (Ezquerro 2014; Horvath 2014; O'Connell 2012; Wallace 2016). Meta-epidemiological evidence demonstrates that incomplete blinding in controlled trials that measure subjective outcomes may exaggerate the observed effect sizes (Savovic 2012; Wood 2008). It is therefore reasonable to expect that incomplete blinding may have exaggerated the effect sizes seen in the current analyses of rTMS and tDCS. It is noteworthy that the largest study of tDCS (Luedtke 2015), also judged at low risk of bias for all criteria except study size, demonstrated no effect of tDCS versus sham.

No study of CES could be judged as having a low risk of bias across all criteria. Despite this, no study from which data were available demonstrated a clear advantage of active over sham stimulation. There was substantial variation in the stimulation parameters used between studies. Notably three studies utilised an 'active placebo' control, in which stimulating current was delivered but at much lower intensities (Gabis 2003; Gabis 2009; Katsnelson 2004). These intensities well exceed those employed in the active stimulation condition of other studies of CES devices and as such it could be hypothesised that they might induce a therapeutic effect themselves. This could possibly disadvantage the active stim-

ulation group in these studies. However, the data available in the meta-analysis do not suggest such a trend and statistical heterogeneity between studies entered into the analysis was low.

All of the included studies may be considered to be small in terms of sample size and we reflected this in our 'Risk of bias' assessment. The prevalence of small studies increases the risk of small study bias and the related issue of publication bias, wherein there is a propensity for small negative studies to not reach full publication. There is evidence that this might lead to an overly positive picture for some interventions (Dechartres 2013; Nüesch 2010). In a review of meta-analyses, Dechartres 2013 demonstrated that trials with fewer than 50 participants, which reflects the majority of studies included in this review, returned effect estimates that were on average 48% larger than the largest trials and 23% larger than estimates from studies with sample sizes of more than 50. Similarly, in Cochrane Reviews of amitriptyline for neuropathic pain and fibromyalgia (Moore 2015a; Moore 2015b), smaller studies were associated with substantially lower numbers needed to treat for an additional beneficial outcome (NNTBs) for treatment response than larger studies. In their recommendations for establishing best practice in chronic pain systematic reviews, the authors of Moore 2010 suggest that study size should be considered an important source of bias. It is therefore reasonable to consider that the evidence base for all non-invasive brain stimulation techniques is at risk of bias on the basis of sample size. In this update we found evidence of small study effects affecting the tDCS evidence, but not for rTMS or CES. However, it is accepted that existing approaches to detecting publication bias are unsatisfactory and lack sensitivity. It should therefore be noted that even where a pooled estimate includes a large number of participants, if it is dominated by small studies, as are all comparisons in this review, then it is prone to small study effects. Funnel plot asymmetry may be explained by reasons other than publication bias, such as methodological quality, or simple chance (Sterne 2011), but for tDCS there is an association between study size and effect size, with smaller studies demonstrating larger effects.

Potential biases in the review process

There is substantial variation between the included studies of rTMS and tDCS. Studies varied in terms of the clinical populations included, the stimulation parameters and location, the number of treatment sessions delivered and in the length of follow-up employed. This heterogeneity is reflected in the I^2 statistic for the overall rTMS and tDCS meta-analyses. However, pre-planned subgroup investigation reduced this heterogeneity in some instances.

Many of the rTMS and tDCS studies specifically recruited participants whose symptoms were resistant to current clinical management and most rTMS studies specifically recruited participants with neuropathic pain. As such it is important to recognise that this analysis in large part reflects the efficacy of rTMS and tDCS for refractory chronic pain conditions and may not accurately reflect their efficacy across all chronic pain conditions.

One study included in the analysis of rTMS studies demonstrated a difference in pain levels between the two groups at baseline that exceeded the size of the difference observed at follow-up (Defrin 2007). Specifically, the group that received sham stimulation reported less pain at baseline than those in the active stimulation group. The use in the current analysis of a between-groups rather than a change-from-baseline comparison is likely to have affected the results although the study contributes only 1.5% weight to the overall meta-analysis and the study itself reported no difference in the degree of pain reduction between the active and sham stimulation groups.

The method used to back-transform the pooled standardised mean difference (SMD) to a 0-10 pain intensity scale and subsequent calculation of the effect as a percentage improvement rests upon the assumption that the standard deviation and the pain levels used are representative of the wider body of evidence and should be considered an estimate at best. Representing average change scores on continuous scales is problematic in chronic pain studies since response to pharmacological treatments has been found to display a bimodal distribution (Moore 2013). More plainly, some participants demonstrate a substantial improvement with pain therapies while many demonstrate little or no change, with few individual participants demonstrating a change similar to the average. As a consequence the meaning of the average effect sizes seen in this review is difficult to interpret. This had led to the recommendation that chronic pain trials employ responder analyses based on predetermined cut-offs for a clinically important response ($\geq$ 30% reduction in pain for a moderate benefit, $\geq$ 50% reduction for a substantial benefit) (Dworkin 2008; Moore 2010). Very few studies identified in this review presented the results of responder analyses and so this type of meta-analysis was not possible. However, where effects were observed in this review they were small, which would indicate that if there is a subgroup of 'responders' to active stimulation who demonstrate moderate or substantial benefits it is likely to include only a small number of participants. We are not aware of any direct evidence that participant outcomes are commonly bimodally distributed following these interventions and a recent analysis of data from trials of various non-surgical interventions for spinal pain did not find evidence for bimodal distribution of outcomes (O'Connell 2017). It is also worth noting that when the effect estimates were back-transformed to a 0 to 10 pain intensity scale they were also below theminimal clinically important difference threshold for the between-group difference of 1 point recently recommended by the OMERACT-12 group (Busse 2015).

Agreements and disagreements with other studies or reviews

The European Academy of Neurology published guidelines on the use of neurostimulation therapy for chronic neuropathic pain in 2017 (Cruccu 2017). Based on a narrative synthesis of the evidence gave "weak recommendations" for the use of rTMS in neuropathic pain and fibromyalgia and "inconclusive recommendations" in CRPS. They offered "inconclusive recommendations" regarding tDCS for fibromyalgia and "weak recommendations" for the use of tDCS for peripheral neuropathic pain. The 'weak' descriptor term used to describe the positive recommendations was based on the low quality of the supporting evidence. Another recent guideline specific to the use of rTMS (Lefaucheur 2014) concluded that there was "level A evidence", which represents "definite efficacy" for the analgesic effect of high frequency rTMS applied to the motor cortex contralateral to the side of pain. In light of our findings we suggest that this assessment of the evidence may not adequately reflect the numerous limitations of the evidence base.

Leung 2009 performed a meta-analysis of individual participant data from studies of motor cortex rTMS for neuropathic pain conditions. Whilst the analysis was restricted to studies that clearly reported the neuroanatomical origin of noxious input (and therefore excluded some of the studies included in the current analysis) the overall analysis suggests a similar effect size of 13.7% improvement in pain (excluding the study of Khedr 2005). The study authors also performed an analysis of the influence of the neuroanatomical origins of noxious input on the effect size. They noted a trend suggestive of a larger treatment effect in central compared with peripheral neuropathic pain states although this did not reach statistical significance. While the data in the current review were not considered sufficient to support a detailed subgroup analysis by neuro-anatomical origin of noxious input, the exclusion of studies that did not specifically investigate neuropathic pain did not significantly affect the overall analysis and the two multiple-dose studies of motor cortex rTMS for central neuropathic pain that were included failed to demonstrate superiority of active over sham stimulation (Defrin 2007; Kang 2009).

All but one of the included studies in the review by Leung 2009 delivered high-frequency ($\geq$ 5 Hz) rTMS and no clear influence of frequency variations was observed within this group. The authors suggest that the number of doses delivered may be more crucial to the therapeutic response than the frequency (within the high-frequency group), based on the larger therapeutic response seen in the study of Khedr 2005, that was excluded from the current analysis. This review preceded the studies by Defrin 2007 and Kang 2009 that did not demonstrate superiority of active over sham stimulation. While there are limited data to test this proposition robustly the result of our subgroup analysis of studies of high-frequency motor cortex rTMS does not suggest a benefit of active stimulation over sham.

Lima and Fregni undertook a systematic review and meta-analysis of motor cortex stimulation for chronic pain (Lima 2008). They pooled data from rTMS and tDCS studies. While the report states that data were collected on mean between-group pain scores they are not presented. The authors present the pooled data for the number of responders to treatment across studies. They conclude that the number of responders is higher following active stimulation compared with sham (risk ratio 2.64, 95% CI 1.63 to 4.30). In their analysis the threshold for treatment response is defined as a global response according to each study's own definition and as such it is difficult to interpret and may not be well standardised. They note a greater response to multiple doses of stimulation, an observation that is not reliably reflected in the current review. Additionally they included the study of Khedr 2005 (excluded from this review due to high risk of bias) and Canavero 2002 (excluded on title and abstract as it is not a randomised or quasi-randomised study). The current review also includes a number of motor cortex rTMS studies in the main analysis published since that review (André-Obadia 2008; Defrin 2007; Hosomi 2013; Jetté 2013; Kang 2009; Lefaucheur 2006; Lefaucheur 2008; Medeiros 2016; Mhalla 2011; Passard 2007; Saitoh 2007; Tekin 2014; Yagci 2014). Neither the review of Leung 2009 nor Lima 2008 applied a formal quality or 'Risk of bias' assessment. While the current review also suggests a small, short-term benefit of high-frequency motor cortex rTMS in the treatment of chronic pain the effect is small, appears short-term and although the pooled estimate approaches the threshold of minimal clinical significance it is possible that it might be inflated by methodological biases in the included studies.

A systematic review of tDCS and rTMS for the treatment of fibromyalgia concluded that the evidence demonstrated reductions in pain similar to US Food and Drug Administration (FDA)-approved pharmaceuticals for this condition and recommended that rTMS or tDCS should be considered, particularly where other therapies have failed (Marlow 2013). This review included randomised and non-randomised studies, did not undertake meta-analysis and took a 'vote-counting' approach to identifying effects based primarily on each included study's report of statistical testing. While our analysis did not specifically investigate a subgroup of studies in fibromyalgia participants, we would suggest that the methodology chosen by Marlow 2013 does not offer the most rigorous approach to establishing effect size, particularly in light of the inconsistency seen among the included studies of that review. Indeed, given the degree of uncertainty that remains regarding the efficacy of these interventions, it could be suggested that the application of tDCS or rTMS for this or other conditions would ideally be limited to the clinical research situation.

Luedtke 2012 systematically reviewed studies of tDCS for chronic pain and experimental pain. Unlike our review they excluded the study by Fenton 2009, as it was judged to be at high risk of bias on the grounds of unclear randomisation procedure and due to a lack of clarity of participant withdrawal, and Boggio 2009 due to the level of dropout. The results of their meta-analysis are broadly consistent with those presented here in that the authors conclude that the evidence is insufficient to allow definite conclusions but that there is low-level evidence that tDCS may be effective for chronic

pain. Moreno-Duarte 2013 recently reviewed the evidence for a variety of electrical and magnetic neural stimulation techniques for the treatment for chronic pain following spinal cord injury, including rTMS, tDCS and CES, including both randomised and non-randomised studies. They found that the results varied across studies, though trials of tDCS were consistently positive, and concluded that further research is needed and that there is a need to develop methods to decrease the variability of treatment response to these interventions. However, it is worth noting that this review did not include the recent negative study of tDCS for post-spinal cord injury pain by Wrigley 2014, and also that variability in observed treatment 'responses' may simply represent the play of chance rather than evidence of a specific group of responders.

Kirsch 2000 reviewed studies of CES in the management of chronic pain and concluded in favour of its use. The review did not report any formalised search strategy, inclusion criteria or quality assessment and discussed a number of unpublished studies that remain unpublished at the time of the current review. Using a more systematic methodology and including papers published since that review, we found that the data that were available for meta-analysis did not suggest a clinically important benefit of active CES over sham. Our analysis included 270 participants. While this is not particularly large it does suggest that if there is an effect of CES on chronic pain it is either small, or that the number of responders is likely to be small.

A recent review of rTMS for chronic pain (Galhardoni 2015) concluded that rTMS has potential utility. This review reported that rTMS was frequently associated with greater that 30% pain relief when compared with a control treatment, though no meta-analysis was reported and no formal assessment of study quality or risk of bias was presented. Our results suggest that, compared with sham, rTMS is associated with somewhat smaller effects and that the effect estimate may be exaggerated by various biases in the literature.

While many reviews have concluded positively regarding the effectiveness and early promise of non-invasive brain stimulation techniques this is frequently based on markers of statistical significance and arguably does not adequately consider the influence of the various biases at play in the literature.

AUTHORS' CONCLUSIONS

Implications for practice

For people with chronic pain

There is a lack of high-quality evidence to support or refute the effectiveness of non-invasive brain stimulation techniques for chronic pain. Due to the small size of included studies and limitations in the way that many studies were conducted, future studies may have a substantial impact upon the estimates of effects presented.

For clinicians

Low- or very low-quality evidence suggests that low-frequency repetitive transcranial magnetic stimulation (rTMS), or rTMS applied to the prefrontal cortex, may not be effective for the treatment of chronic pain. Subgroup analysis suggests that single doses of high-frequency rTMS of the motor cortex may have small, short-term effects on chronic pain that do not meet our threshold of minimum clinical importance (low-quality evidence) and may be exaggerated by the dominance of small studies and other sources of bias. The pooled evidence from multiple-dose studies of high-frequency rTMS to the motor cortex is heterogeneous but does not demonstrate an effect (very low-quality evidence). Very low-quality evidence suggests that transcranial direct current stimulation (tDCS) may have short-term effects on chronic pain but these observed effects may be exaggerated by the dominance of small studies and other sources of bias. Low-quality evidence suggests that cranial electrotherapy stimulation (CES) is not effective. Due to this uncertainty, clinical application of non-invasive brain stimulation techniques would be most appropriate within a clinical research setting rather than in routine clinical care and it is not currently clear if any form of non-invasive brain stimulation is a useful clinical tool.

For policy makers and funders of the intervention

There is a lack of high-quality evidence to support or refute the effectiveness of non-invasive brain stimulation techniques when compared to sham stimulation for people with chronic pain. The short-term effects observed for rTMS and tDCS on pain may be exaggerated by the dominance of small studies and limitations in study methods. There is not currently a strong evidence base for routinely offering these options for the treatment of chronic pain.

Implications for research

General

The existing evidence across all forms of non-invasive brain stimulation is dominated by small studies with unclear risk of bias and there is a need for larger, rigorously controlled trials. It is noteworthy that in the seven years since our original review the number of included studies has risen substantially but our conclusions have not changed. Contrasting the large number of trials included in this review with the persisting lack of certainty over its effectiveness speaks to a problem of research waste.

After our first review of this evidence was completed in 2010 we recommended that there was a need to examine the more promising findings within the existing data through more robust, large,

rigorous, adequately blinded trials that deliver a reasonable dose and investigate effects over a meaningful timescale (O'Connell 2011). Until a body of this type of research is generated there will continue to be uncertainty over the clinical utility of any form of non-invasive brain stimulation for chronic pain. This recommendation is relevant to all other types of non-invasive brain stimulation. The ongoing studies, identified from searching trials registers, predominantly consist of more, relatively small trials and it is unlikely that the results will meaningfully change the findings of this review. A recent consensus statement (Klein 2015) has produced guidelines for future rTMS research on clinical pain with the goal of improving quality and these recommendations should be taken under consideration.

The proliferation of small heterogeneous trials presents a challenge to evidence synthesis. A robust, large scale trial of rTMS or tDCS might fail to reduce uncertainty if included in the same analysis as the existing trials. For future reviews of this evidence base, that seek to answer the question of clinical effectiveness, there may be a case for excluding single-dose trials on the basis of inadequate dose and trials below a threshold size on the basis of imprecision. There is also a case for not updating the current review until trials of adequate size have been added to the evidence base, since an update characterised by the inclusion of more, small heterogeneous trials will sufficiently reduce uncertainty.

Design

Future rTMS research should consider employing recently developed sham coils that control for all of the sensory aspects of stimulation. Such coil systems should be robustly validated as valid sham controls. Future studies should have a strong theoretical basis underpinning the choice of stimulation location and parameters and ensure that stimulation delivered to high technical standards. Future studies of tDCS should give consideration to the integrity of participant blinding, particularly when utilising stimulation intensities that exceed 1 mA. The field should seek to generate consensus on optimal stimulation parameters and procedures.

Outcome measurement

Future trials should also consider the IMMPACT recommendations for the design of trials in chronic pain (Dworkin 2008; Dworkin 2009; Dworkin 2010; Turk 2008), to ensure that outcomes, thresholds for clinical importance and study designs are optimal, and should endeavour to ensure that published study reports are compliant with the CONSORT statement (Schulz 2010). All studies of non-invasive brain stimulation techniques should measure, record and clearly report adverse events from both active and sham stimulation.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Ahmed 2011

Methods	Parallel, quasi-RCT
Participants	Country of study: Egypt Setting: Dept of Neurology, hospital-based Condition: chronic phantom limb pain Prior management details: unresponsive to various pain medications n = 27, 17 active and 10 sham Age, mean (SD): active group 52.01 (12.7) years, sham group 53.3 (13.3) years Duration of symptoms, mean (SD) months: active group 33.4 (39.3), sham group 31.9 (21.9) Gender distribution: active group 13 M, 4 F; sham group 6 M, 4 F
Interventions	Stimulation type: rTMS Stimulation parameters: frequency 20 Hz; coil orientation not specified, number of trains 10; duration of trains 10 s; ITI 50 s; total number of pulses 2000 Stimulation location: M1 stump region Number of treatments: x 5, daily Control type: sham - coil angled away from scalp
Outcomes	Primary: pain VAS (anchors not reported), LANNS When taken: poststimulation session 1 and 5 and at 1 month and 2 months post-treatment Secondary: none relevant
Notes	AEs: not reported COI: not reported Sources of support: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Comment: not true randomisation Quote: "patients were randomly assigned to 2 groups depending on the day of the week on which they were recruited"
Allocation concealment (selection bias)	High risk	Comment: given method of randomisation allocation concealment not viable
Adequate blinding of participants?	Unclear risk	Comment: sham credibility assessment - suboptimal. Coil angled away from scalp. Did not control for sensory characteristics of active stimulation and was visually distinguishable

Ahmed 2011 (*Continued*)

Adequate blinding of assessors?	Low risk	Quote: "The second author evaluated these measures blindly, without knowing the type of TMS"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: levels of dropout not reported
Selective reporting (reporting bias)	Low risk	Comment: primary outcomes presented in full
Study Size	High risk	Comment: < 50 participants per treatment arm
Study duration	Low risk	> 8 weeks' follow-up
Other bias	Low risk	Comment: no other bias detected

Ahn 2017

Methods	Parallel RCT
Participants	Country of study: USA Setting: laboratory Condition: OA knee Prior management details: not reported n = 41 randomised, 40 analysed Age, mean (SD): active group 60.6 (9.8) years, sham group 59.3 (8.6) years Duration of symptoms: not reported Gender distribution: 19 M, 21 F
Interventions	Stimulation type: tDCS Stimulation parameters: tDCS 2mA intensity, 20 min Stimulation location: M1 contralateral to painful side Number of treatments: x 1 daily for 5 days Control type: sham tDCS
Outcomes	Primary: pain NRS anchors 0 = no pain, 10 = worst pain imaginable When taken: 1 d postintervention, 3 weeks postintervention Secondary: WOMAC function score AEs
Notes	Funding source: supported in part by the Claude D. Pepper Older American's Independence Center (P30 AG028740), the Universityof Florida Center for Cognitive Aging and Memory, and NIA Grants K07AG04637 and K01AG050707, and R01AG054077. This Work was also partially supported by VA HSR&D Houston Center for Innovations in Quality, Effectiveness and Safety (CIN# 13-413), Michael E. DeBakey VA Medical Center, Houston, TX COI: study authors declared no COI
Risk of bias	

Ahn 2017 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "randomly assigned with a ratio of 1 to 1 to either the active tDCS (n ¼ 20) or sham tDCS group (n ¼ 20) using a covariate adaptive randomization procedure so that the two groups had approximately equal distribution regarding age, gender and race."
Allocation concealment (selection bias)	Low risk	Quote "Allocation concealment was ensured as the randomization codes were released only after all the interventions and assessments were completed."
Adequate blinding of participants?	Unclear risk	Comment: evidence that participant blinding can be inadequate at intensity of 2 mA. No assessment of blinding success. No formal assessment of blinding success
Adequate blinding of assessors?	Unclear risk	Comment: evidence that assessor blinding can be inadequate at intensity of 2 mA. No assessment of blinding success. No formal assessment of blinding success
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: only one participant withdrew.
Selective reporting (reporting bias)	Low risk	Comment: outcomes reported adequately
Study Size	High risk	Comment: n = 20
Study duration	Unclear risk	Comment: 3-week follow-up
Other bias	Unclear risk	Comment: statistically significant between-group difference in pain NRS scores at baseline

André-Obadia 2006

Methods	Cross-over RCT; 3 conditions
Participants	Country of study: France Setting: laboratory Condition: neuropathic pain (mixed central, peripheral and facial) Prior management details: refractory to drug management, candidates for invasive MCS n = 14 Age: 31-66 years; mean 53 (SD 11) Duration of symptoms: mean 6.9 years (SD 4) Gender distribution: 10 M, 4 F
Interventions	Stimulation type: rTMS figure-of-8 coil Stimulation parameters: Condition 1: frequency 20 Hz; coil orientation posteroanterior; 90% RMT; number of

	trains 20; duration of trains 4 s; ITI 84 s; total number of pulses 1600 Condition 2: frequency 1 Hz; coil orientation lateromedial; number of trains 1; duration of trains 26 min, total number of pulses 1600 Condition 3: sham - same as for condition 2 with coil angled away perpendicular to scalp Stimulation location: M1 contralateral to painful side Number of treatments: 1 for each condition
Outcomes	Primary: VAS 0-10 cm, anchors "no pain" to "unbearable pain" When taken: immediately poststimulation then daily for 1 week Secondary: none
Notes	Data requested from study authors and received Sources of support: Supported in part by a Grant from the Fondation pour la Recherche Médicale (FRM), France COI: no declaration made

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Participants were consecutively assigned to a randomization scheme generated on the web site Randomization.com (Dallal GE, http://www.randomization.com, 2008). We used the second generator, with random permutations for a 3-group trial. The randomization sequence was concealed until interventions were assigned."
Adequate blinding of participants?	Unclear risk	Comment: sham credibility assessment 'suboptimal'. Coil angled away from scalp and not in contact in sham condition. Did not control for sensory characteristics of active stimulation and was visually distinguishable
Adequate blinding of assessors?	Low risk	Quote: "To ensure the double-blind evaluation effects, the physician applying magnetic stimulation was different from the one collecting the clinical data, who in turn was not aware of the modality of rTMS that had been used in each session."
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	2 participants lost to follow-up and not accounted for in the data analysis. Given the small sample size it may influence the results
Selective reporting (reporting bias)	Low risk	Pain outcomes reported for all participants. Change from baseline figures given; point measures requested from study authors and received

André-Obadia 2006 (*Continued*)

Free from carry-over effects?	Low risk	Comment: a 2-week washout period was observed between stimulation conditions and possible carry-over effects were checked and ruled out in the analysis
Study Size	High risk	Comment: < 50 participants per treatment arm
Study duration	High risk	< 2 weeks' follow-up
Other bias	Low risk	Comment: no significant other bias detected

André-Obadia 2008

Methods	Cross-over RCT; 3 conditions
Participants	Country of study: France Setting: laboratory-based Condition: neuropathic pain (mixed central, peripheral and facial) Prior management details: refractory to drug management, candidates for invasive MCS n = 30 Age: 31-72 years, mean 55 (SD 10.5) Duration of symptoms: mean 5 years (SD 3.9) Gender distribution: 23 M, 7 F
Interventions	Stimulation type: rTMS, figure-of-8 coil Stimulation parameters: Condition 1: frequency 20 Hz; coil orientation posteroanterior; 90% RMT; number of trains 20; duration of trains 4 s; ITI 84 s; total number of pulses 1600 Condition 2: frequency 20 Hz, coil orientation lateromedial; number of trains 20; duration of trains 4 s; ITI 84 s; total number of pulses 1600 Condition 3: sham - same as for active conditions with coil angled away perpendicular to scalp Stimulation location: M1 contralateral to painful side Number of treatments: 1 for each condition
Outcomes	Primary: 0-10 NRS (anchors "no pain" to "unbearable pain") When taken: daily for 2 weeks poststimulation Secondary: none
Notes	Data requested from study authors Sources of support: supported in part by a Grant from the Fondation pour la Recherche Médicale (FRM), France COI: study authors declared no COI

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

André-Obadia 2008 (*Continued*)

Random sequence generation (selection bias)	Low risk	Quote: "the order of sessions was randomised (by computerized random-number generation)"
Adequate blinding of participants?	Unclear risk	Comments: sham credibility assessment - suboptimal. Coil angled away from scalp and not in contact in sham condition. Did not control for sensory characteristics of active stimulation and was visually distinguishable
Adequate blinding of assessors?	Low risk	Quote: "The physician who applied the procedure received from a research assistant one sealed envelope containing the order of the rTMS sessions for a given patient. The order remained unknown to the physician collecting clinical data."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: 2 participants apparently lost to follow-up and not obviously accounted for in the analysis. However, this is less than 10% and is unlikely to have strongly influenced the results
Selective reporting (reporting bias)	Low risk	Comment: medial-lateral coil orientation condition data not presented but provided by study authors on request
Free from carry-over effects?	Low risk	Comment: a 2-week washout period was observed between stimulation conditions and possible carry-over effects were checked and ruled out in the analysis
Study Size	High risk	Comment: < 50 participants per treatment arm
Study duration	Unclear risk	Comment: ≥ 2 weeks but < 8 weeks' follow-up
Other bias	Low risk	Comment: no significant other bias detected

André-Obadia 2011

Methods	Cross-over RCT
Participants	Country of study: France Setting: laboratory-based Condition: chronic neuropathic pain (mixed) Prior management details: resistant to conventional pharmacological treatment n = 45 Age: 31-72 years (mean 55) Duration of symptoms: "chronic" Gender distribution: 28 M, 17 F

Interventions	Stimulation type: rTMS Stimulation parameters: frequency 20 Hz; coil orientation not specified, number of trains 20; duration of trains 4 s; ITI 84 s; total number of pulses 1600 Stimulation location: M1 hand area Number of treatments: 1 per group Control type: sham coil - same sound and appearance, no control for sensory cues
Outcomes	Primary: pain NRS anchors 0 = no pain, 10 = unbearable pain When taken: daily for 2 weeks following each stimulation Secondary: none relevant
Notes	AEs: not reported Funding source: charity-funded COI: declaration - no COI

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Comment: method of randomisation not specified but less likely to introduce bias in a cross-over design Quote: "separated into 2 groups determined by the randomization"
Adequate blinding of participants?	Unclear risk	Comment: the study authors state "Because the first step of the procedure (motor hotspot and motor threshold determination) that induced motor contractions was identical in placebo and active sessions and the stimulation differed only when intensities below motor threshold were applied, no patient perceived any difference between the 2 types of rTMS" However, the sensation on the scalp may differ and no formal evaluation of blinding presented
Adequate blinding of assessors?	Unclear risk	Comment: no mention of blinded assessors
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: no mention of dropout/withdrawal
Selective reporting (reporting bias)	Low risk	Comment: primary outcomes reported for all groups and further data made available upon request to authors
Free from carry-over effects?	Low risk	Comment: 2-week washout period observed
Study Size	High risk	Comment: < 50 participants per treatment arm
Study duration	Unclear risk	Comment: ≥ 2 weeks but < 8 weeks' follow-up
Other bias	Low risk	Comment: no other biases detected

Antal 2010

Methods	Cross-over RCT
Participants	Country of study: Germany Setting: laboratory setting Condition: mixed chronic pain, neuropathic and non-neuropathic Prior management details: therapy-resistant n = 23, 10 in parallel (6 active, 4 sham), 13 crossed over Age: active-only group 28-70 years, sham-only group 50-70 years, cross-over group 41-70 years Duration of symptoms: chronic 1.5-25 years (mean 7.4) Gender distribution: 6 M, 17 F
Interventions	Stimulation type: tDCS Stimulation parameters: intensity 1 mA, 35 cm^2 electrodes, duration 20 min Stimulation location: anode - L M1 hand area, cathode right supraorbital Number of treatments: x 5, daily Control type: sham tDCS
Outcomes	Primary: pain VAS 0-10; VAS anchors 0 = no pain, 10 = the worst pain possible When taken: x 3, daily - averaged for daily pain Secondary: none relevant
Notes	Funding: government funding COI: none declared

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "Randomization was performed using the order of entrance into the study." Comment: may not be truly random from description
Allocation concealment (selection bias)	Unclear risk	Comment: not mentioned though unlikely given the randomisation technique. This is a potentially significant source of bias given that only the parallel results were used in this review due to high levels of attrition after the first phase
Adequate blinding of participants?	Low risk	Comment: see above
Adequate blinding of assessors?	Low risk	Comment: 1 mA intensity and operator blinded Quote: "The stimulators were coded using a five letter code, programmed by one of the department members who otherwise did not participate in the study. Therefore neither the investigator not the patient knew the type of the stimulation"
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: the high level of dropout renders the cross-over results at high risk of bias. This is less of an issue where only the parallel results from the first phase were used - first-phase data

Antal 2010 (*Continued*)

		only used in the analysis
Selective reporting (reporting bias)	Low risk	Comment: while not all outcomes at all time points were included in the study report the authors have provided all requested data
Free from carry-over effects?	Low risk	Comment: participants were excluded if pain had not returned to normal. This, however, represents a threat with regard to attrition bias
Study Size	High risk	Comment: < 50 participants per treatment arm
Study duration	Unclear risk	Comment: ≥ 2 weeks but < 8 weeks' follow-up
Other bias	Low risk	Comment: no other sources of bias detected

Attal 2016

Methods	Parallel RCT
Participants	Country of study: France Setting: hospital pain units Condition: lumbar radicular pain Prior management details: stable pharmacological treatment for pain and sleep disorders for at least 1 month prior to study n = 36 Age, mean (SD): active group 53.4 (8) years, sham group 51.5 (13) years Duration of symptoms: not reported Gender distribution: 17 F 18 M
Interventions	Stimulation type: rTMS and tDCS (order randomised in active group) Stimulation parameters: rTMS frequency 10 Hz; coil orientation anteroposterior induced current; 80% RMT; number of trains 30; duration of trains 10 s; ITI 20 s; total number of pulses 3000 tDCS: 2 mA intensity, 30 min Stimulation location: M1 contralateral to painful side Number of treatments: 3 stimulation visits on 3 consecutive days for each stimulation type. 3 week washout period Control type: sham coil - same sound and appearance, no control for sensory cues
Outcomes	Primary: pain NRS anchors 0 = no pain, 10 = maximal pain imaginable When taken: postintervention Secondary: BPI interference scale AEs
Notes	Funding source: The study received financial support from the Institut National de la Sante´ et de la Recherche Médicale (INSERM) COI: the authors declared no COI

Attal 2016 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "The 2 successive randomisations were prepared by a study nurse not involved in the running of the study or in data analysis, using validated software and a centralised randomisation schedule."
Allocation concealment (selection bias)	Low risk	Quote: "The treatment allocation code was kept in a sealed envelope until the completion of the study."
Adequate blinding of participants?	Unclear risk	Comment: rTMS sham described as controlling for sensory, auditory and visual cues. tDCS 2 mA intensity - evidence that blinding can be inadequate at intensity of 2 mA. No formal assessment of blinding success
Adequate blinding of assessors?	Unclear risk	tDCS 2 mA intensity - evidence that blinding can be inadequate at intensity of 2 mA. No formal assessment of blinding success
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: ITT analysis used and low dropout
Selective reporting (reporting bias)	High risk	Comment: point estimates for pain scores not provided - only a responder analysis was presented
Free from carry-over effects?	Unclear risk	Comment: the order of active stimulation types was randomised but it is not clear that there were not baseline differences between pre-rTMS and pre tDCS from the presented data
Study Size	High risk	n = 36
Study duration	High risk	Comment: 5 days post intervention was the longest follow up
Other bias	Low risk	Comment: no other bias detected

Avery 2013

Methods	Parallel RCT
Participants	Country of study: USA Setting: unclear Condition: chronic widespread pain Prior management details: not reported n = 19 Age mean (SD): active 54.86 (7.65) years, sham 52.09 (10.02) years Duration of symptoms (months mean (SD)): active group 11 (4.26), sham group 15.64 (6.93)

Avery 2013 (*Continued*)

	Gender distribution: all F
Interventions	Stimulation type: rTMS Stimulation parameters: frequency 10 Hz; coil orientation not specified; 120% RMT; number of trains 75; duration of trains 4 s; ITI 26 s; total number of pulses 3000 Stimulation location: L DLPFC Number of treatments: 15 sessions over 4 weeks Control type: sham coil - controls for visual, auditory and scalp sensory cues
Outcomes	Primary: pain NRS 0-10 anchors not reported When taken: end of treatment period, 1 month following and 3 months following Secondary: pain interference BPI QoL SF-36 AEs: multiple minor; no clear difference in incidence between active and sham stimulation
Notes	Government-funded study, manufacturer loaned stimulators COI: funded by the National Institute for Arthritis, Musculoskeletal and Skin Diseases, R21 ART053963 and the Bipolar Illness Fund Neuronetics, Inc. loaned the TMS machine to the study Dr. Avery was a consultant for Neuronetics, Inc. for one day, is a member of the Data and Safety Monitoring Board for Cerval Neuortech, Inc., was on the speakers bureau for Eli Lilly and Takeda, was a consultant for Takeda and received a grant from the National Institute of Mental Health. Dr. Roy-Byrne is editor for Journal Watch, Depression and Anxiety, and UpToDate and has stock in Valant Medical Systems. None of the other authors has potential COI

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "At the completion of the baseline assessment, patients were randomly assigned to either real TMS or sham stimulation using a computerized randomization program that uses an adaptive randomization and stratification strategy."
Allocation concealment (selection bias)	Unclear risk	Quote: "Based on the randomization, a "smart card" which determined whether the real TMS or sham coil would be administered was assigned to a particular patient. The card had only a code number that did not reveal the randomization." "The research coordinator blind to the randomization repeated the baseline assessments" Comment: not entirely clear whether the personnel overseeing randomisation was separate from that performing the screening assessment
Adequate blinding of participants?	Low risk	Quote: "... sham stimulation with the electromagnet blocked within the coil by a piece of metal so the cortex was not stimulated. The coils appeared identical. Electrodes were attached

		to the left side of the forehead for each session. Those receiving the sham stimulation received an electrical stimulus to the forehead during the sham stimulation. Those receiving the real TMS received no electrical stimulation to the electrodes. Both groups experienced a sensation in the area of the left forehead. In addition, all subjects were given special earplugs and received an audible noise during the stimulation to mask any possible sound differences between the TMS and sham conditions." Comment: optimal sham - controls for visual, sensory and auditory cues Formal testing - blinding appears robust
Adequate blinding of assessors?	Low risk	Quote: "The research coordinator blind to the randomization repeated the baseline assessments of pain, functional status, depression, fatigue, and sleep before the 1st and after the 5th, the 10th, and the 15th TMS sessions as well as 1 week, 1 month, and 3 months after the last TMS treatment except for the SF-36, neuropsychological tests, audiometry and the dolorimetry which were only done at baseline and one week after the 15th TMS session." Comment: while TMS physicians guessed beyond chance the raters were separate from this process
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "To examine differences in changes in outcomes over time between TMS and comparison group subjects, we estimated random coefficient models following the intent-to-treat principle." "11 were randomized to the sham group and 8 were randomized to the TMS group. However, one subject randomized to the TMS had a baseline BIRS score of 4 which was well below the BIRS score of 8 required for randomization. Because of this incorrect randomization, this subject was excluded from the efficacy analyses, but was included in the analysis of side effects. The clinical characteristics of those correctly randomized are in Table 1. One subject in the TMS dropped out after the 10th session because of lack of response and is included in the analyses." Comment: of 2 dropouts from the TMS group, 1 was excluded (reasons given)
Selective reporting (reporting bias)	Low risk	Comment: all outcomes presented in full in study report
Study Size	High risk	Comment: < 50 participants per treatment arm
Study duration	Low risk	Comment: > 8 weeks' follow-up
Other bias	Low risk	No other bias detected

Ayache 2016

Methods	Cross-over RCT
Participants	Country of study: France Setting: laboratory Condition: MS-related neuropathic pain Prior management details: concomitant medication intake stable throughout protocol n = 16 Age, mean (SD) 48.9 (10) years Duration of symptoms: mean (SD) 11.8 (9.4) months Gender distribution: 13 F, 3 M
Interventions	Stimulation type: tDCS Stimulation parameters: intensity 2 mA, 25 cm^2 electrodes, duration 20 min Stimulation location: anode - L DLPFC, cathode right supraorbital Number of treatments: x 3, daily Control type: sham tDCS
Outcomes	Primary: pain VAS 0 -10; VAS anchors not reported When taken: Postintervention, 7 days postintervention Secondary: AEs
Notes	COI: "AC gave expert testimony for CSL Behring, Novartis, received grants from Biogen, Novartis, CSLBehring, GENeuro, Octapharma, and gave lectures for Genzyme. The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships "that could be construed as potential conflict of interest"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote "The randomization schedule was generated by U.P. prior to the beginning of the study using a dedicated software ("true"random number generation without any restriction, stored in a computer until the patient was assigned to the intervention)."
Adequate blinding of participants?	Unclear risk	Comment: there is evidence that participant blinding of tDCS may be inadequate at 2 mA intensity, particularly in cross-over designs. Results of guessing mode of stimulation not reported
Adequate blinding of assessors?	Unclear risk	Quote: "Only the performing physician (S.S.A) was aware of the stimulation mode (real or sham tDCS). The evaluators (U. P and M.A.C) and the patients were blind to it." Comment: there is evidence that assessor blinding of tDCS may be inadequate at 2 mA intensity

Ayache 2016 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: no attrition reported
Selective reporting (reporting bias)	Low risk	Comment: results reported in full
Free from carry-over effects?	Unclear risk	Comment: baseline scores for each period not reported. No formal analysis for carry-over effects presented
Study Size	High risk	Comment: n = 16
Study duration	High risk	Comment: longest follow-up 7 days after stimulation
Other bias	Low risk	No other bias detected

Bae 2014

Methods	Parallel RCT
Participants	Country of study: South Korea Setting: laboratory Condition: CPSP Prior management details: not reported n = 14 Age, mean (SD): active group 51.1 (3.1) years, sham group 52.3 (2.8) years Duration of symptoms, mean (SD): active group 14.5 (3.2) months, sham group 14.7 (2.7) Gender distribution: 7 M, 7 F
Interventions	Stimulation type: tDCS Stimulation parameters: intensity 2 mA, 35 cm^2 electrodes, duration 20 min Stimulation location: anode - M1 contralateral to painful side, cathode right supraorbital Number of treatments: x 3 per week for 3 weeks Control type: sham tDCS
Outcomes	Primary: pain VAS anchors 0 = no pain, 10 = unbearable When taken: "immediacy", 1 week, 3 weeks (unclear if from end of intervention) Secondary: None relevant
Notes	COI: study authors declared no COI Sources of support: none declared

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: method of randomisation not reported

Bae 2014 (*Continued*)

Allocation concealment (selection bias)	Unclear risk	Comment: no mention of allocation concealment procedures
Adequate blinding of participants?	Unclear risk	Comment: blinding not reported. Evidence that blinding can be inadequate at intensity of 2 mA
Adequate blinding of assessors?	Unclear risk	Comment: blinding not reported. Evidence that blinding can be inadequate at intensity of 2 mA
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: unable to clearly verify if there was any attrition
Selective reporting (reporting bias)	Low risk	Comment: adequate reporting of outcomes
Study Size	High risk	Comment: total n = 14
Study duration	Unclear risk	Comment: 3-week follow-up
Other bias	Low risk	Comment: no other bias detected

Boggio 2009

Methods	Cross-over RCT; 3 conditions
Participants	Country of study: Brazil Setting: laboratory Condition: neuropathic pain (mixed central, peripheral and facial) Prior management details: refractory to drug management n = 8 Age: 40-82 years; mean 63.3 (SD 5.6) Duration of symptoms: 1-20 years; mean 8.3 (SD 5.6) Gender distribution: 2 M, 6 F
Interventions	Stimulation type: tDCS Stimulation parameters: intensity 2 mA, 35 cm^2 electrodes, duration 30 min Condition 1: active tDCS/active TENS Condition 2: active tDCS/sham TENS Condition 3: sham tDCS/sham TENS Stimulation location: M1 contralateral to painful side Number of treatments: 1 for each condition Control type: sham tDCS (switched off after 30 s stimulation)
Outcomes	Primary: VAS 0-10 anchors “no pain” to “worst possible pain” When taken: pre and post each stimulation Secondary: none
Notes	Sources of support: not declared COI: not declared

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "All the patients received the 3 treatments.... in a randomised order (we used a computer generated randomisation list with the order of entrance)."
Adequate blinding of participants?	Unclear risk	Comment: there is evidence that participant blinding of tDCS may be inadequate at 2 mA intensity (see Assessment of risk of bias in included studies)
Adequate blinding of assessors?	Unclear risk	Quote: "All evaluations were carried out by a blinded rater" Comment: there is evidence that assessor blinding of tDCS may be inadequate at 2 mA intensity (see Assessment of risk of bias in included studies)
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: 2 participants lost to follow-up. It is unclear how these data were accounted for as there were no missing data apparent in the results tables. However, this may have an impact given the small sample size
Selective reporting (reporting bias)	Low risk	Comment: primary outcome data presented clearly and in full
Free from carry-over effects?	Low risk	Comment: a 48-h washout period was observed between stimulation conditions and possible carry-over effects were checked and ruled out in the analysis Quote: "To analyze whether there was a carryover effect, we initially performed and showed that the baselines for the 3 conditions were not significantly different (P = 0.51). We also included the variable order in our model and this model also showed that order is not a significant term (P = 0.7)."
Study Size	High risk	Comment: < 50 participants per treatment arm
Study duration	High risk	Comment: < 2 weeks' follow-up
Other bias	Low risk	Comment: no significant other bias detected

Borckardt 2009

Methods	Cross-over RCT; 2 conditions
Participants	Country of study: USA Setting: laboratory Condition: peripheral neuropathic pain Prior management details: not specified n = 4 Age: 33-58 years; mean 46 (SD 11) Duration of symptoms: 5-12 years; mean 10.25 (SD 3.5) Gender distribution: 1 M, 3 F
Interventions	Stimulation type: rTMS, figure-of-8 coil Stimulation parameters: frequency 10 Hz; coil orientation not specified; 100% RMT; number of trains 40; duration of trains 10 s; ITI 20 s; total number of pulses 4000 Stimulation location: L PFC Number of treatments: 3 over a 5-d period Control type: neuronetics sham coil (looks and sounds identical)
Outcomes	Primary: average daily pain 0-10 Likert scale, anchors "no pain at all" to "worst pain imaginable" When taken: post-stimulation for each condition (unclear how many days post) and daily for 3 weeks poststimulation Secondary: none
Notes	AEs: not reported Sources of support: no separate statement provided COI: "Dr. Borckardt receives research funding from the National Institute for Neurological Disorders and Stroke at NIH, Cyberonics Inc, the Neurosciences Institute at MUSC, and is a consultant for Neuropace; however, he has no equity ownership in any device or pharmaceutical company. Dr. George receives research funding from the National Institute for Mental Health, NIDA, and NIAAA at NIH, Jazz Pharmaceuticals, GlaxoSmithKline, and Cyberonics Inc. He is a consultant for Aspect Biomedical, Argolyn, Aventis, Abbott, Bristol-Meyers Squibb, Cephos, Cyberonics, and Neuropace; however, he has no equity ownership in any device or pharmaceutical company. Dr. Nahas receives research funding from the National Institute for Mental Health at NIH and Cyberonics Ind, and is a consultant for Neuropace. Dr. Kozel receives research funding from the National Institute for Mental Health at NIH and the U.S. Department of Defense. MUSC has filed six patents or invention disclosures in one or more of the authors' names regarding brain imaging and stimulation."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The order (real first or sham first) was randomised" Comment: method of randomisation not specified but less critical in cross-over design

Borckardt 2009 (*Continued*)

Adequate blinding of participants?	Unclear risk	Quote: "Two of the four participants (50%) correctly guessed which treatment periods were real and sham, which is equal to chance. All four of the participants initially said that they did not know which was which, and it was not until they were pushed to "make a guess" that they were able to offer an opinion about which sessions were real and which were sham." Comments: sham credibility assessment - suboptimal. Sham coil controlled for auditory cues and was visually indistinguishable from active stimulation but did not control for sensory characteristics of active stimulation
Adequate blinding of assessors?	Unclear risk	Comment: not specified
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: no dropout
Selective reporting (reporting bias)	Low risk	Comment: all results reported clearly and in full
Free from carry-over effects?	Low risk	Comment: a 3-week washout period was observed. Presented average pain values were very similar pre- each condition
Study Size	High risk	Comment: < 50 participants per treatment arm
Study duration	Unclear risk	Comment: ≥ 2 weeks but < 8 weeks' follow-up
Other bias	Low risk	Comment: no significant other bias detected

Boyer 2014

Methods	Parallel RCT
Participants	Country of study: France Setting: specialised pain treatment centre Condition: fibromyalgia Prior management details: stable treatment for more than 1 month before enrolment n = 38 Age, mean (SD): active group 49.1(10.6) years, sham group 47.7 (10.4) years Duration of symptoms, mean (SD): active group 3.7 (4.5) years, sham group 3.6 (3.8) Gender distribution: 37 F, 1 M
Interventions	Stimulation type: rTMS Stimulation parameters: frequency 10 Hz; coil orientation anteroposterior; 90% RMT; number of trains 20; duration of trains 10 s; ITI 50 s; total number of pulses 2000 Stimulation location: L M1 Number of treatments: 14 sessions. 10 sessions in 2 weeks followed by maintenance phase of 1 session at weeks 4, 6, 8 and 10

Boyer 2014 (*Continued*)

	Control type: sham coil - did not control for sensory cues
Outcomes	Primary: pain VAS 0 = no pain, 10 = maximal pain imaginable When taken: 2 weeks, 11 weeks Secondary: FIQ AEs
Notes	Funding source: Supported by Inserm (Centre d'Investigation Clinique, CIC, Hôpital de la Conception, Marseille) and AP-HM (AORC 2008/01) COI: the study authors report no disclosures relevant to the manuscript

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Individuals were randomized by a computer-generated list…"
Allocation concealment (selection bias)	Low risk	Quote: "...which was maintained centrally so no investigators knew the treatment allocation of any patient."
Adequate blinding of participants?	Unclear risk	Quote: "Sham stimulation was conducted with a sham coil of identical size, color, and shape, emitting a sound similar to that emitted by the active coil. Stimulations were administered by the same technologist." Comments: sham credibility assessment - suboptimal. Sham coil controlled for auditory cues and was visually indistinguishable from active stimulation but did not control for sensory characteristics of active stimulation
Adequate blinding of assessors?	Low risk	Quote: "Patients and clinical raters were blinded to treatment"
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote "All patients completed the induction phase, but 9 (23.7%) were excluded during the maintenance phase (3 in the active rTMS group and 6 in the sham rTMS group)" Comment: dropout high, ITT analysis used but no information with regards imputation approach taken (or not)
Selective reporting (reporting bias)	Low risk	Comment: all results reported clearly and in full
Study Size	High risk	Comment: n = 38
Study duration	High risk	Comment: no follow-up after end of maintenance phase
Other bias	Low risk	Comment: no other bias detected

Brietzke 2016

Methods	Parallel RCT
Participants	Country of study: Brazil Setting: laboratory Condition: hepatitis C-related chronic pain Prior management details: not reported n = 28 Age, mean (SD): active group 53.86 (5.76) years, sham group 56.57 (8.52) years Duration of symptoms: not reported Gender distribution: 21 M, 7 F
Interventions	Stimulation type: tDCS Stimulation parameters: intensity 2 mA, 25-35 cm^2 electrodes, duration 20 min Stimulation location: anode - M1 L, cathode right supraorbital Number of treatments: daily, x 5 Control type: sham tDCS
Outcomes	Primary: pain VAS; anchors 0 = no pain, 10 = worst possible pain When taken: end of intervention Secondary: none relevant
Notes	Funding from Brazilian funding agencies: (i) Committee for the Development of Higher Education Personnel (ii) National Council for Scientific and Technological Development-CNPq (iii) Postgraduate Program in Medical Sciences of Medical School of the Federal University of Rio Grande do Sul. (iv) Postgraduate Research Group at the Hospital de Clínicas de Porto Alegre (v) Laboratory of Neuromodulation & Center for Clinical Research Learning (vi) Foundation for Support of Research at Rio Grande do Sul

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomized numbers in a 1:1 ratio were generated using appropriate software (www.randomization.com) to assign each Participant to either active or sham-placebo group."
Allocation concealment (selection bias)	Low risk	Quote: "Envelopes were prepared for randomization process and sealed. After subject's agreement to participate in the trial, one investigator who was not involved with either stimulation or assessments opened the envelope. The allocation concealment was reached since no investigator (stimulators nor accessors) was aware of treatment allocations and had no control over the order of patients randomized."

Brietzke 2016 (*Continued*)

Adequate blinding of participants?	Unclear risk	Comment: evidence that blinding can be inadequate at intensity of 2 mA
Adequate blinding of assessors?	Unclear risk	Quote: "Two independent blinded examiners were trained to apply the pain scales and to conduct the psychological tests Comment: evidence that assessor blinding can be inadequate at intensity of 2 mA. No assessment of blinding success
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: 3 participants dropped out (> 10%) reasons not given. ITT analysis with LOCF
Selective reporting (reporting bias)	Low risk	Comment: outcome data adequately reported
Study Size	High risk	Comment n = 28
Study duration	High risk	Comment: no follow-up after immediate postintervention period
Other bias	Low risk	No other bias detected

Capel 2003

Methods	Partial cross-over RCT. NB: we only considered first-phase results therefore we considered the trial as having a parallel design
Participants	Country of study: UK Setting: residential educational centre Condition: post-SCI pain (unclear whether this was neuropathic or otherwise) Prior management details: unclear n = 30 Age: unclear Duration of symptoms: unclear Gender distribution: unclear
Interventions	Stimulation type: CES Stimulation parameters: frequency 10 Hz; pulse width 2 ms; intensity 1 2 μA; duration 53 min Stimulation location: ear clip electrodes Number of treatments: x 2, daily for 4 days Control type: sham CES unit indistinguishable from active unit
Outcomes	Primary: 0-10 VAS 'level of pain', anchors not specified When taken: daily during the treatment period Secondary: none
Notes	COI: no declaration made Sources of support: Laing Foundation (charity) "financial assistance"

Capel 2003 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Comment: method equivalent to picking out of a hat Quote: "Subjects would be randomly assigned into two groups according to their choice of treatment device... The devices were numbered for identification, but neither the administrators nor the recipients of the treatment could distinguish between the devices."
Allocation concealment (selection bias)	Low risk	Comment: this is achieved through the method of randomisation
Adequate blinding of participants?	Low risk	Quote: "neither the administrators nor the recipients of the treatment could distinguish between the devices."
Adequate blinding of assessors?	Low risk	Quote: "neither the administrators nor the recipients of the treatment could distinguish between the devices."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: 3 participants withdrew (not voluntarily) and while the data were not clearly accounted for in the data analysis this constituted 10% of the overall cohort and was unlikely to have strongly influenced the results Quote: "Three of the 30 subjects included were withdrawn from the study after commencement, one of whom developed an upper respiratory infection, and two others were withdrawn from the study because their medication (either H2 antagonist anti-ulcer or steroidal inhalant) were interacting with the TCET treatment."
Selective reporting (reporting bias)	High risk	Comment: pain score values were not provided for any time point
Study Size	High risk	Comment: < 50 participants per treatment arm
Study duration	High risk	Comment: < 2 weeks' follow-up

Capel 2003 (*Continued*)

Other bias	Low risk	Comment: no significant other bias detected

Carretero 2009

Methods	Parallel randomised clinical trial
Participants	Country of study: Spain Setting: outpatient clinic Condition: fibromyalgia (with major depression) Prior management details: unclear n = 26 Age: active group 47.5 (SD 5.7) years, sham group 54.9 (SD 4.9) years Duration of symptoms: unclear "chronic" Gender distribution: 2 M, 24 F
Interventions	Stimulation type: rTMS Stimulation parameters: frequency 1 Hz; coil orientation not specified; 110% RMT; number of trains 20; duration of trains 60 s; ITI 45 s; number of pulses 1200 Stimulation location: R DLPFC Number of treatments: up to 20 on consecutive working days Control type: coil angled 45º from the scalp
Outcomes	Primary: Likert pain scale 0-10, anchors "no pain" to "extreme pain" When taken: 2 weeks, 4 weeks and 8 weeks from commencement of study Secondary: none
Notes	COI: no declaration made Sources of support: IUNICS Institute, Research Institute of Health Sciences

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: method of randomisation not specified
Allocation concealment (selection bias)	Unclear risk	Comment: allocation concealment not specified
Adequate blinding of participants?	Unclear risk	Comments: sham credibility assessment - suboptimal. Coil angled 45º away from scalp. Did not control for sensory characteristics of active stimulation and was visually distinguishable
Adequate blinding of assessors?	Low risk	Quote: "patients and raters (but not the treating physician) were blind to the procedure"

Carretero 2009 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: only 1 participant in each group did not complete the study. Unlikely to have strongly influenced the findings
Selective reporting (reporting bias)	Low risk	Comment: outcomes presented clearly and in full
Study Size	High risk	Comment: < 50 participants per treatment arm
Study duration	Unclear risk	Comment: ≥ 2 weeks but < 8 weeks' follow-up
Other bias	Low risk	Comment: no significant other bias detected

Chang 2017

Methods	Parallel RCT
Participants	Country of study: Australia Setting: laboratory Condition: knee OA Prior management details: not reported n = 30 Age, mean (SD): active group 59.8 (9.1) years, sham group 64.1 (11.1) years Duration of symptoms mean (SD) years: active group: 7.2 (5.3), sham group 9.0 (7.3) Gender distribution: 10 M, 19 F
Interventions	Stimulation type: tDCS Stimulation parameters: tDCS: 1 mA intensity, 20 min Stimulation location: M1 contralateral to painful side Number of treatments: x 2 weekly for 8 weeks prior to a 30-min supervised strengthening exercise session. 16 sessions Control type: sham tDCS
Outcomes	Primary: pain NRS anchors 0 = no pain, 10 = worst pain imaginable When taken: postintervention Secondary: WOMAC function AEs
Notes	Funding source: Trial funded by Arthritis Australia (The Zimmer Australia Grant). W-JC (1094434), PWH (1002190), KLB (1058440), MBL (1059116) and SMS (1105040) receive salary support from the National Health and Medical Research Council of Australia, RSH from the Australian Research Council (FT#130100175) and VB from a Western Sydney University Postgraduate Research Award COI: study authors declared no COI
Risk of bias	

Chang 2017 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: method of randomisation not described
Allocation concealment (selection bias)	Low risk	Quote: "The randomisation schedule was concealed in consecutively numbered, sealed opaque envelopes. An investigator not involved in recruitment and assessment prepared and provided the envelopes to the treating physiotherapists who revealed group allocation."
Adequate blinding of participants?	Low risk	Comment: blinding likely maintained at 1 mA intensity
Adequate blinding of assessors?	Low risk	Quote: "A single investigator (W-JC), blinded to the group allocation of the participants, performed participant recruitment, screening, and testing."
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: 2 (13% dropout from active group), 3 (20%) from control group. ITT analysis with no imputation of missing values
Selective reporting (reporting bias)	Low risk	Comment: outcomes reported adequately
Study Size	High risk	Comment: n = 30
Study duration	High risk	Comment: postintervention follow-up only (within 1 week)
Other bias	Low risk	Comment: no other bias detected

Cork 2004

Methods	Cross-over RCT (to be considered as parallel - first treatment phase only as 2nd unblinded)
Participants	Country of study: USA Setting: pain clinic Condition: fibromyalgia Prior management details: unclear n = 74 Age: 22-75 years; mean 53 Duration of symptoms: 1-21 years; mean 7.3 Gender distribution: 4 M, 70 F
Interventions	Stimulation type: CES Stimulation parameters: frequency 0.5 Hz; pulse width unclear; intensity 100 μA; waveform shape modified square wave biphasic 50% duty cycle; duration 60 min Stimulation location: ear clip electrodes Number of treatments: ? daily for 3 weeks Control type: sham CES unit indistinguishable from active unit

Cork 2004 (*Continued*)

Outcomes	Primary: 0 -5 pain NRS, anchors "no pain" to "worst pain imaginable" When taken: immediately following the 3-week treatment period Secondary: Oswestry Disability Index When taken: immediately following the 3-week treatment period
Notes	AEs: not reported COI: no declaration made Sources of support: "Supported by a grant from the Department of Anesthesiology, LSU Health Sciences Center. No financial support was received from the makers of the Alpha-Stim™; however, Electromedical Products International, Inc. did loan the authors the Alpha-Stim™ units necessary to do the study."

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: method of randomisation not specified
Allocation concealment (selection bias)	Unclear risk	Comment: allocation concealment not specified
Adequate blinding of participants?	Low risk	Quote: "All staff, the physicians, and the patient were blind to the treatment conditions."
Adequate blinding of assessors?	Low risk	Quote: "All staff, the physicians, and the patient were blind to the treatment conditions."
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: dropout rate not reported
Selective reporting (reporting bias)	High risk	Comment: pain score numerical values not provided clearly with measures of variance for any time point
Study Size	High risk	Comment: < 50 participants per treatment arm (considered as a parallel trial - 1st phase only)
Study duration	High risk	Comment: < 2 weeks' follow-up
Other bias	Low risk	Comment: no significant other bias detected

Curatolo 2017

Methods	Parallel RCT
Participants	Country of study: Italy Setting: laboratory Condition: fibromyalgia Prior management details: not reported n = 20 Age, mean (SD): active group 41.4 (10.25) years, sham group 44.2 (9.81) years Duration of symptoms, mean (SD) years: active group 4.3 (2.62), sham group 5 (5.04) Gender distribution: all F
Interventions	Stimulation type: tRNS Stimulation parameters: tDCS: 1.5 mA intensity, 20 min (randomly oscillating in frequency range 101-640 Hz for 10 min, offset set to 0 ma sham - stimulation turned on for 30 s only) Stimulation location: M1 (side not reported) Number of treatments: x 1 daily, 5 days a week for 2 weeks (x 10 sessions) Control type: sham tRNS
Outcomes	Primary: pain NRS anchors not reported When taken: postintervention Secondary: FIQ AEs not reported
Notes	Funding source: not reported COI: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: method of randomisation not described
Allocation concealment (selection bias)	Unclear risk	Comment: allocation concealment not described
Adequate blinding of participants?	Unclear risk	Comment: method of blinding not reported
Adequate blinding of assessors?	Unclear risk	Comment: method of blinding not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: no dropout reported
Selective reporting (reporting bias)	High risk	Comment: no numeric reporting of primary outcomes
Study Size	High risk	Comment: n = 20
Study duration	High risk	Comment: postintervention follow-up only

Curatolo 2017 (*Continued*)

Other bias	Low risk	Comment: no other bias detected

Dall'Agnol 2014

Methods	Parallel RCT
Participants	Country of study: Brazil Setting: not specified Condition: chronic myofascial pain in the upper body Prior management details: not reported n = 24 Age, mean (SD): active group 45.83 (9.63) years, sham group 44.83 (14.09) years Duration of symptoms: not reported Gender distribution: all F
Interventions	Stimulation type: rTMS Stimulation parameters: frequency 10 Hz; coil orientation 45º from midline, 80% RMT, number of trains 16; duration of trains 10 s; ITI 26 s; total number of pulses 1600 Stimulation location: L M1 Number of treatments: 10 sessions, timescale not specified Control type: sham coil - same sound and appearance and sensation
Outcomes	Primary: pain NRS anchors 0 = no pain, 10 = worst possible pain When taken: postintervention Secondary: AEs
Notes	Funding source: grants and material support from the following Brazilian agencies: Brazilian Innovation Agency (FINEP), process number 1245/13; Committee for the Development of Higher Education Personnel-PNPD/CAPES, process number 023-11, and material support; National Council for Scientific and Technological Development-CNPq (grants WC-301256/2013-6 and ILST- 302345/2011-6); Postgraduate Program in Medical Sciences at the School of Medicine of the Federal University of Rio Grande do Sul (material support); Postgraduate Research Group at the Hospital de Cl nicas de Porto Alegre (grant number 120343 and material support); and Foundation for Support of Research at Rio Grande do Sul (FAPERGS) COI: study authors declared that there was no COI

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "A computer random number generator assigned patients to 1 of 2 groups: rTMS or placebo-sham using a block randomization strategy."
Allocation concealment (selection bias)	Low risk	Quote: "Before the recruitment phase, opaque envelopes containing the protocol materials were prepared. Each opaque envelope was sealed and numbered sequentially, containing 1 in-

Dall'Agnol 2014 (*Continued*)

		tervention allocation."
Adequate blinding of participants?	Low risk	Quote "we used an inactive rTMS coil (MagPro X100; MagVenture Company, Lucernemarken, Denmark) as a sham method by placing it in the identical area as the active coil. Thus, sham patients underwent similar rTMS experience (including rTMS sound) as those receiving active stimulation.....The patient recorded identical experiences (including sound effects and somatic sensations caused by contraction of the muscles of the scalp) as during active stimulation" Comment: assessment indicates that blinding was successful.
Adequate blinding of assessors?	Low risk	Quote "Two independent evaluators who were blinded to the group assignments(W.C. and another) were trained to apply the pain scales and conduct psychophysical and psychological tests. "
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: only 1 dropout
Selective reporting (reporting bias)	High risk	Comment: point estimates for outcomes only reported at one time point
Study Size	High risk	n = 24
Study duration	Low risk	12-week follow-up postintervention
Other bias	Low risk	Comment: no other bias detected

de Oliveira 2014

Methods	Parallel RCT
Participants	Country of study: Brazil Setting: neurology dept Condition: CPSP Prior management details: stable medication for 30 d preceding baseline n = 23 Age, mean (SD): active group 55 (9.67) years, sham group SD 57.8 (11.86) years Duration of symptoms, mean (SD): active group 64.18 (49.27) months, sham group 50.1 (28.04) Gender distribution:active group 45% M, sham group 50% M
Interventions	Stimulation type: rTMS Stimulation parameters: frequency 10 Hz; coil orientation not specified, 120% RMT, number of trains 25; duration of trains 5 s; ITI 25s; total number of pulses 1250 Stimulation location: L premotor/DLPFC Number of treatments: 10 sessions daily for 2 weeks Control type: sham coil - same sound and appearance, no control for sensory cues

Outcomes	Primary: pain NRS anchors not reported When taken: end of intervention, 1, 2 and 4 weeks postintervention Secondary: AEs, QoL (SF-36)
Notes	Funding source: study was supported by the Pain Center of the Department of Neurology and by the Transcranial Magnetic Stimulation Laboratory of the Psychiatry Institute, University of Sao Pau COI: the study authors declared no COI

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote "Participants were randomly assigned into 2 groups, active stimulation (a-rTMS) and sham stimulation (s-rTMS), according to a list automatically generated by an internet-based tool (www.random.org)"
Allocation concealment (selection bias)	Unclear risk	Comment: allocation concealment not reported
Adequate blinding of participants?	Unclear risk	Quote "Sham stimulation was carried out with a sham coil of identical size color and shape emitting a sound similar to that emitted by the active coil (MC-P-B70)." Comment: sham credibility assessment - suboptimal. Sham coil controlled for auditory cues and was visually indistinguishable from active stimulation but did not control for sensory characteristics of active stimulation
Adequate blinding of assessors?	Low risk	Quote: "Pain intensity (VAS) was assessed daily, right before and immediately after each rTMS session, from D1 to D10 by an investigator (M.M.) blinded to the type of rTMS patients were receiving. All clinical assessments were performed by a physician and a neuropsychologist (T.L., M.L.M) who were blinded to the type of treatment and had no other role in the study."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: 1 dropout per group
Selective reporting (reporting bias)	Low risk	Comment: outcomes reported adequately
Study Size	High risk	n = 21
Study duration	Unclear risk	Comment: 4-week follow-up
Other bias	Low risk	Comment: no other bias detected

Deering 2017

Methods	Parallel RCT
Participants	Country of study: USA Setting: "single clinical location" Condition: fibromyalgia Prior management details: FDA-approved fibromyalgia drugs and centrally active analgesics or stimulants "prohibited" n = 46 Age mean (SD) active 12-week programme group 55.7 (8.7) active 8-week programme group 46.6 (10.3), sham group 47.9 (11.2) Duration of symptoms: not reported Gender distribution: reported for completers only 35 F, 3 M
Interventions	Stimulation type: RINCE Stimulation parameters: not reported Stimulation location: parietal region (international 10/20 site PZ),"positioned to create a conduction pathway that includes the primary somatosensory and motor cortex" Number of treatments: Active 12-week group: 24 treatments of 12 weeks Active 8-week group: 16 treatments over 8 weeks followed by 8 sham sessions in 4 weeks Sham group: 24 sham sesssions over 12 weeks Control type: nonactivated identical stimulation unit
Outcomes	Primary: pain VAS; 0 = no pain, 10 = worst pain imaginable When taken: end of treatment period, 4 weeks post-treatment Secondary: total FIQ score AEs
Notes	Sources of support: all funding for this study was provided by Cerephex Corporation who manufacture the device COI: no formal declaration. 5 study authors affiliated to funder - who manufacture the RINCE technology

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: method of random sequence generation unclear
Allocation concealment (selection bias)	Unclear risk	Comment: allocation concealment not clearly established
Adequate blinding of participants?	Unclear risk	Quote: "patients cannot feel the RINCE signal and are therefore blinded to receiving treatment or not….no element of hardware or software gave any indication of group assignment"
Adequate blinding of assessors?	Unclear risk	Quote: "The investigators were blinded to these codes and no element of hardware or software gave any indication of group assignment, thus maintaining a double blinded sham controlled

Deering 2017 (*Continued*)

		condition."
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: 7/14 participants not analysed in the sham group due to "exposure to unexpected signal source". These participants not included in sham analysis. Details on how this was confirmed or what the exposure was are not clear
Selective reporting (reporting bias)	High risk	Comment: point estimates with measures of variance not provided for all groups at all time points
Study Size	High risk	n = 46, divided into 3 groups
Study duration	Unclear risk	Comment: 4-week follow-up period
Other bias	Unclear risk	Comment: full baseline data not tested and only data with 8 excluded sham participants removed were presented

Defrin 2007

Methods	Parallel RCT
Participants	Country of study: Israel Setting: outpatient department Condition: post-SCI central neuropathic pain Prior management details: refractory to drug, physical therapy and complementary therapy management n = 12 Age: 44-60 years; mean 54 (SD 6) Duration of symptoms: > 12 months Gender distribution: 7 M, 4 F
Interventions	Stimulation type: rTMS, figure-of-8 coil Stimulation parameters: frequency 5 Hz; coil orientation not specified; 115% RMT; number of trains 500; duration of trains 10 s; ITI 30 s; total number of pulses 500 reported, likely to have been 25,000 judging by these parameters Stimulation location: M1 - midline Number of treatments: x 10, x 1 daily on consecutive days Control type: sham coil - visually the same and makes similar background noise
Outcomes	Primary: 15 cm 0-10 VAS pain intensity, anchors "no pain sensation" to "most intense pain sensation" When taken: pre and post each stimulation session Secondary: McGill pain questionnaire When taken: 2- and 6-week follow-up period
Notes	AEs: not reported Sources of support: supported by the National Association of the insurance companies COI: study authors declared no COI

Defrin 2007 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: method of randomisation not specified Quote: "Patients were randomised into 2 groups that received either real or sham rTMS"
Allocation concealment (selection bias)	Unclear risk	Comment: allocation concealment not specified
Adequate blinding of participants?	Unclear risk	Quote: "Two coils were used; real and sham, both of which were identical in shape and produced a similar background noise." Comment: sham credibility assessment - suboptimal. Sham coil controlled for auditory cues and was visually indistinguishable from active stimulation, but did not control for sensory characteristics of active stimulation over the scalp. Given that stimulation was delivered at 110% RMT active stimulation, but not sham, it is likely to have elicited muscle twitches in peripheral muscles
Adequate blinding of assessors?	Low risk	Quote: "The patients as well as the person conducting the outcome measurements were blind to the type of treatment received. "
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: only 1 participant withdrew for "logistic reasons". Unlikely to have strongly influenced the findings
Selective reporting (reporting bias)	Low risk	Comment: while group means/SD were not presented in the study report, the study authors provided the requested data
Study Size	High risk	Comment: < 50 participants per treatment arm
Study duration	Unclear risk	Comment: ≥ 2 weeks but < 8 weeks' follow-up
Other bias	Unclear risk	Comment: baseline differences observed in pain intensity levels (higher in active group)

Donnell 2015

Methods	Parallel RCT
Participants	Country of study: USA Setting: laboratory Condition: chronic temperomandibular disorder Prior management details: pain not adequately controlled by previous therapies for more than 1 year n = 24 Age range, mean (SD): active group 34.8 (13.7) years, sham group 35.6 (16.7) years

Donnell 2015 (*Continued*)

	Duration of symptoms: not reported Gender distribution: all F
Interventions	Stimulation type: HD-tDCS Stimulation parameters: intensity 2 mA, 4 electrodes arranged at the corners of a 4 x 4 cm square centred over M1 Stimulation location: anode - M1 contralateral to painful side Number of treatments: daily, x 5 Control type: sham tDCS
Outcomes	Primary: pain VAS; anchors not reported - responder analysis only reported When taken: 1-month follow-up Secondary: AEs
Notes	Sources of funding: this project was funded by grants from the American Academy of Orofacial Pain and the University of Michigan Rackham Graduate School Potential undisclosed COI: 1 study author (Biksom) worked for stimulation device manufacturer Soterix

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote "participants were randomized to the treatment or placebo group using the Taves covariate adaptive randomization method."
Allocation concealment (selection bias)	Unclear risk	Comment: no mention of allocation concealment procedures
Adequate blinding of participants?	Unclear risk	Comment: 2 mA intensity. Evidence that blinding can be inadequate at intensity of 2 mA
Adequate blinding of assessors?	High risk	Comment: study described as single blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: no participant dropout
Selective reporting (reporting bias)	High risk	Comment: pain outcomes not presented for all follow-up time points
Study Size	High risk	n = 24
Study duration	Unclear risk	1-month follow-up postintervention
Other bias	Low risk	Comment: no other bias detected

Fagerlund 2015

Methods	Parallel RCT
Participants	Country of study: Norway Setting: university hospital Condition: fibromyalgia Prior management details: prescription medication stable for 3 months prior to inclusion n = 50 Age, mean (SD): active group 49/04 (8.63) years, sham group 48.17 (10.56) years Duration of symptoms, mean (SD) sham group 17.73 (7.54) years, sham group 18.50 (11.48) Gender distribution: 47 F, 3 M
Interventions	Stimulation type: tDCS Stimulation parameters: intensity 2 mA, 35 cm^2 electrodes, duration 20 min Stimulation location: anode - M1 side not reported, cathode supraorbital contralateral to anode Number of treatments: daily, x 5 Control type: sham tDCS
Outcomes	Primary: pain VAS, anchors not reported When taken: postintervention, mean 30 days postintervention Secondary: FIQ, SF-36, AEs
Notes	Sources of funding: study was funded by a grant from the Norwegian Extra Foundation for Health and Rehabilitation through the Norwegian Fibromyalgia Association Study authors declared no COI

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "The codes were associated with the active or sham tDCS condition and randomized using the online Web service www.randomize.org. The ratio of active and sham codes was 1:1."
Allocation concealment (selection bias)	Unclear risk	Comment: not clearly stated that the sequence generation was separated and concealed
Adequate blinding of participants?	Unclear risk	Comment: evidence that blinding can be inadequate at intensity of 2 mA. Not formal assessment of blinding success
Adequate blinding of assessors?	Low risk	Comment: outcomes collected through text message with little potential for assessors to influence process
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: high noncompletion rate for some outcomes and there is not full clarity on how many participants were analysed
Selective reporting (reporting bias)	Low risk	Comment: full reporting of key outcomes

Fagerlund 2015 (*Continued*)

Study Size	High risk	n = 50
Study duration	Unclear risk	Comment: follow-up 30 days postintervention
Other bias	Low risk	Comment: no other bias detected

Fenton 2009

Methods	Cross-over RCT
Participants	Country of study: USA Setting: unclear Condition: chronic pelvic pain Prior management details: refractory to treatment n = 7 Age: mean 38 years Duration of symptoms: mean 80 months Gender distribution: all F
Interventions	Stimulation type: tDCS Stimulation parameters: intensity 1 mA, 35 cm^2 electrodes, duration 20 min Stimulation location: M1 dominant hemisphere Number of treatments: 2 Control type: sham tDCS (switched off after 30 s stimulation)
Outcomes	Primary: VAS overall pain, pelvic pain, back pain, migraine pain, bladder pain, bowel pain, abdomen pain and pain with intercourse. Anchors not specified When taken: daily during stimulation and then for 2 weeks post-each condition Secondary: none
Notes	Sources of support: no declaration made COI: no declaration made

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Comment: method of randomisation not specified but less critical in cross-over design
Adequate blinding of participants?	Low risk	Quote: "All other personnel in the study, including the investigators, study coordinators, participants, and their families, and all primary medical caregivers, were blinded."
Adequate blinding of assessors?	Low risk	Quote: "All other personnel in the study, including the investigators, study coordinators, participants, and their families, and all primary medical caregivers, were blinded."

Fenton 2009 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: no dropout reported
Selective reporting (reporting bias)	Low risk	Comment: variance measures not presented for group means poststimulation but data provided by study author on request
Free from carry-over effects?	Unclear risk	Comments: pre-stimulation data not presented and no formal investigation for carry-over effects discussed
Study Size	High risk	Comment: < 50 participants per treatment arm
Study duration	Unclear risk	Comment: < 2 weeks' follow-up
Other bias	Low risk	Comment: no significant other bias detected

Fregni 2005

Methods	Cross-over RCT
Participants	Country of study: USA Setting: laboratory Condition: chronic pancreatitis pain Prior management details: not specified n = 5 Age: 44 (SD 11) Duration of symptoms: not specified, "chronic" Gender distribution: not specified
Interventions	Stimulation type: rTMS, figure-of-8 coil Stimulation parameters: frequency 1 Hz or 20 Hz; coil orientation not specified; 90% RMT; number of trains not specified; duration of trains not specified; ITI not specified; total number of pulses 1600 Stimulation location: L and R SII Number of treatments: 1 for each condition Control type: sham, "specially designed sham coil". No further details
Outcomes	Primary: pain VAS, anchors not specified When taken: after each stimulation session Secondary: none
Notes	COI: no declaration made Sources of support: National Pancreas Foundation/ NIH

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Fregni 2005 (*Continued*)

Random sequence generation (selection bias)	Low risk	Quote: "The order of stimulation was randomised and counter-balanced across patients using a Latin square design."
Adequate blinding of participants?	Unclear risk	Comment: sham credibility assessment "unclear". Type of sham coil not specified
Adequate blinding of assessors?	Low risk	Quote: "Patients were blinded to treatment condition, and a blinded rater evaluated analgesic use, patient's responses in a Visual Analogue Scale (VAS) of pain.... immediately after each session of rTMS."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: no dropout reported
Selective reporting (reporting bias)	High risk	Comment: pain NRS values not provided clearly with measures of variance for any time point for the sham condition
Free from carry-over effects?	Low risk	Quote: "Importantly, baseline pain scores were not significantly different across the six conditions of stimulation... speaking against carryover effect."
Study Size	High risk	Comment: < 50 participants per treatment arm
Study duration	High risk	Comment: < 2 weeks' follow-up
Other bias	Low risk	Comment: no significant other bias detected

Fregni 2006a

Methods	Parallel RCT
Participants	Country of study: Brazil Setting: laboratory Condition: post-SCI central neuropathic pain Prior management details: refractory to drug management n = 17 Age: mean 35.7 (SD 13.3) years Duration of symptoms: chronic > 3/12 Gender distribution: 14 M, 3 F
Interventions	Stimulation type: tDCS Stimulation parameters: intensity 2 mA, 35 cm^2 electrodes, duration 20 min Stimulation location: M1 (contralateral to most painful side or dominant hand) Number of treatments: 5, x 1 daily on consecutive days Control type: sham tDCS (switched off after 30 s stimulation)

Fregni 2006a (*Continued*)

Outcomes	Primary: pain VAS 0-10 cm, anchors "no pain" to "worst pain possible" When taken: before and after each stimulation and at 16-day follow-up Secondary: none
Notes	COI: no declaration made Sources of support: support from Harvard Medical School Scholars in Clinical Science programme

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Randomization was performed using the order of entrance in the study and a previous randomisation list generated by a computer using random blocks of six (for each six patients, two were randomised to sham and four to active tDCS) in order to minimize the risk of unbalanced group sizes."
Allocation concealment (selection bias)	Low risk	Comment: the use of a pre-generated randomisation list should ensure this
Adequate blinding of participants?	Unclear risk	Comment: there is evidence that participant blinding of tDCS may be inadequate at 2 mA intensity (see Assessment of risk of bias in included studies)
Adequate blinding of assessors?	Unclear risk	Comment: there is evidence that assessor blinding of tDCS may be inadequate at 2 mA intensity (see Assessment of risk of bias in included studies)
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "... we analyzed the primary and secondary endpoints using the intention-to-treat method including patients who received at least one dose of the randomised treatment and had at least one post-baseline efficacy evaluation. We used the last evaluation carried out to the session before the missed session, assuming no further improvement after the dropout, for this calculation."
Selective reporting (reporting bias)	Unclear risk	Comment: pain score numerical values not provided clearly in the study report with measures of variance for any time point. On request data were available for the primary outcome at one follow-up point but not for other follow-up points
Study Size	High risk	Comment: < 50 participants per treatment arm
Study duration	Unclear risk	Comment: ≥ 2 weeks but < 8 weeks' follow-up
Other bias	Low risk	Comment: no significant other bias detected

Fregni 2006b

Methods	Parallel RCT; 3 conditions
Participants	Country of study: Brazil Setting: laboratory Condition: fibromyalgia Prior management details: unclear n = 32 Age: 53.4 (SD 8.9) years Duration of symptoms: condition 1: 8.4 (SD 9.3) years; condition 2: 10.0 (SD 7.8) years; condition 3: 8.1 (SD 7.5) years Gender distribution: 32 F
Interventions	Stimulation type: tDCS Stimulation parameters: intensity 2 mA, 35 cm^2 electrodes, duration 20 min Stimulation location: condition 1: DLPFC; condition 2: M1; condition 3: sham M1. All conditions contralateral to most painful side or dominant hand Number of treatments: 5, x 1 daily on consecutive days Control type: sham tDCS (switched off after 30 s stimulation)
Outcomes	Primary: pain VAS 0-10 cm, anchors not specified When taken: at the end of the stimulation period and at 21-day follow-up Secondary: QoL: FIQ
Notes	COI: no declaration made Sources of support: support from Harvard Medical School Scholars in Clinical Science programme/ NIH

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Randomization was performed using the order of entry into the study and a previous computer-generated randomisation list, using random blocks of 6 patients (for each 6 patients, 2 were randomised to each group) in order to minimize the risk of unbalanced group sizes."
Allocation concealment (selection bias)	Low risk	Comment: the use of a pre-generated randomisation list should have adequately ensured this
Adequate blinding of participants?	Unclear risk	Comment: there is evidence that participant blinding of tDCS may be inadequate at 2 mA intensity (see Assessment of risk of bias in included studies)
Adequate blinding of assessors?	Unclear risk	Comment: there is evidence that assessor blinding of tDCS may be inadequate at 2 mA intensity (see Assessment of risk of bias in included studies)

Fregni 2006b (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "One patient (in the M1 group) withdrew, and the few missing data were considered to be missing at random. We analyzed data using the intent-to-treat method and the conservative last observation carried forward approach."
Selective reporting (reporting bias)	Unclear risk	Comment: pain score numerical values not provided clearly with measures of variance for most time points in the study report. On request data were available for the primary outcome at 1 follow-up point but not for other follow-up points
Study Size	High risk	Comment: < 50 participants per treatment arm
Study duration	Unclear risk	Comment: ≥ 2 weeks but < 8 weeks' follow-up
Other bias	Low risk	Comment: no significant other bias detected

Fregni 2011

Methods	Parallel RCT
Participants	Country of study: USA Setting: laboratory Condition: chronic visceral pain (chronic pancreatitis) Prior management details: most on continuous opioid therapy, most had received surgery for their pain n = 17, 9 in active group, 8 in sham group Age mean (SD): active group 41.11 (11.27) years, sham group 46.71 (13.03) years Duration of symptoms: > 2 years Gender distribution: 14 F, 3 M
Interventions	Stimulation type: rTMS Stimulation parameters:frequency 1 Hz; coil orientation not specified, number of trains 1; duration of trains not specified; intensity 70% maximum stimulator output, total number of pulses 1600 Stimulation location: SII Number of treatments: 10, x 1 daily (weekdays only) Control type: sham rTMS coil
Outcomes	Primary: pain VAS; 0 = no pain, 10 = most intense pain imaginable When taken: daily pain logs for 3 weeks pre-intervention, daily post-stimulation during intervention period and at 3-week follow-up Secondary: none relevant
Notes	COI: no declaration made Sources of support: support from Harvard Thorndike Clinical Research Center/ NIH

Fregni 2011 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Patients were randomised (using a computer generated list with blocks of 4)"
Allocation concealment (selection bias)	Unclear risk	Comment: allocation concealment not specified
Adequate blinding of participants?	Low risk	Quote "The sham and real TMS coils looked identical and were matched for weight and acoustic artefact. This sham coil induces a similar tapping sensation and generates the same clicking noise as the real TMS coil, but without induction of a significant magnetic field and secondary current." Comment: sham appears optimal
Adequate blinding of assessors?	Low risk	Quote: "The pain evaluation was carried out by a blinded assessor"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: dropout/withdrawal not reported
Selective reporting (reporting bias)	High risk	Comment: reporting of pain scores incomplete across all time points
Study Size	High risk	Comment: < 50 participants per treatment arm
Study duration	Unclear risk	Comment: ≥ 2 weeks but < 8 weeks' follow-up
Other bias	Unclear risk	Comment: baseline values not presented by group for key outcome variables

Gabis 2003

Methods	Parallel RCT
Participants	Country of study: USA Setting: pain clinic Condition: chronic back and neck pain Prior management details: unclear n = 20 Age: 20-77 years Duration of symptoms: 0.5-40 years Gender distribution: 9 M, 11 F
Interventions	Stimulation type: CES Stimulation parameters: frequency 77 Hz; pulse width 3.3 ms; intensity ≤ 4 mA; waveform shape biphasic asymmetric; duration 30 min

Gabis 2003 (*Continued*)

	Stimulation location: 3 electrodes, 1 attached to either mastoid process and 1 to the forehead Number of treatments: 8, x 1 daily on consecutive days Control type: "active placebo" units visually indistinguishable. Delivered 50 Hz frequency, intensity ≤ 0.75 mA. Note: may not be inert
Outcomes	Primary: pain VAS, anchors not specified When taken: pre and post each stimulation Secondary: none
Notes	COI: no declaration made Sources of support: grant by Pulse Mazor instruments, Israel

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "The paramedic administered treatments based on a computer-elicited randomisation list."
Allocation concealment (selection bias)	Low risk	Quote: "The paramedic administered treatments based on a computer-elicited randomisation list. At enrolment in the study, the investigator assigned the next random number in that patient's category. The investigator did not have access to the randomisation list until after the study was completed."
Adequate blinding of participants?	Low risk	Quote: "The active placebo device was indistinguishable to the patient and medical team from the real TCES device - it was designed to give the patient the feeling of being treated, inducing an individual sensation of skin numbness or muscle contraction"
Adequate blinding of assessors?	Low risk	Quote: "The active placebo device was indistinguishable to the patient and medical team."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: all participants completed the study
Selective reporting (reporting bias)	Low risk	Comment: while pain score numerical values were not provided clearly with measures of variance for most time points in the study report, the study authors have provided the requested data
Study Size	High risk	Comment: < 50 participants per treatment arm
Study duration	High risk	Comment: < 2 weeks' follow-up
Other bias	Unclear risk	Comment: an active placebo that delivers current may not be inert and may bias against between group differences (0.75 mA exceeds the intensity of the active arms of other CES trials)

Gabis 2009

Methods	Parallel RCT
Participants	Country of study: Israel Setting: pain clinic Condition: chronic back and neck pain Prior management details: unclear n = 75 (excluding headache participants) Age: mean 53.9 years, range 22-82 Duration of symptoms: 0.5-40 years Gender distribution: 35 M, 40 F
Interventions	Stimulation type: CES Stimulation parameters: frequency 77 Hz; pulse width 3.3 ms; intensity ≤ 4 mA; waveform shape biphasic asymmetric; duration 30 min Stimulation location: 3 electrodes, 1 attached to either mastoid process and 1 to the forehead Number of treatments: 8, x 1 daily on consecutive days Control type: "active placebo" units visually indistinguishable. Delivered 50 Hz frequency, intensity ≤ 0.75 mA. Note: may not be inert
Outcomes	Primary: pain VAS, anchors not specified When taken: pre and post each stimulation; 3 weeks and 3 months following treatment Secondary: none
Notes	AEs: not reported COI: no declaration made Sources of support: no declaration made

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "The paramedic administered treatments based on a computer-elicited randomisation list"
Allocation concealment (selection bias)	Low risk	Quote: "The paramedic administered treatments based on a computer-elicited randomisation list. At enrolment, the investigator assigned the next random number in that patient's category. The investigator did not have access to the randomisation list until study completion."
Adequate blinding of participants?	Low risk	Quote: "The placebo device was indistinguishable from the active device"
Adequate blinding of assessors?	Low risk	Quote: "The investigator did not have access to the randomisation list until study completion"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: no dropout is indicated, comparing the results with the number enrolled

Gabis 2009 (*Continued*)

Selective reporting (reporting bias)	Low risk	Comment: results for primary outcomes reported clearly and in full
Study Size	High risk	Comment: < 50 participants per treatment arm
Study duration	Low risk	Comment: > 8 weeks' follow-up
Other bias	Unclear risk	Comment: an active placebo that delivers current may not be inert and may bias against between group differences (0.75 mA exceeds the intensity of the active arms of other CES trials)

Hagenacker 2014

Methods	Cross-over RCT
Participants	Country of study: Germany Setting: laboratory Condition: trigeminal neuralgia Prior management details: stable medication for 6 months prior to study, no invasive procedures prior to study n = 17 Age range: 32-72 years Duration of symptoms: range 2-27 years, mean 13 Gender distribution: 7 M, 10 F
Interventions	Stimulation type: tDCS Stimulation parameters: intensity 1 mA, 40 cm^2 electrodes, duration 20 min Stimulation location: anode - M1 contralateral to painful side, cathode supraorbital contralateral to anode Number of treatments: daily, self-administered for 14 days Control type: sham tDCS
Outcomes	Primary: pain VAS When taken: postintervention Secondary: AEs
Notes	Study authors' COI statement: "Tim Hagenacker has received research support from Astellas and CSL Behring. Vera Bude, Steffen Naegel have nothing to disclose. Dagny Holle has received research support from Grünental and Allergan. Mark Obermann has received scientific support and/or honoraria from Biogen Idec, Novartis, Sanofi-Aventis, Genzyme, Pfizer, Teva. He received research grants from Allergan, Electrocore, and the German Ministry for Education and Research (BMBF). Hans-Christoph Diener has received honoraria for participation in clinical trials, contribution to advisory boards or lectures from Addex Pharma, Allergan, Almirall, AstraZeneca, Bayer Vital, Berlin Chemie, Coherex Medical, CoLucid, Böhringer Ingelheim, Bristol-Myers Squibb, GlaxoSmithKline, Grünenthal, Janssen-Cilag, Lilly, La Roche, 3M Medica, Minster, MSD, Novartis, Johnson & Johnson, Pierre Fabre, Pfizer, Schaper and Brümmer, SanofiAventis, and Weber & Weber; received research support from Allergan, Almirall, AstraZeneca,

Hagenacker 2014 (*Continued*)

	Bayer, Galaxo-Smith-Kline, Janssen-Cilag, and Pfizer Sources of support: "Headache research at the Department of Neurology in Essen is supported by the German Research Council (DFG), the German Ministry of Education and Research (BMBF), and the European Union."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: method of randomisation not reported
Adequate blinding of participants?	Unclear risk	Comment: method of blinding not clearly stated
Adequate blinding of assessors?	Unclear risk	Comment: method of blinding not clearly stated
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: 7/17 participants discontinued trial. Details of when not clear. Per-protocol analysis
Selective reporting (reporting bias)	Low risk	Comment: all key outcomes reported
Free from carry-over effects?	Unclear risk	No formal assessment of baseline equivalence reported
Study Size	High risk	Comment: n = 17, 10 after attrition
Study duration	High risk	Comment: only immediate postintervention follow-up
Other bias	Low risk	Comment: no other bias detected

Hargrove 2012a

Methods	Parallel RCT
Participants	Country of study: USA Setting: "professional clinical setting" Condition: fibromyalgia Prior management details: no recent remission of symptoms n = 91 Age: active group 48-54.7 years, sham group 51-57 years Duration of symptoms: active group mean 17.12 years, sham group mean 17.5 years Gender distribution: reported for completers only 71 F, 6 M
Interventions	Stimulation type: RINCE Stimulation parameters: current density 0.3 mA/cm^2, stimulation duration 11 min, frequency 10 kHz carrier signal delivered at 40 Hz Stimulation location: parietal region (international 10/20 site PZ), ground leads fixed to earlobes Number of treatments: x 2 weekly for 11 weeks

Hargrove 2012a (*Continued*)

	Control type: non-activated identical stimulation unit
Outcomes	Primary: FIQ pain VAS; 0 = no pain, 10 = unbearable pain When taken: end of treatment period Secondary: total FIQ score
Notes	Lead author declared an intellectual property interest in the technology and is a shareholder in a company seeking to develop the technology for commercialisation

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: method of randomisation not specified
Allocation concealment (selection bias)	Unclear risk	Comment: allocation concealment not reported
Adequate blinding of participants?	Low risk	Quote: "The combined involvement of low driving potentials and high carrier frequencies creates a signal that is subthreshold for perceptibility.....Subjects could not feel the signal regardless of group, and therefore could not tell if they were receiving treatment or not"
Adequate blinding of assessors?	Low risk	Quote: "The investigators were blinded to the settings, and no element of hardware or software gave any indication as to which setting had been assigned to the subject."
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: per-protocol analysis used, dropout rate 6/45 (13%) in active group and 8/46 (17%) in sham group
Selective reporting (reporting bias)	Low risk	Comment: data reported on all outcomes and supplementary data made available by the study author
Study Size	High risk	Comment: < 50 participants per treatment arm
Study duration	High risk	Comment: < 2 weeks' follow-up
Other bias	Low risk	Comment: no other biases detected

Harvey 2017

Methods	Parallel RCT
Participants	Country of study: Canada Setting: laboratory Condition: mixed chronic pain (in the over 60s) Prior management details: not reported

Harvey 2017 (*Continued*)

	n = 16 Age, mean (SD): active group 72 (6) years, sham group 71 (8) years Duration of symptoms mean (SD) years: active group 26 (24), sham group 15 (11) Gender distribution: 11 F, 3 M
Interventions	Stimulation type: tDCS Stimulation parameters: tDCS: 2 mA intensity, 20 min Stimulation location: M1 contralateral to painful side Number of treatments: x 1 daily for 5 days Control type: sham tDCS
Outcomes	Primary: pain NRS anchors 0 = no pain 10 = worst imaginable pain When taken: postintervention Secondary: none relevant AEs not reported
Notes	Funding source: G Léonard is supported by the Fonds de Recherche en Santé (FRQ-S, Montréal, QC, Canada). This project was partially supported by the Neuroscience Centre of Excellence of the Université de Sherbrooke (CeNUS, Sherbrooke, QC, Canada) and an internal start-up fund from the Research Centre on Aging (Initiatives stratégiques du Centre de recherche sur le vieillissement, Sherbrooke, QC, Canada) COI: study authors report no COI

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Randomization to sham or active tDCS was performed using a random numbers table with a ratio of 1:1, based on order of entry of the participants in the study."
Allocation concealment (selection bias)	Unclear risk	Comment: allocation concealment not reported
Adequate blinding of participants?	Unclear risk	Comment: blinding can be compromised at 2 mA intensity. No formal blinding assessment reported
Adequate blinding of assessors?	Unclear risk	Comment: blinding can be compromised at 2 mA intensity. No formal blinding assessment reported
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: 2/8 (25%) in active group withdrew. Data appear to have been excluded from analysis
Selective reporting (reporting bias)	Low risk	Comment: outcomes reported adequately
Study Size	High risk	Comment: n = 14
Study duration	High risk	Comment: 1 week postintervention follow-up

Harvey 2017 (*Continued*)

Other bias	High risk	Comment: baseline imbalance in average daily pain

Hazime 2017

Methods	Parallel RCT
Participants	Country of study: Brazil Setting: laboratory Condition: chronic low back pain Prior management details: not reported n = 92, relevant to this review 46 Age, mean (SD): active group 51.9 (9.9) years, sham group 54.1 (9.8) years Duration of symptoms mean (SD) months: active group 91.6 (108.3) sham group 69.2 (92.7) months Gender distribution: 10 M, 36 F
Interventions	Stimulation type: tDCS Stimulation parameters: tDCS: 2 mA intensity, 20 min Stimulation location: M1 contralateral to painful side Number of treatments: x 3 per week for 4 weeks. 12 sessions in total Control type: sham tDCS
Outcomes	Primary: pain NRS anchors 0 = no pain 10 = worst pain possible When taken: postintervention, 3 months, 6 months Secondary: disability (RMDQ) AEs
Notes	Funding source: none COI: study authors declared no COI

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "The patients were allocated to one of the four treatment groups by means of random-number-generating software."
Allocation concealment (selection bias)	Low risk	Quote: "The randomization and allocation concealment were carried out by an external collaborator, not a research participant, who organized patients and their previously allocated treatments in individual opaque envelopes."
Adequate blinding of participants?	Unclear risk	Comment: evidence that blinding can be inadequate at intensity of 2 mA. No formal assessment of blinding success

Hazime 2017 (*Continued*)

Adequate blinding of assessors?	Unclear risk	Comment: evidence that blinding can be inadequate at intensity of 2mA. No assessment of blinding success. No formal assessment of blinding success
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: minimal loss to follow-up
Selective reporting (reporting bias)	Low risk	Comment: outcomes reported adequately
Study Size	High risk	Comment: n = 46
Study duration	Low risk	Comment: 6-month follow-up
Other bias	Low risk	Comment: no other bias detected

Hirayama 2006

Methods	Cross-over RCT; 5 conditions
Participants	Country of study: Japan Setting: laboratory Condition: intractable deafferentation pain (mixed central, peripheral and facial) Prior management details: intractable n = 20 Age: 28-72 years Duration of symptoms: 1.5-24.3 years, mean 6.4 (SD 6) Gender distribution: 13 M, 7 F
Interventions	Stimulation type: rTMS, figure-of-8 coil Stimulation parameters: frequency 5 Hz; coil orientation not specified; 90% RMT; number of trains 10; duration of trains 10 s; ITI 50 s; total number of pulses 500 Stimulation location: condition 1: M1; condition 2: primary sensory cortex; condition 3: pre-motor area; condition 4: supplementary motor area; condition 5: sham Number of treatments: 1 for each condition Control type: coil angled 45º from scalp with synchronised electrical scalp stimulations to mask sensation
Outcomes	Primary: pain intensity VAS, anchors not specified When taken: 0, 30, 60, 90, 180 min poststimulation Secondary: none
Notes	COI: no declaration made Sources of support: no declaration made

Risk of bias

Bias	Authors' judgement	Support for judgement

Hirayama 2006 (*Continued*)

Random sequence generation (selection bias)	Low risk	Quote: "All targets were stimulated in random order" Comment: method of randomisation not specified but less critical in cross-over design
Adequate blinding of participants?	Unclear risk	Quote: "The patients were unable to distinguish sham stimulation from actual rTMS, because the synchronized electrical stimulation applied to the forehead made the forehead spasm, as was the case with actual TMS" Comment: sham credibility assessment - suboptimal. Sensory and auditory aspects controlled for but angulation of coil away from the scalp may be visually distinguishable
Adequate blinding of assessors?	Unclear risk	Comment: blinding of assessors not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "All 20 patients underwent all planned sessions of navigation- guided rTMS"
Selective reporting (reporting bias)	Low risk	Comment: pain score numerical values not provided clearly with measures of variance for any time point but data provided upon request
Free from carry-over effects?	Low risk	Comment: study authors provided requested data. Appears free of carry-over effects
Study Size	High risk	Comment: < 50 participants per treatment arm
Study duration	High risk	Comment: < 2 weeks' follow-up
Other bias	Low risk	Comment: no significant other bias detected

Hosomi 2013

Methods	Cross-over RCT
Participants	Country of study: Japan Setting: multicentre, laboratory-based Condition: mixed neuropathic pain Prior management details: pain persisted despite "adequate treatments" n = 70 of whom 64 analysed Age mean (SD): 60.7 (10.6) years Duration of symptoms: 58.2 (10.6) months Gender distribution: 40 M, 24 F
Interventions	Stimulation type: rTMS Stimulation parameters: frequency 5 Hz; coil orientation parasagittal, number of trains

	10; duration of trains 10 s; ITI 50 s, intensity 90% RMT, total number of pulses per session 500 Stimulation location: M1 corresponding to painful region Number of treatments: 10, x 1 daily (consecutive working days) Control type: sham coil
Outcomes	Current daily pain 0-100 VAS (anchors not reported), SF McGill AEs
Notes	COI: study authors declared no COI Sources of support: "funded by the Japanese Ministry of Health, Labour and Welfare with a Health and Labour Sciences Research Grant. This research was partly supported by Japanese MEXT SRPBS"

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Before the patient enrolment, the independent data center developed a randomization program to assign each patient to one of 2 treatment groups (1:1). A real rTMS period was followed by a sham period in group A, and a real rTMS period came after a sham period in group B. We used Pocock and Simon's minimization method to stratify treatment groups according to institution, age (< 60 or P60 years), sex, and underlying disease (a cerebral lesion or not), and the Mersenne twister for random number generation."
Allocation concealment (selection bias)	Low risk	Quote: "After confirmation of patient eligibility, the data center received a registration form from an assessor who collected questionnaires and assessed adverse events, and then sent an assignment notice to an investigator who conducted the rTMS intervention. Patients were identified by sequential numbers that were assigned by the data center. Patients and assessors were blind to group assignment until the study was completed. The data center was responsible for assigning patients to a treatment group, data management, central monitoring, and statistical analyses."
Adequate blinding of participants?	Low risk	Quote: "Realistic sham stimulation [32] was implemented in this study. Ten trains of electrical stimuli at 2 times the intensity of the sensory threshold (one train, 50 stimuli at 5 Hz; inter train interval, 50 s) were delivered with a conventional electrical stimulator through the electrodes fixed on the head. The cortical effect of the cutaneous electrical stimulation was considered to be negligible at this intensity because of the high electrical resistance of the skull and brief duration of the stimulation [32]. A figure-8 coil, which did not connect to a magnetic stimulator, was placed on the head in the same manner as a real rTMS session. Another coil, which discharged simultaneously with the electrical stimuli,

Hosomi 2013 (*Continued*)

		was placed near the unconnected coil to produce the same sound as real rTMS, but not to stimulate the brain." Comment: sham controls for sensory auditory and visual cues
Adequate blinding of assessors?	Low risk	Quote: "Patients and assessors were blind to group assignment until the study was completed."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: dropout low (total 6 from recruited 70 participants) Quote: "Seventy patients were enrolled and randomly assigned to 2 groups. Of these patients, one patient never came to the hospital after the registration, and a suicidal wish became apparent before the start of the intervention in another patient. Sixty-eight patients received the interventions and 64 patients were included in the intention-to-treat analysis after excluding 4 patients without any data collection."
Selective reporting (reporting bias)	Low risk	Comment: while full numerical means and SDs were not reported for all time points all data were made available upon request to the study authors
Free from carry-over effects?	Low risk	Quote: "To evaluate carry-over effects, Grizzle's test for carry-over effect was applied to the values at day 0 for each period ... Grizzle's test showed no carry-over effects in VAS and SF-MPQ"
Study Size	Unclear risk	Comment: > 50 but < 200 participants per treatment condition
Study duration	Unclear risk	Comment: ≥ 2 weeks but < 8 weeks' follow-up
Other bias	Low risk	Comment: no other bias detected

Irlbacher 2006

Methods	Cross-over RCT; 3 conditions
Participants	Country of study: Germany Setting: laboratory Condition: PLP and CNP Prior management details: unclear n = 27 Age: (median) PLP 46.6 years, CNP 51.1 years Duration of symptoms: mean PLP 15.2 (SD 14.8), CNP 3.9 (SD 4.1) years Gender distribution: 16 M, 11 F
Interventions	Stimulation type: rTMS, figure-of-8 coil Stimulation parameters: Condition 1: frequency 1 Hz; coil orientation not specified; 95% RMT; number of trains not specified; duration of trains not specified; ITI not specified; total number of pulses 500

	Condition 2: frequency 5 Hz; coil orientation not specified; 95% RMT; number of trains not specified; duration of trains not specified; ITI not specified; total number of pulses 500 Condition 3: sham frequency 2 Hz; coil orientation not specified; number of trains not specified; duration of trains not specified; ITI not specified; total number of pulses 500 Stimulation location: M1, contralateral to painful side Number of treatments: x 1 for each condition Control type: sham coil; mimics sight and sound of active treatment
Outcomes	Primary: 0-100 mm VAS pain intensity, anchors "no pain" and "most intense pain imaginable" When taken: pre- and post-stimulation Secondary: none
Notes	Sources of support: no reporting of source of support COI: study authors decare no COI

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Comment: method of randomisation not specified but less critical in cross-over design
Adequate blinding of participants?	Unclear risk	Sham credibility assessment - suboptimal. Sham coil controlled for auditory cues and was visually indistinguishable from active stimulation but did not control for sensory characteristics of active stimulation
Adequate blinding of assessors?	Unclear risk	Comment: blinding of assessors not reported
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: 13 of 27 participants did not complete all treatment conditions and this dropout is not clearly accounted for in the analysis
Selective reporting (reporting bias)	Low risk	Comment: primary outcome data presented clearly and in full
Free from carry-over effects?	Low risk	Quote: "The VAS values before the stimulation showed no significant differences in the various types of treatment"
Study Size	High risk	Comment: < 50 participants per treatment arm
Study duration	High risk	Comment: < 2 weeks' follow-up
Other bias	Low risk	Comment: no significant other bias detected

Jales Junior 2015

Methods	Parallel RCT
Participants	Country of study: Brazil Setting: laboratory Condition: fibromyalgia Prior management details: continued using pharmacological and nonpharmacological therapies n = 20 Age mean (SD): 46.4 (10.62) years Duration of symptoms: not reported Gender distribution: all F
Interventions	Stimulation type: tDCS Stimulation parameters: intensity 1 mA, 15 cm^2 electrodes, duration 20 min Stimulation location: anode - M1 L, cathode right supraorbital Number of treatments: x 1 per week for 10 weeks Control type: sham tDCS
Outcomes	Primary: pain VAS; anchors not reported When taken: postintervention Secondary: FIQ, SF-36
Notes	No reporting of sources of support or COI

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: method of randomisation not reported
Allocation concealment (selection bias)	Unclear risk	Comment: no reporting of concealment procedures
Adequate blinding of participants?	Low risk	Quote "Patients, as well as investigator in charge and evaluators, were blind to the nature of applied stimulation" Comment: blinding likely at 1 mA intensity
Adequate blinding of assessors?	Low risk	Quote "Patients, as well as investigator in charge and evaluators, were blind to the nature of applied stimulation" Comment: blinding likely at 1 mA intensity
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: attrition not reported
Selective reporting (reporting bias)	Low risk	Comment: results reported adequately
Study Size	High risk	Comment: n = 20
Study duration	High risk	Comment: postintervention follow-up only

Jales Junior 2015 (*Continued*)

Other bias	Unclear risk	Comment: no reporting of baseline comparability

Jensen 2013

Methods	Cross-over RCT
Participants	Country of study: USA Setting: laboratory Condition: post-SCI pain (neuropathic and non-neuropathic) Prior management details: not reported n = 31 randomised Age: 22-77 years Duration of symptoms (months): > 6 months Gender distribution: 22 M, 8 F
Interventions	Stimulation type: tDCS Stimulation parameters: intensity 2 mA, 35 cm^2 electrodes, duration 20 min Stimulation location: M1 contralateral to painful side or on L where pain bilateral Number of treatments: 1 Control type: sham tDCS (switched off after 30 s stimulation)
Outcomes	Primary: 0-10 NRS; 0 = no pain, 10 = most intense pain sensation imaginable. An average of current, least, worst and average pain scores When taken: poststimulation Secondary: none relevant
Notes	AEs not reported Government-funded

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote "The remaining 31 individuals were randomly assigned to receive the five procedure conditions in one of five orders, using a Latin square design."
Adequate blinding of participants?	Unclear risk	Comment: there is evidence that participant blinding of tDCS may be inadequate at 2 mA intensity (see Assessment of risk of bias in included studies)
Adequate blinding of assessors?	Unclear risk	Comment: there is evidence that assessor blinding of tDCS may be inadequate at 2 mA intensity (see Assessment of risk of bias in included studies)
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: of 31 randomised there were data from 28 following active tDCS and 27 following sham

Jensen 2013 (*Continued*)

Selective reporting (reporting bias)	Low risk	Comment: outcomes adequately reported
Free from carry-over effects?	Low risk	Comment: baseline pain levels pre active and sham tDCS session appear equivalent
Study Size	High risk	Comment: < 50 participants per treatment arm
Study duration	High risk	Comment: < 2 weeks' follow-up
Other bias	Low risk	Comment: no other bias detected

Jetté 2013

Methods	Cross-over RCT
Participants	Country of study: Canada Setting: outpatient rehabilitation centre Condition: post-SCI neuropathic pain Prior management details: almost all participants in various medications n = 18 Age: range 31-69 years, mean (SD) 50 (9) Duration of symptoms: not reported Gender distribution: 11 M, 5 F
Interventions	Stimulation type: rTMS Stimulation parameters: frequency 10 Hz; coil orientation 45º posterolateral, 90% RMT for hand, 110% RMTA for leg, number of trains 40; duration of trains 5 s; ITI 25 s; total number of pulses 2000 Stimulation location: M1 hand or leg area with neuronavigation Number of treatments: single session per condition, 1 session of sham Control type: sham coil - same sound and appearance and sensation
Outcomes	Primary: pain NRS anchors 0 = no pain, 10 = worst possible pain When taken: immediately poststimulation, 20 min poststimulation Secondary: AEs - though no formal assessment reported
Notes	Funding source: supported by the Canadian Institutes of Health Research (CIHR), Grant Number MOP-79370. C. Mercier was supported by salary awards from the CIHR and the Fonds de recherche du Québec, Santé (FRQS). F. Jetté was supported by a fellowship from Université Laval and H. B. Meziane by a fellowship from the Réseau Provincial de Recherche en Adaptation-Réadaptation (REPAR-FRQS). Support was provided by the Consortium d'Imagerie en Neuroscience et Santé Mentale de Québec (CINQ) for MRI acquisition COI: the study authors declared no potential COI
Risk of bias	

Jetté 2013 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote "2 active rTMS sessions (hand/leg M1 area) and 1 sham rTMS session in a randomized, counterbalanced order." Comment: method of randomisation not described
Adequate blinding of participants?	Low risk	Quote "Sham rTMS, using a sham coil (mimicking the noise and scalp sensations), was applied over the hand area using the same parameters
Adequate blinding of assessors?	Low risk	Quote "The researcher running the pre-post assessment (as well as data analysis) was blind relative to the applied rTMS protocol (as was the participant), with the rTMS application being performed by a different researcher
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: dropout levels low - 2 in total
Selective reporting (reporting bias)	Low risk	Comment: data provided upon author request
Free from carry-over effects?	Unclear risk	Comment: 2-week washout period observed but no analysis or data presented to confirm baseline comparability
Study Size	High risk	Comment: n = 16
Study duration	High risk	Comment: immediate poststimulation measurement only
Other bias	Low risk	Comment: no other bias detected

Kang 2009

Methods	Cross-over RCT
Participants	Country of study: South Korea Setting: university hospital outpatient setting Condition: post-SCI central neuropathic pain Prior management details: resistant to drug, physical or complementary therapies n = 11 Age: 33-75 years, mean 54.8 Duration of symptoms: chronic Gender distribution: 6 M, 5 F
Interventions	Stimulation type: rTMS Stimulation parameters: frequency 10 Hz; coil orientation angled 45º posterolaterally; 80% RMT; number of trains 20; duration of trains 5 s; ITI 55 s; total number pulses 1000 Stimulation location: R M1, hand area Number of treatments: 5, x 1 daily

Kang 2009 (*Continued*)

	Control type: coil elevated and angled away from the scalp
Outcomes	Primary: NRS average pain over last 24 h, anchors "no pain sensation" to "most intense pain sensation imaginable" When taken: immediately after the 3rd and 5th treatments and 1, 3, 5 and 7 weeks after the end of the stimulation period Secondary: BPI - pain interference (surrogate measure of disability) When taken: as for the NRS
Notes	AEs: not reported COI: studu authors declared no COI Sources of support: supported by the Seoul National University Bundang Hospital

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "The real and sham rTMS stimulations were separated by 12 weeks and performed in a random order according to the prepared allocation code." Comment: method of randomisation not specified but less critical in cross-over design
Adequate blinding of participants?	Unclear risk	Comments: sham credibility assessment - suboptimal. Coil angled away from scalp and not in contact in sham condition. Didnot control for sensory characteristics of active stimulation and was visually distinguishable
Adequate blinding of assessors?	Low risk	Quote: "... a different researcher collected the clinical data; the latter researcher was not aware of the type of rTMS (real or sham)"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: no participants withdrew after receiving the first treatment condition
Selective reporting (reporting bias)	Low risk	Comment: results for primary outcomes reported clearly and in full
Free from carry-over effects?	Low risk	Comment: a 12-week washout period was observed. The pre-stimulation baseline scores closely match
Study Size	High risk	Comment: < 50 participants per treatment arm
Study duration	Unclear risk	Comment: ≥ 2 weeks but < 8 weeks' follow-up
Other bias	Low risk	Comment: no significant other bias detected

Katsnelson 2004

Methods	Parallel RCT; 3 conditions
Participants	Country of study: Russia Setting: unclear Condition: hip and knee OA Prior management details: unclear n = 64 Age: unclear Duration of symptoms: unclear Gender distribution: unclear
Interventions	Stimulation type: CES Stimulation parameters: frequency not specified; pulse width not specified; intensity 11-15 mA; waveform shape: condition 1 symmetric, condition 2 asymmetric; duration 40 min Stimulation location: appears to be 1 electrode attached to either mastoid process and 1 to the forehead Number of treatments: 5, x 1 daily for 5 consecutive Control type: sham unit - visually indistinguishable from active units
Outcomes	Primary: 0-10 NRS, anchors "no pain" to "very painful" When taken: unclear. Likely to be pre and post each stimulation session and then daily for 1 week after Secondary: none
Notes	AEs: not reported COI: no declaration made Sources of support: no declaration made

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "If subjects passed all criteria they were randomly assigned to one of the two active treatments or the sham treatment." Comment: method of randomisation not specified
Allocation concealment (selection bias)	Unclear risk	Comment: not specified
Adequate blinding of participants?	Low risk	Quote: "The physicians, like all other participants in the study, were unaware of which treatment each subject received."
Adequate blinding of assessors?	Low risk	Quote: "The physicians, like all other participants in the study, were unaware of which treatment each subject received."

Katsnelson 2004 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: dropout level not specified
Selective reporting (reporting bias)	High risk	Comment: it is unclear in the report which time points were reported for primary outcomes
Study Size	High risk	Comment: < 50 participants per treatment arm
Study duration	High risk	Comment: < 2 weeks' follow-up
Other bias	Unclear risk	Comment: the reporting of baseline group characteristics is insufficient

Khedr 2005

Methods	Parallel RCT
Participants	Country of study: Egypt Setting: university hospital neurology department Condition: neuropathic pain, mixed central (poststroke) and facial (trigeminal neuralgia) pain Prior management details: refractory to drug management n = 48 Age: poststroke 52.3 (SD 10.3) years, trigeminal neuralgia 51.5 (SD 10.7) years Duration of symptoms: poststroke 39 months (SD 31), trigeminal neuralgia 18 months (SD 17) Gender distribution: 8 M, 16 F
Interventions	Stimulation type: rTMS Stimulation parameters: frequency 20 Hz; coil orientation not specified; 80% RMT; number of trains 10; duration of trains 10 s; ITI 50 s; total number of pulses 2000 Stimulation location: M1 contralateral to the side of worst pain Number of treatments: 5, x 1 on consecutive days Control type: coil elevated and angled away from scalp
Outcomes	Primary: pain VAS, anchors not specified When taken: post 1st, 4th and 5th stimulation session and 15 days after the last session Secondary: none
Notes	AEs: not reported COI: study authors declared no COI Sources of support: no declaration made

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Khedr 2005 (*Continued*)

Random sequence generation (selection bias)	High risk	Quote: "Patients were randomly assigned to one of the two groups, depending on the day of the week on which they were recruited." Comment: not truly random
Allocation concealment (selection bias)	High risk	Comment: the method of sequence generation makes concealment of allocation unlikely
Adequate blinding of participants?	Unclear risk	Comments: sham credibility assessment - suboptimal. Coil angled away from scalp and not in contact in sham condition. Did not control for sensory characteristics of active stimulation and was visually distinguishable
Adequate blinding of assessors?	Low risk	Quote: "The second author evaluated these measures blindly-that is, without knowing the type of rTMS"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: no dropout apparent from the data presented
Selective reporting (reporting bias)	Low risk	Comment: while pain score numerical values were not provided clearly with measures of variance for all time points in the study report, the study authors have provided the requested data
Study Size	High risk	Comment: < 50 participants per treatment arm
Study duration	Unclear risk	Comment: ≥ 2 weeks but < 8 weeks' follow-up
Other bias	Low risk	Comment: no significant other bias detected

Khedr 2017

Methods	Parallel RCT
Participants	Country of study: Egypt Setting: laboratory Condition: fibromyalgia Prior management details: not reported n = 40, 36 after attrition Age, mean (SD): active group 31.3 (10.99) years, sham group 33.89 (11.18) years Duration of symptoms, mean (SD) months, active group 6.1 (2.65), sham group 6.05 (2.5) Gender distribution: 34 F, 2 M
Interventions	Stimulation type: tDCS Stimulation parameters: tDCS: 2 mA intensity, 20 min Stimulation location: L M1 Number of treatments: x 1 daily for 5 days per week for 2 weeks - 10 sessions in total

Khedr 2017 (*Continued*)

	Control type: sham tDCS
Outcomes	Primary: pain VAS anchors not reported When taken: postintervention, 2 weeks and 1 month postintervention Secondary: none relevant AEs
Notes	Funding source: no funding reported COI: study authors declared no COI

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Each patient was given a serial number from a computer generated randomization table, and was placed in the appropriate group after opening the corresponding sealed envelope."
Allocation concealment (selection bias)	Low risk	Quote: "Allocation concealment was done using serially numbered closed, opaque envelopes."
Adequate blinding of participants?	Unclear risk	Comment: evidence that blinding can be inadequate at intensity of 2 mA. No formal assessment of blinding success
Adequate blinding of assessors?	Unclear risk	Comment: evidence that blinding can be inadequate at intensity of 2 mA. No formal assessment of blinding success
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: 10% dropout per group
Selective reporting (reporting bias)	Low risk	Comment: outcomes reported adequately
Study Size	High risk	Comment: n = 20 per group
Study duration	Unclear risk	Comment: 1 month postintervention follow-up
Other bias	Low risk	Comment: no other bias detected

Kim 2013

Methods	Parallel RCT
Participants	Country of study: South Korea Setting: laboratory Condition: chronic painful diabetic polyneuropathy Prior management details: persistent pain after taking medications. Stable doses of analgesics for 2 months prior to commencement n = 72, 60 after dropout, outcome data only given on this 60

Kim 2013 (*Continued*)

	Age, mean (SD): active M1 group 59.60 (13.15) years, active DLPFC group 63.5 (8.75) years, sham group 61.6 (10.27) years Duration of symptoms: all participants had had pain for > 2 years Gender distribution: 25 M, 35 F (after dropout)
Interventions	Stimulation type: tDCS Stimulation parameters: intensity 2 mA, 25-35 cm^2 electrodes, duration 20 min Stimulation location: group 1: anode - M1, side not specified, group 2 anode DLPFC side not specified, group 3 M1 sham, cathode contralateral supraorbital Number of treatments: daily, x 5 Control type: sham tDCS
Outcomes	Primary: pain VAS; 0 = no pain, 10 = "worst possible pain" When taken: end of intervention, 2 weeks, 4 weeks Secondary: AEs
Notes	Funding: supported by Eulji University COI: study authors declared no potential COI

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Randomization was performed using the order of entry into the study and a computer-generated randomization chart with random blocks of six patients each."
Allocation concealment (selection bias)	Unclear risk	Comment: allocation concealment procedure not described
Adequate blinding of participants?	Unclear risk	Comment: blinding can be compromised at intensities of 2 mA, no formal assessment of blinding success
Adequate blinding of assessors?	Unclear risk	Comment: blinding can be compromised at intensities of 2 mA, no formal assessment of blinding success
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: 15% dropout, even across groups, analysis appears to be per-protocol
Selective reporting (reporting bias)	High risk	Comment: point estimates and measures of variance for primary outcome only reported at selected time points
Study Size	High risk	Comment: n = 72, 3 groups
Study duration	Unclear risk	Comment: 4-week follow-up
Other bias	Low risk	Comment: no other bias detected

Lagueux 2017

Methods	Parallel RCT
Participants	Country of study: Canada Setting: laboratory Condition: CRPS type I Prior management details: not reported n = 22 Age, mean (SD): active group 40.9 (8.8) years, sham group 52.7 (10.5) years Duration of symptoms, mean (SD) months: active group 36.3 (25.6), sham group 36.6 (25.8) Gender distribution: 14 F, 8 M
Interventions	Stimulation type: tDCS (combined with graded motor imagery) Stimulation parameters: tDCS: 2 mA intensity, 20 min Stimulation location: M1 contralateral to painful side Number of treatments: x 5 weekly for 2 weeks, x 1 weekly for 4 weeks - 14 sessions in total over 6 weeks Control type: sham tDCS (combined with grade motor imagery)
Outcomes	Primary: average pain NRS anchors 0 = no pain, 10 = worst possible pain When taken: 1 month post intervention Secondary: physical function (BPI pain interference), QoL (SF36-SF) AEs
Notes	Funding source: this study was supported by grants from the Canadian Pain Society (CPS), the Quebec Pain Research Network (QPRN), as well as the Inflammation and Pain Axis and the Faculty of Medicine and Health Sciences from the Université de Sherbrooke COI: the study authors declared no COI

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: precise method for randomisation not reported
Allocation concealment (selection bias)	Low risk	Quote: "order to avoid a potential concealment bias, the randomization sequence was concealed from the investigators, where only an independent research agent held the allocation list."
Adequate blinding of participants?	Low risk	Comment: 2 mA can affect blinding negatively but formal assessment of participant blinding suggests success
Adequate blinding of assessors?	Unclear risk	Comment: evidence that assessor blinding can be inadequate at intensity of 2 mA

Lagueux 2017 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: no loss to follow-up
Selective reporting (reporting bias)	Low risk	Comment: results reported adequately
Study Size	High risk	Comment: n = 22
Study duration	Unclear risk	Comment: 1 month postinterventionfollow-up
Other bias	Low risk	Comment: no other bias detected

Lee 2012

Methods	Parallel RCT
Participants	Country of study: Korea Setting: outpatient clinic Condition: fibromyalgia Prior management details: none reported n = 22 Age mean (SD): low-frequency group 45.6 (9.6) years, high-frequency group 53 (4.2) years, sham group 51.3 (6.2) years Duration of symptoms (months mean (SD)): low-frequency group: 47.2 (20.1), high-frequency group 57.1 (6.4), sham group 44.7 (10.3) Gender distribution: all F
Interventions	Stimulation type: rTMS Stimulation parameters: Low-frequency group: frequency 1 Hz; coil orientation not specified, number of trains 2; duration of trains 800 s; ITI 60 s; total number of pulses 1600 High-frequency group: frequency 10 Hz; coil orientation not specified, number of trains 25; duration of trains 8 s; ITI 10 s; total number of pulses 2000 Stimulation location: right DLPFC (low-frequency), L M1 (high-frequency) Number of treatments: 10, x 1 daily (weekdays only) for 2 weeks Control type: sham - coil orientated away from scalp
Outcomes	Primary: 0-100 mm pain VAS; 0 = none, 100 = an extreme amount of pain When taken: post-treatment and at 1 month follow-up Secondary: FIQ
Notes	Comment: no information on AEs given relating to those participants who did not complete all sessions COI: study authors declared no COI Sources of support: no declaration made

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Lee 2012 (*Continued*)

Random sequence generation (selection bias)	Unclear risk	Comment: method of randomisation not specified
Allocation concealment (selection bias)	Unclear risk	Comment: allocation concealment not specified
Adequate blinding of participants?	Unclear risk	Comment: sham credibility assessment - suboptimal. Coil angled away from scalp. Did not control for sensory characteristics of active stimulation and was visually distinguishable
Adequate blinding of assessors?	Unclear risk	Comment: blinding of assessors not specified
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: no ITT analysis described - appears to be per protocol. 3/8 in low-frequency group, 2/5 in high-frequency group and 2/5 in sham group
Selective reporting (reporting bias)	Low risk	Comment: point measures presented in full for all outcomes
Study Size	High risk	Comment: < 50 participants per treatment arm
Study duration	Unclear risk	Comment: ≥ 2 weeks but < 8 weeks' follow-up
Other bias	Low risk	Comment: no other biases detected

Lefaucheur 2001a

Methods	Cross-over RCT
Participants	Country of study: France Setting: laboratory Condition: intractable neuropathic pain (mixed central and facial) Prior management details: refractory to drug management n = 14 Age: 34-80 years, mean 57.2 Duration of symptoms: not specified "chronic" Gender distribution: 6 M, 8 F
Interventions	Stimulation type: rTMS, figure-of-8 coil Stimulation parameters: frequency 10 Hz; coil orientation not specified; 80% RMT; number of trains 20; duration of trains 5 s; ITI 55 s; total number of pulses 1000 Stimulation location: M1, contralateral to painful side Number of treatments: x 1 for each condition Control type: sham coil used (? inert)
Outcomes	Primary: 0-10 VAS, anchors not specified When taken: daily for 12 days poststimulation Secondary: none

Lefaucheur 2001a (*Continued*)

Notes	COI: no declaration made Sources of support: grant from the 'Institut UPSA de la douleur'

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Two different sessions of rTMS separated by 3 weeks at least were randomly performed in each patient." Comment: method of randomisation not specified but less critical in cross-over design
Adequate blinding of participants?	Unclear risk	Comments: sham credibility assessment - suboptimal. This study used the same sham coil as that used in Lefaucheur 2004, which in that paper was stated as not meeting the criteria for an ideal sham
Adequate blinding of assessors?	Unclear risk	Comment: blinding of assessors not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: no dropout apparent from the data presented
Selective reporting (reporting bias)	Low risk	Comment: pain score numerical values not provided clearly with measures of variance for any time point in the report but were provided by study authors on request
Free from carry-over effects?	Low risk	Comment: 3/52 washout period makes carry-over effects unlikely
Study Size	High risk	Comment: < 50 participants per treatment arm
Study duration	High risk	Comment: < 2 weeks' follow-up
Other bias	Low risk	Comment: no significant other bias detected

Lefaucheur 2001b

Methods	Cross-over RCT
Participants	Country of study: France Setting: laboratory Condition: neuropathic pain (mixed central and peripheral) Prior management details: refractory to drug management n = 18 Age: 28-75 years, mean 54.7 Duration of symptoms: not specified "chronic" Gender distribution: 11 M, 7 F

Lefaucheur 2001b (*Continued*)

Interventions	Stimulation type: rTMS, figure-of-8 coil Stimulation parameters: Condition 1: frequency 10 Hz; coil orientation posteroanterior; 80% RMT; number of trains 20; duration of trains 5 s; ITI 55 s; total number of pulses 1000 Condition 2: frequency 0.5 Hz; coil orientation posteroanterior; number of trains 1; duration of trains 20 min; total number of pulses 600 Condition 3: sham - same as for condition 1 with sham coil Stimulation location: M1 contralateral to painful side Number of treatments: x 1 for each condition
Outcomes	Primary: 0-10 VAS pain, anchors not specified When taken: 5-10 min poststimulation Secondary: none
Notes	COI: no declaration made Sources of support: grant from the 'Institut UPSA de la douleur'

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "To study the influence of the frequency of stimulation, three different sessions of rTMS separated by three weeks at least were randomly performed in each patient" Comment: method of randomisation not specified but less critical in cross-over design
Adequate blinding of participants?	Unclear risk	Comments: sham credibility assessment - suboptimal. This study used the same sham coil as that used in Lefaucheur 2004, which in that paper was stated as not meeting the criteria for an ideal sham
Adequate blinding of assessors?	Unclear risk	Comment: blinding of assessors not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: no dropout apparent from the data presented
Selective reporting (reporting bias)	Low risk	Comment: results for primary outcomes reported clearly and in full
Free from carry-over effects?	Low risk	Comment: 3-week washout observed and no clear imbalance in pre-stimulation pain scores between conditions
Study Size	High risk	Comment: < 50 participants per treatment arm
Study duration	High risk	Comment: < 2 weeks' follow-up

Lefaucheur 2001b (*Continued*)

Other bias	Unclear risk	Comment: the results of some of the planned data analysis (ANOVA of group differences after each condition) not reported. However, adequate data were available for inclusion in the meta-analysis

Lefaucheur 2004

Methods	Cross-over RCT
Participants	Country of study: France Setting: laboratory Condition: neuropathic pain (mixed central, peripheral and facial) Prior management details: refractory to drug management n = 60 Age: 27-79 years, mean 54.6 Duration of symptoms: not specified "chronic" Gender distribution: 28 M, 32 F
Interventions	Stimulation type: rTMS, figure-of-8 coil Stimulation parameters: frequency 10 Hz; coil orientation posteroanterior; 80% RMT; number of trains 20; duration of trains 5 s; ITI 55 s; total number of pulses 1000 Stimulation location: M1 contralateral to painful side Number of treatments: x 1 for each condition Control type: sham coil
Outcomes	Primary: 0-10 VAS pain, anchors not specified When taken: 5 min poststimulation Secondary: none
Notes	COI: study authors declared no COI Sources of support: grant from the 'Institut UPSA de la douleur'

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "one of the following two protocols was applied in a random order" Comment: method of randomisation not specified but less critical in cross-over design
Adequate blinding of participants?	Unclear risk	Quote: "ideal sham...which should be performed by means of a coil similar to the real one in shape, weight, and location on the scalp, producing a similar sound and similar scalp skin sensation, but generating no electrical field within the cortex. Such a sham coil has not yet been designed, and at present, the sham coil used in this study is to our knowledge the more valid for clinical trials."

Lefaucheur 2004 (*Continued*)

		Comments: sham credibility assessment - suboptimal
Adequate blinding of assessors?	Unclear risk	Comment: blinding of assessors not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: no dropout apparent from the data presented
Selective reporting (reporting bias)	Low risk	Comment: results for primary outcomes reported clearly and in full
Free from carry-over effects?	Low risk	Comment: 3-week washout observed and no clear imbalance in pre-stimulation pain scores between conditions
Study Size	Unclear risk	Comment: > 50 but < 200 participants per treatment condition
Study duration	High risk	Comment: < 2 weeks' follow-up
Other bias	Low risk	Comment: no significant other bias detected

Lefaucheur 2006

Methods	Cross-over RCT, 3 conditions
Participants	Country of study: France Setting: laboratory Condition: unilateral chronic neuropathic pain (mixed central and peripheral) Prior management details: refractory to drug management n = 22 Age: 28-75 years, mean 56.5 (SD 2.9) Duration of symptoms: 2-18 years, mean 5.4 (SD 4.1) Gender distribution: 12 M, 10 F
Interventions	Stimulation type: rTMS, figure-of-8 coil Stimulation parameters: Condition 1: frequency 10 Hz; coil orientation posteroanterior; 90% RMT; number of trains 20; duration of trains 6 s; ITI 54 s; total number of pulses 1200 Condition 2: frequency 1 Hz; coil orientation posteroanterior; 90% RMT; number of trains 1; duration of trains 20 min; total number of pulses 1200 Condition 3: sham coil Stimulation location: M1 contralateral to painful side Number of treatments: x 1 for each condition
Outcomes	Primary: 0-10 VAS pain, anchors not specified When taken: pre- and poststimulation Secondary: none
Notes	AEs: not reported COI: no declaration made

Lefaucheur 2006 (*Continued*)

	Sources of support: grant from the 'Institut UPSA de la douleur'

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Three sessions of motor cortex rTMS, separated by at least 3 weeks, were performed in random order" Comment: method of randomisation not specified but less critical in cross-over design
Adequate blinding of participants?	Unclear risk	Comments: sham credibility assessment - suboptimal. This study used the same sham as Lefaucheur 2004, which in that paper was stated as not meeting the criteria for an ideal sham
Adequate blinding of assessors?	Unclear risk	Comment: blinding of assessors only reported for measures of cortical excitability
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: level of dropout not reported and unclear from the data presented
Selective reporting (reporting bias)	Low risk	Comment: pain score numerical values not provided clearly with measures of variance for any time point in the study report but were provided by the study authors on request
Free from carry-over effects?	Low risk	Quote: "Post hoc tests did not reveal any differences between the three pre-rTMS assessments regarding excitability values or pain levels"
Study Size	High risk	Comment: < 50 participants per treatment arm
Study duration	High risk	Comment: < 2 weeks' follow-up
Other bias	Low risk	Comment: no significant other bias detected

Lefaucheur 2008

Methods	Cross-over RCT, 3 conditions
Participants	Country of study: France Setting: laboratory Condition: neuropathic pain (mixed central, peripheral and facial) Prior management details: refractory to drug management for at least 1 year n = 46 Age: 27-79 years, mean 54.2

Lefaucheur 2008 (*Continued*)

	Duration of symptoms: chronic > 1 year Gender distribution: 23 M, 23 F
Interventions	Stimulation type: rTMS, figure-of-8 coil Stimulation parameters: Condition 1: frequency 10 Hz; coil orientation posteroanterior; 90% RMT; number of trains 20; duration of trains 6 s; ITI 54 s; total number of pulses 1200 Condition 2: frequency 1 Hz; coil orientation posteroanterior; 90% RMT; number of trains 1; duration of trains 20 min; total number of pulses 1200 Condition 3: sham coil Stimulation location: M1 contralateral to painful side Number of treatments: x 1 for each condition
Outcomes	Primary: 0-10 VAS, anchors not specified When taken: pre- and poststimulation Secondary: none
Notes	AEs: not reported COI: study authors declared no COI Sources of support: grant from the 'Institut UPSA de la douleur'

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Three different sessions of rTMS..... were performed in a random order" Comment: method of randomisation not specified but less critical in cross-over design
Adequate blinding of participants?	Unclear risk	Comments: sham credibility assessment - suboptimal. This study used the same sham coil as that used in Lefaucheur 2004, which in that paper was stated as not meeting the criteria for an ideal sham
Adequate blinding of assessors?	Low risk	Quote: "In all cases, the examiner was blinded to the type of rTMS administered."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: 2 participants dropped out but this is < 5% of the cohort. Unlikely to have strongly influenced the findings
Selective reporting (reporting bias)	Low risk	Comment: results for all outcomes reported clearly and in full
Free from carry-over effects?	Low risk	Comment: 3-week washout observed and no clear imbalance in pre-stimulation pain scores between conditions

Lefaucheur 2008 (*Continued*)

Study Size	High risk	Comment: < 50 participants per treatment arm
Study duration	High risk	Comment: < 2 weeks' follow-up
Other bias	Low risk	Comment: no significant other bias detected

Lichtbroun 2001

Methods	Parallel RCT
Participants	Country of study: USA Setting: outpatient fibromyalgia clinic Condition: fibromyalgia Prior management details: unclear n = 60 Age: 23-82 years, mean 50 Duration of symptoms: 1-40 years, mean 11 Gender distribution: 2 M, 58 F
Interventions	Stimulation type: CES Stimulation parameters: frequency 0.5 Hz; 50% duty cycle; intensity 100 μA; waveform shape biphasic square wave; duration 60 min Stimulation location: ear clip electrodes Number of treatments: 30, x 1 daily for consecutive days Control type: sham unit - indistinguishable from active unit
Outcomes	Primary: 10-point self-rating pain scale, anchors not specified When taken: poststimulation (not precisely defined) Secondary: QoL: 0-10 VAS scale (data not reported)
Notes	AEs: not reported COI: no declaration made Sources of support: no declaration made

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "the subjects were randomly assigned into three separate groups by an office secretary who drew their names, which were on separate sealed slips of paper in a container"
Allocation concealment (selection bias)	Low risk	Comment: probably, given the quote above
Adequate blinding of participants?	Low risk	Comment: see previous quote

Lichtbroun 2001 (*Continued*)

Adequate blinding of assessors?	Low risk	Quote: "All subjects, staff, the examining physician and the psychometrician remained blind to the treatment conditions"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Dropout levels not specified in the report. ITT analysis not discussed in the report
Selective reporting (reporting bias)	High risk	Comment: pain score numerical values not provided clearly with measures of variance for any time points in the study report
Study Size	High risk	Comment: < 50 participants per treatment arm
Study duration	High risk	Comment: < 2 weeks' follow-up
Other bias	Low risk	Comment: no significant other bias detected

Luedtke 2015

Methods	Parallel RCT
Participants	Country of study: Germany Setting: back pain clinic Condition: chronic nonspecific low back pain Prior management details: excluded if had spinal surgery in previous 6 months n = 135 Age range: 26-64 years, mean (SD) active group 45(9), sham group 44 (10) Duration of symptoms, mean (SD) active group 45 (9) months, sham group 44 (10) Gender distribution: 63 F, 72 M
Interventions	Stimulation type: tDCS Stimulation parameters: intensity 2 mA, 35 cm^2 electrodes, duration 20 min Stimulation location: anode L M1, cathode right supraorbital area Number of treatments: x1 dally for 5 d Control type: sham tDCS
Outcomes	Primary: pain VAS anchors not reported When taken: end of intervention, 4, 12 and 24 weeks postintervention Secondary: Oswestry Disability Index
Notes	Sources of support: "This study was funded by the Deutsche Forschungsgemeinschaft DFG (MA 1862/10-1)." Competing interests: "AM, TJ, KL, and AP had financial support from DFG (MA 1862/10-1) and NeuroImageNord for the submitted work."

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Luedtke 2015 (*Continued*)

Random sequence generation (selection bias)	Low risk	Quote: "We randomised 160 stimulation codes (80 triggering active stimulation, 80 triggering sham stimulation) by custom written software into two separate lists."
Allocation concealment (selection bias)	Low risk	Quote: "An independent researcher created the randomisation lists. To achieve allocation concealment the recruiter provided participants with the next unused stimulation code from the randomised lists. The recruiter had no access to the randomisation list."
Adequate blinding of participants?	Low risk	Quote: "Blinding of participants and the treating physiotherapist was achieved by using a sham paradigm identical to the anodal stimulation procedure…. " kappa agreement -0.120 Comment While 2 mA intensity can be inadequately blinded, assessment suggests blinding successful
Adequate blinding of assessors?	Low risk	Comment: while 2 mA intensity can be inadequately blinded, formal assessment suggests blinding successful
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: only 3 in each group discontinued in stimulation period. ITT approach
Selective reporting (reporting bias)	Low risk	Comment: reporting of all core outcomes
Study Size	Unclear risk	Comment: n = 67 and 68 per group
Study duration	Low risk	Comment: 24-week follow-up
Other bias	Low risk	Comment: no other bias detected

Malavera 2013

Methods	Parallel RCT
Participants	Country of study: Colombia Setting: rehabilitation department Condition: phantom limb pain Prior management details: no difference across groups in use of NSAIDS, physical rehabilitation or psychological therapy n = 54 Age, mean (SD): active group 33.1 (6.6) years, sham group 8.2 (6.3) years Duration of symptoms: not reported Gender distribution: 50 M, 4 F
Interventions	Stimulation type: rTMS Stimulation parameters: frequency 10 Hz; coil orientation 45° angle from midline, 90% RMT number of trains 20; duration of trains 6 s; ITI 54 s; total number of pulses 1200 Stimulation location: M1 contralateral to painful side, no neuronavigation

Malavera 2013 (*Continued*)

	Number of treatments: 10 sessions x 1 per work day for 2 weeks Control type: sham coil - same sound and appearance, no control for sensory cues
Outcomes	Primary: pain NRS anchors 0 = no pain, 10 = worst pain possible When taken: 15 d and 30 d after treatment Secondary: AEs
Notes	Funding source: study was partially supported by a grant from the Colombian Science and Technology Institute (COLCIENCIAS, project code: 6566-49-326169). Felipe Fregni is the principal investigator at Spaulding Rehabilitation Hospital of a research grant funded by NIH (5R01HD082302-02) COI: study authors declared no COI

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "a computer-generated randomization method with a permuted block size of 6 was used to allocate subjects to the sham or active rTMS interventions"
Allocation concealment (selection bias)	Low risk	Quote: "The randomization code was only given to the treating investigator on the first day of treatment session by an independent investigator not involved with any other aspect of the trial. "
Adequate blinding of participants?	Low risk	Comment: while sham coil did not control for scalp sensation blinding assessment suggested adequate blinding Quote: "Subjects and investigators did not guess correctly the treatment allocation beyond chance (P = .704; P = .571)."
Adequate blinding of assessors?	Low risk	Quote: "All evaluations were performed by an investigator blinded to treatment allocation."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: 1 participant per group dropped out at 15 days and 2 per group at 30 days. ITT analysis performed Quote "We analyzed the end point of the study using the intention-to-treat method including patients who attended at least 1 of the rTMS sessions. The missing data were considered at random, thus we used a regression imputation method to handle this issue."
Selective reporting (reporting bias)	Low risk	Comment: key outcomes presented at all follow-up points
Study Size	High risk	Comment: n = 27 per group
Study duration	Unclear risk	Comment: 15-day follow-up postintervention

Malavera 2013 (*Continued*)

Other bias	Low risk	Comment: no other bias detected

Medeiros 2016

Methods	Factorial RCT
Participants	Country of study: Brazil Setting: not specified Condition: chronic myofascial pain syndrome Prior management details: not reported n = 46, of which 23 relevant to this review Age, mean (SD): active group 45.83 (9.63) years, sham group 46.73 (13.09) years Duration of symptoms: not reported Gender distribution: all F
Interventions	Stimulation type: rTMS Stimulation parameters: frequency 10 Hz; coil orientation 45° from midline, 80% RMT, number of trains not reported; duration of trains not reported; ITI s not reported; total number of pulses 1600 Stimulation location: L M1 Number of treatments: 10 days of stimulation Control type: sham coil - no details provided
Outcomes	Primary: pain NRS anchors 0 = no pain, 10 = worst possible pain When taken: at end of intervention Secondary: none relevant
Notes	Funding source: supported by Brazilian funding agencies: National Council for Scientific and Technological Development-CNPq (Dr. I.L.S. Torres, W. Caumo, L.F. Medeiros; J. Dussan-Sarria, A. Souza, V.L. Scarabelot); Graduate Research Group (GPPG) of Hospital de Cl ´ nicas de Porto Alegre (Dr W. Caumo- Grant # 100196 and Dr. I.L.S. Torres # 100276); Coordination for the Improvement of Higher Education Personnel-CAPES (A. Deitos); International Cooperation Program-CAPES (n8023/11) COI: authors declared no COI

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote "Participants were randomized to one of the four groups, using a stratified blocked randomization scheme and appropriate statistical Random Allocation Software."
Allocation concealment (selection bias)	Low risk	Quote: "Each envelope was sealed and numbered sequentially and contained the allocated treatment. During the entire protocol timeline, two investigators who were not involved in patient evaluation were responsible for then blinding and randomization procedures"

Medeiros 2016 (*Continued*)

Adequate blinding of participants?	Unclear risk	Quote: "A sham coil was used" Comment: insufficient description to know whether it controlled for all aspects on the experience. No formal assessment of blinding provided
Adequate blinding of assessors?	Low risk	Quote: "All participants were instructed not to discuss their group assignment during the treatment sessions or with the project staff collecting outcomes data, all of them were also blind to the group assignments. Independent evaluators' blind to the group assignments were trained to apply the pain scales and cortical excitability parameter."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: low levels of dropout (2 participants in total)
Selective reporting (reporting bias)	Unclear risk	Comment: pain diary data not reported in the results with no clear explanation offered for the omission
Study Size	High risk	Comment: group sizes ranged from 11-12 participants
Study duration	High risk	Comment: only follow-up immediately postintervention
Other bias	Low risk	Comment: no other bias detected

Mendonca 2011

Methods	Parallel RCT
Participants	Country of study: Brazil/USA Setting: laboratory Condition: fibromyalgia Prior management details: not reported n = 30 (6 per group) Age, mean (SD): 43.2 (9.8) years Duration of symptoms: not reported Gender distribution: 28 F, 2 M
Interventions	Stimulation type: tDCS Stimulation parameters: simulation intensity 2 mA, 20 min duration Stimulation location: Group 1 cathodal M1; Group 2 cathodal supraorbital; Group 3 anodal M1; Group 4 anodal supraorbital; Group 5 sham Number of treatments: 1 session Control type: sham tDCS (switched off after 30 s stimulation)
Outcomes	Primary: pain VAS; 0 = no pain, 10 = worst possible pain When taken: immediately poststimulation Secondary: none relevant

Mendonca 2011 (*Continued*)

Notes	COI: study authors declared no COI Sources of support: NIH

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: method of randomisation not specified
Allocation concealment (selection bias)	Unclear risk	Comment: allocation concealment not specified
Adequate blinding of participants?	Unclear risk	Comment: 2 mA intensity used - empirical evidence that participant blinding may be suboptimal at this intensity
Adequate blinding of assessors?	Unclear risk	Comment: 2 mA intensity used - empirical evidence that assessor blinding may be suboptimal at this intensity
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: no dropouts occurred
Selective reporting (reporting bias)	High risk	No numerical data provided for any post-treatment clinical outcome. Data not provided upon request to study authors
Study Size	High risk	Comment: < 50 participants per treatment arm
Study duration	High risk	Comment: < 2 weeks' follow-up
Other bias	Low risk	No other bias detected

Mendonca 2016

Methods	Parallel RCT
Participants	Country of study: Brazil Setting: laboratory Condition: fibromyalgia Prior management details: excluded if undergoing physical treatment or were on stable pain control medication for "less than 2 months" n = 45 (of which 30 relevant to this review) Age, mean (SD): active group 44.5 (14) years, sham group 48 (11.8) years Duration of symptoms, mean (SD): active group 140.6 (72.2) months, sham group 149.3 (111.1) Gender distribution: 29 F, 1 M
Interventions	Stimulation type: tDCS Stimulation parameters: intensity 2 mA, 35 cm^2 electrodes, duration 20 min Stimulation location: anode L M1, cathode right supraorbital area

	Number of treatments: x 1 daIly for 5 days Control type: sham tDCS	
Outcomes	Primary: pain VAS, anchors 0 = no pain, 10 = worst pain imaginable When taken: postintervention, 1 month postintervention, 2 months postintervention Secondary: QoL SF-36 AEs	
Notes	Study authors declared that there were no COI	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "Randomization was performed by a blinded therapist using sealed envelopes for each individual." Comment: no description of the actual allocation sequence generation
Allocation concealment (selection bias)	Low risk	Quote: "Randomization was performed by a blinded therapist using sealed envelopes for each individual." Comment: likely to be a concealed process
Adequate blinding of participants?	Unclear risk	Quote: "Participants were blinded to the intervention groups, as were the therapists who performed the evaluation." Comment: evidence that blinding can be inadequate at intensity of 2 mA No formal assessment of blinding success
Adequate blinding of assessors?	Unclear risk	Quote: "Participants were blinded to the intervention groups, as were the therapists who performed the evaluation." Comment: Evidence that assessor blinding can be inadequate at intensity of 2 mA. No formal assessment of blinding success
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: ITT analysis using LOCF. Low for postintervention (< 10%) and high for 2/12 follow-up
Selective reporting (reporting bias)	Low risk	Comment: adequate reporting of core outcomes
Study Size	High risk	n = 45 in 3 groups of which n = 30 relevant to this review
Study duration	Low risk	2-month postintervention follow-up
Other bias	Low risk	Comment: no other bias detected

Mhalla 2011

Methods	Parallel RCT
Participants	Country of study: France Setting: laboratory Condition: fibromyalgia Prior management details: not reported but concomitant treatments allowed n = 40 Age, mean (SD): active group 51.8 (11.6) years, sham group 49.6 (10) years Duration of symptoms (mean (SD) years): active group 13 (12.9), sham group 14.1 (11.9) Gender distribution: all F
Interventions	Stimulation type: rTMS Stimulation parameters: frequency 10 Hz; coil orientation posteroanterior, number of trains 15; duration of trains 10 s; ITI 50 s, intensity 80% RMT, total number of pulses 1500 Stimulation location: L M1 Number of treatments: 14, x 1 daily for 5 days, x 1 weekly for 3 weeks, x 1 every two weeks for 6 weeks, x 1 monthly for 3 months Control type: sham coil, did not control for sensory cues
Outcomes	Primary: pain NRS; 0 = no pain, 10 = maximal pain imaginable When taken: day 5, 3 weeks, 9 weeks, 21 weeks, 25 weeks Secondary: BPI interference scale, FIQ
Notes	COI: study authors declared no COI Sources of support: Grants from the "Fondation APICIL" and the "Fondation de France

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients were randomly assigned to 2 groups...with equal numbers in each group. A study nurse prepared the concealed allocation schedule by computer randomisation of these 2 treatment groups to a consecutive number series; the nurse had no further participation in the trial. Patients were assigned in turn to the next consecutive number."
Allocation concealment (selection bias)	Low risk	Comment: see quote above
Adequate blinding of participants?	Unclear risk	Comment: sham credibility assessment - sham coil controls for sound and appearance but not the skin sensation of stimulation
Adequate blinding of assessors?	Low risk	Quote: "Both patients and investigators were blind to treatment group. Cortical excitability measurements and transcranial stimulation were performed by an independent investigator not involved in the selection or clinical assessment of the patients."

Mhalla 2011 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: 25% dropout at long-term follow-up but intention-to-treat analysis used with BOCF imputation
Selective reporting (reporting bias)	Low risk	Comment: no numeric point measures provided for the primary outcome but provided upon request to the authors
Study Size	High risk	Comment: < 50 participants per treatment arm
Study duration	Low risk	Comment: > 8 weeks' follow-up
Other bias	Low risk	Comment: no other biases detected

Mori 2010

Methods	Parallel RCT
Participants	Country of study: Italy Setting: laboratory Condition: neuropathic pain secondary to multiple sclerosis Prior management details: refractory to drug management and medication discontinued over previous month n = 19 Age: 23-69 years, mean 44.8 (SD 27.5) Duration of symptoms: 1-10 years, mean 2.79 (SD 2.64) Gender distribution: 8 M, 11 F
Interventions	Stimulation type: tDCS Stimulation parameters: intensity 2 mA, 35 cm^2 electrodes, duration 20 min Stimulation location: M1, contralateral to painful side Number of treatments: 5, x 1 daily on consecutive days Control type: sham tDCS (switched off after 30 s stimulation)
Outcomes	Primary: 0-100 mm VAS pain, anchors "no pain" to "worst possible pain" When taken: end of treatment period and x 1 weekly over 3-week follow-up Secondary: QoL, multiple sclerosis QoL-54 scale (MSQoL-54) When taken: as for primary outcome
Notes	AEs: none COI: no declaration made Sources of support: "Italian National Ministero dell'Universita' e della Ricerca, by the Italian National Ministero della Salute, by the Fondazione Italiana Sclerosi Multipla (FISM) to DC, and by the Agenzia Spaziale Italiana to GB"

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Mori 2010 (*Continued*)

Random sequence generation (selection bias)	Low risk	Quote: "Randomization was performed using the order of entrance in the study and a previous randomization list generated by a computer."
Allocation concealment (selection bias)	Low risk	Comment: likely given that the randomisation list was generated pre-study
Adequate blinding of participants?	Unclear risk	Comment: there is evidence that participant blinding of tDCS may be inadequate at 2 mA intensity (see Assessment of risk of bias in included studies)
Adequate blinding of assessors?	Unclear risk	Comment: there is evidence that assessor blinding of tDCS may be inadequate at 2 mA intensity (see Assessment of risk of bias in included studies)
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: no dropouts observed Quote: "... none of the patients enrolled discontinued the study. "
Selective reporting (reporting bias)	Low risk	Comment: between-group means not presented clearly to allow meta-analysis but data provided on request
Study Size	High risk	Comment: < 50 participants per treatment arm
Study duration	Unclear risk	Comment: ≥ 2 weeks but < 8 weeks' follow-up
Other bias	Low risk	Comment: no significant other bias detected

Nardone 2017

Methods	Parallel RCT
Participants	Country of study: Italy and Austria Setting: laboratory Condition: below level post SCI, predominantly neuropathic pain Prior management details: > 4/10 pain despite rehabilitation and pharmacological treatment. All participants previously treated with antidepressant, anticonvulsants and analgesics for a minimum period of 6 months n = 12 Age, mean (range): active group 43.7 (26-56) years, sham group 42.5 (24-62) years Duration of symptoms: not reported Gender distribution: 9 M, 3 F
Interventions	Stimulation type: rTMS Stimulation parameters: frequency 10 Hz; coil orientation AP direction, 120% RMT, number of trains 25; duration of trains 5 s; ITI 25s; total number of pulses 1250 Stimulation location: L PFC (no neuronavigation) Number of treatments: 10 sessions daily x 5 per week for 2 weeks

Nardone 2017 (*Continued*)

	Control type: sham coil - same sound and appearance, no control for sensory cues
Outcomes	Primary: pain VAS anchors not reported When taken: postintervention, 1 month postintervention Secondary: none relevant AEs
Notes	Funding source: no statement provided regarding funding COI: the study authors declared no COI

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: method of randomisation not reported
Allocation concealment (selection bias)	Unclear risk	Comment: allocation concealment not reported
Adequate blinding of participants?	Unclear risk	Quote: "Sham stimulation was carried out with a sham coil of identical size color and shape emitting a sound similar to that emitted by the active coil." Comment: Sham suboptimal - no control for cutaneous sensation associated with stimulation
Adequate blinding of assessors?	Low risk	Quote "Pain was assessed by an investigator blinded to the type of rTMS subjects were receiving."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: no loss to follow-up
Selective reporting (reporting bias)	Low risk	Comment: data reported adequately
Study Size	High risk	Comment: n = 12
Study duration	Unclear risk	Comment: 1 month postintervention follow-up
Other bias	Low risk	Comment: no other bias detected

Ngernyam 2015

Methods	Cross-over RCT
Participants	Country of study: Thailand Setting: laboratory Condition: neuropathic pain associated with SCI Prior management details: refractory to medication including antidepressants, antiepileptics and opioids

	n = 20 Age, mean (SD) 44.5 (9.16) years Duration of symptoms: 50.1 (37.05) months Gender distribution: 15 M 5 F
Interventions	Stimulation type: tDCS Stimulation parameters: intensity 2 mA, 35 cm^2 electrodes, duration 20 min Stimulation location: anode M1 contralateral to most painful side, cathode supraorbital area contralateral to anode Number of treatments: x 1 session Control type: sham tDCS
Outcomes	Primary: pain VAS, anchors 0 = no pain, 10 = the most possible pain When taken: immediately poststimulation Secondary: AEs
Notes	No author declaration of COI made Sources of support "This work was supported by an invitation research grant, Faculty of Medicine, Khon Kaen University, Thailand (Grant number I 55229), the Higher Education Research Promotion and National Research University Project of Thailand, Office of the Higher Education Commission and Faculty of Social Science, Naresuan University, Phitsanulok, Thailand."

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "participants were randomized to receive either active tDCS followed by sham tDCS, or sham tDCS stimulation followed by active tDCS in a 1:1 ratio using a computer generated list of random numbers in blocks of four randomizations."
Adequate blinding of participants?	Unclear risk	Comment: evidence that blinding can be inadequate at intensity of 2 mA. No formal assessment of blinding success
Adequate blinding of assessors?	Unclear risk	Comment: evidence that assessor blinding can be inadequate at intensity of 2 mA. No formal assessment of blinding success
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: < 10% dropout rate
Selective reporting (reporting bias)	Low risk	Comment: numeric data on pain outcomes not presented in the paper. All data provided by study authors upon request
Free from carry-over effects?	Low risk	Comment: preliminary ANOVA analyses yielded no significant main or interaction effects involving condition order
Study Size	High risk	Comment: n = 20

Ngernyam 2015 (*Continued*)

Study duration	High risk	Comment: maximum follow-up 1 week postintervention
Other bias	Low risk	Comment: no other bias detected

Nurmikko 2016

Methods	Cross-over RCT
Participants	Country of study: UK Setting: laboratory Condition: mixed refractory neuropathic pain Prior management details: no benefit from medication or other stimulation approaches n = 40 (27 after loss to follow-up) Age, range: 27-79 years Duration of symptoms: not reported Gender distribution: 23 M, 17 F
Interventions	Stimulation type: rTMS Stimulation parameters: frequency 10 Hz; coil orientation AP direction, 90% RMT, number of trains 20; duration of trains 10 s; ITI 1 min; total number of pulses 2000 Stimulation location: Site A: M1 hotspot, Site B M1 reorganised area, Site C (sham) occipital fissure Number of treatments: 3-5 sessions per week for 5 sessions Control type: sham active stimulation of occipital fissure
Outcomes	Primary: pain NRS anchors 0 = no pain 10 = worst pain imagined When taken: postintervention, 3 weeks postintervention Secondary: none relevant AEs
Notes	Funding source: research funded by the National Institute for Health Research (NIHR) under Research for Patient Benefit (RfPB) Programme (Grant Reference Number PB-PG-0110-20321) COI: Prof. Nurmikko has received travel sponsorship from Nexstim Ltd. None of the other authors report any COI

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Patients were randomly allocated to receive three cycles of rTMS in 5 sessions at sites A, B, and SHAM. Randomization order was computer generated."
Adequate blinding of participants?	Low risk	Comment: sham was active stimulation of a non target brain area- likely indistinguishable from active stimulation
Adequate blinding of assessors?	Low risk	Comment: outcomes self-reported via pain diaries

Nurmikko 2016 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: 40 randomised, 38 received rTMS, 27 included in per-protocol analysis (33% attrition). Responder analysis n = 33 (17% dropout) Reasons for dropout not reported
Selective reporting (reporting bias)	Low risk	Comment: outcomes reported adequately
Free from carry-over effects?	Low risk	Comment: 3 weeks washout period observed. Baseline pain levels for each condition appear equivalent
Study Size	High risk	Comment: n = 40, 27 after loss to follow-up
Study duration	Unclear risk	Comment: 3 week follow-up
Other bias	Low risk	Comment: no other bias detected

Oliveira 2015

Methods	Parallel RCT
Participants	Country of study: Brazil Setting: laboratory Condition: chronic temporomandibular disorder Prior management details: excluded if received any type of physiotherapy in preceding month n = 32 Age, mean (SD): active group 23.80 (7.3) years sham group 25.5 (6.3) years Duration of symptoms, months mean (SD): active group 29.8 (17.1), sham group 33.7 (22.8) Gender distribution: 3 M, 29 F
Interventions	Stimulation type: tDCS Stimulation parameters: intensity 2 mA, 35 cm^2 electrodes, duration 20 min Stimulation location: anode M1 contralateral to painful side, cathode supraorbital area, contralateral to anode Number of treatments: daily sessions for 5 consecutive days. Then twice a week for 3 weeks, up to 10 sessions Control type: sham tDCS
Outcomes	Primary: pain VAS, anchors not reported When taken: 5 months postintervention, no data reported from formal study period Secondary: QoL WHO-QoL, AEs
Notes	Sources of support: study was carried out without funding COI: study authors decare no COI
Risk of bias	

Oliveira 2015 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "After the first comprehensive evaluation, the secretary of the clinical facility, who was not involved with any other procedures of the study, randomised participants who fulfilled the inclusion criteria for treatment and accepted to participate in the study. Randomisation occurred by the simple random method, in which each subject was invited to remove a small sealed envelope from a larger opaque envelope indicating two treatment groups."
Allocation concealment (selection bias)	Low risk	Quote: "After the first comprehensive evaluation, the secretary of the clinical facility, who was not involved with any other procedures of the study, randomised participants who fulfilled the inclusion criteria for treatment and accepted to participate in the study."
Adequate blinding of participants?	Unclear risk	Comment: evidence that blinding can be inadequate at intensity of 2 mA. 15 guessed stimulation condition correctly in active group vs 7 in sham group
Adequate blinding of assessors?	Unclear risk	Comment: evidence that assessor blinding can be inadequate at intensity of 2 mA. No formal assessment of blinding success
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: no attrition noted for core follow-up points
Selective reporting (reporting bias)	Low risk	Comment: no numeric reporting of point estimates for most outcomes but data provided upon request
Study Size	High risk	Comment: n = 32
Study duration	Unclear risk	Comment: formal follow-up for 3 weeks postintervention
Other bias	Low risk	Commet: no other bias detected

Onesti 2013

Methods	Cross-over RCT
Participants	Country of study: Italy Setting: laboratory n = 25 Condition: neuropathic pain from diabetic neuropathy Prior management details: resistant to standard therapies for at least 1 year Age mean (SD): 70.6 (8.5) years Duration of symptoms (months mean (SD)): not reported Gender distribution: 9 F, 14 M

Onesti 2013 (*Continued*)

Interventions	Stimulation type: rTMS using H-coil Stimulation parameters: frequency 20 Hz; coil orientation H coil, number of trains 30; duration of trains 2.5 s; ITI 30 s, intensity 100% RMT, total number of pulses 1500 Stimulation location: M1 lower limb (deep in central sulcus) Number of treatments: 5 per condition on consecutive days Control type: sham coil, controlled for scalp sensory, auditory and visual cues
Outcomes	Primary: pain VAS 0-100, no pain to worst possible pain When taken: immediately poststimulation, 3 weeks poststimulation Secondary: none relevant
Notes	COI: 2 authors have links to the manufacturer of the H-coil Sources of support: no declaration made

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "After enrolment, patients were randomly assigned in a 1:1 ratio to two counterbalanced arms by receiving a sequential number from a computer-generated random list."
Adequate blinding of participants?	Low risk	Quote: "Sham stimulation was delivered with a sham coil placed in the helmet encasing the active rTMS coil. The sham coil produced a similar acoustic artefact and scalp sensation as the active coil and could also mimic the facial muscle activation induced by the active coil. It induced only a negligible electric field inside the brain because its non-tangential orientation on the scalp and components cancelling the electric field ensured that it rapidly reduced the field as a function of distance" Comment: controlled for visual auditory and sensory aspects of stimulation
Adequate blinding of assessors?	Unclear risk	Comment: while study described as "double blind" there was no specific mention of blinding assessors
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: only 2 participants lost to follow-up
Selective reporting (reporting bias)	High risk	Comment: data not presented by stimulation condition - rather they were grouped by the order in which interventions were delivered. No SDs presented. Data requested
Free from carry-over effects?	Low risk	Comment: 5-week washout period observed with no difference at T3
Study Size	High risk	Comment: < 50 participants per treatment arm

Onesti 2013 (*Continued*)

Study duration	Unclear risk	Comment: ≥ 2 weeks but < 8 weeks' follow-up
Other bias	Low risk	Comment: no other bias detected

Palm 2016

Methods	Cross-over RCT
Participants	Country of study: France Setting: laboratory Condition: MS-related neuropathic pain Prior management details: stable pharmacological and physical therapies for at least 1 month n = 16 Age, mean (SD) 47.4 (8.9) years Duration of symptoms: not reported for pain Gender distribution: 13 F, 3 M
Interventions	Stimulation type: tRNS Stimulation parameters: Intensity 1 mA, 25 cm^2 electrodes, duration 20 min, VARIANCE 650/2 μA Stimulation location: M1 contralateral to most painful side Number of treatments: x 1 daily for 3 days Control type: sham tRNS
Outcomes	Primary: pain VAS, anchors not reported When taken: average for 7 days postintervention Secondary: BPI interference, AEs
Notes	COI: "FP has received grants from neuroConn GmbH, Ilmenau, Germany. The other authors declare no conflict" Sources of support: not reported

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: method of randomisation not reported
Adequate blinding of participants?	Low risk	Quote: "Neither the patients nor the evaluators were aware about the nature of the stimulation block." Comment: assessment of participant blinding integrity suggests success
Adequate blinding of assessors?	Low risk	Quote: "Neither the patients nor the evaluators were aware about the nature of the stimulation block."

Palm 2016 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: 2 participants (13%) withdrew and data were excluded
Selective reporting (reporting bias)	Low risk	Comment: outcomes adequately reported
Free from carry-over effects?	Unclear risk	Comment: 3-week washout period observed but no formal assessment of carry-over effects
Study Size	High risk	Comment: n = 16
Study duration	High risk	Comment: postintervention follow-up only
Other bias	Low risk	Comment: no other bias detected

Passard 2007

Methods	Parallel RCT
Participants	Country of study: France Setting: laboratory Condition: fibromyalgia Prior management details: unclear n = 30 Age: active group: 52.6 (SD 7.8) years, sham group 55.3 (SD 8.9) years Duration of symptoms: active group: 8.1 (SD 7.9), sham group: 10.8 (SD 8.6) Gender distribution: 1 M, 29 F
Interventions	Stimulation type: rTMS, figure-of-8 coil Stimulation parameters: frequency 10 Hz; coil orientation posteroanterior; 80% RMT; number of trains 25; duration of trains 8 s; ITI 52 s; total number of pulses 2000 Stimulation location: M1 contralateral to painful side Number of treatments: 10, x 1 daily for 10 working days Control type: sham rTMS coil. Mimics sight and sound of active treatment
Outcomes	Primary: 0-10 NRS of average pain intensity over last 24 h, anchors "no pain" to "maximal pain imaginable" When taken: daily during treatment period and at 15, 30 and 60 days post-treatment follow-up Secondary: FIQ When taken: as for primary outcome
Notes	COI: no declaration made Sources of support: no declaration made

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Passard 2007 (*Continued*)

Random sequence generation (selection bias)	Low risk	Quote: "patients who met all inclusion criteria were randomly assigned, according to a computer-generated list, to two groups"
Allocation concealment (selection bias)	Unclear risk	Comment: allocation concealment not specified
Adequate blinding of participants?	Unclear risk	Quote: "Sham stimulation was carried out with the 'Magstim placebo coil system', which physically resembles the active coil and makes similar sounds." Comment: sham credibility assessment - suboptimal. Sham coil controlled for auditory cues and was visually indistinguishable from active stimulation but did not control for sensory characteristics of active stimulation over the scalp
Adequate blinding of assessors?	Low risk	Quote: "... investigators were blind to treatment group."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: equal dropout in each group and appropriately managed in the data analysis Quote: "All randomized patients with a baseline and at least one post-baseline visit with efficacy data were included in the efficacy analyses (intent to treat analysis)." "All the patients received the full course of treatment and were assessed on D15 and D30. Four patients (two in each treatment group) withdrew from the trial between days 30 and 60."
Selective reporting (reporting bias)	Low risk	Comment: while pain score numerical values not provided clearly with measures of variance for all time points in the study report, the study authors provided the requested data
Study Size	High risk	Comment: < 50 participants per treatment arm
Study duration	Low risk	Comment: ≥ 8 weeks' follow-up
Other bias	Low risk	Comment: no significant other bias detected

Picarelli 2010

Methods	Parallel RCT
Participants	Country of study: Brazil Setting: laboratory Condition: CRPS type I Prior management details: refractory to best medical treatment n = 23 Age mean (SD): active group 43.5 (12.1) years, sham group 40.6 (9.9) years Duration of symptoms (months mean (SD)): active group 82.33 (34.5), sham group 79.27 (32.1) Gender distribution: 14 F, 9 M

Picarelli 2010 (*Continued*)

Interventions	Stimulation type: rTMS Stimulation parameters: frequency 10 Hz; coil orientation posteroanterior, number of trains 25; duration of trains 10 s; ITI 60 s, intensity 100% RMT, total number of pulses 2500 Stimulation location: M1 contralateral to painful limb Number of treatments: 10, x 1 daily on consecutive weekdays Control type: sham coil - did not control for sensory cues
Outcomes	Primary: pain VAS; 0 = "no pain", 10 = "most severe pain" When taken: after first and last session then 1 and 3 months post-treatment Secondary: QoL SF-36, not reported
Notes	COI: study authors declared no COI Sources of support: University of Sao Paolo, Brazil

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: while stated "randomized" the method of randomisation not reported
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not reported
Adequate blinding of participants?	Unclear risk	Comment: sham suboptimal as it did not control for scalp sensation. Study reported that number who guessed the condition correctly was similar but no formal data or analysis reported
Adequate blinding of assessors?	Unclear risk	Comment: study described as "double-blinded" but assessor blinding not specifically reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: only 1 participant dropped out at follow-up
Selective reporting (reporting bias)	Low risk	Comment: data presented for primary outcome. While this was not adequate for meta-analysis it did not really constitute selectivity. No response received to request for full data access
Study Size	High risk	Comment: < 50 participants per treatment arm
Study duration	Low risk	Comment: ≥ 8 weeks' follow-up
Other bias	Low risk	Comment: no other biases detected

Pleger 2004

Methods	Cross-over RCT
Participants	Country of study: Germany Setting: laboratory Condition: CRPS type I Prior management details: drug management ceased for 48 h prior to study n = 10 Age: 29-72 years, mean 51 Duration of symptoms: 24-72 months, mean 35 Gender distribution: 3 M, 7 F
Interventions	Stimulation type: rTMS Stimulation parameters: frequency 10 Hz; coil orientation unspecified; 110% RMT; number of trains 10; duration of trains 1.2 s; ITI 10 s; total number of pulses 120 Stimulation location: M1 hand area Number of treatments: 1 for each condition Control type: coil angled 45º away from scalp
Outcomes	Primary: 0-10 VAS current pain intensity, anchors "no pain" to "most extreme pain" When taken: 30 s, 15, 45 and 90 min poststimulation Secondary: none When taken: 30 s, 15, 45 and 90 min poststimulation
Notes	AEs: not reported COI: no declaration made Sources of support: "grant from the BMBF (NR. 01EM0102) and by a grant of the Scientific Research Council of BG-Kliniken Bergmannsheil, Bochum."

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Using a computerized random generator, five patients were first assigned to the placebo group (sham rTMS), while the others were treated using verum rTMS"
Adequate blinding of participants?	Unclear risk	Comments: sham credibility assessment - suboptimal. Coil angled 45º away from scalp. Did not control for sensory characteristics of active stimulation and was visually distinguishable
Adequate blinding of assessors?	Unclear risk	Comment: blinding of assessors not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: no dropout apparent from the data presented
Selective reporting (reporting bias)	Low risk	Comment: while sham group results not presented in the study report, the study authors provided the requested data

Pleger 2004 (*Continued*)

Free from carry-over effects?	Low risk	Quote: "The initial pain intensities (VAS) were similar prior to verum and sham rTMS (Student's paired t-test, P = 0.47). The level of intensity was also independent of whether the patients were first subjected to sham or verum rTMS (P > 0.05)."
Study Size	High risk	Comment: < 50 participants per treatment arm
Study duration	High risk	Comment: < 2 weeks' follow-up
Other bias	Low risk	Comment: no significant other bias detected

Portilla 2013

Methods	Cross-over RCT
Participants	Country of study: USA Setting: laboratory Condition: postburn neuropathic pain Prior management details: varied n = 3 Age range: 34-52 years Duration of symptoms: > 6 months Gender distribution: 2 F, 1 M
Interventions	Stimulation type: tDCS Stimulation parameters: intensity 2 mA, duration 20 min Stimulation location: M1 contralateral to most painful side Number of treatments: 1 per condition Control type: sham tDCS (switched off after 30 s stimulation)
Outcomes	Primary: pain VAS; 0 = "no pain", 10 = "worst pain ever felt" When taken: before and after stimulation Secondary: none relevant
Notes	COI: study authors declared no COI Sources of support: departmentally funded

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "subjects were randomized to either active tDCS or sham stimulation." Comment: method of randomisation not specified but less critical in cross-over design

Portilla 2013 (*Continued*)

Adequate blinding of participants?	Unclear risk	Comment: there is evidence that participant blinding of tDCS may be inadequate at 2 mA intensity (see Assessment of risk of bias in included studies)
Adequate blinding of assessors?	Unclear risk	Comment: there is evidence that participant blinding of tDCS may be inadequate at 2 mA intensity (see Assessment of risk of bias in included studies)
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: all 3 participants completed study
Selective reporting (reporting bias)	High risk	Comment: no numeric data provided for pain outcomes
Free from carry-over effects?	Unclear risk	Comment: 1-week washout observed but no data reported for pain outcome so unable to assess this issue
Study Size	High risk	Comment: < 50 participants per treatment arm
Study duration	High risk	Comment: < 2 weeks' follow-up
Other bias	Low risk	Comment: no other bias detected

Riberto 2011

Methods	Parallel RCT
Participants	Country of study: Brazil Setting: rehabilitation clinic Condition: fibromyalgia Prior management details: none reported n = 23 Age mean (SD): active group 58.3 (12.1) years, sham group 52.4 (11.5) years Duration of symptoms, months (mean (SD)): active group 9.9 (11.8), sham group 6.4 (10.3) Gender distribution: all F
Interventions	Stimulation type: tDCS Stimulation parameters: intensity 2 mA, duration 20 min Stimulation location: M1 (contralateral to most painful side or dominant hand) Number of treatments: 10, x 1 weekly for 10 weeks Control type: sham tDCS (switched off after 30 s stimulation) Both groups received 4 months rehabilitation programme
Outcomes	Primary: pain VAS; 0 = "no pain", 10 = "worst pain" When taken: immediately at end of 4-month rehabilitation programme Secondary: QoL SF36, FIQ

Riberto 2011 (*Continued*)

Notes	AEs: not reported COI: study authors declared no COI Sources of support: no declaration made

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: stated simple randomisation method but method not described
Allocation concealment (selection bias)	Unclear risk	Comment: allocation concealment not reported
Adequate blinding of participants?	Unclear risk	Comment: 2 mA used, which may threaten assessor blinding, though formal analysis of blinding appears acceptable
Adequate blinding of assessors?	Unclear risk	Comment: 2 mA intensity used - empirical evidence that assessor blinding may be suboptimal at this intensity
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: no dropouts
Selective reporting (reporting bias)	Low risk	Comment: while numeric data on the primary outcome not reported in study report the authors made it available upon request
Study Size	High risk	Comment: < 50 participants per treatment arm
Study duration	High risk	Comment: < 2 weeks' follow-up
Other bias	Unclear risk	Comment: there were group imbalances at baseline on the duration of pain, education, age and economic activity

Rintala 2010

Methods	Parallel RCT
Participants	Country of study: USA Setting: outpatient clinic, participants took device home Condition: pain related to Parkinson's disease Prior management details: not reported n = 19 (reduced to 13 through dropout) Age mean (SD): active group 74.7 (7.8) years, sham group 74.4 (8.3) years Duration of symptoms: > 6 months Gender distribution: 15 M, 4 F

Interventions	Stimulation type: CES Stimulation parameters: frequency not specified; pulse width not specified; intensity 100 μA; waveform shape not specified; duration 40 min per session Stimulation location: earlobe clips Number of treatments: 42, x 1 daily for 42 days Control type: sham CES unit indistinguishable from active unit
Outcomes	Primary: pain VAS 0 -10, anchors not reported When taken: at the end of the treatment period Secondary: none
Notes	Sources of support: equipment provided by CES manufacturer as an "unrestricted gift" COI: no declaration made

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: stated randomised but method of randomisation not reported
Allocation concealment (selection bias)	Unclear risk	Comment: allocation concealment not reported
Adequate blinding of participants?	Low risk	Comment: see above comment
Adequate blinding of assessors?	Low risk	Comment: participants and the study co-ordinator were blinded to group assignment and the code sheet indicating which devices were active and which were sham was kept by another person who was not in contact with the participants
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: > 30% dropout
Selective reporting (reporting bias)	Low risk	Comment: mean (SD) pain scores reported for both groups pre- and poststimulation
Study Size	High risk	Comment: < 50 participants per treatment arm
Study duration	High risk	Comment: < 2 weeks' follow-up
Other bias	Low risk	Comment: no other bias detected

Rollnik 2002

Methods	Cross-over RCT
Participants	Country of study: Germany Setting: pain clinic Condition: chronic pain (mixed musculoskeletal and neuropathic) Prior management details: "intractable" n = 12 Age: 33-67 years, mean 51.3 (SD 12.6) Duration of symptoms: mean 2.7 (SD 2.4) Gender distribution: 6 M, 6 F
Interventions	Stimulation type: rTMS, circular coil for arm symptoms, double cone coil for leg symptoms Stimulation parameters: frequency 20 Hz; coil orientation not specified; 80% RMT; number of trains 20; duration of trains 2 s; ITI not specified; total number of pulses 800; treatment duration 20 min Stimulation location: M1 (midline) Number of treatments: x 1 for each condition Control type: coil angled 45º away from the scalp
Outcomes	Primary: 0-100 mm VAS pain intensity, anchors "no pain" to "unbearable pain" When taken: 0, 5, 10 and 20 min post-stimulation Secondary: none
Notes	Sources of support: supported by Deutsche Forschungsgemeinschaft COI: no declaration made

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "sham and active stimulation were given in a random order" Comment: method of randomisation not specified but less critical in cross-over design
Adequate blinding of participants?	Unclear risk	Comments: sham credibility assessment - suboptimal. Coil angled 45º away from scalp. Did not control for sensory characteristics of active stimulation over the scalp and was visually distinguishable. Given that stimulation was delivered at 110% RMT active stimulation, but not sham, likely to have elicited muscle twitches in peripheral muscles
Adequate blinding of assessors?	Unclear risk	Comment: blinding of assessors not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: only 1 participant withdrew due to "headaches". Unlikely to have strongly influenced the findings

Rollnik 2002 (*Continued*)

Selective reporting (reporting bias)	Low risk	Comment: while pain score numerical values not provided clearly with measures of variance for all time points in the study report, the study authors provided the requested data
Free from carry-over effects?	Low risk	Comment: not clearly demonstrated in the study report but clear from unpublished data provided by the study authors (baseline mean group pain scores: active stimulation 65.1 (SD 16), sham stimulation 66.9 (SD 17.4))
Study Size	High risk	Comment: < 50 participants per treatment arm
Study duration	High risk	Comment: < 2 weeks' follow-up
Other bias	Low risk	Comment: no significant other bias detected

Saitoh 2007

Methods	Cross-over RCT, 4 conditions
Participants	Country of study: Japan Setting: laboratory Condition: neuropathic pain (mixed central and peripheral) Prior management details: intractable n = 13 Age: 29-76 years, mean 59.4 Duration of symptoms: 2-35 years, mean 10.2 (SD 9.7) Gender distribution: 7 M, 6 F
Interventions	Stimulation type: rTMS figure-of-8 coil Stimulation parameters: Condition 1: frequency 10 Hz; coil orientation not specified; 90% RMT; number of trains 5; duration of trains 10 s; ITI 50 s; total number of pulses 500 Condition 2: frequency 5 Hz; coil orientation not specified; 90% RMT; number of trains 10; duration of trains 10 s; ITI 50 s; total number of pulses 500 Condition 3: frequency 1 Hz; coil orientation not specified; 90% RMT; number of trains 1; duration of trains 500 s; total number of pulses 500 Condition 4: sham, coil angled 45º from scalp with synchronised electrical scalp stimulations to mask sensation Stimulation location: M1 over the representation of the painful area Number of treatments: 1 for each condition
Outcomes	Primary: VAS pain, anchors not specified When taken: 0, 15, 30, 60, 90 and 180 minutes poststimulation Secondary: none
Notes	Sources of support: no declaration made COI: no declaration made

Saitoh 2007 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "rTMS was applied to all the patients at frequencies of 1, 5, and 10 Hz and as a sham procedure in random order" Comment: method of randomisation not specified but less critical in cross-over design
Adequate blinding of participants?	Unclear risk	Comment: sham credibility assessment - suboptimal. Sensory and auditory aspects controlled for but angulation of coil away from the scalp may be visually distinguishable
Adequate blinding of assessors?	Unclear risk	Comment: blinding of assessors not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "All 13 patients participated in all planned sessions of navigation-guided rTMS" Comment: no dropouts observed
Selective reporting (reporting bias)	Low risk	Comment: while pain score numerical values not provided clearly with measures of variance for all time points in the study report, the study authors provided the requested data
Free from carry-over effects?	Low risk	Comment: not clearly demonstrated in the study report but paired t-tests on unpublished baseline data provided by the study authors suggest that carry-over was not a significant issue
Study Size	High risk	Comment: < 50 participants per treatment arm
Study duration	High risk	Comment: < 2 weeks' follow-up
Other bias	Low risk	Comment: no significant other bias detected

Sakrajai 2014

Methods	Parallel RCT
Participants	Country of study: Thailand Setting: laboratory Condition: myofascial pain syndrome (affecting shoulder) Prior management details: stable analgesic use for 3 months preceding study n = 31 Age mean (SD): active group 49.94 (8.25) years, sham group 45.93 (10.24) years

	Duration of symptoms, mean(SD) active group 5.91 (2.55) months, sham group 45.93 (10.24) Gender distribution: 22 F, 9 M
Interventions	Stimulation type: tDCS Stimulation parameters: intensity 1 mA, 35 cm^2 electrodes, duration 20 min Stimulation location: anode M1 contralateral to most painful side, cathode supraorbital area contralateral to anode Number of treatments: x 1 daily for 5 days Control type: sham tDCS
Outcomes	Primary: pain VAS, anchors 0 = no pain, 10 = the most possible pain When taken: post-treatment, average of daily score in week 1 postintervention, week 2, 3, 4 postintervention. Only responder analysis presented Secondary: QoL WHO-QoL, data not reported AEs
Notes	COI: "M.P.J. is a consultant to Noninvasive Brain Stimulation Research Group of Thailand. The remaining authors declare no conflict of interest." Sources of support: "Supported in part by Grant Number R21 HD058049 from the National Institutes of Health, National Institute of Child Health and Human Development, Rockville, MD; and National Center for Medical Rehabilitation Research, Rockville, MD."

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: method of sequence generation not described
Allocation concealment (selection bias)	Unclear risk	Comment: allocation concealment procedures not described
Adequate blinding of participants?	Low risk	Comment: "The tDCS device was designed to allow for masked (sham) stimulation. Specifically, the control switch was in front of the instrument, which was covered by an opaque adhesive during stimulation. The power indicator was on the front of the machine, which lit up during the time of stimulation both in active and sham stimulations."
Adequate blinding of assessors?	Unclear risk	Comment: blinding of assessors not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: only 1 dropout
Selective reporting (reporting bias)	Low risk	Comment: no numeric reporting of pain score or QoL point estimates in the paper. All data provided by study authors upon request

Sakrajai 2014 (*Continued*)

Study Size	High risk	Comment: n = 31
Study duration	Unclear risk	Comment: 4-week follow-up postintervention
Other bias	Low risk	Comment: no other bias detected

Short 2011

Methods	Parallel RCT
Participants	Country of study: USA Setting: laboratory Condition: fibromyalgia Prior management details: naive to TMS n = 20 Age mean (SD): active group 54.2 (8.28) years, sham group 51.67 (18.19) years Duration of symptoms, years mean (SD): active group 12.1 (7.75), sham group 10.10 (12.81) Gender distribution: 84% F
Interventions	Stimulation type: rTMS Stimulation parameters: frequency 10 Hz; coil orientation parasagittal, number of trains 80; duration of trains 5 s; ITI 10 s, intensity 120% RMT, total number of pulses per session 4000 Stimulation location: L DLPFC Number of treatments: 10, x 1 daily (working days) for 2 weeks Control type: sham coil
Outcomes	Primary: pain VAS; 0 = "no pain", 10 = "worst pain" When taken: after 1 and 2 weeks of treatment, then 1 week and 2 weeks posttreatment Secondary: FIQ, BPI function scale
Notes	AEs: no data provided COI: 1 researcher received research grants from the device manufacturer and holds patents for TMS technology Sources of support: Multidisciplinary Clinical, Research Center Grant P60 AR049459 The Office of the Provost and Vice President for Research

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Patients were randomly assigned (random generator software developed by JJB in the Brain Stimulation Laboratory) "
Allocation concealment (selection bias)	Low risk	Quote: "A co investigator not directly involved in ratings or treatment released treatment condition to the TMS operator"

Short 2011 (*Continued*)

Adequate blinding of participants?	Low risk	Quote: "A specially designed sham TMS coil is used for all sham conditions that produces auditory signals identical to active coils but shielded so that actual stimulation does not occur. However, subjects do experience sensory stimulation that is difficult to distinguish from real rTMS" Comment: sensory, auditory and visual cues controlled for
Adequate blinding of assessors?	Low risk	Quote: "A masked continuous rater assessed patients at baseline, at the end of each treatment week, and at the 2 follow-up weeks. Importantly the continuous rater did not administer the TMS, minimizing the chances of unmasking due to events during the TMS treatment session."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: no loss to follow-up
Selective reporting (reporting bias)	Low risk	Comment: full reporting of primary outcomes
Study Size	High risk	Comment: < 50 participants per treatment arm
Study duration	High risk	Comment: < 2 weeks' follow-up
Other bias	Low risk	Comment: no other biases detected

Soler 2010

Methods	Parallel RCT
Participants	Country of study: Spain Setting: laboratory Condition: post-SCI neuropathic pain Prior management details: stable pharmacological treatment for at least 2 weeks prior to start of treatment. Unresponsive to medication n = 39 Age mean (SD): 45 (15.5) years Duration of symptoms: not reported Gender distribution: 30 M, 9 F
Interventions	Stimulation type: tDCS Stimulation parameters: intensity 2 mA, duration 20 min Stimulation location: M1 (contralateral to most painful side or dominant hand) Number of treatments: 10, x 1 daily (working days) for 2 weeks Control type: 4 groups, tDCS + visual illusion, sham tDCS + visual illusion, tDCS + control illusion, sham tDCS + control illusion
Outcomes	Primary: pain VAS; 0 = no pain, 10 = unbearable pain; mean over previous 24 h When taken: end of treatment period, 12 and 24 d post-treatment Secondary: BPI pain interference scale

Soler 2010 (*Continued*)

Notes	COI: no declaration made Sources of support: "grants from a BBVA Translational Research Chair in Biomedicine, the International Brain Research Foundation (IBRF) and National Institutes of Health grant K 24 RR018875 to A.P.L., the Foundation La Marato´ TV3 (071931) and grant PI082004 and TERCEL funds from the Instituto de Salud Carlos III"

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "We used a computer generated list as randomisation strategy."
Allocation concealment (selection bias)	Unclear risk	Comment: allocation concealment not reported
Adequate blinding of participants?	Unclear risk	Comment: 2 mA may threaten blinding but assessment of blinding seemed OK
Adequate blinding of assessors?	Unclear risk	Comment: 2 mA intensity used - empirical evidence that assessor blinding may be suboptimal at this intensity
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: only 3 dropouts, 1 in each group
Selective reporting (reporting bias)	Low risk	Comment: all main outcomes reported
Study Size	High risk	Comment: < 50 participants per treatment arm
Study duration	Unclear risk	Comment: ≥ 2 weeks but < 8 weeks' follow-up
Other bias	Low risk	Comment: no other biases detected

Souto 2014

Methods	Parallel RCT
Participants	Country of study: Brazil Setting: reference centre for integrated and multidisciplinary treatment for human T-lymphotropic virus 1 (HTLV-1) and viral hepatitis Condition: JTLVI-infected patients with chronic low back or lower limb pain Prior management details: stable pharmacotherapy in the preceding month n = 20 Age, mean (SD): active group 48.8 (11.6) years, sham group 56.2 (14) years Duration of symptoms: not reported Gender distribution: 15 F, 5 M

Interventions	Stimulation type: tDCS Stimulation parameters: intensity 2 mA, 25 cm^2 electrodes, duration 20 min Stimulation location: anode L M1, cathode right supraorbital area Number of treatments: x 1 dAlly for 5 days Control type: sham tDCS
Outcomes	Primary: pain VAS; 0 = no pain, 10 = worst possible pain When taken: postintervention, responder analysis 30%, 50% pain relief Secondary: AEs
Notes	COI: the study authors declared no COI Sources of support: "G.S.G. was funded by FAPESB, Salvador, BA/Brazil (Fundação de Amparo à Pesquisa do Estado da Bahia) and M.E.M by CAPES, Brasília, DF/Brazil (Coordenação de Aperfeiçoamento Pessoal de Nível Superior)"

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Participants were randomized using a stratified randomization strategy with pain as the stratification factor."
Allocation concealment (selection bias)	Low risk	Quote "A previously generated randomization list was used to allocate the patients to each stratum, in accordance with the order of their entrance into the study. A researcher who was not involved with assessments or interaction with participants randomized and allocated the patients"
Adequate blinding of participants?	Unclear risk	Comment: evidence that blinding can be inadequate at intensity of 2 mA. No formal assessment of blinding success
Adequate blinding of assessors?	Unclear risk	Comment: evidence that assessor blinding can be inadequate at intensity of 2 mA. No formal assessment of blinding success
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: 2 dropouts (20%) from sham group, imputation with LOCF
Selective reporting (reporting bias)	Low risk	Comment: outcomes reported adequately
Study Size	High risk	Comment: n = 20
Study duration	High risk	Comment: postintervention follow-up only
Other bias	Low risk	Comment: no other bias detected

Tan 2000

Methods	Cross-over RCT
Participants	Country of study: USA Setting: tertiary care teaching hospital Condition: neuromuscular pain (excluding fibromyalgia) Prior management details: unclear n = 28 Age: 45-65 years, mean 55.6 Duration of symptoms: 4-45 years, mean 15 Gender distribution: 25 M, 3 F
Interventions	Stimulation type: CES Stimulation parameters: frequency 0.5 Hz; pulse width not specified; intensity 10-600 μA; waveform shape not specified Stimulation location: ear clip electrodes Number of treatments: 12, frequency of treatment not specified Control type: sham CES unit indistinguishable from active unit
Outcomes	Primary: VAS 0-5 pain intensity When taken: pre- and post- each treatment Secondary: life interference scale, sickness impact profile - Roland Scale When taken: not specified
Notes	AEs: not reported COI: no declaration made Sources of support: no declaration made

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "each subject was randomly assigned to receive either the active or the sham treatment first" Comment: method of randomisation not specified but less critical in cross-over design
Adequate blinding of participants?	Low risk	Quote: "sham treatment was made possible by having the treatment delivered via a black box" Comment: sham and active stimulators visually indistinguishable
Adequate blinding of assessors?	Unclear risk	Comment: blinding of assessors not reported
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: only 17 participants completed the study and this dropout (over 50%) is not clearly accounted for in the analysis
Selective reporting (reporting bias)	Low risk	Comment: primary outcome data presented clearly

Tan 2000 (*Continued*)

Free from carry-over effects?	Low risk	Quote: "Note that there were no significant differences in pain ratings pre-post changes between the active and sham groups"
Study Size	High risk	Comment: < 50 participants per treatment arm
Study duration	High risk	Comment: < 2 weeks' follow-up
Other bias	Unclear risk	Comment: participants also received local stimulation to the painful area that may have elicited a therapeutic effect

Tan 2006

Methods	Parallel RCT
Participants	Country of study: USA Setting: medical centre Condition: post-SCI pain (not clearly neuropathic) Prior management details: unclear n = 40 Age: 38-82 years Duration of symptoms: chronic > 6 months Gender distribution: all M
Interventions	Stimulation type: CES Stimulation parameters: frequency not specified; pulse width not specified; intensity 100-500 μA; waveform shape not specified; duration 1 h per session Stimulation location: ear clip electrodes Number of treatments: 21, x 1 daily for consecutive days Control type: sham CES unit indistinguishable from active unit
Outcomes	Primary: BPI (0-10 NRS), anchors "no pain" to "pain as bad as you can imagine" When taken: post-treatment period Secondary: pain interference subscale of BPI When taken: as for primary outcome
Notes	AEs: not reported COI: no declaration made Sources of support: no declaration made

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "The participants were then randomly assigned to either the active or sham CES treatment groups" Comment: method of randomisation not specified

Tan 2006 (*Continued*)

Allocation concealment (selection bias)	Unclear risk	Comment: allocation concealment not specified
Adequate blinding of participants?	Low risk	Comment: see quote above
Adequate blinding of assessors?	Low risk	Quote: "The investigators,research assistant (RA), and participants were blinded to treatment type until the end of the initial phase."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: only 2 (5%) participants withdrew from the study. Unlikely to have strongly influenced the findings
Selective reporting (reporting bias)	Low risk	Comment: primary outcomes presented clearly and in full
Study Size	High risk	Comment: < 50 participants per treatment arm
Study duration	High risk	Comment: < 2 weeks' follow-up
Other bias	Low risk	Comment: no significant other bias detected

Tan 2011

Methods	Parallel RCT
Participants	Country of study: USA Setting: 4 Veterans Affairs medical centres and 1 private rehabilitation clinic Condition: post-SCI neuropathic pain Prior management details: not reported n = 105 Age mean (SD): active group 52.1 (10.5) years, sham group 52.5 (11.7) years Gender distribution: 90 M, 15 F
Interventions	Stimulation type: CES Stimulation parameters: frequency not specified; pulse width not specified; intensity 100 μA; waveform shape not specified; duration 1 h per session Stimulation location: earlobe clips Number of treatments: 21, x 1 daily Control type: sham CES unit indistinguishable from active unit
Outcomes	Primary: BPIpain intensity VAS 0-100, anchors not reported When taken: at end of treatment period Secondary: QoL SF-12 physical and mental component subscales
Notes	COI: study authors declared no COI Sources of support: funded by Veterans Affairs rehabilitation research and development service
Risk of bias	

Tan 2011 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The equipment was set up for a double-blind study by the manufacturer such that the participants could not differentiate active from sham CES devices. Research staff members who interacted with the participants (e.g. recruited and trained participants, administered questionnaires, followed up by telephone) did not know which devices were sham and which were active. Randomization was achieved by selecting a device from a box initially containing equal numbers of active and sham devices." Comment: whilst unconventional it appeared to avoid a systematic bias
Allocation concealment (selection bias)	Low risk	Comment: see quote/comment above
Adequate blinding of participants?	Low risk	Comment: stimulation subsensory and units indistinguishable
Adequate blinding of assessors?	Low risk	Comment: stimulation subsensory and units indistinguishable
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: available case analysis with small loss to follow-up
Selective reporting (reporting bias)	Low risk	Comment: key outcomes fully reported
Study Size	Unclear risk	Comment: > 50 but < 200 participants per treatment condition
Study duration	High risk	Comment: < 2 weeks' follow-up
Other bias	Unclear risk	Comment: baseline between-group imbalances on BPI pain interference, SF-36 pain subscale and coping strategies

Taylor 2013

Methods	Parallel RCT
Participants	Country of study: USA Setting: community rheumatology practices Condition: fibromyalgia Prior management details: not reported but continued stable medication usage n = 57 (46 after dropout) Age mean (SD): active group 51 (10.6) years, sham group 51.5 (10.9) years, usual care group 48.6 (9.8) years Duration of symptoms: not reported Gender distribution: 43 F, 3 M (data reported on completers)

Taylor 2013 (*Continued*)

Interventions	Stimulation type: CES Stimulation parameters: frequency 0.5 Hz; pulse width not specified; intensity 100 μA; waveform shape square wave biphasic, duration 1 h per session Stimulation location: earlobe clip electrodes Number of treatments: x 1 daily for 8 weeks Control type: sham CES unit indistinguishable from active unit
Outcomes	Primary: pain VAS, anchors not reported When taken: at the end of each week of treatment period Secondary: FIQ
Notes	COI: no declaration made Sources of support: University of Virginia. Center for the study of Complementary and Alternative Therapies. Devices loaned by Electromedical Products International

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: described as randomised but method of randomisation not reported
Allocation concealment (selection bias)	Unclear risk	Comment: allocation concealment not reported
Adequate blinding of participants?	Low risk	Comment: identical devices given to sham and active group with subsensory stimulation parameters
Adequate blinding of assessors?	Low risk	Comment: participants self-rated at home
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: of 57, 11 did not complete - unclear if ITT analysis employed. However, only 2-4 per group and balanced, mostly due to assessment burden
Selective reporting (reporting bias)	Low risk	Comment: while no numeric data were provided on primary outcomes in the study report, these data were provided upon request to the authors
Study Size	High risk	Comment: < 50 participants per treatment arm
Study duration	High risk	Comment: < 2 weeks' follow-up
Other bias	Low risk	Comment: no other source of bias detected

Tekin 2014

Methods	Parallel RCT
Participants	Country of study: Turkey Setting: Rehabilitation outpatient unit Condition: fibromyalgia Prior management details: no analgesic use for 1 month prior to enrolment n = 51 Age mean (SD): active group 42.4 (78.63) years, sham group 46.5 (8.36) years Duration of symptoms: mean (SD) active group 10.81 (6.31) years, sham group 13.33 (6.65) Gender distribution: 47 F, 4 M
Interventions	Stimulation type: rTMS Stimulation parameters: frequency 10 Hz; coil orientation 45º angle from the midline, 100% RMT number of trains 30; duration of trains 5 s; ITI 12 s; total number of pulses 1500 Stimulation location: M1 midline, no neuronavigation Number of treatments: 10 sessions daily - unclear whether only work days Control type: sham coil - same sound and appearance, no control for sensory cues
Outcomes	Primary: pain NRS anchors 0 = no pain, 10 = most severe pain When taken: end of intervention Secondary: WHQoL-BREF
Notes	Funding source: none reported COI: the study authors declared no COI

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote "Randomisation was completed with the help of a software programme that produces random allocation"
Allocation concealment (selection bias)	Unclear risk	Comment: allocation concealment not reported
Adequate blinding of participants?	Unclear risk	Comment: placebo coil did not control for the sensory aspects of stimulation. No formal assessment of blinding success reported
Adequate blinding of assessors?	Low risk	Quote: "the investigator who conducted the clinical evaluation received no information about patient admission, randomisation or mode of treatment"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: only 1 participant lost to follow-up
Selective reporting (reporting bias)	Low risk	Comment: no suggestion of selective outcome reporting
Study Size	High risk	Comment: 25 and 27 participants in each group

Tekin 2014 (*Continued*)

Study duration	High risk	Comment: only immediate postintervention follow-up
Other bias	Low risk	Comment: no other bias detected

Thibaut 2017

Methods	Parallel RCT
Participants	Country of study: USA Setting: laboratory Condition: post-SCI neuropathic pain (sublesion) Prior management details: not reported n = 33 (14 after loss to follow-up in phase one) Age, mean (SD): active group 51.38 (14.89) years, sham group 51 (10.11) years Duration of symptoms: not reported Gender distribution: 24 M, 9 F
Interventions	Stimulation type: tDCS Stimulation parameters: tDCS: 2 mA intensity, 20 min Stimulation location: M1 contralateral to painful side Number of treatments: x1 daily for 5 days in phase one. Phase 2 not relevant to this review Control type: sham tDCS
Outcomes	Primary: pain VAS anchors 0 = no pain 10 = pain as bad as you can imagine When taken: postintervention, 1 week postintervention, 3 months postintervention Secondary: QoL (PHQ-9) AEs
Notes	Funding source: this project was supported by the National Institute on Disability, Independent Living, and Rehabilitation Research (NIDILRR grant numbers 90DP0035 and H133N110010) COI: study authors declared no COI

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: method of randomisation not reported
Allocation concealment (selection bias)	Unclear risk	Comment: allocation concealment not reported
Adequate blinding of participants?	Unclear risk	Comment: blinding can be compromised at 2 mA intensity. No formal blinding assessment reported

Thibaut 2017 (*Continued*)

Adequate blinding of assessors?	Unclear risk	Comment: blinding can be compromised at 2 mA intensity. No formal blinding assessment reported
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: while ITT analysis reported with multiple imputation, at the end of phase one, dropout was 57%
Selective reporting (reporting bias)	Low risk	Comment: data reported adequately
Study Size	High risk	Comment: n = 33 (14 after loss to follow-up)
Study duration	Low risk	Comment: 3-month follow-up for phase 1
Other bias	Low risk	Comment: no other bias detected

Tzabazis 2013

Methods	Unclear, likely parallel RCT (for 1 Hz only), 10 Hz data open-label therefore excluded from this review
Participants	Country of study: USA Setting: not reported, likely laboratory Condition: fibromyalgia Prior management details: "moderate to severe despite current and stable treatment regime" n = unclear, abstract report (Schneider 2012 (see Tzabazis 2013)) stated 45, but full paper stated 16 Age mean (SD): 53.2 (8.9) years Duration of symptoms, years mean (SD): not reported Gender distribution: 14 F, 2 M
Interventions	Stimulation type: rTMS 4-coil configuration Stimulation parameters: frequency 1 Hz; no of trains not reported; duration of trains not reported; ITI not reported, intensity 110% RMT, total number of pulses per session 1800, stimulation duration 30 min Stimulation location: targeted to the anterior cingulate cortex Number of treatments: 20, x 1 daily (working days) for 4 weeks Control type: sham coil
Outcomes	Primary: BPI average pain last 24 h, NRS, anchors not reported When taken: end of treatment, 4 weeks post-treatment Secondary: FIQ
Notes	COI: 3 study authors have acted as paid consultants to the manufacturer of the stimulation device, of which 2 hold stock in the company and 1 founded the company, is its chief medical officer and has intellectual property rights Sources of support: no declaration made

Tzabazis 2013 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: no description of the sequence generation process used
Allocation concealment (selection bias)	Unclear risk	Comment: no description of allocation concealment
Adequate blinding of participants?	Unclear risk	Comment: no description of blinding of participants for clinical part of study. Sham coil controlled for auditory cues and was visually indistinguishable from active stimulation but did not control for sensory characteristics of active stimulation over the scalp
Adequate blinding of assessors?	Unclear risk	Comment: no description or mention of blinding assessors for clinical part of study
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: no mention of the degree of dropout or how it was managed. However, 45 participants with fibromyalgia reported in the abstract of the same study (Schneider 2012 (Tzabazis 2013)), but only 16 reported in the full paper
Selective reporting (reporting bias)	High risk	Comment: no presentation of numeric pain data with measures of variance
Study Size	High risk	Comment: < 50 participants per treatment arm
Study duration	Unclear risk	Comment: ≥ 2 weeks but < 8 weeks' follow-up
Other bias	Unclear risk	Comment: baseline and demographic data not presented for clinical group

Umezaki 2016

Methods	Parallel RCT
Participants	Country of study: USA Setting: not reported Condition: burning mouth syndrome Prior management details: not reported

Umezaki 2016 (*Continued*)

	n = 26 Age mean (SD): active group 63.36 (10.78) years, sham group 64.42 (8.35) years Duration of symptoms, mean (SD): active group 61.57 (32.10) months, sham group 65.58 (55.52) Gender distribution: active group 93% F, sham group 92% F
Interventions	Stimulation type: rTMS Stimulation parameters: frequency 10 Hz; coil orientation not specified, 100% RMT, number of trains 10; duration of trains 5 s; ITI 10 s; total number of pulses 3000 Stimulation location: L DLPFC Number of treatments: 10 x 1 daily on work days Control type: sham coil - same sound and appearance and sensory cues
Outcomes	Primary: pain NRS anchors 0 = no pain, 10 = extreme amount When taken: end of stimulation and 15, 30, 60 days after start of treatment Secondary: AEs
Notes	Funding source: no information provided COI: no information provided

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Patients who met all inclusion criteria were randomly assigned to one of two groups - one given active and the other sham stimulation - using a web-based randomization generator"
Allocation concealment (selection bias)	Unclear risk	Comment: allocation concealment procedures not reported
Adequate blinding of participants?	Low risk	Comment: sham controls for all aspects of stimulation Quote: "The coil used in the sham group was the same configuration as that used with the real group but shielded so that actual stimulation does not occur. All subjects had ECT electrodes placed under the TMS coil. For those receiving active TMS, the electrodes were disconnected, such that there was no current flowing through during stimulation. In contrast, the electrodes were connected during sham, so participants received a small electrical stimulation through the electrodes, precisely when the TMS was being triggered." "Ten of 12 (83%) patients in the real group and 4 of 8 (50%) patients in the sham group thought that they were in the real group. There was no significant difference for the belief of the allocated group between two groups ($\chi 2$ = 2.54,1, NS), suggesting that blinding for the subjects in this study was kept. The high percentage of correct guessing in the active group is concerning. However, when asked why they guessed the way they did, it was based on whether they had BMS symptom reduction.

Umezaki 2016 (*Continued*)

		If this occurred, then they guessed the active group. There were no instances of patient unblinding."
Adequate blinding of assessors?	High risk	Comment: assessor was not blinded to group allocation
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: 2/14 (14%) randomised did not receive active stim, 4/12 (33%) randomised to sham did not receive sham. Excluded from the analysis
Selective reporting (reporting bias)	High risk	Comment: pain intensity data only presented in graphical form without numeric point estimates/precision estimates
Study Size	High risk	Comment: combined n = 26 (per protocol = 20)
Study duration	Unclear risk	Comment: 7-week follow-up
Other bias	Low risk	Comment: no other risks of bias detected

Valle 2009

Methods	Parallel RCT, 3 conditions
Participants	Country of study: Brazil Setting: laboratory Condition: fibromyalgia Prior management details: refractory to medical intervention n = 41 Age: mean 54.8 (SD 9.6) years Duration of symptoms: condition 1: 7.54 (SD 3.93) years; condition 2: 8.39 (SD 2.06) years; condition 3: 8.69 (SD 3.61) years Gender distribution: 0 M, 41 F
Interventions	Stimulation type: tDCS Stimulation parameters: intensity 2 mA, 35 cm^2 electrodes, duration 20 min Stimulation location: condition 1: L DLPFC; condition 2: L M1, condition 3; sham L M1 Number of treatments: 10, x 1 daily on consecutive working days Control type: sham tDCS (switched off after 30 s stimulation)
Outcomes	Primary: pain VAS 0-10 cm, anchors not specified When taken: immediately post-treatment, averaged over 3 d post-treatment, 30 and 60 d post-treatment Secondary: QoL; FIQ
Notes	COI: no declaration made Sources of support: no declaration made
Risk of bias	

Valle 2009 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomization was performed using the order of entrance in the study and a previous randomisation list generated by a computer"
Allocation concealment (selection bias)	Low risk	Comment: the use of a pregenerated randomisation list should have adequately ensured this
Adequate blinding of participants?	Unclear risk	Comment: there is evidence that participant blinding of tDCS may be inadequate at 2 mA intensity (see Assessment of risk of bias in included studies)
Adequate blinding of assessors?	Unclear risk	Comment: there is evidence that assessor blinding of tDCS may be inadequate at 2 mA intensity (see Assessment of risk of bias in included studies)
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: no dropout occurred
Selective reporting (reporting bias)	High risk	Comment: pain score numerical values not provided clearly with measures of variance for any post-treatment time point in the study report
Study Size	High risk	Comment: < 50 participants per treatment arm
Study duration	Low risk	Comment: ≥ 8 weeks' follow-up
Other bias	Low risk	Comment: no significant other bias detected

Villamar 2013

Methods	Cross-over RCT
Participants	Country of study: USA Setting: laboratory Condition: fibromyalgia Prior management details: pain refractory to common analgesics and muscle relaxants n = 18 randomised of which 17 allocated Age mean (SD): 50.3 (8.5) years Duration of symptoms (years) mean (SD): 10.7 (6.8) Gender distribution: 15 F, 3 M
Interventions	Stimulation type: HD-tDCS Stimulation parameters: intensity 2 mA, duration 20 min, anodal/cathodal/sham 4 x 1-ring configuration Stimulation location: L M1 Number of treatments: x 1 per condition

Villamar 2013 (*Continued*)

	Control type: sham tDCS
Outcomes	Primary: pain visual numerical scale; 0 = complete absence of pain, 10 = worst pain imaginable When taken: baseline, immediately poststimulation, 30 min poststimulation Secondary: adapted QoL scale for persons with chronic illness (7 points: 1 = terrible, 7 = delighted)
Notes	COI: no declaration made Sources of support: no declaration made

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "the order of stimulation was counterbalanced and randomly assigned for each individual" Comment: method of randomisation not specified but less likely to introduce bias in a cross-over design
Adequate blinding of participants?	Unclear risk	Comment: there is evidence that participant blinding of tDCS may be inadequate at 2 mA intensity (see Assessment of risk of bias in included studies)
Adequate blinding of assessors?	Unclear risk	Comment: there is evidence that participant blinding of tDCS may be inadequate at 2 mA intensity (see Assessment of risk of bias in included studies)
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: only 1 loss to follow-up and multiple imputation used
Selective reporting (reporting bias)	Low risk	Comment: primary outcomes reported in full
Free from carry-over effects?	Low risk	Comment: 7-day washout periods observed. Data similar at baseline
Study Size	High risk	Comment: < 50 participants per treatment arm
Study duration	High risk	Comment: < 2 weeks' follow-up
Other bias	Low risk	Comment: no other bias detected

Volz 2016

Methods	Parallel RCT
Participants	Country of study: Germany Setting: laboratory Condition: chronic abdominal pain with inflammatory bowel disease Prior management details: participants allowed to continue anti-inflammatory drugs and acute pain medication n = 20 Age, mean (SD) active group 40.6 (12.5) years, sham group 34.4 (13.2) years Duration of symptoms: active group 10 (8.9) years, sham group 34.4 (13.2) Gender distribution: 13 F, 7 M
Interventions	Stimulation type: tDCS Stimulation parameters: intensity 2 mA, 35 cm^2 electrodes, duration 20 min Stimulation location: anode M1 contralateral to painful side, cathode supraorbital area, contralateral to anode Number of treatments: x 1 daIly for 5 days Control type: sham tDCS
Outcomes	Primary: pain VAS, anchors 0 = no pain, 10 = the worst pain possible When taken: postintervention, 1 week postintervention Secondary: inflammatory bowel disease QoL questionnaire AEs
Notes	COI: study authors declared no COI Sources of support: "This study has been supported by the grant "Patientenorientierte Forschung bei CED 2014" of the "Deutsche Morbus Crohn/Colitis ulcerosa Vereinigung e.V." (Not industry)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomization was performed by the unblinded researcher (A.F.) in blocks of 4 generated from a computer-based random allocation."
Allocation concealment (selection bias)	Unclear risk	Quote: "Quote: "Randomization was performed by the unblinded researcher (A.F.)" Comment: no apparent steps to conceal allocation
Adequate blinding of participants?	Unclear risk	Evidence that assessor blinding can be inadequate at intensity of 2 mA. No formal assessment of blinding success
Adequate blinding of assessors?	Unclear risk	Evidence that assessor blinding can be inadequate at intensity of 2 mA. No formal assessment of blinding success
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: levels of dropout, if any, not reported

Volz 2016 (*Continued*)

Selective reporting (reporting bias)	Low risk	Comment: outcomes reported adequately
Study Size	High risk	Comment: n = 20
Study duration	High risk	Comment: 1-week postintervention maximum follow-up.
Other bias	Low risk	Comment: no further bias detected

Wrigley 2014

Methods	Cross-over RCT
Participants	Country of study: Australia Setting: laboratory Condition: chronic neuropathic pain post-SCI Prior management details; none n = 10 Age mean (SD): 56.1 (14.9) years Duration of symptoms: 15.8 (11.3) years Gender distribution: 8 M, 2 F
Interventions	Stimulation type: tDCS Stimulation parameters: intensity 2 mA, duration 20 min Stimulation location: M1 (contralateral to most painful side or dominant hand) Number of treatments: 5, x 1 daily 5 days Control type: sham tDCS (switched off after 30 s stimulation)
Outcomes	Primary: pain VAS; 0 = "no pain", 10 = "worst possible pain" When taken: at end of treatment, 4 weeks post-treatment Secondary: none relevant
Notes	COI: no declaration made Sources of support: no declaration made

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Comment: method of randomisation not specified but less important for cross-over design Quote: "A randomized crossover design was used so that all subjects participated in an active treatment (transcranial direct current stimulation) and sham treatment period. Both the subject and the response assessor were blinded to the randomization sequence."

Wrigley 2014 (*Continued*)

Adequate blinding of participants?	Unclear risk	Comment: there is evidence that participant blinding of tDCS may be inadequate at 2 mA intensity (see Assessment of risk of bias in included studies)
Adequate blinding of assessors?	Unclear risk	Comment: there is evidence that assessor blinding of tDCS may be inadequate at 2 mA intensity (see Assessment of risk of bias in included studies)
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: no loss to follow-up
Selective reporting (reporting bias)	Low risk	Comment: primary outcomes reported in full
Free from carry-over effects?	Low risk	Comment: 4-week washout period observed and data appear free of carry-over effects
Study Size	High risk	Comment: < 50 participants per treatment arm
Study duration	Unclear risk	Comment: ≥ 2 weeks but < 8 weeks' follow-up
Other bias	Low risk	Comment: no other bias detected

Yagci 2014

Methods	Parallel RCT
Participants	Country of study: Turkey Setting: not reported Condition: fibromyalgia Prior management details: no improvement in cases of using medical treatment for fibromyalgia for at least 3 months n = 28 Age mean (SD): active group 45.25 (9.33) years, sham group 43 (7.63) years Duration of symptoms, mean(SD): active group 53 (29.15) months, sham group 54.92 (30.44) Gender distribution: all F
Interventions	Stimulation type: rTMS Stimulation parameters: frequency 1 Hz; coil orientation not reported, 90% RMT, number of trains 20; duration of trains 60 s; ITI 45 s; total number of pulses 1200 Stimulation location: L M1, no neuronavigation Number of treatments: 10 sessions, weekdays for 2 weeks Control type: sham coil - same sound and appearance, no control for sensory cues
Outcomes	Primary: pain NRS anchors 0 = no pain, 10 = maximum pain imaginable When taken: end of intervention, 1 month, 3 months Secondary: FIQ AEs

Yagci 2014 (*Continued*)

Notes	Funding source: the study authors declared that this study received no financial support COI: no COI was declared by the authors

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: method of randomisation not outlined Quote: "patients were randomly assigned to be in either a real stimulation group or a sham stimulation group by another clinician"
Allocation concealment (selection bias)	Low risk	Quote: "masked clinician evaluated the patients clinically and provided the diagnosis of FM. The patients were randomly assigned to be in either a real stimulation group or a sham stimulation group by another clinician."
Adequate blinding of participants?	Unclear risk	Comment: sham coil did not control for sensory aspects of stimulation Quote: "Sham stimulation was carried out with the same parabolic coil, which was placed at 90° angles to the motor cortex area"
Adequate blinding of assessors?	Low risk	Quote: "A masked clinician evaluated the patients clinically and provided the diagnosis of FM [fibromyalgia]"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: 3 participants dropped out though this exceeds 10% of total number, the group they withdrew from and point of withdrawal were not clear
Selective reporting (reporting bias)	Low risk	Comment: outcomes adequately reported
Study Size	High risk	N = 28 (per protocol 25)
Study duration	Low risk	Comment: 3-month follow-up
Other bias	Low risk	Comment: no other risk of bias detected

Yilmaz 2014

Methods	Parallel RCT
Participants	Country of study: Turkey Setting: rehabilitation unit Condition: post-SCI below lesion neuropathic pain Prior management details: pain that is resistant to pharmacological (anticonvulsants, antidepressants, narcotics) and interventional treatments n = 17

Yilmaz 2014 (*Continued*)

	Age mean (SD): active group: 40 (5.1) years, sham group 36.94 (8) years Duration of symptoms mean (SD): active group 32.3 (25.9) months, sham group 35.4 (17.9) Gender distribution: all M
Interventions	Stimulation type: rTMS Stimulation parameters: frequency 10 Hz; coil orientation handle pointing posteriorly, number of trains 30; duration of trains 5 s; ITI 25 s; total number of pulses 1500 Stimulation location: M1 midline Number of treatments: daily for 10 weekdays Control type: coil angled away - same sound and appearance, did not control for visual or sensory cues
Outcomes	Primary: pain NRS anchors 0 = no pain, 10 = worst pain imaginable When taken: end of intervention, 6 weeks, 6 months postintervention Secondary: none relevant
Notes	Funding source: no information reported COI: no information reported

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "A computer-generated randomization schedule was used."
Allocation concealment (selection bias)	Unclear risk	Comment: allocation concealment not reported
Adequate blinding of participants?	Unclear risk	Comment: sham condition did not control for visual or sensory aspects of stimulation
Adequate blinding of assessors?	Low risk	Quote: "The patients and the researcher evaluating the patients were blinded to type of rTMS."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: only one participant dropped out
Selective reporting (reporting bias)	Low risk	Comment: key outcomes adequately reported
Study Size	High risk	Comment: n = 16
Study duration	Low risk	Comment: 6-month follow-up
Other bias	Low risk	Comment: no other bias detected

AE: adverse event; **ANOVA**: analysis of variance; **BIRS**: Gracely Box Intensity Scale (BIRS); **BOCF**: baseline observation carried forward; **BPI**: Brief Pain Inventory; **CES**: cranial electrotherapy stimulation; **CNP**: central neuropathic pain; **COI**: conflict of

interest; **CPSP**: central poststroke pain; **CRPS**: complex regional pain syndrome; **DLPFC**: dorsolateral prefrontal cortex; **F**: female; **FIQ**: Fibromyalgia Impact Questionnaire; **HD-tDCS**: High definition tDCS; **ITI**: inter-train interval; **ITT**: intention-to-treat; **L**: left; **LANSS**: Leeds Assessment of Neuropathic Symptoms and Signs pain scale; **LOCF**: last observation carried forward; **M**: male; **M1**: primary motor cortex; **MCS**: motor cortex stimulation (MCS); **NIH**: National Institutes of Health; **NRS**: numerical rating scale; **NSAIDS**: nonsteroidal anti-imflammatory drugs; **OA**: osteoarthritis; **PFC**: prefrontal cortex; **PLP**: phantom limb pain; **QoL**: Quality of Life; **R**: right; **RCT**: randomised controlled trial; **RINCE**: reduced impedance non-invasive cortical electrostimulation; **RMDQ**: Roland Morris Disability Questionnaire; **RMT**: resting motor threshold; **rTMS**: repetitive transcranial magnetic stimulation; **SCI**: spinal cord injury; **SII**: secondary somatosensory area; **SD**: standard deviation; **TCES**: transcranial electrical stimulation; **tDCS**: transcranial direct current stimulation; **TENS**: transcutaneous electrical nerve stimulation; **TMS**: transcranial magnetic stimulation; **VAS**: visual analogue scale; **WOMAC**: Western Ontario and McMaster Universities Arthritis Index

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Avery 2007	The duration of painful symptoms is unclear. May not be exclusively chronic pain
Belci 2004	Pain is not measured as an outcome
Bolognini 2013	Inclusion of acute and chronic pain patients
Bolognini 2015	Not clearly a chronic population
Carraro 2010	Not a study of electrical brain stimulation
Choi 2012b	Study of acute pain
Choi 2012a	Study of acute pain
Choi 2014	Not clearly a chronic population
Cummiford 2016	Allocation not randomised
Evtiukhin 1998	A study of postoperative pain. No sham control employed
Frentzel 1989	Not a study of brain stimulation
Hargrove 2012b	Uncontrolled long-term follow-up data from Hargrove 2012a
Johnson 2006	Self-reported pain is not measured
Katz 1991	Study not confined to chronic pain
Khedr 2015	Not clearly a chronic population
Lindholm 2015	Allocation not randomised
Longobardi 1989	Not clearly studying chronic pain

(*Continued*)

Ma 2015	Not clearly a chronic population
Maestu 2013	Not electrical brain stimulation - magnetic fields unlikely to induce electrical currents
Morin 2017	Not clearly a chronic pain population - provoked vestibulodynia
Nelson 2010	Intervention not designed to alter cortical activity directly by electrical stimulation - a neuro feedback intervention
O'Connell 2013	Not a RCT or quasi-RCT - no randomisation specifically to treatment group or order
Pujol 1998	Participants are a mixture of acute and chronic pain patients
Schabrun 2014	Not clearly a chronic population
Seada 2013	No sham control employed
Sichinava 2012	No sham control employed
Silva 2007	A single case report
Smania 2005	Not a study of brain stimulation
Yoon 2014	Allocation not randomised
Zaghi 2009	Single case study

RCT: randomised controlled trial

Characteristics of studies awaiting assessment *[ordered by study ID]*

Acler 2012

Methods	Parallel RCT
Participants	Post-polio patients, n = 32
Interventions	tDCS, bi-anodal, bilateral motor cortex, 1.5 mA, 20 min, daily for 5 days
Outcomes	Pain, QoL
Notes	Published as conference abstract only. Attempts to contact study authors currently unsuccessful

Albu 2011

Methods	Sham-controlled study, unclear whether randomised
Participants	Post-SCI chronic neuropathic pain, n = 30
Interventions	tDCS motor cortex, 2 mA, 10 sessions
Outcomes	Pain intensity
Notes	Published as conference abstract only. Attempts to contact study authors currently unsuccessful

Fricova 2009

Methods	Sham-controlled trial, unclear whether randomised
Participants	Chronic neurogenic orofacial pain, n = 26
Interventions	rTMS motor cortex, frequency unclear, appears to be a single session of stimulation per condition
Outcomes	Pain VAS
Notes	Published as conference abstract only. Attempts to contact study authors currently unsuccessful

Fricova 2011

Methods	Sham-controlled trial, unclear whether randomised, likely to be a cross-over design
Participants	Chronic neurogenic orofacial pain, n = 26
Interventions	rTMS motor cortex, frequency unclear, appears to be a single session of stimulation per condition
Outcomes	Pain VAS
Notes	Published as conference abstract only. Likely to be a duplicate report of Fricova 2009. Attempts to contact study authors currently unsuccessful

Fricová 2013

Methods	Sham-controlled parallel trial - unclear if randomised
Participants	Chronic orofacial pain n = 59
Interventions	rTMS, 10 Hz and 20 Hz, location not clear
Outcomes	Pain VAS
Notes	Published as conference abstract only. Attempt to contact study authors currently unsuccessful

Hwang 2015

Methods	Parallel RCT
Participants	CRPS type I, n = 18
Interventions	rTMS, 10 Hz, 10 treatment sessions
Outcomes	Pain, disability, QoL
Notes	Published as conference abstract only. Attempts to contact study author currently unsuccessful

Klirova 2010

Methods	Parallel RCT
Participants	Neuropathic orofacial pain, n = 29
Interventions	rTMS, motor cortex, 10 Hz, 5 treatment sessions
Outcomes	Pain VAS
Notes	Published as conference abstract only. Attempts to contact study authors currently unsuccessful

Klirova 2011

Methods	Parallel RCT
Participants	Neuropathic orofacial pain, medication resistant, n = 29
Interventions	rTMS, motor cortex, 10 Hz, 5 treatment sessions
Outcomes	Pain VAS
Notes	Published as conference abstract only. Likely to be a duplicate report of Klirova 2010. Attempts to contact authors currently unsuccessful

Knotkova 2011

Methods	Parallel RCT
Participants	CRPS type I, n = 25
Interventions	tDCS, motor cortex, 2 mA, 20 min per session, daily for 5 days
Outcomes	Pain, QoL, physical activity
Notes	Currently published as conference abstract only. Correspondence with study authors - data unavailable as currently being re-analysed

Mattoo 2017

Methods	Parallel RCT
Participants	Fibromyalgia n = 50
Interventions	Low-frequency rTMS DLPFC
Outcomes	Pain
Notes	Published as conference abstract only. Attempt to contact study authors currently unsuccessful

Moreno-Duarte 2013a

Methods	Cross-over RCT
Participants	Post-SCI pain, n = 6
Interventions	tDCS and visual illusion
Outcomes	Pain
Notes	Published as conference abstract only. Attempt to contact study authors currently unsuccessful

Mylius 2013

Methods	Parallel RCT
Participants	Chronic neuropathic pain
Interventions	Low-frequency rTMS, M1 or DLPFC
Outcomes	Pain
Notes	Published as conference abstract only. Attempts to contact study authors currently unsuccessful

Parhizgar 2011

Methods	Parallel RCT
Participants	Current and former opioid abusers - pain status unclear. n = 60
Interventions	tDCS M1, number of sessions unclear
Outcomes	Not clear whether pain intensity was measured
Notes	Published as conference abstract only. Attempts to contact study authors currently unsuccessful

Pellaprat 2012

Methods	Cross-over RCT
Participants	Parkinson's disease with related pain, n = 19
Interventions	rTMS 20 Hz motor cortex, ? whether single session
Outcomes	Pain VAS
Notes	Published as conference abstract only. Attempts to contact study authors currently unsuccessful

Shklar 1997

Methods	Unable to retrieve study report
Participants	-
Interventions	-
Outcomes	-
Notes	-

Tanwar 2016

Methods	Parallel RCT
Participants	Fibromyalgia n = 48
Interventions	Low-frequency rTMS DLPFC
Outcomes	Pain
Notes	Published as conference abstract only. Attempt to contact study authors currently unsuccessful

Vatashsky 1997

Methods	Unable to retrieve study report
Participants	-
Interventions	-
Outcomes	-
Notes	-

Williams 2014

Methods	Parallel RCT
Participants	Fibromyalgia n = 20
Interventions	rTMS, L DLPFC, 10 treatment sessions
Outcomes	? whether pain intensity measured as an outcome
Notes	Published as conference abstract only. Attempt to contact study authors currently unsuccessful

CRPS: complex regional pain syndrome; **DLPFC**: dorsolateral prefrontal cortex; **FIQ**: Fibromyalgia Impact Questionnaire: **L**: left; **M1**: primary motor cortex; **QoL**: quality of life; **RCT**: randomised controlled trial; **rTMS**: repetitive transcranial magnetic stimulation; **SCI**: spinal cord injury; **tDCS**: transcranial direct current stimulation; **VAS**: visual analogue scale

Characteristics of ongoing studies *[ordered by study ID]*

ACTRN12612001155886

Trial name or title	Investigating the role of transcranial direct current stimulation for pain relief in fibromyalgia and myalgic encephalomyelitis/chronic fatigue syndrome patients
Methods	Parallel RCT
Participants	Fibromyalgia syndrome Myalgic encephalomyelitis/chronic fatigue syndrome
Interventions	tDCS Sham tDCS
Outcomes	Pain, fatigue, FIQ, stimulation condition
Starting date	
Contact information	Ms Hannah Bereznicki, hannah.bereznicki@deakin.edu.au
Notes	TRIAL WITHDRAWN

ACTRN12613000561785

Trial name or title	The effectiveness of repetitive transcranial magnetic stimulation in the treatment of fibromyalgia
Methods	Parallel RCT
Participants	Fibromyalgia

ACTRN12613000561785 (*Continued*)

Interventions	rTMS to DLPFC 10 Hz sham rTMS
Outcomes	Pain severity QoL
Starting date	17 May 2013
Contact information	Dr Bernadette Fitzgibbon, bernadette.fitzgibbon@monash.edu
Notes	Correspondence with authors 21 December 2016 - data collection ongoing

ACTRN12613001232729

Trial name or title	Modulation of chronic pain perception with noninvasive central and peripheral nervous system stimulation
Methods	RCT
Participants	Chronic musculoskeletal pain
Interventions	Intervention group 1: participants receive tDCS and TENS only Comparator group 1: participants receive tDCS and sham TENS only Comparator group 2: participants receive TENS and sham tDCS only Control group 1: participants receive sham tDCSand sham TENS only
Outcomes	Pain VAS WHO-QOL
Starting date	11 November 2013
Contact information	Prof Allan Abbott, aabbott@bond.edu.au
Notes	Correspondence with authors 22 December 2016- trial did not go ahead due to "changes in project personnel and funding."

ACTRN12614001247662

Trial name or title	The effects of non-invasive brain stimulation on chronic arm pain
Methods	RCT
Participants	Neuropathic pain in the upper limb
Interventions	tDCS Sham

ACTRN12614001247662 (*Continued*)

Outcomes	Arm pain Upper limb function
Starting date	16 April 2014
Contact information	A/Prof Gwyn Lewis, gwyn.lewis@aut.ac.nz
Notes	Correspondence with authors 21 December 2016, data collection ongoing

ACTRN12615000110583

Trial name or title	The impact of non-invasive brain stimulation on motor cortex excitability and cognition in chronic lower back pain
Methods	RCT
Participants	Chronic low back pain
Interventions	tDCS Sham
Outcomes	Pain, HR-QoL
Starting date	9 March 2015
Contact information	Dr Andrea Loftus, andrea.loftus@curtin.edu.au
Notes	Correspondence with authors 3 January 2017, data collection ongoing

ACTRN12616000624482

Trial name or title	Safety and feasibility of transcranial direct current stimulation (tDCS) combined with sensorimotor retraining in chronic low back pain: a pilot randomised controlled trial
Methods	RCT
Participants	Chronic nonspecific low back pain
Interventions	tDCS + sensorimotor training sham tDCS + sensorimotor training
Outcomes	Pain severity Physical function
Starting date	8 August 2016

ACTRN12616000624482 (*Continued*)

Contact information	Dr Siobhan Schabrun, s.schabrun@westernsydney.edu.au
Notes	Correspondance with authors 22 December 2016, trial beginning recruitment

Ansari 2013

Trial name or title	
Methods	Parallel RCT
Participants	Fibromyalgia, n = 118
Interventions	rTMS right DLPFC, low-frequency, 20 sessions
Outcomes	Unclear whether self-reported pain scores were collected
Starting date	
Contact information	
Notes	Published as conference abstract only. Correspondance with study authors - paper currently in press awaiting publication

ChiCTR-INR-17011706

Trial name or title	Transcranial magnetic stimulation induced motor evoked potential in the expression of brain-derived neurotrophic factor BDNF, pathological pain and quality of life in patients with spinal cord injury
Methods	Parallel RCT
Participants	Post-SCI pain, n = 60
Interventions	rTMS
Outcomes	Pain, QoL
Starting date	01 July 2017
Contact information	Dr Shi Jiajia 707529535@qq.com
Notes	Contact with study authors unsuccessful

CTRI/2013/12/004228

Trial name or title	Effect of transcranial magnetic stimulation on pain modulation status in fibromyalgia patients
Methods	Parallel RCT
Participants	Fibromyalgia
Interventions	rTMS
Outcomes	Pain
Starting date	01 September 2013
Contact information	Dr Rathmi Mashur, mathurashmi@yahoo.co.in
Notes	Contact with study authors unsuccessful

Muniswamy 2016

Trial name or title	
Methods	Parallel RCT
Participants	Mixed chronic pain
Interventions	tDCS, M1, DLPFC, number of sessions not clear
Outcomes	Pain, QoL
Starting date	
Contact information	
Notes	Published as conference abstract only. Correspondence with study authors - study ongoing

NCT00815932

Trial name or title	The effect of transcranial direct current stimulation (t-DCS) On the P300 component of event-related potentials in patients with chronic neuropathic pain due to CRPS or diabetic neuropathy
Methods	Cross-over RCT
Participants	Chronic neuropathic pain due to CRPS or diabetic neuropathy
Interventions	tDCS or sham, 2 mA, 20 min, x 1 session, location not specified
Outcomes	Pain intensity
Starting date	February 2009

NCT00815932 (*Continued*)

Contact information	Dr Pesach Schvartzman, spesah@bgu.ac.il
Notes	Contact in 2010 - study ongoing, recent attempts to contact for update unsuccessful

NCT00947622

Trial name or title	Occipital transcranial direct current stimulation in fibromyalgia
Methods	Cross-over RCT
Participants	Fibromyalgia
Interventions	tDCS or sham, parameters not specified
Outcomes	Pain VAS and FIQ
Starting date	July 2009
Contact information	Dr Mark Plazier, mark.plazier@uza.be
Notes	Attempts to contact study authors currently unsuccessful

NCT01112774

Trial name or title	Application of transcranial direct current stimulation in patients with chronic pain after spinal cord injury
Methods	Parallel RCT
Participants	Chronic pain after SCI, proposed n = 60
Interventions	tDCS 2 mA, 10 sessions
Outcomes	Pain VAS, QoL
Starting date	April 2010
Contact information	Dr Felipe Fregni, ffregni@neuromodulationlab.org, Kayleen Weaver, kmweaver@partners.org
Notes	Contact with study author - study at "to be analysed and reported" stage

NCT01220323

Trial name or title	Transcranial direct current stimulation for chronic pain relief
Methods	Cross-over RCT
Participants	Chronic pain patients, proposed n = 100
Interventions	tDCS, motor cortex, 2 mA, daily for 5 days
Outcomes	Pain relief
Starting date	November 2010
Contact information	Dr Silvio Brill, Tel Aviv Sourasky Medical Centre
Notes	Correspondence with study authors: study ongoing

NCT01402960

Trial name or title	Exploration of parameters of transcranial direct current stimulation in chronic pain
Methods	Parallel RCT
Participants	Chronic pain following traumatic SCI, n = 60
Interventions	tDCS or sham, 2 mA, motor cortex, 20 min, x 1 daily for 5 days
Outcomes	Pain
Starting date	April 2010
Contact information	Dr Felipe Fregni, ffregni@partners.org; Kayleen Weaver, kmweaver@partners.org
Notes	Contact with study author - study at “to be analysed and reported” stage

NCT01404052

Trial name or title	Effects of transcranial direct current stimulation and transcranial ultrasound on osteoarthritis pain of the knee
Methods	Parallel RCT
Participants	Chronic knee OA pain, n = 30
Interventions	tDCS or sham, 20 min, 2 mA, motor cortex, 5 sessions
Outcomes	Pain
Starting date	January 2011

NCT01404052 (*Continued*)

Contact information	Dr Felipe Fregni, ffregni@partners.org; Kayleen Weaver, kmweaver@partners.org
Notes	Contact with study author - study at "to be analysed and reported" stage

NCT01575002

Trial name or title	Effects of transcranial direct current stimulation in chronic corneal pain
Methods	Cross-over RCT
Participants	Chronic corneal pain
Interventions	tDCS, active or sham, 1 session of each, parameters not reported
Outcomes	Pain VAS
Starting date	January 2012
Contact information	Dr Felipe Fregni, ffregni@partners.org; Kayleen Weaver, kmweaver@partners.org
Notes	Contact with study author - study at "to be analysed and reported" stage

NCT01746355

Trial name or title	Assessment and treatment patients with atypical facial pain through repetitive transcranial magnetic stimulation
Methods	Parallel RCT
Participants	Atypical facial pain, n = 40
Interventions	rTMS or sham, parameters not reported, 5 sessions
Outcomes	Pain VAS
Starting date	March 2011
Contact information	Ricardo Galhardoni
Notes	Correspondence with study authors: study near completion

NCT01747070

Trial name or title	Effect of cranial stimulation and acupuncture on pain, functional capability and cerebral function in osteoarthritis
Methods	Parallel RCT
Participants	Chronic OA pain, n = 80
Interventions	4 groups, real tDCS + electroacupuncture sham; sham tDCS + electroacupuncture sham, sham tDCS + electroacupuncture, real tDCS + electroacupuncture tDCS 2 mA motor cortex. All single session
Outcomes	Daily pain intensity, WOMAC
Starting date	January 2012
Contact information	Dr Wolnei Caumo, caumo@cpovo.net
Notes	Correspondence with study authors: study ongoing

NCT01781065

Trial name or title	The effects of transcranial direct current stimulation on central pain in patients with spinal cord injury
Methods	RCT
Participants	Central neuropathic pain post-SCI
Interventions	tDCS Sham
Outcomes	Pain, average 24 h Pain interference
Starting date	March 2008
Contact information	Hyung-Ik Shin, Associate Professor, Seoul National University Bundang Hospital
Notes	Contact with study authors unsuccessful

NCT01795079

Trial name or title	Effects of transcranial direct current stimulation (tDCS) on neuropathic symptoms following burn injury
Methods	RCT
Participants	Burn injury

NCT01795079 (*Continued*)

Interventions	tDCS Sham
Outcomes	Pain QoL
Starting date	January 2013
Contact information	Dr Felipe Fregni, ffregni@partners.org
Notes	Contact with authors unsuccessful

NCT01857492

Trial name or title	tDCS for the management of chronic visceral pain in patients with chronic pancreatitis (tDCS)
Methods	RCT
Participants	Chronic pancreatitis pain
Interventions	tDCS Sham
Outcomes	Pain QoL
Starting date	March 2013
Contact information	Steven Freedman, MD PhD
Notes	Contact with study author 20 December 2016 - stated all results published but did not respond to request to identify the published paper. Trial register record implies the study was withdrawn prior to enrolment

NCT01875029

Trial name or title	tDCS effects on chronic low back pain
Methods	RCT
Participants	Chronic nonspecific low back pain, n = 45
Interventions	Real-tDCS + back school Sham tDCS + back school
Outcomes	Pain
Starting date	January 2012

NCT01875029 (*Continued*)

Contact information	Sofia Straudi, MD
Notes	Contact with study authors unsuccessful

NCT01904097

Trial name or title	Functional neuroimaging in fibromyalgia patients receiving tDCS
Methods	RCT
Participants	Fibromyalgia, n = 34
Interventions	tDCS + pregabalin Sham tDCS + pregabalin
Outcomes	Pain FIQ WH-QoL
Starting date	March 2013
Contact information	Wolnei Caumo, MD, caumo@cpovo.net
Notes	Contact with study authors unsuccessful

NCT01932905

Trial name or title	Deep rTMS in central neuropathic pain syndromes (DRTMS)
Methods	RCT
Participants	Central pain, n = 90
Interventions	rTMS double cone coil rTMS H-coil Sham rTMS
Outcomes	Pain VAS
Starting date	March 2011
Contact information	Daniel Ciampi, MD, PhD, ciampi@usp.br
Notes	Correspondence with authors 22 December 2016, data collection complete, analysis ongoing

NCT01960400

Trial name or title	Investigation of the efficacy of tDCS in the treatment of complex regional pain syndrome (CRPS) Type 1
Methods	RCT
Participants	CRPS type 1, n = 22
Interventions	tDCS + GMI
Outcomes	sham tDCS + GMI
Starting date	April 2013
Contact information	Yannick Tousignant-Laflamme, PT Ph.D, Université de Sherbrooke
Notes	Correspondence with study authors - manuscript under review for publication

NCT02051959

Trial name or title	Long-term effects of transcranial direct current stimulation (tDCS) on patients with phantom limb pain (PLP)
Methods	Cross-over RCT
Participants	Phantom limb pain, n = 24
Interventions	Anodal tDCS Cathodal tDCS Sham TDCS
Outcomes	Pain AEs
Starting date	May 2015
Contact information	Itzhak Siev-Ner, MD
Notes	Contact with study authors unsuccessful

NCT02059096

Trial name or title	Analgesic dffect of repetitive transcranial magnetic stimulation (rTMS) for central neuropathic pain in multiple sclerosis (STIMASEP)
Methods	RCT
Participants	Central neuropathic pain due to multiple sclerosis, n = 66

NCT02059096 (*Continued*)

Interventions	rTMS Theta burst TMS Sham rTMS
Outcomes	Pain
Starting date	February 2014
Contact information	Patrick Lacarin placarin@chu-clermontferrand.fr
Notes	Contact with study authors unsuccessful

NCT02070016

Trial name or title	Transcranial magnetic stimulation for low back pain
Methods	Cross-over RCT
Participants	Chronic low back pain
Interventions	rTMS ? comparator
Outcomes	Pain
Starting date	January 2014
Contact information	Sean Mackey, Chief, Division of Pain Medicine, Stanford University
Notes	Contact with study authors unsuccessful. Register record states this study was withdrawn prior to enrolment. Reasons not given

NCT02161302

Trial name or title	The effect of tDCS in the treatment of chronic pelvic pain associated with endometriosis (tDCS)
Methods	Parallel RCT
Participants	Painful endometriosis, n = 30
Interventions	tDCS Sham tDCS
Outcomes	Pain AEs QoL

NCT02161302 (*Continued*)

Starting date	June 2014
Contact information	Wolnei Caumo, MD, PhD, caumo@cpovo.net
Notes	Contact with study authors unsuccessful

NCT02277912

Trial name or title	Efficacy of transcranial magnetic stimulation (TMS) in central post stroke pain (CPSP)
Methods	RCT
Participants	Central poststroke pain, n = 20
Interventions	Navigated rTMS Sham rTMS
Outcomes	Pain intensity QoL AEs
Starting date	June 2013
Contact information	Eija Kalso, PhD, Helsinki University Central Hospital
Notes	Register record notes "The recruitment status of this study is unknown. The completion date has passed and the status has not been verified in more than two years." Correspondence with study authors 05 January 2017: data analysis ongoing

NCT02330315

Trial name or title	Effects of tDCS and tUS on pain perception in OA of the knee
Methods	Parallel RCT
Participants	OA of the knee, n = 28
Interventions	Active tDCS + active tUS Sham tDCS + sham tUS
Outcomes	Pain AEs QoL
Starting date	March 2015
Contact information	Felipe Fregni, Principal Investigator, Spaulding Rehabilitation Hospital

NCT02330315 (*Continued*)

Notes	Contact with study authors unsuccessful

NCT02386969

Trial name or title	Repetitive transcranial magnetic stimulation in central neuropathic pain
Methods	Cross-over RCT
Participants	Central neuropathic pain, n = 50
Interventions	rTMS Sham rTMS
Outcomes	Pain VAS, average and responder analysis
Starting date	November 2015
Contact information	Charles Quesada, Roland Peyron
Notes	Contact with study authors unsuccessful

NCT02393391

Trial name or title	A novel non invasive brain stimulation based treatment for chronic low back pain (CLBP)
Methods	Parallel RCT
Participants	Chronic low back pain, n = 80
Interventions	tDCS/tACS stimulation Sham tDCS
Outcomes	Pain
Starting date	May 2015
Contact information	Dr Silviu Brill, paincenter@tlvmc.gov.il
Notes	Contact with study authors unsuccessful

NCT02483468

Trial name or title	The effects of cognitive behavioral therapy and transcranial current stimulation (tDCS) on chronic lower back pain
Methods	Parallel RCT
Participants	Chronic low back pain, n = 120
Interventions	tDCS of DLPFC + CBT Sham tDCS + CBT
Outcomes	Pain
Starting date	January 2015
Contact information	Jeffrey Borckardt, Professor, Medical University of South Carolina
Notes	Contact with study authors unsuccessful

NCT02487966

Trial name or title	Optimizing rehabilitation for phantom limb pain using mirror therapy and transcranial direct current stimulation (tDCS)
Methods	Factorial RCT
Participants	Chronic phantom limb pain, n = 132
Interventions	Active tDCS and active mirror therapy Active tDCS and sham mirror therapy Sham tDCS and active mirror therapy Sham tDCS and sham mirrory therapy
Outcomes	Pain QoL (short version SF-36) AEs
Starting date	July 2015
Contact information	Dr Felipe Fregni ffregni@partners.org
Notes	Contact with study authors unsuccessful

NCT02615418

Trial name or title	Non invasive brain stimulation treatment for CLBP (NIBSTCLBP)
Methods	Cross-over RCT
Participants	Chronic low back pain, n = 60
Interventions	tDCS Sham tDCS "partially active- first 2.5 weeks will receive sham treatment followed by active"
Outcomes	Pain Disability
Starting date	January 2016
Contact information	Iftach Dolev, PhD
Notes	Contact with study authors unsuccessful

NCT02652988

Trial name or title	Home-based transcranial direct current stimulation in fibromyalgia patients
Methods	Parallel RCT
Participants	Fibromyalgia, n = 32
Interventions	tDCS Sham tDCS
Outcomes	Pain Functional capacity
Starting date	January 2016
Contact information	Wolnei Caumo caumo@cpovo.net Aline Brietzke aline_brietzke@yahoo.com.br
Notes	Contact with study authors unsuccessful

NCT02665988

Trial name or title	Adjunctive transcranial direct current stimulation (tDCS)
Methods	Parallel RCT
Participants	Chronic pain, n = 36

NCT02665988 (*Continued*)

Interventions	tDCS Sham tDCS
Outcomes	Pain Physical activity
Starting date	January 2016
Contact information	Alok Madan, PhD amadan@menninger.edu Gladys Jimenez, PhD gjtorres@menninger.edu
Notes	Correspondance with study authors 20 December 2016 - data collection ongoing

NCT02687360

Trial name or title	Imaging the effects of rTMS on chronic pain
Methods	Parallel RCT
Participants	Chronic neuropathic pain, n = 60
Interventions	Active rTMS, prefrontal Sham rTMS
Outcomes	Pain QoL
Starting date	March 2016
Contact information	Diana Martinez, MD, dm437@cumc.columbia.edu
Notes	Contact with study authors unsuccessful

NCT02723175

Trial name or title	The effects of CBT and (tDCS) on fibromyalgia patients
Methods	Parallel RCT
Participants	Fibromyalgia, n = 72
Interventions	tDCS + CBT Sham tDCS + CBT
Outcomes	Pain QoL

NCT02723175 (*Continued*)

Starting date	November 2014
Contact information	Jeffrey Borckardt, Ph.D. borckard@musc.edu
Notes	Contact with study authors unsuccessful

NCT02723929

Trial name or title	Effects of tDCS and tUS on pain perception in OA of the knee
Methods	Parallel RCT
Participants	OA knee, n = 64
Interventions	Active tDCS/active tUS Sham tDCS/sham tUS
Outcomes	Pain
Starting date	September 2016
Contact information	Felipe Fregni, Spaulding Rehabilitation Hospital
Notes	Contact with study authors unsuccessful

NCT02768129

Trial name or title	Transcranial direct current stimulation for chronic low back pain
Methods	Parallel RCT
Participants	Chronic low back pain, n = 60
Interventions	tDCS Sham tDCS
Outcomes	Pain
Starting date	November 2014
Contact information	Butler Hospital, individual not specified
Notes	Contact with study authors unsuccessful

NCT02771990

Trial name or title	tDCS for chronic low back pain
Methods	Parallel RCT
Participants	Chronic low back pain, n = 40
Interventions	tDCS Sham tDCS
Outcomes	Pain
Starting date	October 2013
Contact information	Frederick Burgess, MD, PhD Benjamin Greenberg, MD, PhD Providence VA Medical Center
Notes	Correspondence with study authors 21 December 2017, study in progress

NCT02813629

Trial name or title	tDCS associated with peripheral electrical stimulation for pain control in individuals with sickle cell disease (tDCS/PES_SCD)
Methods	Parallel RCT
Participants	Sickle cell disease, n = 80
Interventions	ss-tDCS (active) plus PES (active) ss-tDCS (active) plus PES (simulated) ss-tDCS (simulated) plus PES (active) ss-tDCS (simulated) plus PES (simulated) sc-tDCS (active) plus PES (active) sc-tDCS (active) plus PES (simulated) sc-tDCS (simulated) plus PES (active) sc-TDCS (simulated) plus PES (simulated)
Outcomes	Pain Function
Starting date	March 2016
Contact information	Prof. Abrahão F Baptista, afbaptista@ufba.br Tiago S. Lopes, Sr, tiago.lopes56@yahoo.com
Notes	Contact with study authors unsuccessful

NCT03015558

Trial name or title	Analgesic effect of non invasive stimulation: transcranial direct current stimulation of opercular-insular cortex
Methods	Parallel RCT
Participants	CRPS, n = 40
Interventions	tDCS of operculo-insular cortex
Outcomes	Pain
Starting date	November 2016
Contact information	luis.garcia-larrea@univ-lyon1.fr
Notes	

NCT03137472

Trial name or title	TMS for complex regional pain syndrome
Methods	Parallel RCT
Participants	CRPS, n = 40
Interventions	Theta-burst rTMS
Outcomes	Pain
Starting date	24 April 2017
Contact information	vsalmasi@stanford.edu
Notes	

RBR-9dxp3k

Trial name or title	Effectiveness of transcranial direct current stimulation combined with kinesiotherapy in patients with chronic temporomandibular disorders (TMJ): clinical, randomized, double-blind, placebo controlled trial
Methods	Parallel RCT
Participants	Chronic temporomandibular pain
Interventions	tDCS + kinesiotherapy Sham tDCS + kinesiotherapy
Outcomes	Pain

RBR-9dxp3k (*Continued*)

Starting date	December 2013
Contact information	Maitê de Freitas, maite_famaral@hotmail.com
Notes	Correspondence with study authors 31 December 2016 - study report under peer review for publication

AE: adverse events; **CBT**: cognitive behavioural therapy; **CRPS**: complex regional pain syndrome; **DLPFC**: dorsolateral prefrontal cortex; **FIQ**: Fibromyalgia Impact Questionnaire; **GMI**: graded motor imagery; **HR-QoL**: health-related quality of life; **OA**: osteoarthritis; **PES**: peripheral electrical stimulation; **QoL**: quality of life; **RCT**: randomised controlled trial; **rTMS**: repetitive transcranial magnetic stimulation; **SCI**: spinal cord injury; **tACS**: transcranial alternating current stimulation; **tDCS**: transcranial direct current stimulation; **TENS**: transcutaneous electrical nerve stimulation; **tUS**: transcranial ultrasound; **VAS**: visual analogue scale; **WHO-QOL**: World Health Organization-QoL; **WOMAC**: Western Ontario and McMaster Universities Arthritis Index

DATA AND ANALYSES

Comparison 1. Repetitive transcranial magnetic stimulation (rTMS)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pain: short-term follow-up	27		Std. Mean Difference (Fixed, 95% CI)	-0.22 [-0.29, -0.16]
1.1 Low-frequency ≤ 1 Hz	7		Std. Mean Difference (Fixed, 95% CI)	0.13 [-0.03, 0.28]
1.2 High-frequency ≥ 5 Hz	25		Std. Mean Difference (Fixed, 95% CI)	-0.30 [-0.37, -0.23]
2 Pain: short-term follow-up, subgroup analysis: multiple-dose vs single-dose studies	27		Std. Mean Difference (Random, 95% CI)	-0.26 [-0.40, -0.13]
2.1 Single-dose studies	13		Std. Mean Difference (Random, 95% CI)	-0.23 [-0.36, -0.10]
2.2 Multiple-dose studies	14		Std. Mean Difference (Random, 95% CI)	-0.40 [-0.76, -0.05]
3 Pain: short-term follow-up, subgroup analysis, neuropathic pain participants only	17		Std. Mean Difference (Fixed, 95% CI)	-0.20 [-0.28, -0.13]
3.1 Low-frequency ≤ 1 Hz	5		Std. Mean Difference (Fixed, 95% CI)	0.15 [-0.02, 0.32]
3.2 High-frequency ≥ 5 Hz	17		Std. Mean Difference (Fixed, 95% CI)	-0.28 [-0.36, -0.20]
4 Pain: short-term follow-up, subgroup analysis, non-neuropathic pain participants only	8		Std. Mean Difference (Fixed, 95% CI)	-0.39 [-0.61, -0.17]
4.1 Low-frequency ≤ 1 Hz	1		Std. Mean Difference (Fixed, 95% CI)	0.16 [-0.29, 0.61]
4.2 High-frequency ≥ 5 Hz	7		Std. Mean Difference (Fixed, 95% CI)	-0.56 [-0.81, -0.31]
5 Pain: short-term follow-up, subgroup analysis: motor cortex studies only, low-frequency studies excluded	21		Std. Mean Difference (Random, 95% CI)	-0.37 [-0.51, -0.22]
5.1 Single-dose studies	13		Std. Mean Difference (Random, 95% CI)	-0.38 [-0.49, -0.27]
5.2 Multiple-dose studies	8		Std. Mean Difference (Random, 95% CI)	-0.34 [-0.73, 0.05]
6 Sensitivity analysis - imputed correlation coefficient increased. Pain: short-term follow-up	29		Std. Mean Difference (Random, 95% CI)	-0.27 [-0.40, -0.14]
6.1 Low-frequency ≤ 1 Hz	7		Std. Mean Difference (Random, 95% CI)	0.15 [0.01, 0.29]
6.2 High-frequency ≥ 5 Hz	28		Std. Mean Difference (Random, 95% CI)	-0.35 [-0.49, -0.22]
7 Sensitivity analysis - imputed correlation coefficient decreased. Pain: short-term follow-up	28		Std. Mean Difference (Random, 95% CI)	-0.26 [-0.40, -0.13]
7.1 Low-frequency ≤ 1 Hz	7		Std. Mean Difference (Random, 95% CI)	0.13 [-0.06, 0.33]
7.2 High-frequency ≥ 5 Hz	26		Std. Mean Difference (Random, 95% CI)	-0.34 [-0.49, -0.19]

8 Sensitivity analysis - imputed correlation increased. Pain: short-term follow-up, subgroup analysis: motor cortex studies only, low-frequency studies excluded	20		Std. Mean Difference (Random, 95% CI)	-0.37 [-0.50, -0.24]
8.1 Single-dose studies	13		Std. Mean Difference (Random, 95% CI)	-0.39 [-0.50, -0.28]
8.2 Multiple-dose studies	7		Std. Mean Difference (Random, 95% CI)	-0.33 [-0.71, 0.04]
9 Sensitivity analysis - imputed correlation decreased. Pain: short-term follow-up, subgroup analysis: motor cortex studies only, low-frequency studies excluded	20		Std. Mean Difference (Random, 95% CI)	-0.37 [-0.52, -0.22]
9.1 Single-dose studies	13		Std. Mean Difference (Random, 95% CI)	-0.37 [-0.47, -0.26]
9.2 Multiple-dose studies	7		Std. Mean Difference (Random, 95% CI)	-0.36 [-0.81, 0.09]
10 Sensitivity analysis - inclusion of high risk of bias studies. Pain: short-term follow-up	31		Std. Mean Difference (Fixed, 95% CI)	-0.27 [-0.34, -0.20]
10.1 Low-frequency ≤ 1 Hz	10		Std. Mean Difference (Fixed, 95% CI)	0.07 [-0.07, 0.22]
10.2 High-frequency ≥ 5 Hz	28		Std. Mean Difference (Fixed, 95% CI)	-0.36 [-0.44, -0.29]
11 Sensitivity analysis - inclusion of high risk of bias studies. Pain: short-term follow-up, subgroup analysis: motor cortex studies only, low-frequency studies excluded	24		Std. Mean Difference (Random, 95% CI)	-0.41 [-0.55, -0.26]
11.1 Single-dose studies	15		Std. Mean Difference (Random, 95% CI)	-0.35 [-0.46, -0.24]
11.2 Multiple-dose studies	10		Std. Mean Difference (Random, 95% CI)	-0.53 [-0.91, -0.15]
12 Pain: short-term follow-up, subgroup analysis: prefrontal cortex studies only	6		Std. Mean Difference (Random, 95% CI)	-0.67 [-1.48, 0.15]
12.1 Low frequency ≤ 1 Hz	1		Std. Mean Difference (Random, 95% CI)	0.16 [-0.29, 0.61]
12.2 High frequency ≥ 5 Hz	5		Std. Mean Difference (Random, 95% CI)	-0.92 [-1.95, 0.12]
13 Sensitivity analysis - inclusion of high risk of bias studies. Pain: short-term follow-up, subgroup analysis: prefrontal cortex studies only	7		Std. Mean Difference (Random, 95% CI)	-0.64 [-1.36, 0.08]
13.1 Multiple-dose studies	7		Std. Mean Difference (Random, 95% CI)	-0.64 [-1.36, 0.08]
14 Pain: short term responder analysis 30% pain reduction	2	89	Risk Ratio (M-H, Random, 95% CI)	2.11 [1.17, 3.80]
15 Sensitivity analysis- inclusion of high risk of bias studies. Disability: medium-term follow-up	5		Std. Mean Difference (Random, 95% CI)	-0.42 [-1.01, 0.17]
16 Pain: medium-term follow-up	11		Std. Mean Difference (Random, 95% CI)	-0.28 [-0.61, 0.05]
16.1 Low-frequency ≤ 1 Hz	2		Std. Mean Difference (Random, 95% CI)	0.14 [-0.41, 0.69]
16.2 High-frequency ≥ 5 Hz	9		Std. Mean Difference (Random, 95% CI)	-0.36 [-0.73, 0.00]
17 Sensitivity analysis - inclusion of high risk of bias studies. Pain: medium-term follow-up	15		Std. Mean Difference (Random, 95% CI)	-0.50 [-0.80, -0.20]

17.1 Low-frequency ≤ 1 Hz	3		Std. Mean Difference (Random, 95% CI)	0.02 [-0.52, 0.56]
17.2 High-frequency ≥ 5 Hz	13		Std. Mean Difference (Random, 95% CI)	-0.57 [-0.90, -0.25]
18 Pain: medium-term follow-up, subgroup analysis: motor cortex studies only	6		Std. Mean Difference (Random, 95% CI)	-0.22 [-0.46, 0.02]
18.1 Low frequency ≤ 1Hz	1		Std. Mean Difference (Random, 95% CI)	-0.08 [-0.86, 0.70]
18.2 High-frequency ≥ 5 Hz	5		Std. Mean Difference (Random, 95% CI)	-0.23 [-0.49, 0.03]
19 Pain: medium-term follow-up, subgroup analysis: prefrontal cortex studies only	5		Std. Mean Difference (Random, 95% CI)	-1.08 [-2.49, 0.32]
19.1 Low frequency ≤ 1 Hz	1		Std. Mean Difference (Random, 95% CI)	0.36 [-0.41, 1.13]
19.2 High-frequency ≥ 5 Hz	4		Std. Mean Difference (Random, 95% CI)	-1.74 [-3.66, 0.19]
20 Pain: long-term follow-up	4		Std. Mean Difference (Random, 95% CI)	-0.14 [-0.44, 0.17]
21 Sensitivity analysis - inclusion of high risk of bias studies. Pain: long-term follow-up	5		Std. Mean Difference (Random, 95% CI)	-0.40 [-0.89, 0.10]
22 Disability: short-term follow-up	5		Std. Mean Difference (Random, 95% CI)	-0.29 [-0.87, 0.29]
23 Sensitivity analysis- inclusion of high risk of bias studies. Disability: short-term follow-up	7		Std. Mean Difference (Random, 95% CI)	-0.30 [-0.72, 0.12]
24 Disability: medium-term follow-up	4		Std. Mean Difference (Random, 95% CI)	-0.37 [-1.07, 0.33]
25 Pain: short term responder analysis 50% pain reduction	1	54	Risk Ratio (M-H, Random, 95% CI)	1.89 [1.03, 3.47]
26 Disability: long-term follow-up	3		Std. Mean Difference (Random, 95% CI)	-0.23 [-0.62, 0.16]
27 Sensitivity analysis - inclusion of high risk of bias studies. Disability: long-term follow-up	4		Std. Mean Difference (Random, 95% CI)	-0.41 [-0.87, 0.05]
28 Quality of life: short-term follow-up (Fibromyalgia Impact Questionnaire)	4	105	Mean Difference (IV, Random, 95% CI)	-10.80 [-15.04, -6.55]
29 Quality of life: medium-term follow-up (Fibromyalgia Impact Questionnaire)	4	105	Mean Difference (IV, Fixed, 95% CI)	-11.49 [-16.73, -6.25]
30 Sensitivity analysis - inclusion of high risk of bias studies. Quality of life: medium-term follow-up (Fibromyalgia Impact Questionnaire)	5	143	Mean Difference (IV, Fixed, 95% CI)	-8.93 [-13.49, -4.37]
31 Quality of life: long-term follow-up	2	51	Mean Difference (IV, Fixed, 95% CI)	-6.78 [-13.43, -0.14]
32 Sensitivity analysis - inclusion of high risk of bias studies. Quality of life: long-term follow-up	3	89	Mean Difference (IV, Fixed, 95% CI)	-8.58 [-13.84, -3.33]

Comparison 2. Cranial electrotherapy stimulation (CES)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pain: short-term follow-up	5	270	Std. Mean Difference (IV, Random, 95% CI)	-0.24 [-0.48, 0.01]
2 Quality of life: short term follow up	1		Mean Difference (IV, Random, 95% CI)	Subtotals only

Comparison 3. Transcranial direct current stimulation (tDCS)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pain: short-term follow-up	26		Std. Mean Difference (Random, 95% CI)	-0.43 [-0.63, -0.22]
1.1 Single-dose studies	4		Std. Mean Difference (Random, 95% CI)	-0.18 [-0.38, 0.02]
1.2 Multiple-dose studies	22		Std. Mean Difference (Random, 95% CI)	-0.51 [-0.77, -0.25]
2 Pain: short-term sensitivity analysis: correlation increased	26		Std. Mean Difference (Random, 95% CI)	-0.43 [-0.62, -0.23]
3 Pain: short-term sensitivity analysis: correlation decreased	26		Std. Mean Difference (Random, 95% CI)	-0.44 [-0.64, -0.23]
4 Pain: short term sensitivity analysis, inclusion of high risk of bias studies	31		Std. Mean Difference (Random, 95% CI)	-0.48 [-0.67, -0.29]
4.1 Single-dose studies	4		Std. Mean Difference (Random, 95% CI)	-0.18 [-0.38, 0.02]
4.2 Multiple-dose studies	27		Std. Mean Difference (Random, 95% CI)	-0.56 [-0.79, -0.32]
5 Pain: short-term follow-up, subgroup analysis: motor cortex studies only	25		Std. Mean Difference (Random, 95% CI)	-0.47 [-0.67, -0.28]
5.1 Single-dose studies	4		Std. Mean Difference (Random, 95% CI)	-0.18 [-0.38, 0.02]
5.2 Multiple-dose studies	21		Std. Mean Difference (Random, 95% CI)	-0.58 [-0.84, -0.33]
6 Pain: short-term follow-up, subgroup analysis: motor cortex studies only, sensitivity analysis: correlation increased	26		Std. Mean Difference (Random, 95% CI)	-0.45 [-0.64, -0.26]
6.1 Single-dose studies	4		Std. Mean Difference (Random, 95% CI)	-0.18 [-0.37, 0.01]
6.2 Multiple-dose studies	22		Std. Mean Difference (Random, 95% CI)	-0.55 [-0.81, -0.30]
7 Pain: short-term follow-up, subgroup analysis: motor cortex studies only, sensitivity analysis: correlation decreased	26		Std. Mean Difference (Random, 95% CI)	-0.40 [-0.58, -0.22]
7.1 Single-dose studies	4		Std. Mean Difference (Random, 95% CI)	-0.18 [-0.38, 0.03]
7.2 Multiple-dose studies	22		Std. Mean Difference (Random, 95% CI)	-0.49 [-0.72, -0.26]
8 Pain: short-term follow-up, subgroup analysis, neuropathic and non neuropathic pain	25		Std. Mean Difference (Random, 95% CI)	-0.37 [-0.56, -0.19]
8.1 Neuropathic	9		Std. Mean Difference (Random, 95% CI)	-0.26 [-0.53, 0.01]
8.2 Non neuropathic	16		Std. Mean Difference (Random, 95% CI)	-0.42 [-0.67, -0.17]

9 Pain: short term follow-up responder analysis 30% pain reduction	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
10 Pain: short term follow-up responder analysis 50% pain reduction	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
11 Pain: medium-term follow-up	14		Std. Mean Difference (Random, 95% CI)	-0.43 [-0.72, -0.13]
12 Pain: medium term follow-up responder analysis 30% pain reduction	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
13 Pain: medium term follow-up responder analysis 50% pain reduction	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
14 Sensitivity analysis - inclusion of high risk of bias studies. Pain: medium-term follow-up	16		Std. Mean Difference (Random, 95% CI)	-0.45 [-0.72, -0.18]
15 Pain: long-term follow-up	3		Std. Mean Difference (Random, 95% CI)	-0.01 [-0.43, 0.41]
16 Disability: short-term follow-up	4	212	Std. Mean Difference (IV, Random, 95% CI)	-0.01 [-0.28, 0.26]
17 Disability: medium-term follow-up	1		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
18 Quality of life: short-term follow-up	4	82	Std. Mean Difference (IV, Random, 95% CI)	0.66 [0.21, 1.11]
19 Quality of life: medium-term follow-up	3	87	Std. Mean Difference (IV, Random, 95% CI)	0.34 [-0.09, 0.76]

Comparison 4. Reduced impedance non-invasive cortical electrostimulation (RINCE)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pain: short-term follow-up	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
2 Sensitivity analysis - inclusion of high risk of bias studies. Pain: short-term follow-up	2	115	Std. Mean Difference (IV, Random, 95% CI)	-0.59 [-0.99, -0.18]
3 Quality of Life: short term follow-up	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
4 Sensitivity analysis - inclusion of high risk of bias studies. Quality of life: short term follow-up	2	115	Std. Mean Difference (IV, Random, 95% CI)	-0.45 [-0.91, 0.02]

Comparison 5. Transcranial random noise stimulation

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pain	1		Std. Mean Difference (Fixed, 95% CI)	-0.19 [-0.64, 0.26]

Analysis 1.1. Comparison 1 Repetitive transcranial magnetic stimulation (rTMS), Outcome 1 Pain: short-term follow-up.

Review: Non-invasive brain stimulation techniques for chronic pain

Comparison: 1 Repetitive transcranial magnetic stimulation (rTMS)

Outcome: 1 Pain: short-term follow-up

Study or subgroup	Std. Mean Difference (SE)	Std. Mean Difference IV,Fixed,95% CI	Weight	Std. Mean Difference IV,Fixed,95% CI
1 Low-frequency ≤ 1 Hz				
Andr -Obadia 2006	-0.016296 (0.259415)		1.7 %	-0.02 [-0.52, 0.49]
Carretero 2009	0.15649 (0.230164)		2.1 %	0.16 [-0.29, 0.61]
Lefaucheur 2001b	0.156 (0.162229)		4.3 %	0.16 [-0.16, 0.47]
Lefaucheur 2006 (1)	0.37847 (0.21421)		2.5 %	0.38 [-0.04, 0.80]
Lefaucheur 2008	0.14778 (0.140854)		5.7 %	0.15 [-0.13, 0.42]
Saitoh 2007	-0.169857 (0.332186)		1.0 %	-0.17 [-0.82, 0.48]
Yagci 2014	-0.46 (0.408163)		0.7 %	-0.46 [-1.26, 0.34]
Subtotal (95% CI)			**18.0 %**	**0.13 [-0.03, 0.28]**
Heterogeneity: Chi^2 = 4.62, df = 6 (P = 0.59); I^2 =0.0%				
Test for overall effect: Z = 1.59 (P = 0.11)				
2 High-frequency ≥ 5 Hz				
Andr -Obadia 2006	-0.066506 (0.259685)		1.7 %	-0.07 [-0.58, 0.44]
Andr -Obadia 2008 (2)	-0.41092 (0.191008)		3.1 %	-0.41 [-0.79, -0.04]
Andr -Obadia 2008 (3)	-0.287518 (0.187174)		3.2 %	-0.29 [-0.65, 0.08]
Andr -Obadia 2011	-0.383319 (0.105999)		10.1 %	-0.38 [-0.59, -0.18]
Avery 2013	0.57 (0.494898)		0.5 %	0.57 [-0.40, 1.54]
Borckardt 2009	-2.717609 (0.743356)		0.2 %	-2.72 [-4.17, -1.26]

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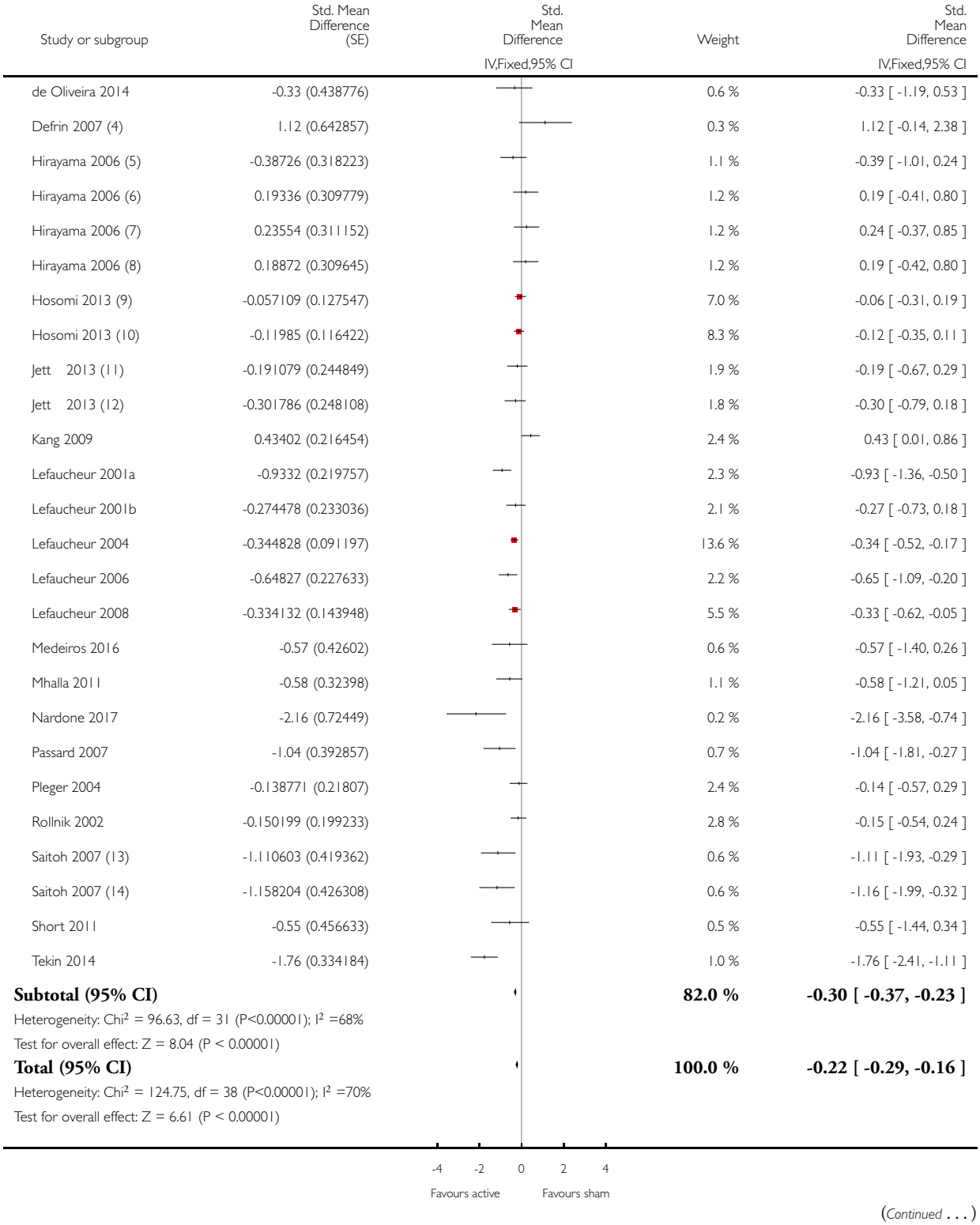

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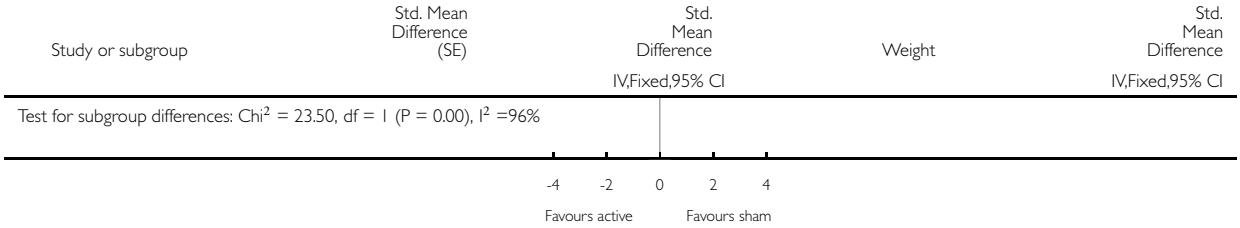

(1) 1Hz

(2) antero-posterior coil orientation

(3) medial-lateral coil orientation

(4) Pain score higher at baseline in active stim group

(5) M1

(6) PMA

(7) S1

(8) SMA

(9) M1 Group A (real followed by sham)

(10) M1 Group B (sham followed by real)

(11) Leg area M1

(12) hand area M1

(13) 10 Hz

(14) 5Hz

Analysis 1.2. Comparison 1 Repetitive transcranial magnetic stimulation (rTMS), Outcome 2 Pain: short-term follow-up, subgroup analysis: multiple-dose vs single-dose studies.

Review: Non-invasive brain stimulation techniques for chronic pain

Comparison: 1 Repetitive transcranial magnetic stimulation (rTMS)

Outcome: 2 Pain: short-term follow-up, subgroup analysis: multiple-dose vs single-dose studies

Study or subgroup	Std. Mean Difference (SE)	Std. Mean Difference IV,Random,95% CI	Weight	Std. Mean Difference IV,Random,95% CI
1 Single-dose studies				
Andr -Obadia 2006 (1)	-0.016296 (0.259415)		2.8 %	-0.02 [-0.52, 0.49]
Andr -Obadia 2006 (2)	-0.066506 (0.259685)		2.8 %	-0.07 [-0.58, 0.44]
Andr -Obadia 2008 (3)	-0.41092 (0.191008)		3.3 %	-0.41 [-0.79, -0.04]
Andr -Obadia 2008 (4)	-0.287518 (0.187174)		3.4 %	-0.29 [-0.65, 0.08]
Andr -Obadia 2011	-0.383319 (0.105999)		4.0 %	-0.38 [-0.59, -0.18]
Hirayama 2006 (5)	0.18872 (0.309645)		2.4 %	0.19 [-0.42, 0.80]
Hirayama 2006 (6)	0.19336 (0.309779)		2.4 %	0.19 [-0.41, 0.80]
Hirayama 2006 (7)	0.23554 (0.311152)		2.4 %	0.24 [-0.37, 0.85]
Hirayama 2006 (8)	-0.38726 (0.318223)		2.3 %	-0.39 [-1.01, 0.24]
Jett 2013	-0.301786 (0.248108)		2.9 %	-0.30 [-0.79, 0.18]
Jett 2013	-0.191079 (0.244849)		2.9 %	-0.19 [-0.67, 0.29]
Lefaucheur 2001a	-0.9332 (0.219757)		3.1 %	-0.93 [-1.36, -0.50]
Lefaucheur 2001b (9)	-0.274478 (0.233036)		3.0 %	-0.27 [-0.73, 0.18]
Lefaucheur 2001b (10)	0.156 (0.230164)		3.0 %	0.16 [-0.30, 0.61]
Lefaucheur 2004	-0.344828 (0.091197)		4.1 %	-0.34 [-0.52, -0.17]
Lefaucheur 2006 (11)	-0.64827 (0.227633)		3.0 %	-0.65 [-1.09, -0.20]
Lefaucheur 2006 (12)	0.37847 (0.21421)		3.1 %	0.38 [-0.04, 0.80]
Lefaucheur 2008 (13)	-0.334132 (0.143948)		3.8 %	-0.33 [-0.62, -0.05]
Lefaucheur 2008 (14)	0.14778 (0.140854)		3.8 %	0.15 [-0.13, 0.42]
Pleger 2004	-0.138771 (0.21807)		3.1 %	-0.14 [-0.57, 0.29]
Rollnik 2002	-0.150199 (0.199233)		3.3 %	-0.15 [-0.54, 0.24]
Saitoh 2007 (15)	-0.169857 (0.332186)		2.2 %	-0.17 [-0.82, 0.48]
Saitoh 2007 (16)	-1.158204 (0.426308)		1.7 %	-1.16 [-1.99, -0.32]

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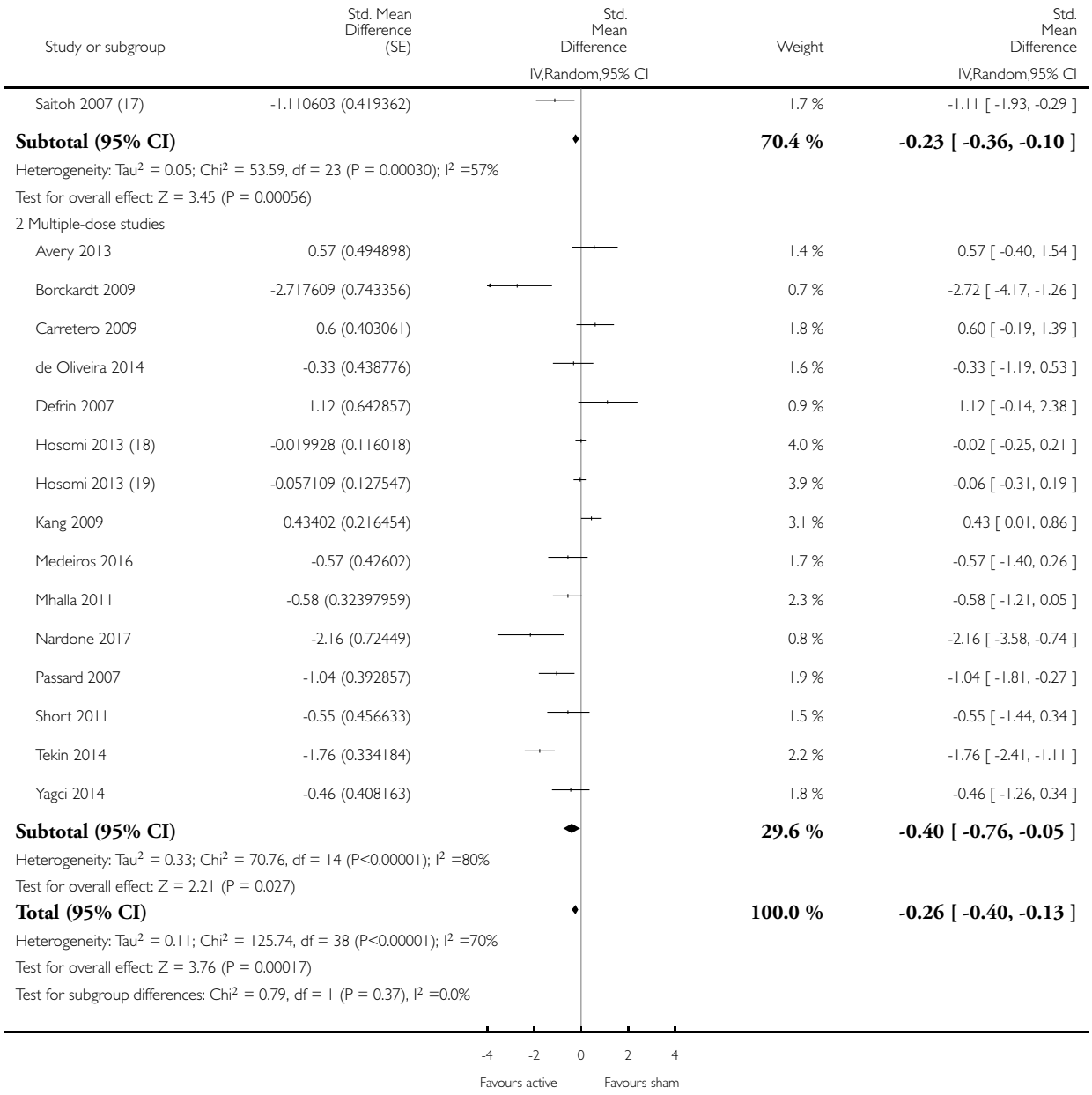

(1) 1Hz

(2) 20Hz

(3) 20Hz antero-posterior coil orientation

(4) 20 Hz medial-lateral coil orientation

(5) SMA

(6) PMA

(7) S1

(8) M1

(9) 10Hz

(10) 0.5 Hz

(11) 10Hz

(12) 1Hz

(13) 10 Hz

(14) 1Hz

(15) 1Hz

(16) 5Hz

(17) 10Hz

(18) M1 Group A real followed by sham

(19) M1 Sham followed by real

Analysis 1.3. Comparison 1 Repetitive transcranial magnetic stimulation (rTMS), Outcome 3 Pain: short-term follow-up, subgroup analysis, neuropathic pain participants only.

Review: Non-invasive brain stimulation techniques for chronic pain

Comparison: 1 Repetitive transcranial magnetic stimulation (rTMS)

Outcome: 3 Pain: short-term follow-up, subgroup analysis, neuropathic pain participants only

Study or subgroup	Std. Mean Difference (SE)	Std. Mean Difference IV,Fixed,95% CI	Weight	Std. Mean Difference IV,Fixed,95% CI
1 Low-frequency ≤ 1 Hz				
Andr -Obadia 2006	-0.016296 (0.259415)		1.9 %	-0.02 [-0.52, 0.49]
Lefaucheur 2001b	0.156 (0.162229)		4.9 %	0.16 [-0.16, 0.47]
Lefaucheur 2006 (1)	0.37847 (0.21421)		2.8 %	0.38 [-0.04, 0.80]
Lefaucheur 2008	0.14778 (0.140854)		6.5 %	0.15 [-0.13, 0.42]
Saitoh 2007	-0.169857 (0.332186)		1.2 %	-0.17 [-0.82, 0.48]
Subtotal (95% CI)			**17.3 %**	**0.15 [-0.02, 0.32]**
Heterogeneity: Chi^2 = 2.48, df = 4 (P = 0.65); I^2 =0.0%				
Test for overall effect: Z = 1.71 (P = 0.087)				
2 High-frequency ≥ 5 Hz				
Andr -Obadia 2006	-0.066506 (0.259685)		1.9 %	-0.07 [-0.58, 0.44]
Andr -Obadia 2008 (2)	-0.41092 (0.191008)		3.5 %	-0.41 [-0.79, -0.04]
Andr -Obadia 2008 (3)	-0.287518 (0.187174)		3.7 %	-0.29 [-0.65, 0.08]
Andr -Obadia 2011	-0.383319 (0.105999)		11.5 %	-0.38 [-0.59, -0.18]
Borckardt 2009	-2.717609 (0.743356)		0.2 %	-2.72 [-4.17, -1.26]
de Oliveira 2014	-0.33 (0.438776)		0.7 %	-0.33 [-1.19, 0.53]
Defrin 2007 (4)	1.12 (0.642857)		0.3 %	1.12 [-0.14, 2.38]
Hirayama 2006 (5)	0.23554 (0.311152)		1.3 %	0.24 [-0.37, 0.85]
Hirayama 2006 (6)	0.19336 (0.309779)		1.3 %	0.19 [-0.41, 0.80]
Hirayama 2006 (7)	0.18872 (0.309645)		1.3 %	0.19 [-0.42, 0.80]
Hirayama 2006 (8)	-0.38726 (0.318223)		1.3 %	-0.39 [-1.01, 0.24]
Hosomi 2013 (9)	-0.057109 (0.127547)		7.9 %	-0.06 [-0.31, 0.19]
Hosomi 2013 (10)	-0.11985 (0.116422)		9.5 %	-0.12 [-0.35, 0.11]
Jett 2013	-0.191079 (0.244849)		2.2 %	-0.19 [-0.67, 0.29]
Jett 2013	-0.301786 (0.248108)		2.1 %	-0.30 [-0.79, 0.18]

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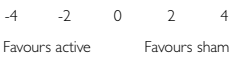
Study or subgroup	Std. Mean Difference (SE)	Std. Mean Difference IV,Fixed,95% CI	Weight	Std. Mean Difference IV,Fixed,95% CI
Kang 2009	0.43402 (0.216454)		2.8 %	0.43 [0.01, 0.86]
Lefaucheur 2001a	-0.9332 (0.219757)		2.7 %	-0.93 [-1.36, -0.50]
Lefaucheur 2001b	-0.274478 (0.233036)		2.4 %	-0.27 [-0.73, 0.18]
Lefaucheur 2004	-0.344828 (0.091197)		15.5 %	-0.34 [-0.52, -0.17]
Lefaucheur 2006	-0.64827 (0.227633)		2.5 %	-0.65 [-1.09, -0.20]
Lefaucheur 2008	-0.334132 (0.143948)		6.2 %	-0.33 [-0.62, -0.05]
Nardone 2017	-2.16 (0.72449)		0.2 %	-2.16 [-3.58, -0.74]
Saitoh 2007 (11)	-1.110603 (0.419362)		0.7 %	-1.11 [-1.93, -0.29]
Saitoh 2007 (12)	-1.158204 (0.426308)		0.7 %	-1.16 [-1.99, -0.32]
Subtotal (95% CI)			**82.7 %**	**-0.28 [-0.36, -0.20]**
Heterogeneity: Chi^2 = 68.06, df = 23 (P<0.00001); I^2 =66%				
Test for overall effect: Z = 7.05 (P < 0.00001)				
Total (95% CI)			**100.0 %**	**-0.20 [-0.28, -0.13]**
Heterogeneity: Chi^2 = 90.72, df = 28 (P<0.00001); I^2 =69%				
Test for overall effect: Z = 5.70 (P < 0.00001)				
Test for subgroup differences: Chi^2 = 20.19, df = 1 (P = 0.00), I^2 =95%				



(1) 1Hz

(2) antero-posterior coil orientation

(3) medial-lateral coil orientation

(4) Pain score higher at baseline in active stim group

(5) S1

(6) PMA

(7) SMA

(8) M1

(9) M1 Group A (real followed by sham)

(10) M1 Group B (sham followed by real)

(11) 10 Hz

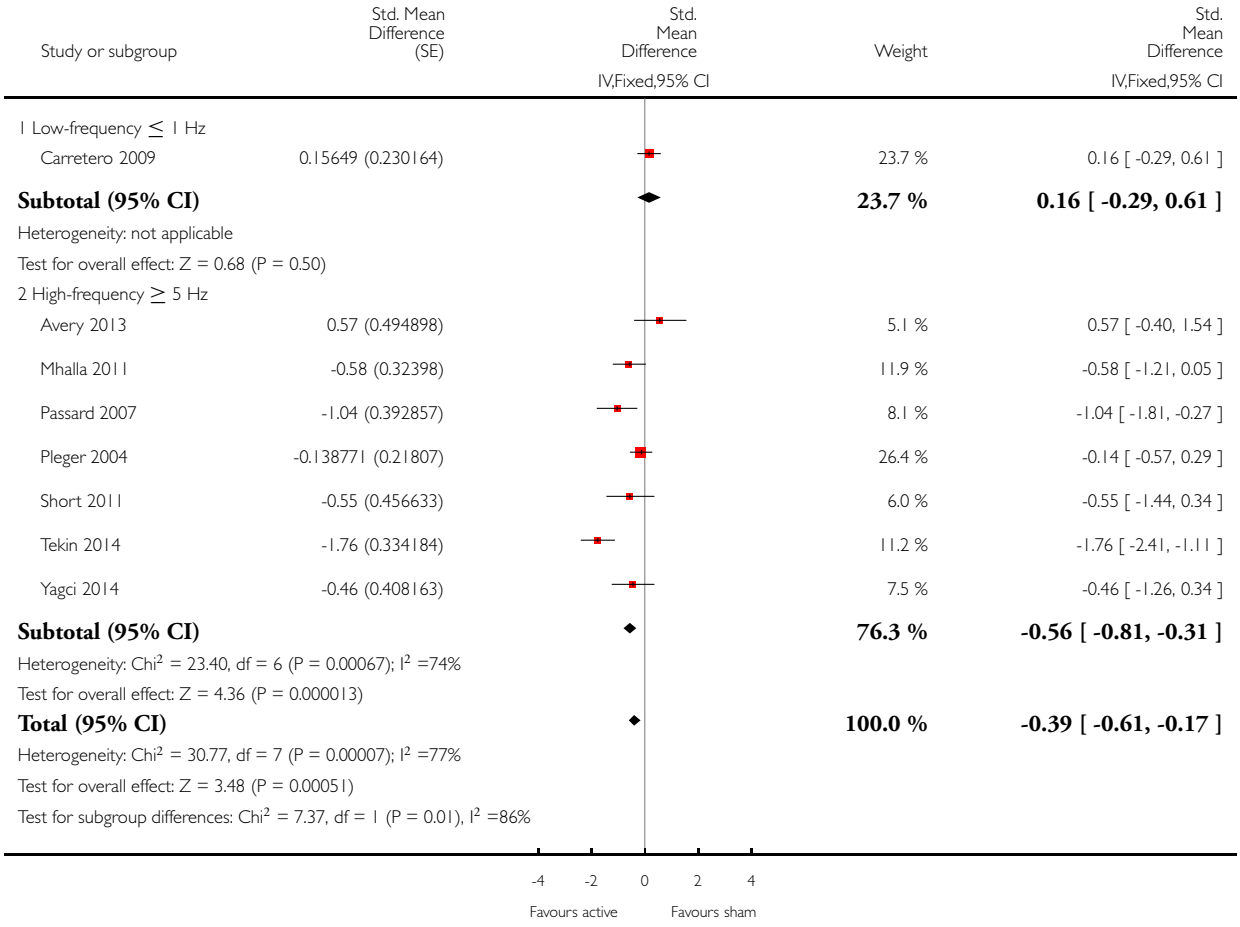
(12) 5Hz

Analysis 1.4. Comparison 1 Repetitive transcranial magnetic stimulation (rTMS), Outcome 4 Pain: short-term follow-up, subgroup analysis, non-neuropathic pain participants only.

Review: Non-invasive brain stimulation techniques for chronic pain

Comparison: 1 Repetitive transcranial magnetic stimulation (rTMS)

Outcome: 4 Pain: short-term follow-up, subgroup analysis, non-neuropathic pain participants only



Analysis 1.5. Comparison 1 Repetitive transcranial magnetic stimulation (rTMS), Outcome 5 Pain: short-term follow-up, subgroup analysis: motor cortex studies only, low-frequency studies excluded.

Review: Non-invasive brain stimulation techniques for chronic pain

Comparison: 1 Repetitive transcranial magnetic stimulation (rTMS)

Outcome: 5 Pain: short-term follow-up, subgroup analysis: motor cortex studies only, low-frequency studies excluded

Study or subgroup	Std. Mean Difference (SE)	Std. Mean Difference IV,Random,95% CI	Weight	Std. Mean Difference IV,Random,95% CI
1 Single-dose studies				
Andr -Obadia 2006	-0.066506 (0.259685)		3.8 %	-0.07 [-0.58, 0.44]
Andr -Obadia 2008 (1)	-0.287518 (0.187174)		4.9 %	-0.29 [-0.65, 0.08]
Andr -Obadia 2008 (2)	-0.41092 (0.191008)		4.9 %	-0.41 [-0.79, -0.04]
Andr -Obadia 2011	-0.383319 (0.105999)		6.3 %	-0.38 [-0.59, -0.18]
Hirayama 2006	-0.38726 (0.318223)		3.1 %	-0.39 [-1.01, 0.24]
Jett 2013	-0.191079 (0.244849)		4.0 %	-0.19 [-0.67, 0.29]
Jett 2013	-0.301786 (0.248108)		4.0 %	-0.30 [-0.79, 0.18]
Lefaucheur 2001a	-0.9332 (0.219757)		4.4 %	-0.93 [-1.36, -0.50]
Lefaucheur 2001b	-0.274478 (0.233036)		4.2 %	-0.27 [-0.73, 0.18]
Lefaucheur 2004	-0.344828 (0.091197)		6.5 %	-0.34 [-0.52, -0.17]
Lefaucheur 2006	-0.64827 (0.227633)		4.3 %	-0.65 [-1.09, -0.20]
Lefaucheur 2008	-0.334132 (0.143948)		5.7 %	-0.33 [-0.62, -0.05]
Pleger 2004	-0.138771 (0.21807)		4.4 %	-0.14 [-0.57, 0.29]
Rollnik 2002	-0.150199 (0.199233)		4.7 %	-0.15 [-0.54, 0.24]
Saitoh 2007	-1.110603 (0.419362)		2.2 %	-1.11 [-1.93, -0.29]
Saitoh 2007	-1.158204 (0.426308)		2.1 %	-1.16 [-1.99, -0.32]
Subtotal (95% CI)			**69.6 %**	**-0.38 [-0.49, -0.27]**
Heterogeneity: Tau² = 0.01; Chi² = 19.48, df = 15 (P = 0.19); I² =23%				
Test for overall effect: Z = 6.75 (P < 0.00001)				
2 Multiple-dose studies				
Defrin 2007	1.12 (0.642857)		1.1 %	1.12 [-0.14, 2.38]
Hosomi 2013 (3)	-0.057109 (0.127547)		5.9 %	-0.06 [-0.31, 0.19]
Hosomi 2013 (4)	-0.019928 (0.116018)		6.1 %	-0.02 [-0.25, 0.21]
Kang 2009	0.43402 (0.216454)		4.5 %	0.43 [0.01, 0.86]

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Study or subgroup	Std. Mean Difference (SE)	Std. Mean Difference IV,Random,95% CI	Weight	Std. Mean Difference IV,Random,95% CI
Medeiros 2016	-0.57 (0.42602)		2.1 %	-0.57 [-1.40, 0.26]
Mhalla 2011	-0.58 (0.32397959)		3.0 %	-0.58 [-1.21, 0.05]
Passard 2007	-1.04 (0.392857)		2.4 %	-1.04 [-1.81, -0.27]
Tekin 2014	-1.76 (0.334184)		2.9 %	-1.76 [-2.41, -1.11]
Yagci 2014	-0.46 (0.408163)		2.3 %	-0.46 [-1.26, 0.34]
Subtotal (95% CI)			**30.4 %**	**-0.34 [-0.73, 0.05]**
Heterogeneity: Tau^2 = 0.25; Chi^2 = 44.59, df = 8 (P<0.00001); I^2 =82%				
Test for overall effect: Z = 1.71 (P = 0.086)				
Total (95% CI)			**100.0 %**	**-0.37 [-0.51, -0.22]**
Heterogeneity: Tau^2 = 0.08; Chi^2 = 71.66, df = 24 (P<0.00001); I^2 =67%				
Test for overall effect: Z = 4.93 (P < 0.00001)				
Test for subgroup differences: Chi^2 = 0.03, df = 1 (P = 0.87), I^2 =0.0%				

(1) medial-lateral coil orientation

(2) antero-posterior coil orientation

(3) Group B sham followed by real

(4) Group A real followed by sham

Analysis 1.6. Comparison 1 Repetitive transcranial magnetic stimulation (rTMS), Outcome 6 Sensitivity analysis - imputed correlation coefficient increased. Pain: short-term follow-up.

Review: Non-invasive brain stimulation techniques for chronic pain

Comparison: 1 Repetitive transcranial magnetic stimulation (rTMS)

Outcome: 6 Sensitivity analysis - imputed correlation coefficient increased. Pain: short-term follow-up

Study or subgroup	Std. Mean Difference (SE)	Weight	Std. Mean Difference IV,Random,95% CI
1 Low-frequency ≤ 1 Hz			
Andr -Obadia 2006	-0.016296 (0.200013)	2.9 %	-0.02 [-0.41, 0.38]
Carretero 2009	0.6 (0.403061)	1.6 %	0.60 [-0.19, 1.39]
Lee 2012	-0.59 (0.760204)	0.6 %	-0.59 [-2.08, 0.90]
Lefaucheur 2001b	0.15649 (0.17746)	3.1 %	0.16 [-0.19, 0.50]
Lefaucheur 2006 (1)	0.37847 (0.165159)	3.2 %	0.38 [0.05, 0.70]
Lefaucheur 2008	0.14778 (0.097135)	3.7 %	0.15 [-0.04, 0.34]
Saitoh 2007	-0.169857 (0.256121)	2.5 %	-0.17 [-0.67, 0.33]
Subtotal (95% CI)		**17.4 %**	**0.15 [0.01, 0.29]**
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 6.36$, df = 6 (P = 0.38); $I^2 = 6\%$			
Test for overall effect: Z = 2.13 (P = 0.033)			
2 High-frequency ≥ 5 Hz			
Andr -Obadia 2006	-0.066506 (0.200221)	2.9 %	-0.07 [-0.46, 0.33]
Andr -Obadia 2008 (2)	-0.287518 (0.144314)	3.3 %	-0.29 [-0.57, 0.00]
Andr -Obadia 2008 (3)	-0.41092 (0.14727)	3.3 %	-0.41 [-0.70, -0.12]
Andr -Obadia 2011	-0.383319 (0.081727)	3.8 %	-0.38 [-0.54, -0.22]
Avery 2013	0.57 (0.494898)	1.2 %	0.57 [-0.40, 1.54]
Borckardt 2009	-2.717609 (0.57314)	1.0 %	-2.72 [-3.84, -1.59]
de Oliveira 2014	-0.33 (0.438776)	1.4 %	-0.33 [-1.19, 0.53]
Defrin 2007	1.12 (0.642857)	0.8 %	1.12 [-0.14, 2.38]
Fregni 2005	0 (0)		Not estimable
Hirayama 2006 (4)	0.23554 (0.239903)	2.6 %	0.24 [-0.23, 0.71]
Hirayama 2006 (5)	0.19336 (0.238845)	2.6 %	0.19 [-0.27, 0.66]
Hirayama 2006 (6)	0.18872 (0.238741)	2.6 %	0.19 [-0.28, 0.66]
Hirayama 2006 (7)	-0.38726 (0.245355)	2.5 %	-0.39 [-0.87, 0.09]

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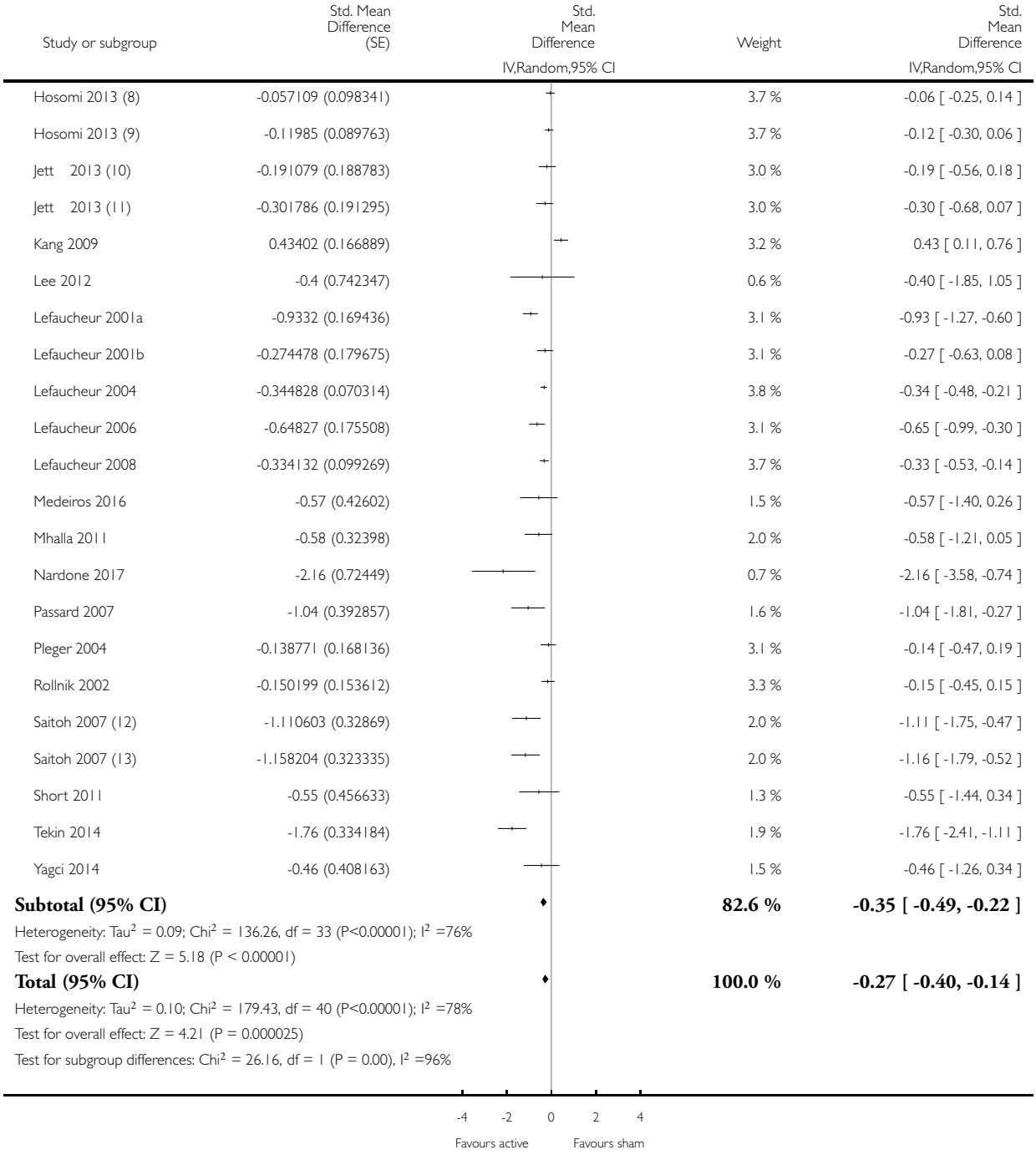

(1) 1Hz

(2) medial-lateral coil orientation

(3) antero-posterior coil orientation

(4) S1

(5) PMA

(6) SMA

(7) M1

(8) M1 Group A (real followed by sham)

(9) M1 Group B (sham followed by real)

(10) M1 leg area

(11) M1 hand area

(12) 5Hz

(13) 10 Hz

Analysis 1.7. Comparison 1 Repetitive transcranial magnetic stimulation (rTMS), Outcome 7 Sensitivity analysis - imputed correlation coefficient decreased. Pain: short-term follow-up.

Review: Non-invasive brain stimulation techniques for chronic pain

Comparison: 1 Repetitive transcranial magnetic stimulation (rTMS)

Outcome: 7 Sensitivity analysis - imputed correlation coefficient decreased. Pain: short-term follow-up

Study or subgroup	Std. Mean Difference (SE)	Std. Mean Difference IV,Random,95% CI	Weight	Std. Mean Difference IV,Random,95% CI
1 Low-frequency ≤ 1 Hz				
Andr -Obadia 2006	-0.016296 (0.311698)		2.3 %	-0.02 [-0.63, 0.59]
Carretero 2009	0.6 (0.403061)		1.8 %	0.60 [-0.19, 1.39]
Lefaucheur 2001b	0.15649 (0.276551)		2.6 %	0.16 [-0.39, 0.70]
Lefaucheur 2006	0.37847 (0.257382)		2.7 %	0.38 [-0.13, 0.88]
Lefaucheur 2008	0.14778 (0.151374)		3.6 %	0.15 [-0.15, 0.44]
Saitoh 2007	-0.169857 (0.355683)		2.0 %	-0.17 [-0.87, 0.53]
Yagci 2014	-0.46 (0.408163)		1.7 %	-0.46 [-1.26, 0.34]
Subtotal (95% CI)			**16.9 %**	**0.13 [-0.06, 0.33]**
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 5.33$, df = 6 (P = 0.50); $I^2 = 0.0\%$				
Test for overall effect: Z = 1.35 (P = 0.18)				
2 High-frequency ≥ 5 Hz				
Andr -Obadia 2006	-0.066506 (0.312022)		2.3 %	-0.07 [-0.68, 0.55]
Andr -Obadia 2008 (1)	-0.41092 (0.229504)		3.0 %	-0.41 [-0.86, 0.04]
Andr -Obadia 2008 (2)	-0.287518 (0.224898)		3.0 %	-0.29 [-0.73, 0.15]
Andr -Obadia 2011	-0.383319 (0.127363)		3.8 %	-0.38 [-0.63, -0.13]
Avery 2013	0.57 (0.494898)		1.4 %	0.57 [-0.40, 1.54]
Borckardt 2009	-2.717609 (0.893174)		0.5 %	-2.72 [-4.47, -0.97]
de Oliveira 2014	-0.33 (0.438776)		1.6 %	-0.33 [-1.19, 0.53]
Defrin 2007	1.12 (0.642857)		0.9 %	1.12 [-0.14, 2.38]
Hirayama 2006 (3)	0.23554 (0.239903)		2.9 %	0.24 [-0.23, 0.71]
Hirayama 2006 (4)	-0.38726 (0.245355)		2.8 %	-0.39 [-0.87, 0.09]
Hirayama 2006 (5)	0.19336 (0.238845)		2.9 %	0.19 [-0.27, 0.66]
Hirayama 2006 (6)	0.18872 (0.238741)		2.9 %	0.19 [-0.28, 0.66]
Hosomi 2013 (7)	-0.11985 (0.139886)		3.7 %	-0.12 [-0.39, 0.15]

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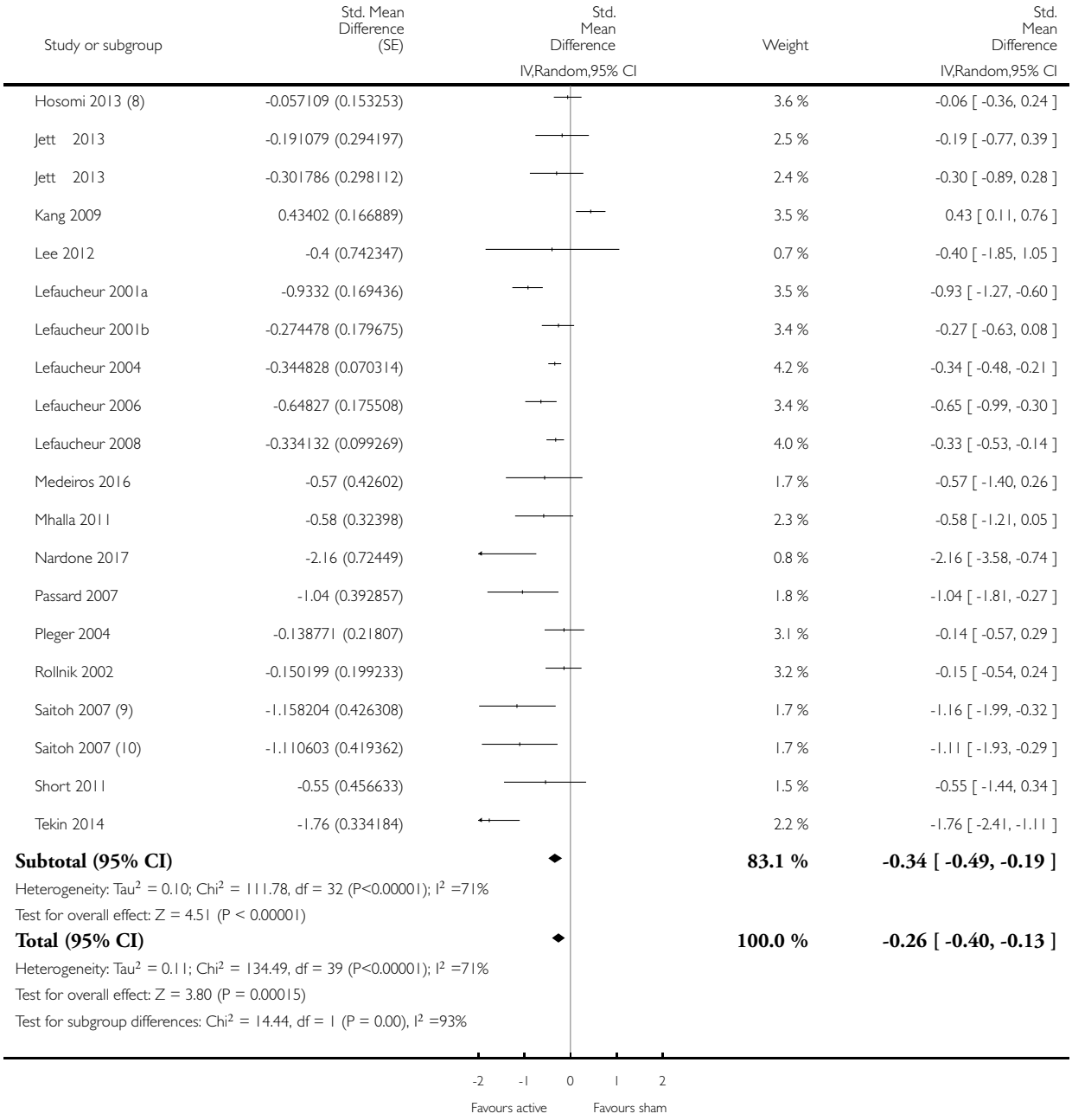


(1) antero-posterior coil orientation

(2) medial-lateral coil orientatioin

(3) S1

(4) M1

(5) PMA

(6) SMA

(7) M1 Group B (sham followed by real)

(8) M1 Group A (real followed by sham)

(9) 5Hz

(10) 10 Hz

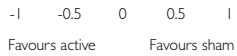
Analysis 1.8. Comparison 1 Repetitive transcranial magnetic stimulation (rTMS), Outcome 8 Sensitivity analysis - imputed correlation increased. Pain: short-term follow-up, subgroup analysis: motor cortex studies only, low-frequency studies excluded.

Review: Non-invasive brain stimulation techniques for chronic pain

Comparison: 1 Repetitive transcranial magnetic stimulation (rTMS)

Outcome: 8 Sensitivity analysis - imputed correlation increased. Pain: short-term follow-up, subgroup analysis: motor cortex studies only, low-frequency studies excluded

Study or subgroup	Std. Mean Difference (SE)	Std. Mean Difference IV,Random,95% CI	Weight	Std. Mean Difference IV,Random,95% CI
1 Single-dose studies				
Andr -Obadia 2006	-0.066506 (0.200221)		4.2 %	-0.07 [-0.46, 0.33]
Andr -Obadia 2008 (1)	-0.287518 (0.144314)		5.1 %	-0.29 [-0.57, 0.00]
Andr -Obadia 2008 (2)	-0.41092 (0.14727)		5.1 %	-0.41 [-0.70, -0.12]
Andr -Obadia 2011	-0.383319 (0.081727)		6.0 %	-0.38 [-0.54, -0.22]
Hirayama 2006	-0.38726 (0.245355)		3.6 %	-0.39 [-0.87, 0.09]
Jett 2013 (3)	-0.301786 (0.191295)		4.3 %	-0.30 [-0.68, 0.07]
Jett 2013 (4)	-0.191079 (0.188783)		4.4 %	-0.19 [-0.56, 0.18]
Lefaucheur 2001a	-0.9332 (0.169436)		4.7 %	-0.93 [-1.27, -0.60]



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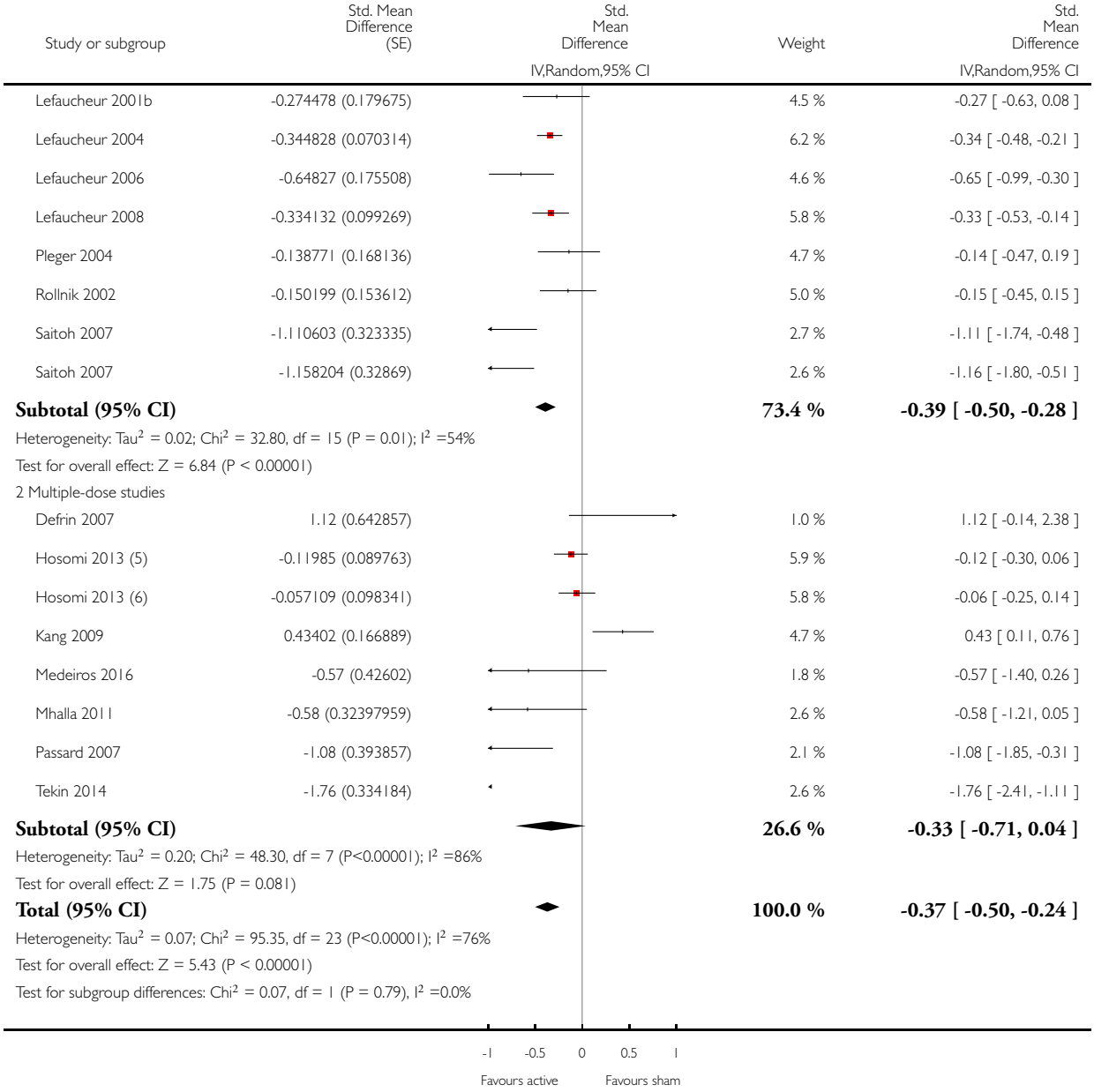

(1) medial-lateral coil orientation

(2) antero-posterior coil orientation

(3) m1 hand area

(4) M1 leg area

(5) Group B (sham followed by real)

(6) Group A (real followed by sham)

Analysis 1.9. Comparison 1 Repetitive transcranial magnetic stimulation (rTMS), Outcome 9 Sensitivity analysis - imputed correlation decreased. Pain: short-term follow-up, subgroup analysis: motor cortex studies only, low-frequency studies excluded.

Review: Non-invasive brain stimulation techniques for chronic pain

Comparison: 1 Repetitive transcranial magnetic stimulation (rTMS)

Outcome: 9 Sensitivity analysis - imputed correlation decreased. Pain: short-term follow-up, subgroup analysis: motor cortex studies only, low-frequency studies excluded

Study or subgroup	Std. Mean Difference (SE)	Std. Mean Difference IV,Random,95% CI	Weight	Std. Mean Difference IV,Random,95% CI
1 Single-dose studies				
Andr -Obadia 2006	-0.066506 (0.312022)		3.6 %	-0.07 [-0.68, 0.55]
Andr -Obadia 2008 (1)	-0.287518 (0.224898)		5.0 %	-0.29 [-0.73, 0.15]
Andr -Obadia 2008 (2)	-0.41092 (0.229504)		4.9 %	-0.41 [-0.86, 0.04]
Andr -Obadia 2011	-0.383319 (0.127363)		6.9 %	-0.38 [-0.63, -0.13]
Hirayama 2006	-0.38726 (0.382358)		2.8 %	-0.39 [-1.14, 0.36]
Jett 2013	-0.301786 (0.298112)		3.8 %	-0.30 [-0.89, 0.28]
Jett 2013	-0.191079 (0.294197)		3.9 %	-0.19 [-0.77, 0.39]
Lefaucheur 2001a	-0.9332 (0.264047)		4.3 %	-0.93 [-1.45, -0.42]
Lefaucheur 2001b	-0.274478 (0.280003)		4.1 %	-0.27 [-0.82, 0.27]
Lefaucheur 2004	-0.344828 (0.109577)		7.2 %	-0.34 [-0.56, -0.13]
Lefaucheur 2006	-0.64827 (0.312022)		3.6 %	-0.65 [-1.26, -0.04]
Lefaucheur 2008	-0.334132 (0.1547)		6.3 %	-0.33 [-0.64, -0.03]
Pleger 2004	-0.138771 (0.262021)		4.4 %	-0.14 [-0.65, 0.37]
Rollnik 2002	-0.150199 (0.239386)		4.7 %	-0.15 [-0.62, 0.32]
Saitoh 2007	-1.110603 (0.503881)		1.9 %	-1.11 [-2.10, -0.12]
Saitoh 2007	-1.158204 (0.512227)		1.8 %	-1.16 [-2.16, -0.15]
Subtotal (95% CI)			**69.3 %**	**-0.37 [-0.47, -0.26]**
Heterogeneity: Tau² = 0.0; Chi² = 13.26, df = 15 (P = 0.58); I² =0.0%				
Test for overall effect: Z = 6.79 (P < 0.00001)				
2 Multiple-dose studies				
Defrin 2007	1.12 (0.642857)		1.3 %	1.12 [-0.14, 2.38]
Hosomi 2013 (3)	-0.11985 (0.139886)		6.6 %	-0.12 [-0.39, 0.15]

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Study or subgroup	Std. Mean Difference (SE)	Std. Mean Difference IV,Random,95% CI	Weight	Std. Mean Difference IV,Random,95% CI
Hosomi 2013 (4)	-0.057109 (0.153253)		6.4 %	-0.06 [-0.36, 0.24]
Kang 2009	0.43402 (0.260078)		4.4 %	0.43 [-0.08, 0.94]
Medeiros 2016	-0.57 (0.42602)		2.4 %	-0.57 [-1.40, 0.26]
Mhalla 2011	-0.58 (0.32397959)		3.5 %	-0.58 [-1.21, 0.05]
Passard 2007	-1.08 (0.392857)		2.7 %	-1.08 [-1.85, -0.31]
Tekin 2014	-1.76 (0.334184)		3.3 %	-1.76 [-2.41, -1.11]
Subtotal (95% CI)			**30.7 %**	**-0.36 [-0.81, 0.09]**
Heterogeneity: Tau^2 = 0.31; Chi^2 = 40.25, df = 7 (P<0.00001); I^2 =83%				
Test for overall effect: Z = 1.58 (P = 0.11)				
Total (95% CI)			**100.0 %**	**-0.37 [-0.52, -0.22]**
Heterogeneity: Tau^2 = 0.07; Chi^2 = 55.72, df = 23 (P = 0.00015); I^2 =59%				
Test for overall effect: Z = 4.70 (P < 0.00001)				
Test for subgroup differences: Chi^2 = 0.00, df = 1 (P = 0.98), I^2 =0.0%				

(1) medial-lateral coil orientation

(2) antero-posterior coil orientation

(3) Group A (sham followed by real)

(4) Group A (real followed by sham)

Analysis 1.10. Comparison 1 Repetitive transcranial magnetic stimulation (rTMS), Outcome 10 Sensitivity analysis - inclusion of high risk of bias studies. Pain: short-term follow-up.

Review: Non-invasive brain stimulation techniques for chronic pain

Comparison: 1 Repetitive transcranial magnetic stimulation (rTMS)

Outcome: 10 Sensitivity analysis - inclusion of high risk of bias studies. Pain: short-term follow-up

Study or subgroup	Std. Mean Difference (SE)	Std. Mean Difference IV,Fixed,95% CI	Weight	Std. Mean Difference IV,Fixed,95% CI
1 Low-frequency ≤ 1 Hz				
Andr -Obadia 2006	-0.016296 (0.259415)		1.7 %	-0.02 [-0.52, 0.49]
Carretero 2009	0.15649 (0.230164)		2.2 %	0.16 [-0.29, 0.61]
Fregni 2011	0 (0)			Not estimable
Irlbacher 2006	-0.178283 (0.188266)		3.3 %	-0.18 [-0.55, 0.19]
Lee 2012 (1)	-0.59 (0.760204)		0.2 %	-0.59 [-2.08, 0.90]
Lefaucheur 2001b	0.156 (0.162229)		4.4 %	0.16 [-0.16, 0.47]
Lefaucheur 2006 (2)	0.37847 (0.21421)		2.5 %	0.38 [-0.04, 0.80]
Lefaucheur 2008	0.14778 (0.140854)		5.9 %	0.15 [-0.13, 0.42]
Saitoh 2007	-0.169857 (0.332186)		1.1 %	-0.17 [-0.82, 0.48]
Yagci 2014	-0.46 (0.408163)		0.7 %	-0.46 [-1.26, 0.34]
Subtotal (95% CI)			**22.0 %**	**0.07 [-0.07, 0.22]**
Heterogeneity: Chi^2 = 7.61, df = 8 (P = 0.47); I^2 =0.0%				
Test for overall effect: Z = 1.02 (P = 0.31)				
2 High-frequency ≥ 5 Hz				
Ahmed 2011	-3.58 (0.660714)		0.3 %	-3.58 [-4.87, -2.29]
Andr -Obadia 2006	-0.066506 (0.259685)		1.7 %	-0.07 [-0.58, 0.44]
Andr -Obadia 2008 (3)	-0.41092 (0.191008)		3.2 %	-0.41 [-0.79, -0.04]
Andr -Obadia 2008 (4)	-0.287518 (0.187174)		3.3 %	-0.29 [-0.65, 0.08]
Andr -Obadia 2011	-0.383319 (0.105999)		10.4 %	-0.38 [-0.59, -0.18]
Avery 2013	0.57 (0.494898)		0.5 %	0.57 [-0.40, 1.54]
Borckardt 2009	-2.717609 (0.743356)		0.2 %	-2.72 [-4.17, -1.26]
Dall'Agnol 2014	-0.59 (0.418367)		0.7 %	-0.59 [-1.41, 0.23]
de Oliveira 2014	-0.33 (0.438776)		0.6 %	-0.33 [-1.19, 0.53]
Defrin 2007 (5)	1.12 (0.642857)		0.3 %	1.12 [-0.14, 2.38]

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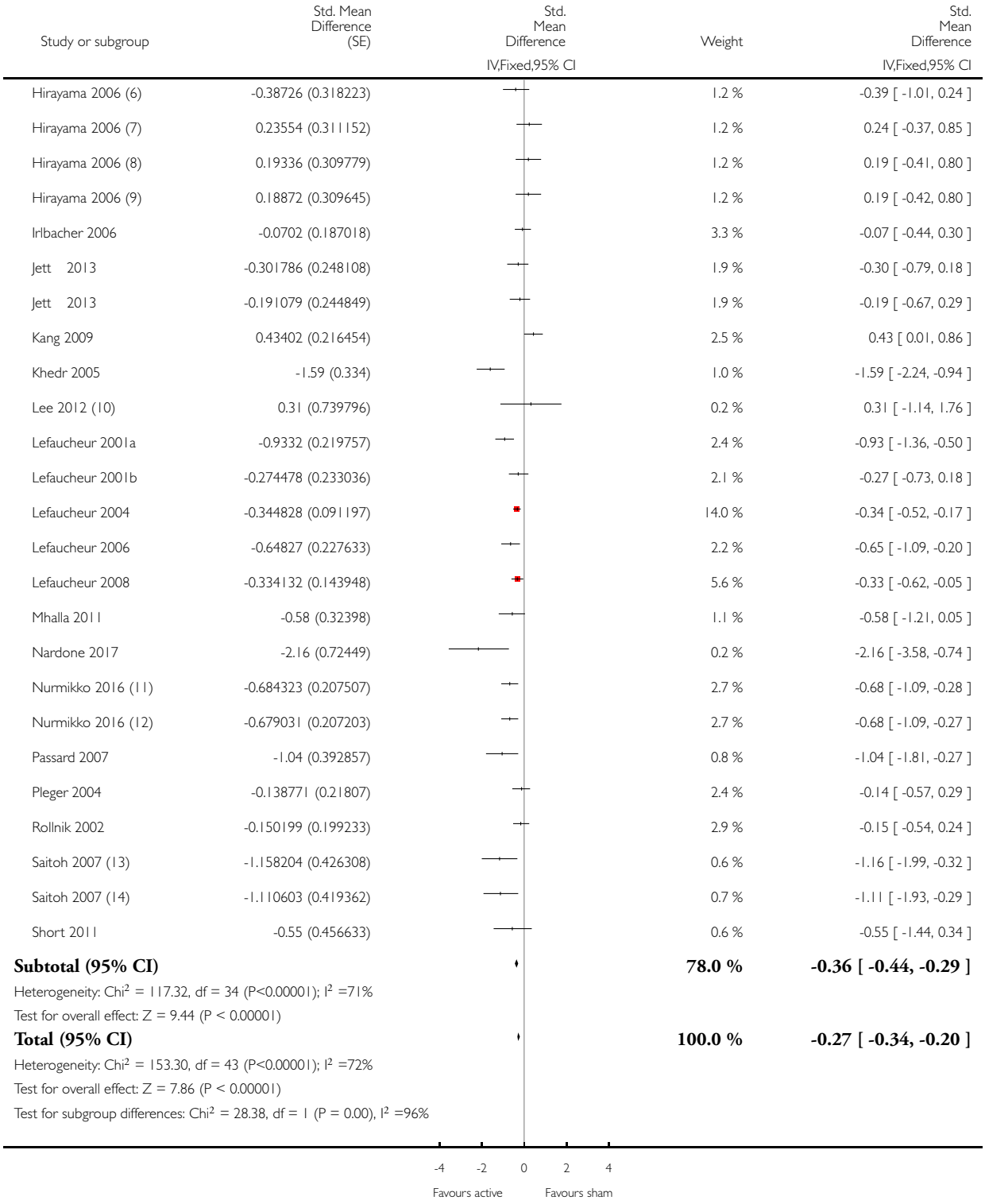

(1) right DLPFC

(2) 1Hz

(3) antero-posterior coil orientation

(4) medial-lateral coil orientation

(5) Pain score higher at baseline in active stim group

(6) M1

(7) S1

(8) PMA

(9) SMA

(10) left M1

(11) M1 hotspot

(12) M1 reorganised area

(13) 5Hz

(14) 10 Hz

Analysis 1.11. Comparison 1 Repetitive transcranial magnetic stimulation (rTMS), Outcome 11 Sensitivity analysis - inclusion of high risk of bias studies. Pain: short-term follow-up, subgroup analysis: motor cortex studies only, low-frequency studies excluded.

Review: Non-invasive brain stimulation techniques for chronic pain

Comparison: 1 Repetitive transcranial magnetic stimulation (rTMS)

Outcome: 11 Sensitivity analysis - inclusion of high risk of bias studies. Pain: short-term follow-up, subgroup analysis: motor cortex studies only, low-frequency studies excluded

Study or subgroup	Std. Mean Difference (SE)	Std. Mean Difference IV,Random,95% CI	Weight	Std. Mean Difference IV,Random,95% CI
1 Single-dose studies				
Andr -Obadia 2006	-0.066506 (0.259685)		3.4 %	-0.07 [-0.58, 0.44]
Andr -Obadia 2008 (1)	-0.287518 (0.187174)		4.2 %	-0.29 [-0.65, 0.08]
Andr -Obadia 2008 (2)	-0.41092 (0.191008)		4.1 %	-0.41 [-0.79, -0.04]
Andr -Obadia 2011	-0.383319 (0.149906)		4.6 %	-0.38 [-0.68, -0.09]
Hirayama 2006	-0.38726 (0.318223)		2.8 %	-0.39 [-1.01, 0.24]
Irlbacher 2006	-0.0702 (0.187018)		4.2 %	-0.07 [-0.44, 0.30]
Jett 2013	-0.301786 (0.248108)		3.5 %	-0.30 [-0.79, 0.18]
Jett 2013	-0.191079 (0.244849)		3.5 %	-0.19 [-0.67, 0.29]
Lefaucheur 2001a	-0.9332 (0.219757)		3.8 %	-0.93 [-1.36, -0.50]
Lefaucheur 2001b	-0.274478 (0.233036)		3.6 %	-0.27 [-0.73, 0.18]
Lefaucheur 2004	-0.344828 (0.091197)		5.2 %	-0.34 [-0.52, -0.17]
Lefaucheur 2006	-0.64827 (0.227633)		3.7 %	-0.65 [-1.09, -0.20]
Lefaucheur 2008	-0.334132 (0.143948)		4.6 %	-0.33 [-0.62, -0.05]
Mhalla 2011	-0.21 (0.316327)		2.8 %	-0.21 [-0.83, 0.41]
Pleger 2004	-0.138771 (0.21807)		3.8 %	-0.14 [-0.57, 0.29]
Rollnik 2002	-0.150199 (0.199233)		4.0 %	-0.15 [-0.54, 0.24]
Saitoh 2007	-1.110603 (0.419362)		2.0 %	-1.11 [-1.93, -0.29]
Saitoh 2007	-1.158204 (0.426308)		2.0 %	-1.16 [-1.99, -0.32]
Subtotal (95% CI)			**65.7 %**	**-0.35 [-0.46, -0.24]**
Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 22.07$, df = 17 (P = 0.18); $I^2 = 23\%$				
Test for overall effect: Z = 6.36 (P < 0.00001)				
2 Multiple-dose studies				
Ahmed 2011	-3.58 (0.660714)		1.0 %	-3.58 [-4.87, -2.29]

(*Continued* . . .)

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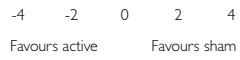
Study or subgroup	Std. Mean Difference (SE)	Std. Mean Difference IV,Random,95% CI	Weight	Std. Mean Difference IV,Random,95% CI
Dall'Agnol 2014	-0.59 (0.418367)		2.0 %	-0.59 [-1.41, 0.23]
Defrin 2007	1.12 (0.642857)		1.1 %	1.12 [-0.14, 2.38]
Hosomi 2013 (3)	-0.11985 (0.116422)		4.9 %	-0.12 [-0.35, 0.11]
Hosomi 2013 (4)	-0.057109 (0.127547)		4.8 %	-0.06 [-0.31, 0.19]
Kang 2009	0.43402 (0.216454)		3.8 %	0.43 [0.01, 0.86]
Khedr 2005	-1.59 (0.334)		2.7 %	-1.59 [-2.24, -0.94]
Lee 2012	0.26 (0.635204)		1.1 %	0.26 [-0.98, 1.50]
Mhalla 2011	-0.58 (0.32397959)		2.7 %	-0.58 [-1.21, 0.05]
Nurmikko 2016 (5)	-0.679031 (0.207203)		3.9 %	-0.68 [-1.09, -0.27]
Nurmikko 2016 (6)	-0.684323 (0.207507)		3.9 %	-0.68 [-1.09, -0.28]
Passard 2007	-1.04 (0.392857)		2.2 %	-1.04 [-1.81, -0.27]
Subtotal (95% CI)			**34.3 %**	**-0.53 [-0.91, -0.15]**
Heterogeneity: Tau^2 = 0.32; Chi^2 = 74.26, df = 11 (P<0.00001); I^2 =85%				
Test for overall effect: Z = 2.75 (P = 0.0059)				
Total (95% CI)			**100.0 %**	**-0.41 [-0.55, -0.26]**
Heterogeneity: Tau^2 = 0.10; Chi^2 = 96.89, df = 29 (P<0.00001); I^2 =70%				
Test for overall effect: Z = 5.41 (P < 0.00001)				
Test for subgroup differences: Chi^2 = 0.79, df = 1 (P = 0.37), I^2 =0.0%				



(1) medial-lateral coil orientation

(2) antero-posterior coil orientation

(3) Group A (sham followed by real)

(4) Group B (real followed by sham)

(5) M1 hotspot

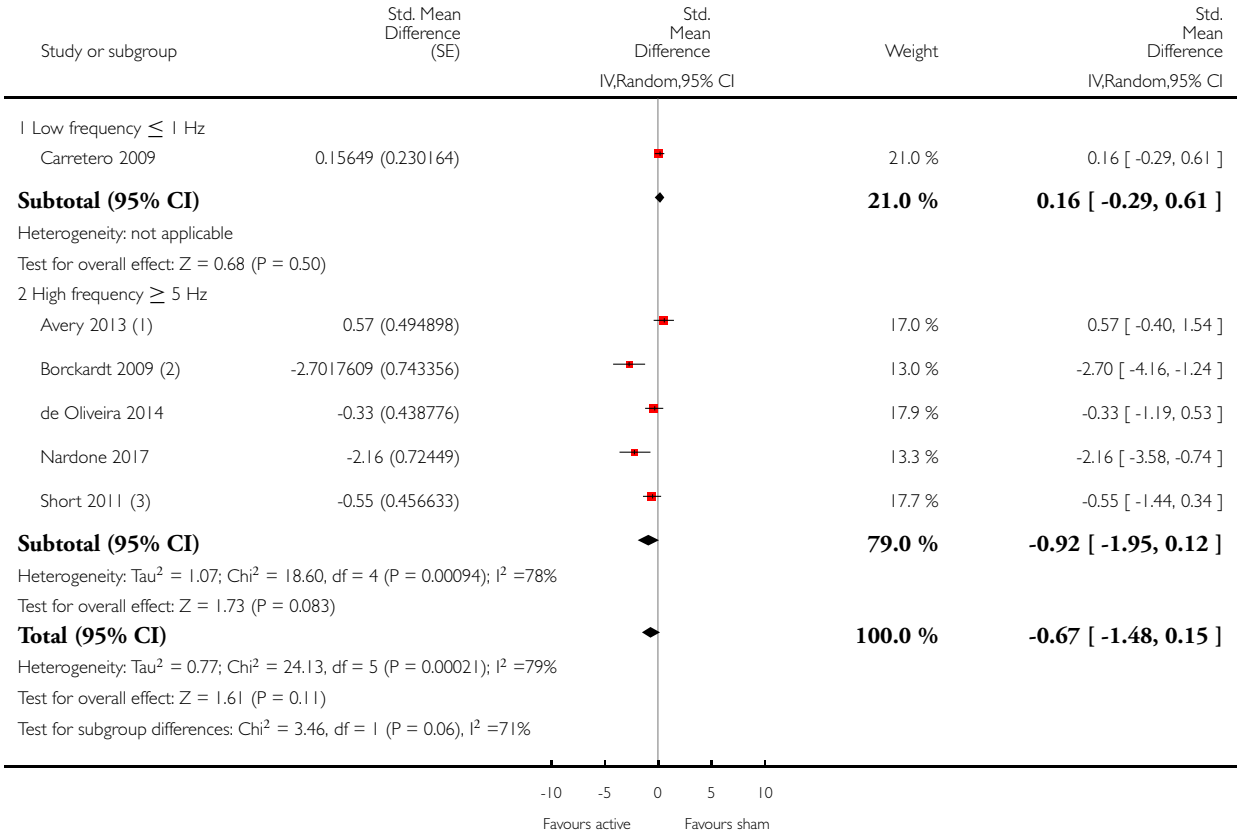
(6) M1 reogranised area

Analysis 1.12. Comparison 1 Repetitive transcranial magnetic stimulation (rTMS), Outcome 12 Pain: short-term follow-up, subgroup analysis: prefrontal cortex studies only.

Review: Non-invasive brain stimulation techniques for chronic pain

Comparison: 1 Repetitive transcranial magnetic stimulation (rTMS)

Outcome: 12 Pain: short-term follow-up, subgroup analysis: prefrontal cortex studies only



(1) 10Hz

(2) 10Hz

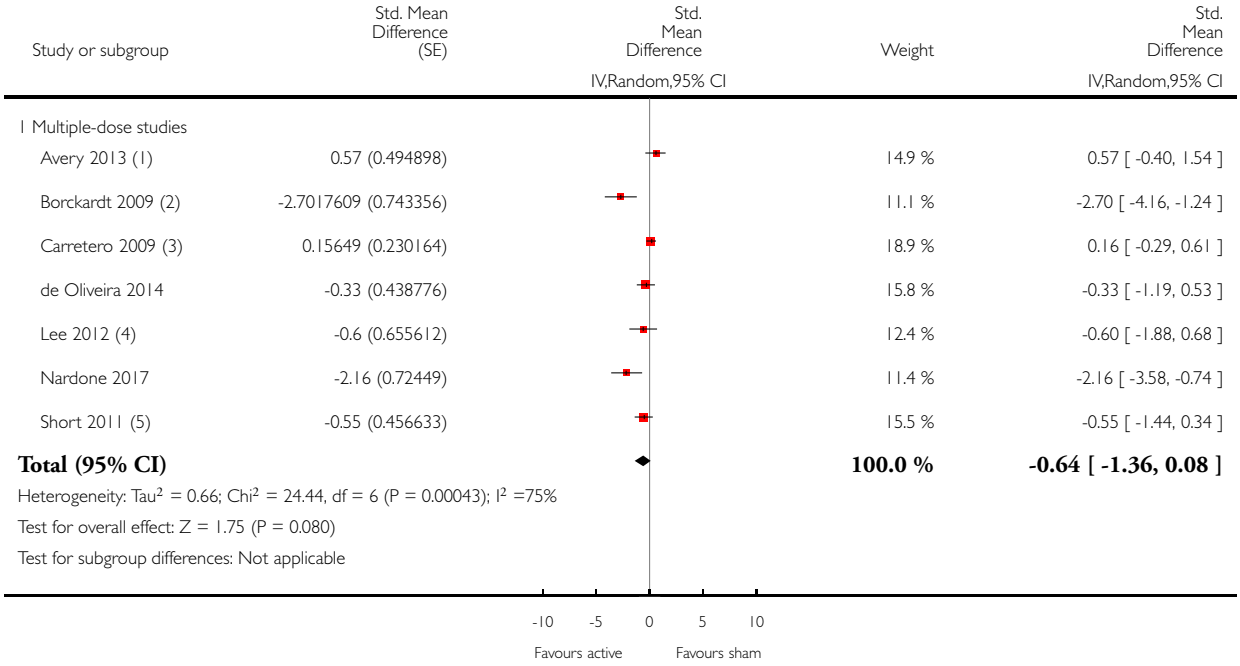
(3) 10Hz

Analysis 1.13. Comparison 1 Repetitive transcranial magnetic stimulation (rTMS), Outcome 13 Sensitivity analysis - inclusion of high risk of bias studies. Pain: short-term follow-up, subgroup analysis: prefrontal cortex studies only.

Review: Non-invasive brain stimulation techniques for chronic pain

Comparison: 1 Repetitive transcranial magnetic stimulation (rTMS)

Outcome: 13 Sensitivity analysis - inclusion of high risk of bias studies. Pain: short-term follow-up, subgroup analysis: prefrontal cortex studies only



(1) 10Hz

(2) 10Hz

(3) 1 Hz

(4) 1Hz

(5) 10Hz

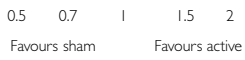
Analysis 1.14. Comparison 1 Repetitive transcranial magnetic stimulation (rTMS), Outcome 14 Pain: short term responder analysis 30% pain reduction.

Review: Non-invasive brain stimulation techniques for chronic pain

Comparison: 1 Repetitive transcranial magnetic stimulation (rTMS)

Outcome: 14 Pain: short term responder analysis 30% pain reduction

Study or subgroup	Active n/N	Sham n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Attal 2016	0/23	0/12			Not estimable
Malavera 2013	19/27	9/27		100.0 %	2.11 [1.17, 3.80]
Total (95% CI)	**50**	**39**		**100.0 %**	**2.11 [1.17, 3.80]**
Total events: 19 (Active), 9 (Sham)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.50 (P = 0.013)					
Test for subgroup differences: Not applicable					

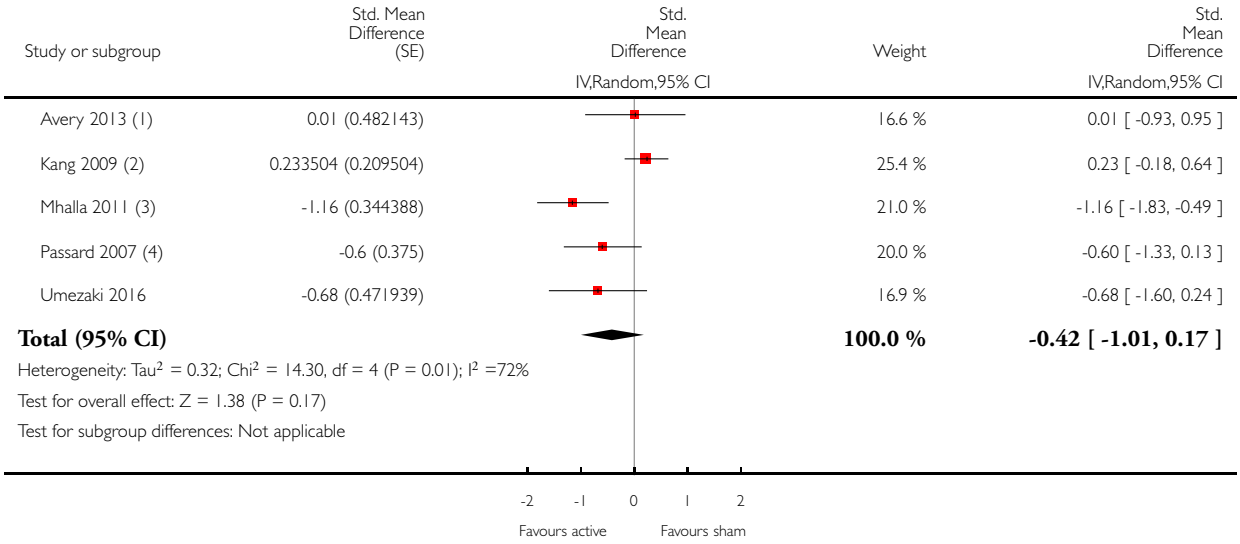


Analysis 1.15. Comparison 1 Repetitive transcranial magnetic stimulation (rTMS), Outcome 15 Sensitivity analysis- inclusion of high risk of bias studies. Disability: medium-term follow-up.

Review: Non-invasive brain stimulation techniques for chronic pain

Comparison: 1 Repetitive transcranial magnetic stimulation (rTMS)

Outcome: 15 Sensitivity analysis- inclusion of high risk of bias studies. Disability: medium-term follow-up



(1) BPI interference 1 month follow up

(2) BPI total (excl. walking subscale) 1 week post stim period

(3) BPI interference 1 month post treatment

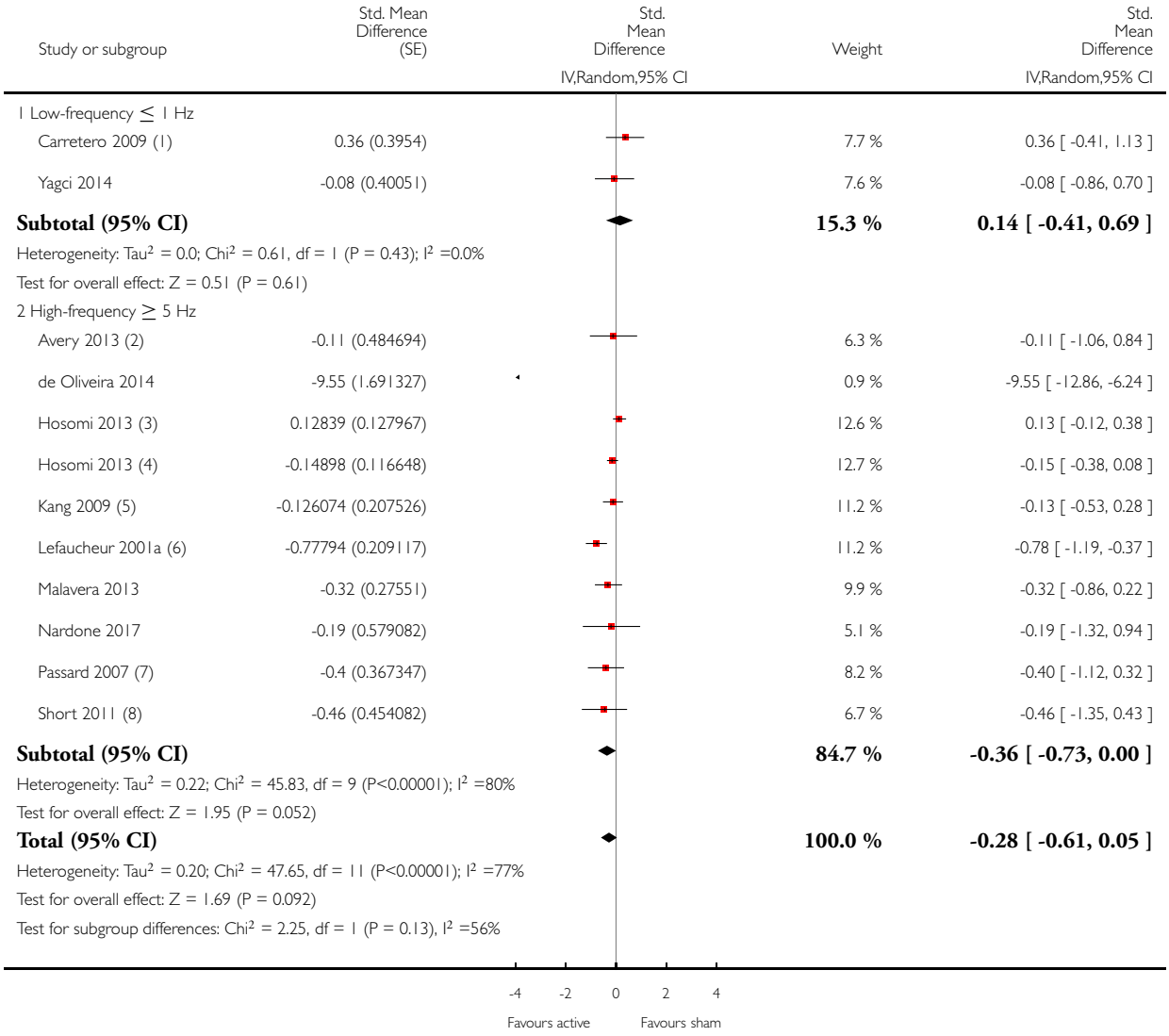
(4) BPI general activity subscale. 16 days post stim period

Analysis 1.16. Comparison 1 Repetitive transcranial magnetic stimulation (rTMS), Outcome 16 Pain: medium-term follow-up.

Review: Non-invasive brain stimulation techniques for chronic pain

Comparison: 1 Repetitive transcranial magnetic stimulation (rTMS)

Outcome: 16 Pain: medium-term follow-up



(1) DLPFC, 1 Hz 4 weeks post treatment

(2) DLPFC 10Hz 1 month follow up

(3) M1 10Hz, Group A real followed by sham, 17 days post treatment

(4) M1 10Hz, Group B sham followed by real, 17 days post treatment

(5) M1, 10Hz, 3 week follow up

(6) M1, 10HZ, 12 days post stimulation

(7) M1, 10Hz, 15 days post first stim (likely 2 weeks post intervention)

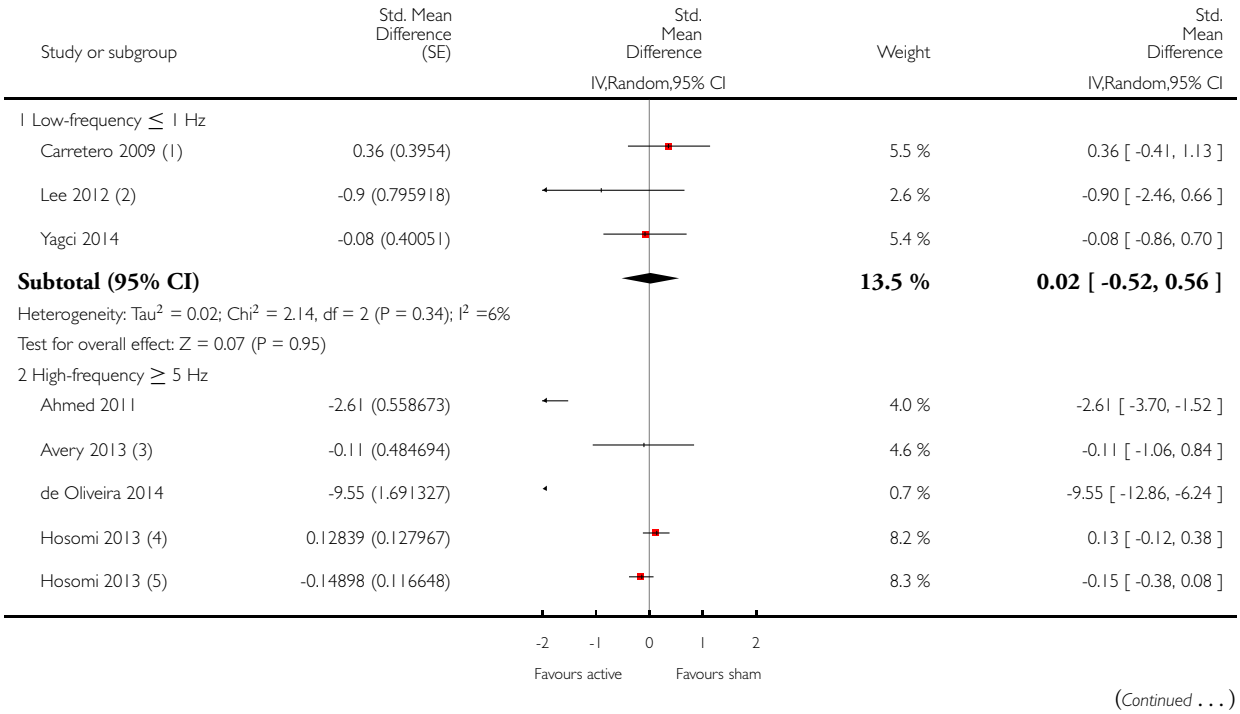
(8) DLPFC,10Hz, 2 weeks post treatment

Analysis 1.17. Comparison 1 Repetitive transcranial magnetic stimulation (rTMS), Outcome 17 Sensitivity analysis - inclusion of high risk of bias studies. Pain: medium-term follow-up.

Review: Non-invasive brain stimulation techniques for chronic pain

Comparison: 1 Repetitive transcranial magnetic stimulation (rTMS)

Outcome: 17 Sensitivity analysis - inclusion of high risk of bias studies. Pain: medium-term follow-up



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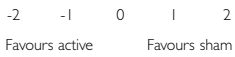
Study or subgroup	Std. Mean Difference (SE)	Std. Mean Difference IV,Random,95% CI	Weight	Std. Mean Difference IV,Random,95% CI
Kang 2009 (6)	-0.126074 (0.207526)		7.5 %	-0.13 [-0.53, 0.28]
Khedr 2005	-1.16 (0.313776)		6.4 %	-1.16 [-1.77, -0.55]
Lee 2012	0.06 (0.729592)		2.9 %	0.06 [-1.37, 1.49]
Lefaucheur 2001a (7)	-0.77794 (0.209117)		7.5 %	-0.78 [-1.19, -0.37]
Malavera 2013	-0.32 (0.27551)		6.8 %	-0.32 [-0.86, 0.22]
Nardone 2017	-0.19 (0.579082)		3.8 %	-0.19 [-1.32, 0.94]
Nurmikko 2016 (8)	-0.55342 (0.200581)		7.6 %	-0.55 [-0.95, -0.16]
Nurmikko 2016 (9)	-0.716703 (0.209405)		7.5 %	-0.72 [-1.13, -0.31]
Passard 2007 (10)	-0.4 (0.367347)		5.8 %	-0.40 [-1.12, 0.32]
Short 2011 (11)	-0.46 (0.454082)		4.9 %	-0.46 [-1.35, 0.43]
Subtotal (95% CI)			**86.5 %**	**-0.57 [-0.90, -0.25]**
Heterogeneity: Tau^2 = 0.28; Chi^2 = 79.44, df = 14 (P<0.00001); I^2 =82%				
Test for overall effect: Z = 3.44 (P = 0.00059)				
Total (95% CI)			**100.0 %**	**-0.50 [-0.80, -0.20]**
Heterogeneity: Tau^2 = 0.26; Chi^2 = 83.18, df = 17 (P<0.00001); I^2 =80%				
Test for overall effect: Z = 3.29 (P = 0.0010)				
Test for subgroup differences: Chi^2 = 3.35, df = 1 (P = 0.07), I^2 =70%				



(1) DLPFC 4 weeks post treatment

(2) dlpfc 4 weeks post treatment

(3) 10Hz DLPFC 1 month follow up

(4) M1 Group A real followed by sham, around 17 days post treatment

(5) M1 Group B sham followed by real, around 17 days post treatment

(6) M1 3 week follow up

(7) M1 12 days post

(8) M1 reorganised area

(9) M1 hotspot

(10) M1 15 days post first stim (likely 2 weeks post internvetion)

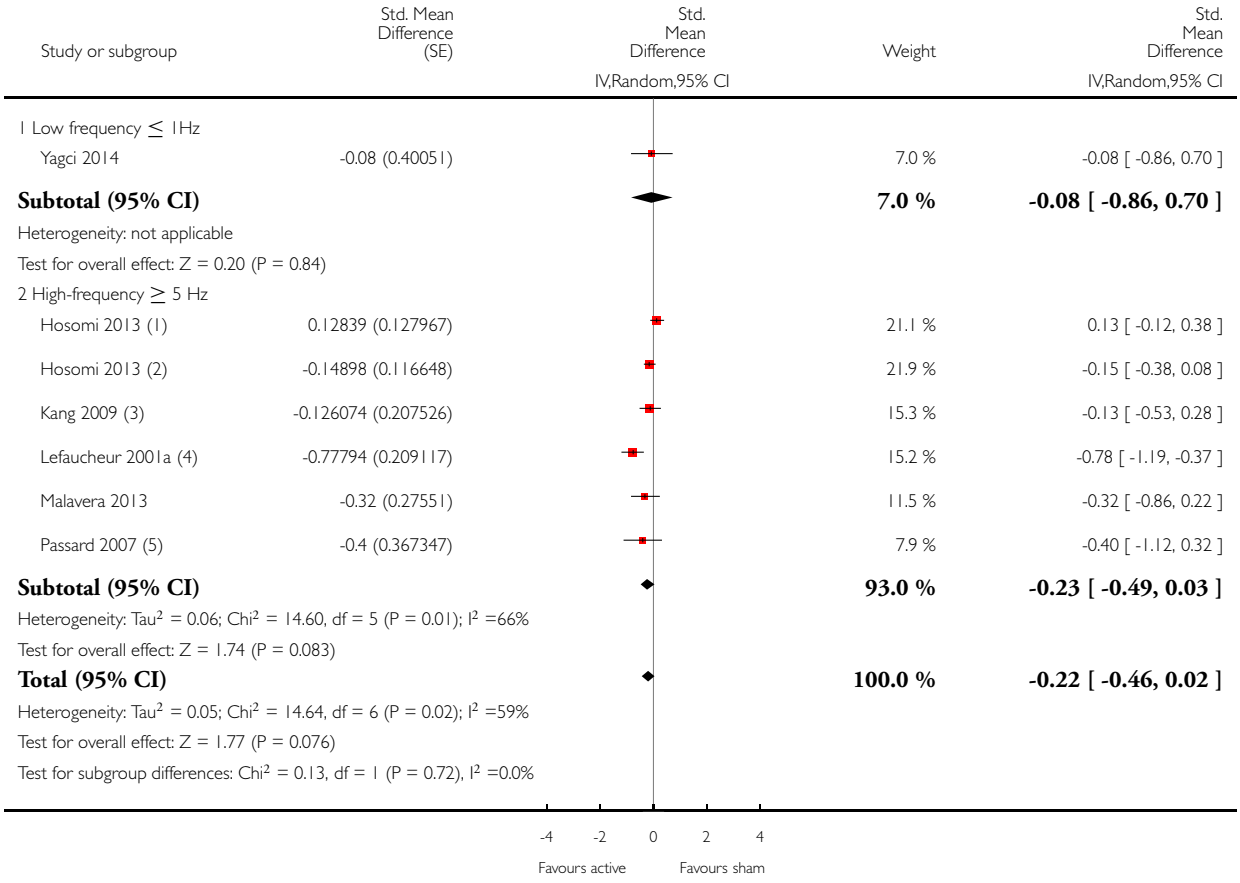
(11) DLPFC 2 weeks post treatment

Analysis 1.18. Comparison 1 Repetitive transcranial magnetic stimulation (rTMS), Outcome 18 Pain: medium-term follow-up, subgroup analysis: motor cortex studies only.

Review: Non-invasive brain stimulation techniques for chronic pain

Comparison: 1 Repetitive transcranial magnetic stimulation (rTMS)

Outcome: 18 Pain: medium-term follow-up, subgroup analysis: motor cortex studies only



(1) M1 10Hz, Group A real followed by sham, 17 days post treatment

(2) M1 10Hz, Group B sham followed by real, 17 days post treatment

(3) M1, 10Hz, 3 week follow up

(4) M1, 10HZ, 12 days post stimulation

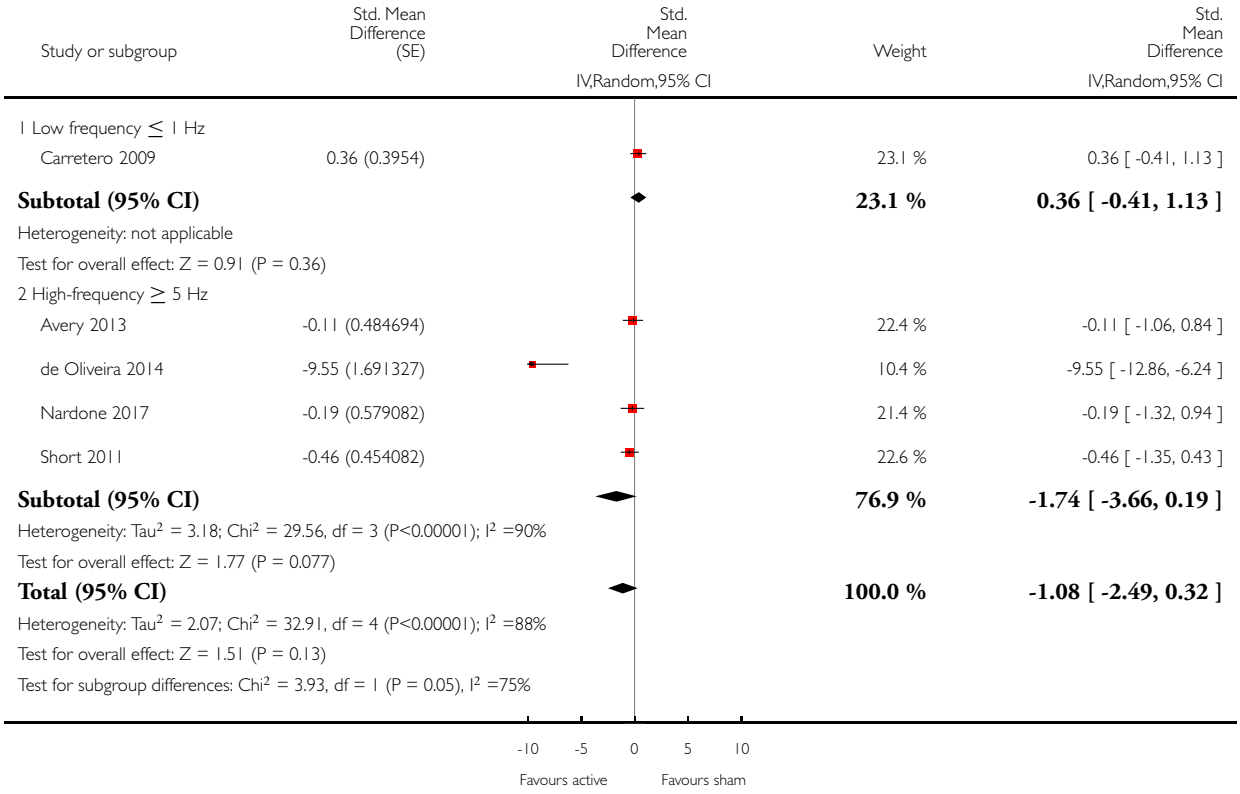
(5) M1, 10Hz, 15 days post first stim (likely 2 weeks post intervention)

Analysis 1.19. Comparison 1 Repetitive transcranial magnetic stimulation (rTMS), Outcome 19 Pain: medium-term follow-up, subgroup analysis: prefrontal cortex studies only.

Review: Non-invasive brain stimulation techniques for chronic pain

Comparison: 1 Repetitive transcranial magnetic stimulation (rTMS)

Outcome: 19 Pain: medium-term follow-up, subgroup analysis: prefrontal cortex studies only

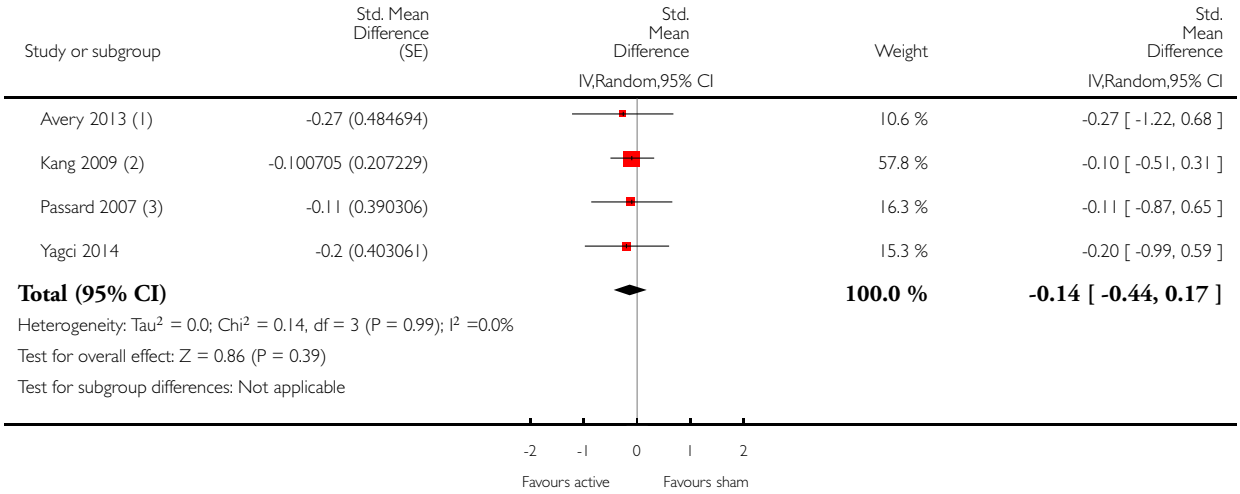


Analysis 1.20. Comparison 1 Repetitive transcranial magnetic stimulation (rTMS), Outcome 20 Pain: long-term follow-up.

Review: Non-invasive brain stimulation techniques for chronic pain

Comparison: 1 Repetitive transcranial magnetic stimulation (rTMS)

Outcome: 20 Pain: long-term follow-up



(1) 3 month follow up

(2) 7 week follow up

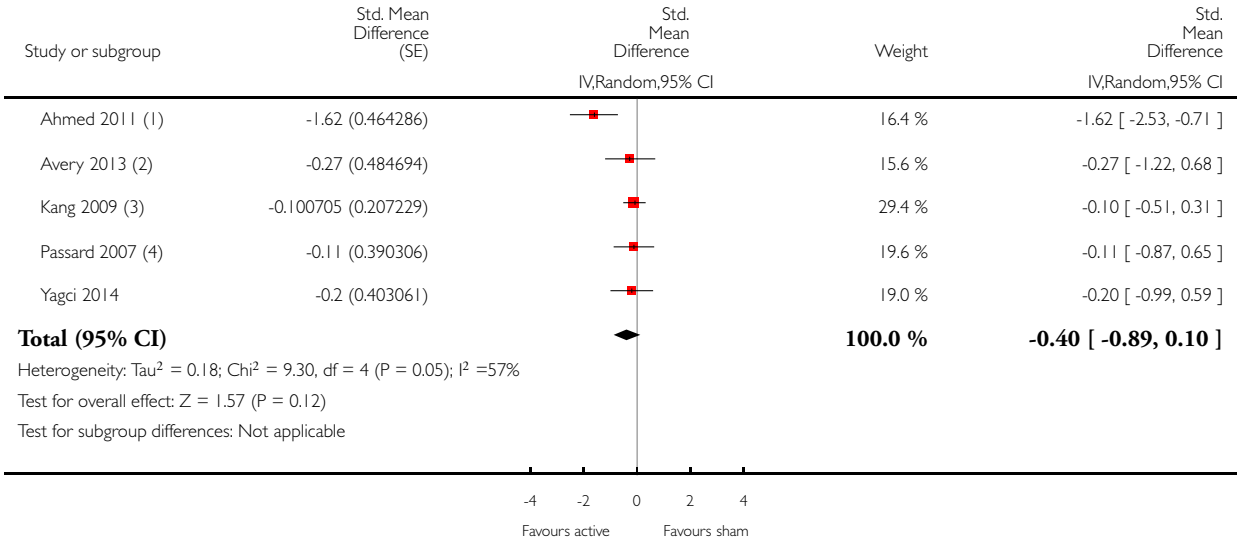
(3) 60 day follow up

Analysis 1.21. Comparison 1 Repetitive transcranial magnetic stimulation (rTMS), Outcome 21 Sensitivity analysis - inclusion of high risk of bias studies. Pain: long-term follow-up.

Review: Non-invasive brain stimulation techniques for chronic pain

Comparison: 1 Repetitive transcranial magnetic stimulation (rTMS)

Outcome: 21 Sensitivity analysis - inclusion of high risk of bias studies. Pain: long-term follow-up



(1) 20Hz, M1, 2 month follow up

(2) 10Hz DLPFC 3 month follow up

(3) 10Hz, M1, 7 week follow up

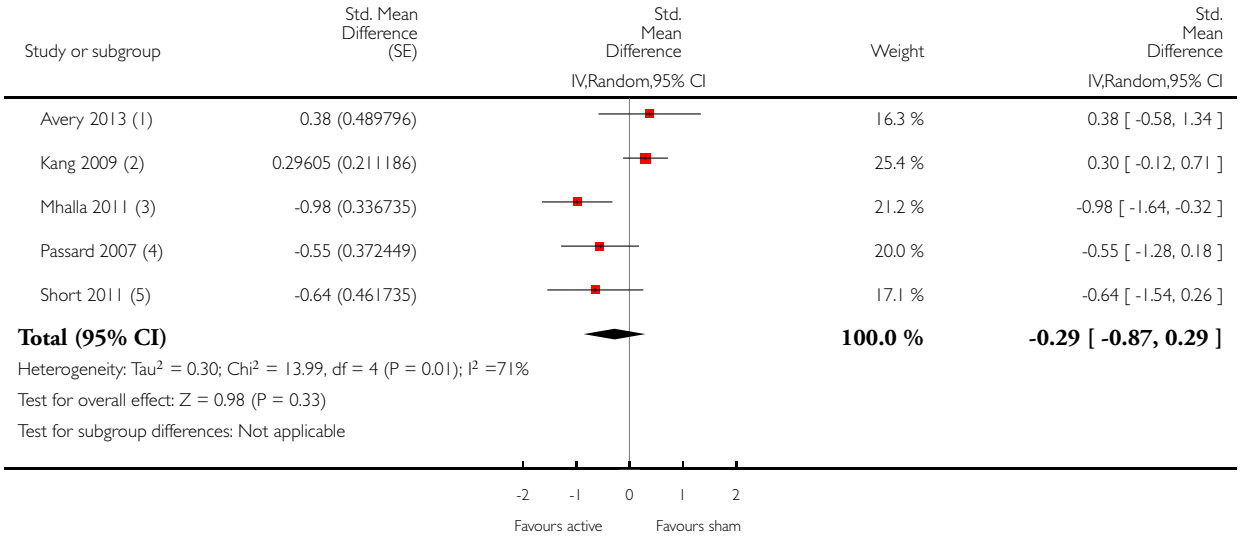
(4) 10Hz, M1, 60 day follow up

Analysis 1.22. Comparison 1 Repetitive transcranial magnetic stimulation (rTMS), Outcome 22 Disability: short-term follow-up.

Review: Non-invasive brain stimulation techniques for chronic pain

Comparison: 1 Repetitive transcranial magnetic stimulation (rTMS)

Outcome: 22 Disability: short-term follow-up



(1) BPI interference end of treatment period

(2) BPI total (excl. walking subscale) end of 5 day stim period

(3) BPI interference end of 9 week treatment period (only monthly maintenance stim to go)

(4) BPI general activity subscale. 1 day post stim period

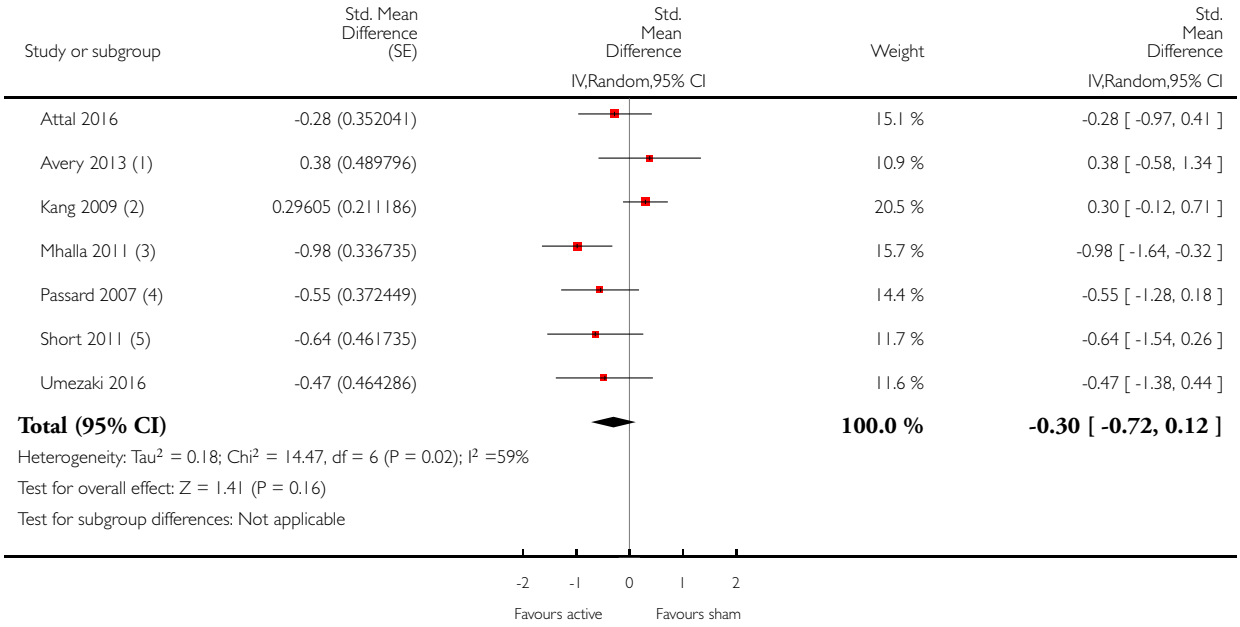
(5) BPI functional impairment end of 2 week treatment period

Analysis 1.23. Comparison 1 Repetitive transcranial magnetic stimulation (rTMS), Outcome 23 Sensitivity analysis- inclusion of high risk of bias studies. Disability: short-term follow-up.

Review: Non-invasive brain stimulation techniques for chronic pain

Comparison: 1 Repetitive transcranial magnetic stimulation (rTMS)

Outcome: 23 Sensitivity analysis- inclusion of high risk of bias studies. Disability: short-term follow-up



(1) BPI interference end of treatment period

(2) BPI total (excl. walking subscale) end of 5 day stim period

(3) BPI interference end of 9 week treatment period (only monthly maintenance stim to go)

(4) BPI general activity subscale. 1 day post stim period

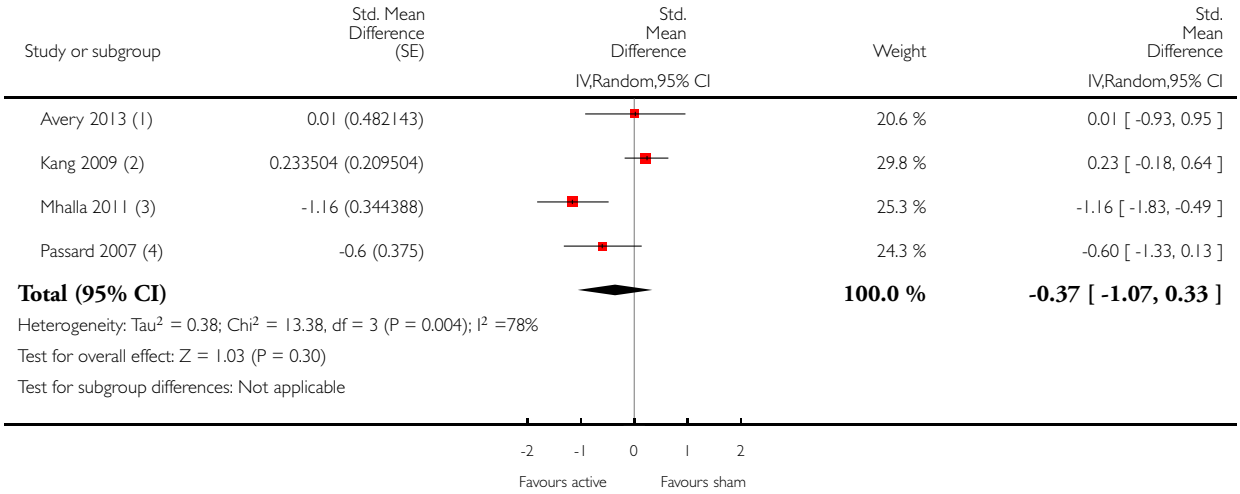
(5) BPI functional impairment end of 2 week treatment period

Analysis 1.24. Comparison 1 Repetitive transcranial magnetic stimulation (rTMS), Outcome 24 Disability: medium-term follow-up.

Review: Non-invasive brain stimulation techniques for chronic pain

Comparison: 1 Repetitive transcranial magnetic stimulation (rTMS)

Outcome: 24 Disability: medium-term follow-up



(1) BPI interference 1 month follow up

(2) BPI total (excl. walking subscale) 1 week post stim period

(3) BPI interference 1 month post treatment

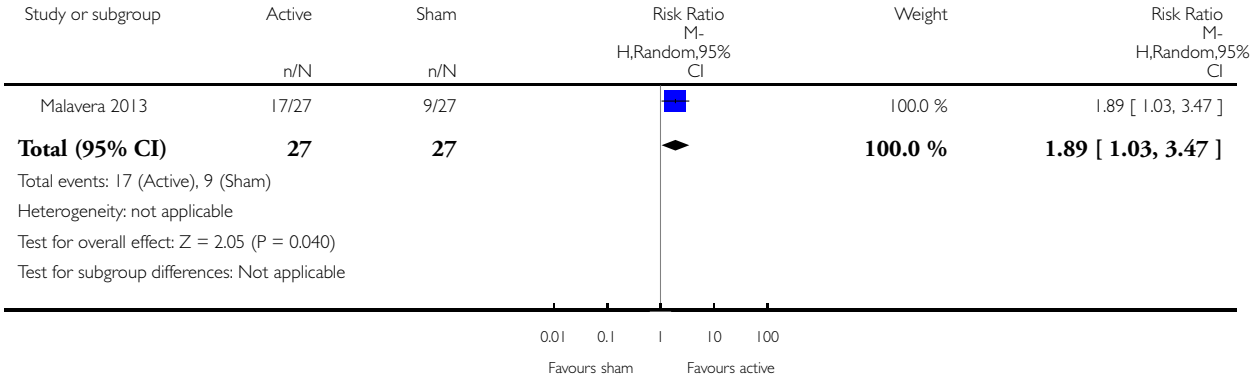
(4) BPI general activity subscale. 16 days post stim period

Analysis 1.25. Comparison 1 Repetitive transcranial magnetic stimulation (rTMS), Outcome 25 Pain: short term responder analysis 50% pain reduction.

Review: Non-invasive brain stimulation techniques for chronic pain

Comparison: 1 Repetitive transcranial magnetic stimulation (rTMS)

Outcome: 25 Pain: short term responder analysis 50% pain reduction

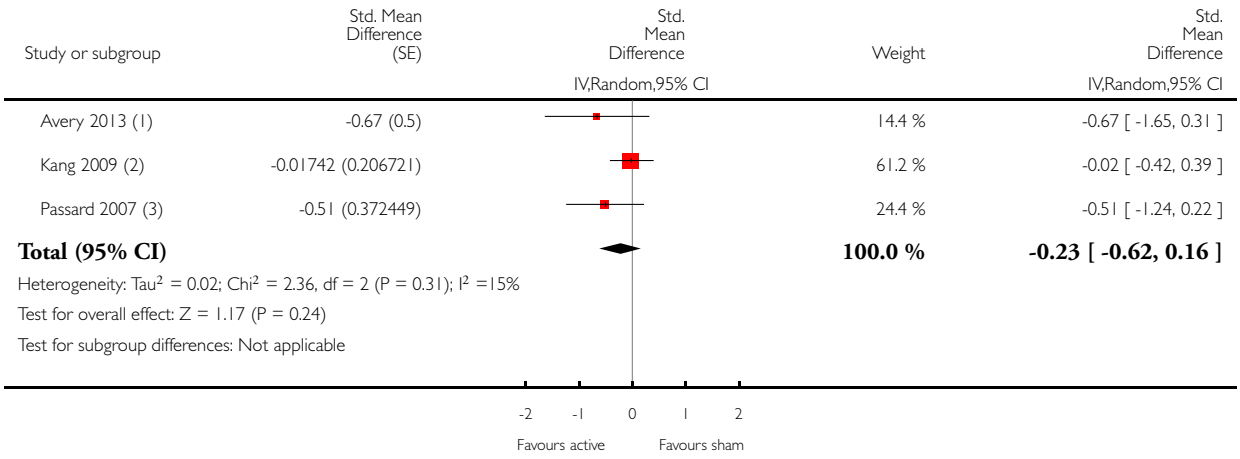


Analysis 1.26. Comparison 1 Repetitive transcranial magnetic stimulation (rTMS), Outcome 26 Disability: long-term follow-up.

Review: Non-invasive brain stimulation techniques for chronic pain

Comparison: 1 Repetitive transcranial magnetic stimulation (rTMS)

Outcome: 26 Disability: long-term follow-up



(1) BPI interference 3 month follow up

(2) BPI total (excl. walking subscale) 7 weeks post stim period

(3) BPI general activity subscale. 46 days post stim period

Analysis 1.27. Comparison 1 Repetitive transcranial magnetic stimulation (rTMS), Outcome 27 Sensitivity analysis - inclusion of high risk of bias studies. Disability: long-term follow-up.

Review: Non-invasive brain stimulation techniques for chronic pain

Comparison: 1 Repetitive transcranial magnetic stimulation (rTMS)

Outcome: 27 Sensitivity analysis - inclusion of high risk of bias studies. Disability: long-term follow-up

Study or subgroup	Std. Mean Difference (SE)	Std. Mean Difference IV,Random,95% CI	Weight	Std. Mean Difference IV,Random,95% CI
Avery 2013 (1)	-0.67 (0.5)		16.3 %	-0.67 [-1.65, 0.31]
Kang 2009 (2)	-0.01742 (0.206721)		42.6 %	-0.02 [-0.42, 0.39]
Passard 2007 (3)	-0.51 (0.372449)		24.4 %	-0.51 [-1.24, 0.22]
Umezaki 2016	-1.03 (0.492347)		16.7 %	-1.03 [-1.99, -0.07]
Total (95% CI)			**100.0 %**	**-0.41 [-0.87, 0.05]**

Heterogeneity: $Tau^2 = 0.09$; $Chi^2 = 4.92$, df = 3 (P = 0.18); $I^2 = 39\%$

Test for overall effect: Z = 1.76 (P = 0.078)

Test for subgroup differences: Not applicable

(1) BPI interference 3 month follow up

(2) BPI total (excl. walking subscale) 7 weeks post stim period

(3) BPI general activity subscale. 46 days post stim period

Analysis 1.28. Comparison 1 Repetitive transcranial magnetic stimulation (rTMS), Outcome 28 Quality of life: short-term follow-up (Fibromyalgia Impact Questionnaire).

Review: Non-invasive brain stimulation techniques for chronic pain

Comparison: 1 Repetitive transcranial magnetic stimulation (rTMS)

Outcome: 28 Quality of life: short-term follow-up (Fibromyalgia Impact Questionnaire)

Study or subgroup	Active stimulation		Sham stimulation		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Random,95% CI		IV,Random,95% CI
Mhalla 2011 (1)	16	55 (16.6)	14	65.7 (11)		18.1 %	-10.70 [-20.67, -0.73]
Passard 2007 (2)	15	47.4 (8.1)	15	57.8 (6.8)		62.9 %	-10.40 [-15.75, -5.05]
Short 2011 (3)	10	42.07 (18.13)	10	51.5 (17.32)		7.5 %	-9.43 [-24.97, 6.11]
Yagci 2014 (4)	13	44.8 (15.77)	12	58.8 (16.1)		11.5 %	-14.00 [-26.51, -1.49]
Total (95% CI)	**54**		**51**			**100.0 %**	**-10.80 [-15.04, -6.55]**

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.30$, df = 3 (P = 0.96); $I^2 = 0.0\%$

Test for overall effect: Z = 4.99 (P < 0.00001)

Test for subgroup differences: Not applicable

(1) M1, 10Hz

(2) M1, 10Hz

(3) DLPFC, 10Hz

(4) M1, 1Hz

Analysis 1.29. Comparison 1 Repetitive transcranial magnetic stimulation (rTMS), Outcome 29 Quality of life: medium-term follow-up (Fibromyalgia Impact Questionnaire).

Review: Non-invasive brain stimulation techniques for chronic pain

Comparison: 1 Repetitive transcranial magnetic stimulation (rTMS)

Outcome: 29 Quality of life: medium-term follow-up (Fibromyalgia Impact Questionnaire)

Study or subgroup	Active stimulation		Sham stimulation		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Fixed,95% CI		IV,Fixed,95% CI
Mhalla 2011 (1)	16	56 (17.7)	14	63.3 (15)		20.1 %	-7.30 [-19.00, 4.40]
Passard 2007 (2)	15	48.7 (10.4)	15	62.2 (8.9)		57.3 %	-13.50 [-20.43, -6.57]
Short 2011 (3)	10	38.99 (19.44)	10	47.93 (14.7)		12.0 %	-8.94 [-24.05, 6.17]
Yagci 2014	13	38.35 (23.25)	12	49.8 (17.7)		10.6 %	-11.45 [-27.58, 4.68]
Total (95% CI)	**54**		**51**			**100.0 %**	**-11.49 [-16.73, -6.25]**

Heterogeneity: $Chi^2 = 0.93$, df = 3 (P = 0.82); $I^2 = 0.0\%$

Test for overall effect: Z = 4.29 (P = 0.000018)

Test for subgroup differences: Not applicable

(1) M1, 10Hz

(2) M1, 10Hz

(3) DLPFC, 10Hz

Analysis 1.30. Comparison 1 Repetitive transcranial magnetic stimulation (rTMS), Outcome 30 Sensitivity analysis - inclusion of high risk of bias studies. Quality of life: medium-term follow-up (Fibromyalgia Impact Questionnaire).

Review: Non-invasive brain stimulation techniques for chronic pain

Comparison: 1 Repetitive transcranial magnetic stimulation (rTMS)

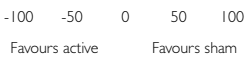
Outcome: 30 Sensitivity analysis - inclusion of high risk of bias studies. Quality of life: medium-term follow-up (Fibromyalgia Impact Questionnaire)

Study or subgroup	Active stimulation		Sham stimulation		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Fixed,95% CI		IV,Fixed,95% CI
Boyer 2014	19	0.3 (18.2)	19	1.3 (9.5)		24.4 %	-1.00 [-10.23, 8.23]
Mhalla 2011 (1)	16	56 (17.7)	14	63.3 (15)		15.2 %	-7.30 [-19.00, 4.40]
Passard 2007 (2)	15	48.7 (10.4)	15	62.2 (8.9)		43.3 %	-13.50 [-20.43, -6.57]
Short 2011 (3)	10	38.99 (19.44)	10	47.93 (14.7)		9.1 %	-8.94 [-24.05, 6.17]
Yagci 2014	13	38.35 (23.25)	12	49.8 (17.7)		8.0 %	-11.45 [-27.58, 4.68]
Total (95% CI)	**73**		**70**			**100.0 %**	**-8.93 [-13.49, -4.37]**

Heterogeneity: $Chi^2 = 4.68$, df = 4 (P = 0.32); $I^2 = 14\%$

Test for overall effect: Z = 3.84 (P = 0.00012)

Test for subgroup differences: Not applicable



(1) M1, 10Hz

(2) M1, 10Hz

(3) DLPFC, 10Hz

Analysis 1.31. Comparison 1 Repetitive transcranial magnetic stimulation (rTMS), Outcome 31 Quality of life: long-term follow-up.

Review: Non-invasive brain stimulation techniques for chronic pain

Comparison: 1 Repetitive transcranial magnetic stimulation (rTMS)

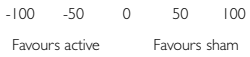
Outcome: 31 Quality of life: long-term follow-up

Study or subgroup	Experimental N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Passard 2007	13	57.2 (10.1)	13	63.1 (8.8)		83.3 %	-5.90 [-13.18, 1.38]
Yagci 2014	13	36.95 (24.27)	12	48.13 (16.79)		16.7 %	-11.18 [-27.44, 5.08]
Total (95% CI)	**26**		**25**			**100.0 %**	**-6.78 [-13.43, -0.14]**

Heterogeneity: $Chi^2 = 0.34$, df = 1 (P = 0.56); $I^2 = 0.0\%$

Test for overall effect: Z = 2.00 (P = 0.045)

Test for subgroup differences: Not applicable



Analysis 1.32. Comparison 1 Repetitive transcranial magnetic stimulation (rTMS), Outcome 32 Sensitivity analysis - inclusion of high risk of bias studies. Quality of life: long-term follow-up.

Review: Non-invasive brain stimulation techniques for chronic pain

Comparison: 1 Repetitive transcranial magnetic stimulation (rTMS)

Outcome: 32 Sensitivity analysis - inclusion of high risk of bias studies. Quality of life: long-term follow-up

Study or subgroup	Experimental N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Boyer 2014	19	-9.6 (16.7)	19	2 (9.3)		37.4 %	-11.60 [-20.19, -3.01]
Passard 2007	13	57.2 (10.1)	13	63.1 (8.8)		52.1 %	-5.90 [-13.18, 1.38]
Yagci 2014	13	36.95 (24.27)	12	48.13 (16.79)		10.5 %	-11.18 [-27.44, 5.08]
Total (95% CI)	**45**		**44**			**100.0 %**	**-8.58 [-13.84, -3.33]**

Heterogeneity: $Chi^2 = 1.09$, df = 2 (P = 0.58); $I^2 = 0.0\%$

Test for overall effect: Z = 3.20 (P = 0.0014)

Test for subgroup differences: Not applicable

Analysis 2.1. Comparison 2 Cranial electrotherapy stimulation (CES), Outcome 1 Pain: short-term follow-up.

Review: Non-invasive brain stimulation techniques for chronic pain

Comparison: 2 Cranial electrotherapy stimulation (CES)

Outcome: 1 Pain: short-term follow-up

Study or subgroup	Active stimulation		Sham stimulation		Std. Mean Difference	Weight	Std. Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Random,95% CI		IV,Random,95% CI
Gabis 2003	10	2.83 (2.07)	10	2.65 (2.49)		7.6 %	0.08 [-0.80, 0.95]
Gabis 2009 (1)	17	3.82 (2.86)	16	5.25 (2.29)		12.0 %	-0.54 [-1.23, 0.16]
Gabis 2009 (2)	19	3.26 (2.79)	23	4.65 (2.62)		15.3 %	-0.51 [-1.12, 0.11]
Tan 2006	18	5.73 (2.56)	20	6 (2.41)		14.3 %	-0.11 [-0.74, 0.53]
Tan 2011	45	5 (1.92)	55	5 (1.93)		37.5 %	0.0 [-0.39, 0.39]
Taylor 2013 (3)	19	5.12 (1.69)	18	6.36 (2.11)		13.3 %	-0.64 [-1.30, 0.03]
Total (95% CI)	**128**		**142**			**100.0 %**	**-0.24 [-0.48, 0.01]**

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 4.87$, df = 5 (P = 0.43); $I^2 = 0.0\%$

Test for overall effect: Z = 1.91 (P = 0.056)

Test for subgroup differences: Not applicable

(1) back pain

(2) neck pain

(3) Effect predominantly due to increase in pain in sham group

Analysis 2.2. Comparison 2 Cranial electrotherapy stimulation (CES), Outcome 2 Quality of life: short term follow up.

Review: Non-invasive brain stimulation techniques for chronic pain

Comparison: 2 Cranial electrotherapy stimulation (CES)

Outcome: 2 Quality of life: short term follow up

Study or subgroup	Active stimulation		Sham stimulation		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Random,95% CI		IV,Random,95% CI
Taylor 2013 (1)	18	45.05 (16.27)	18	70.1 (22.34)			-25.05 [-37.82, -12.28]

Test for subgroup differences: Not applicable

(1) Fibromyalgia Impact Questionnaire

Analysis 3.1. Comparison 3 Transcranial direct current stimulation (tDCS), Outcome 1 Pain: short-term follow-up.

Review: Non-invasive brain stimulation techniques for chronic pain

Comparison: 3 Transcranial direct current stimulation (tDCS)

Outcome: 1 Pain: short-term follow-up

Study or subgroup	Std. Mean Difference (SE)	Std. Mean Difference IV,Random,95% CI	Weight	Std. Mean Difference IV,Random,95% CI
1 Single-dose studies				
Boggio 2009	-0.417904 (0.314924)		4.1 %	-0.42 [-1.04, 0.20]
Jensen 2013	-0.146424 (0.165274)		5.7 %	-0.15 [-0.47, 0.18]
Ngernyam 2015	-0.17 (0.192387)		5.4 %	-0.17 [-0.55, 0.21]
Villamar 2013 (1)	-0.393703 (0.29557)		4.3 %	-0.39 [-0.97, 0.19]
Villamar 2013 (2)	0.11545 (0.285689)		4.4 %	0.12 [-0.44, 0.68]
Subtotal (95% CI)			**23.9 %**	**-0.18 [-0.38, 0.02]**
Heterogeneity: Tau^2 = 0.0; Chi^2 = 2.21, df = 4 (P = 0.70); I^2 =0.0%				
Test for overall effect: Z = 1.75 (P = 0.080)				
2 Multiple-dose studies				
Ahn 2017	-0.88 (0.334184)		3.9 %	-0.88 [-1.53, -0.23]
Ayache 2016	-0.3 (0.354592)		3.7 %	-0.30 [-0.99, 0.39]
Bae 2014	0.15 (0.556122)		2.3 %	0.15 [-0.94, 1.24]
Brietzke 2016	-0.51 (0.535714)		2.4 %	-0.51 [-1.56, 0.54]
Chang 2017	-0.45 (0.405612)		3.3 %	-0.45 [-1.24, 0.34]
Fagerlund 2015	-0.37 (0.290816)		4.3 %	-0.37 [-0.94, 0.20]
Fenton 2009	0.06593 (0.323217)		4.0 %	0.07 [-0.57, 0.70]
Fregni 2006a	-1.32 (0.568878)		2.2 %	-1.32 [-2.43, -0.21]
Fregni 2006b (3)	1.11 (0.477041)		2.7 %	1.11 [0.18, 2.04]
Fregni 2006b (4)	-0.73 (0.556122)		2.3 %	-0.73 [-1.82, 0.36]
Hazime 2017	-0.85 (0.308763)		4.2 %	-0.85 [-1.46, -0.24]
Jales Junior 2015	-0.87 (0.471939)		2.8 %	-0.87 [-1.79, 0.05]
Khedr 2017	-1.81 (0.403061)		3.3 %	-1.81 [-2.60, -1.02]
Lagueux 2017	-0.56 (0.436224)		3.0 %	-0.56 [-1.41, 0.29]
Luedtke 2015	0.04 (0.181122)		5.5 %	0.04 [-0.31, 0.39]

(*Continued* . . .)

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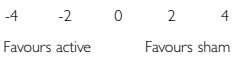
Study or subgroup	Std. Mean Difference (SE)	Std. Mean Difference IV,Random,95% CI	Weight	Std. Mean Difference IV,Random,95% CI
Mendonca 2016	-0.3 (0.367347)		3.6 %	-0.30 [-1.02, 0.42]
Mori 2010	-1.19 (0.507653)		2.5 %	-1.19 [-2.18, -0.20]
Oliveira 2015	-0.97 (0.378)		3.5 %	-0.97 [-1.71, -0.23]
Riberto 2011	0.02 (0.4158)		3.2 %	0.02 [-0.79, 0.83]
Sakrajai 2014	-1.58 (0.418367)		3.2 %	-1.58 [-2.40, -0.76]
Soler 2010 (5)	-0.55 (0.45663)		2.9 %	-0.55 [-1.44, 0.34]
Volz 2016	-0.85 (0.471939)		2.8 %	-0.85 [-1.77, 0.07]
Wrigley 2014	0.35377 (0.278353)		4.5 %	0.35 [-0.19, 0.90]
Subtotal (95% CI)			**76.1 %**	**-0.51 [-0.77, -0.25]**
Heterogeneity: $Tau^2 = 0.25$; $Chi^2 = 61.73$, df = 22 (P = 0.00001); I^2 =64%				
Test for overall effect: Z = 3.79 (P = 0.00015)				
Total (95% CI)			**100.0 %**	**-0.43 [-0.63, -0.22]**
Heterogeneity: $Tau^2 = 0.16$; $Chi^2 = 67.25$, df = 27 (P = 0.00003); I^2 =60%				
Test for overall effect: Z = 4.14 (P = 0.000035)				
Test for subgroup differences: $Chi^2 = 3.90$, df = 1 (P = 0.05), I^2 =74%				



(1) cathodal

(2) anodal

(3) DLPFC

(4) M1

(5) tDCS+ sham illusion vs sham tDCS + sham illusion

Analysis 3.2. Comparison 3 Transcranial direct current stimulation (tDCS), Outcome 2 Pain: short-term sensitivity analysis: correlation increased.

Review: Non-invasive brain stimulation techniques for chronic pain

Comparison: 3 Transcranial direct current stimulation (tDCS)

Outcome: 2 Pain: short-term sensitivity analysis: correlation increased

Study or subgroup	Std. Mean Difference (SE)	Std. Mean Difference IV,Random,95% CI	Weight	Std. Mean Difference IV,Random,95% CI
Ahn 2017	-0.88 (0.334184)		3.7 %	-0.88 [-1.53, -0.23]
Ayache 2016	-0.3 (0.354592)		3.5 %	-0.30 [-0.99, 0.39]
Bae 2014	0.15 (0.556122)		2.1 %	0.15 [-0.94, 1.24]
Boggio 2009	-0.417904 (0.268318)		4.4 %	-0.42 [-0.94, 0.11]
Brietzke 2016	-0.51 (0.385204)		3.3 %	-0.51 [-1.26, 0.24]
Chang 2017	-0.45 (0.405612)		3.1 %	-0.45 [-1.24, 0.34]
Fagerlund 2015	-0.37 (0.290816)		4.1 %	-0.37 [-0.94, 0.20]
Fenton 2009	0.06593 (0.275383)		4.3 %	0.07 [-0.47, 0.61]
Fregni 2006a	-1.32 (0.568878)		2.1 %	-1.32 [-2.43, -0.21]
Fregni 2006b (1)	1.11 (0.477041)		2.6 %	1.11 [0.18, 2.04]
Fregni 2006b (2)	-0.73 (0.556122)		2.1 %	-0.73 [-1.82, 0.36]
Hazime 2017	-0.85 (0.308673)		4.0 %	-0.85 [-1.45, -0.25]
Jales Junior 2015	-0.87 (0.471939)		2.6 %	-0.87 [-1.79, 0.05]
Jensen 2013	-0.146424 (0.140815)		5.7 %	-0.15 [-0.42, 0.13]
Khedr 2017	-1.81 (0.403061)		3.1 %	-1.81 [-2.60, -1.02]
Lagueux 2017	-0.56 (0.436224)		2.9 %	-0.56 [-1.41, 0.29]
Luedtke 2015	0.04 (0.181122)		5.3 %	0.04 [-0.31, 0.39]
Mendonca 2016	-0.3 (0.367347)		3.4 %	-0.30 [-1.02, 0.42]
Mori 2010	-1.19 (0.507653)		2.4 %	-1.19 [-2.18, -0.20]
Ngernyam 2015	-0.17 (0.163915)		5.5 %	-0.17 [-0.49, 0.15]
Oliveira 2015	-0.97 (0.3775)		3.3 %	-0.97 [-1.71, -0.23]
Riberto 2011	0.02 (0.4158)		3.0 %	0.02 [-0.79, 0.83]
Sakrajai 2014	-1.58 (0.418367)		3.0 %	-1.58 [-2.40, -0.76]
Soler 2010 (3)	-0.55 (0.45663)		2.7 %	-0.55 [-1.44, 0.34]

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Study or subgroup	Std. Mean Difference (SE)	Std. Mean Difference IV,Random,95% CI	Weight	Std. Mean Difference IV,Random,95% CI
Soler 2010 (4)	-0.74 (0.479592)		2.6 %	-0.74 [-1.68, 0.20]
Villamar 2013 (5)	0.11545 (0.298113)		4.1 %	0.12 [-0.47, 0.70]
Villamar 2013 (6)	-0.393703 (0.308424)		4.0 %	-0.39 [-1.00, 0.21]
Volz 2016	-0.85 (0.471939)		2.6 %	-0.85 [-1.77, 0.07]
Wrigley 2014	0.35377 (0.237244)		4.7 %	0.35 [-0.11, 0.82]
Total (95% CI)			**100.0 %**	**-0.43 [-0.62, -0.23]**

Heterogeneity: $Tau^2 = 0.15$; $Chi^2 = 71.32$, df = 28 (P = 0.00001); $I^2 = 61\%$

Test for overall effect: Z = 4.33 (P = 0.000015)

Test for subgroup differences: Not applicable

(1) DLPFC

(2) M1

(3) tDCS+ sham illusion vs sham TDCS + sham illusion

(4) tDCS+ illusion vs sham TDCS + illusion

(5) anodal

(6) cathodal

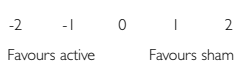
Analysis 3.3. Comparison 3 Transcranial direct current stimulation (tDCS), Outcome 3 Pain: short-term sensitivity analysis: correlation decreased.

Review: Non-invasive brain stimulation techniques for chronic pain

Comparison: 3 Transcranial direct current stimulation (tDCS)

Outcome: 3 Pain: short-term sensitivity analysis: correlation decreased

Study or subgroup	Std. Mean Difference (SE)	Std. Mean Difference IV,Random,95% CI	Weight	Std. Mean Difference IV,Random,95% CI
Ahn 2017	-0.88 (0.334184)		4.0 %	-0.88 [-1.53, -0.23]
Ayache 2016	-0.3 (0.354592)		3.8 %	-0.30 [-0.99, 0.39]
Bae 2014	0.15 (0.556122)		2.3 %	0.15 [-0.94, 1.24]
Boggio 2009	-0.417904 (0.355472)		3.8 %	-0.42 [-1.11, 0.28]
Brietzke 2016	-0.51 (0.385204)		3.5 %	-0.51 [-1.26, 0.24]
Chang 2017	-0.45 (0.405612)		3.3 %	-0.45 [-1.24, 0.34]
Fagerlund 2015	-0.37 (0.290816)		4.4 %	-0.37 [-0.94, 0.20]
Fenton 2009	0.06593 (0.364833)		3.7 %	0.07 [-0.65, 0.78]
Fregni 2006a	-1.32 (0.568878)		2.2 %	-1.32 [-2.43, -0.21]
Fregni 2006b (1)	1.11 (0.477041)		2.8 %	1.11 [0.18, 2.04]
Fregni 2006b (2)	-0.73 (0.556122)		2.3 %	-0.73 [-1.82, 0.36]
Hazime 2017	-0.85 (0.308673)		4.3 %	-0.85 [-1.45, -0.25]
Jales Junior 2015	-0.55 (1.13)		0.7 %	-0.55 [-2.76, 1.66]
Jensen 2013	-0.146424 (0.186554)		5.6 %	-0.15 [-0.51, 0.22]
Khedr 2017	-1.81 (0.403061)		3.4 %	-1.81 [-2.60, -1.02]
Lagueux 2017	-0.56 (0.436224)		3.1 %	-0.56 [-1.41, 0.29]
Luedtke 2015	0.04 (0.181122)		5.7 %	0.04 [-0.31, 0.39]
Mendonca 2016	-0.3 (0.367347)		3.7 %	-0.30 [-1.02, 0.42]
Mori 2010	-1.19 (0.507653)		2.6 %	-1.19 [-2.18, -0.20]
Ngernyam 2015	-0.17 (0.21716)		5.3 %	-0.17 [-0.60, 0.26]
Oliveira 2015	-0.97 (0.3775)		3.6 %	-0.97 [-1.71, -0.23]
Riberto 2011	0.02 (0.4158)		3.3 %	0.02 [-0.79, 0.83]
Sakrajai 2014	-1.58 (0.418367)		3.2 %	-1.58 [-2.40, -0.76]
Soler 2010 (3)	-0.55 (0.45663)		2.9 %	-0.55 [-1.44, 0.34]



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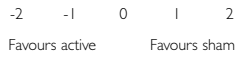
Study or subgroup	Std. Mean Difference (SE)	Std. Mean Difference IV,Random,95% CI	Weight	Std. Mean Difference IV,Random,95% CI
Soler 2010 (4)	-0.74 (0.479592)		2.8 %	-0.74 [-1.68, 0.20]
Villamar 2013 (5)	0.11545 (0.394946)		3.4 %	0.12 [-0.66, 0.89]
Villamar 2013 (6)	-0.393703 (0.408606)		3.3 %	-0.39 [-1.19, 0.41]
Volz 2016	-0.85 (0.471939)		2.8 %	-0.85 [-1.77, 0.07]
Wrigley 2014	0.35377 (0.314305)		4.2 %	0.35 [-0.26, 0.97]
Total (95% CI)			**100.0 %**	**-0.44 [-0.64, -0.23]**

Heterogeneity: $Tau^2 = 0.16$; $Chi^2 = 63.46$, df = 28 (P = 0.00014); $I^2 = 56\%$

Test for overall effect: Z = 4.21 (P = 0.000025)

Test for subgroup differences: Not applicable



(1) DLPFC

(2) M1

(3) tDCS+ sham illusion vs sham TDCS + sham illusion

(4) tDCS+ illusion vs sham TDCS + illusion

(5) anodal

(6) cathodal

Analysis 3.4. Comparison 3 Transcranial direct current stimulation (tDCS), Outcome 4 Pain: short term sensitivity analysis, inclusion of high risk of bias studies.

Review: Non-invasive brain stimulation techniques for chronic pain

Comparison: 3 Transcranial direct current stimulation (tDCS)

Outcome: 4 Pain: short term sensitivity analysis, inclusion of high risk of bias studies

Study or subgroup	Std. Mean Difference (SE)	Std. Mean Difference IV,Random,95% CI	Weight	Std. Mean Difference IV,Random,95% CI
1 Single-dose studies				
Boggio 2009	-0.417904 (0.314924)		3.4 %	-0.42 [-1.04, 0.20]
Jensen 2013	-0.146424 (0.165274)		4.7 %	-0.15 [-0.47, 0.18]
Ngernyam 2015	-0.17 (0.192387)		4.5 %	-0.17 [-0.55, 0.21]
Villamar 2013 (1)	-0.393703 (0.29557)		3.6 %	-0.39 [-0.97, 0.19]
Villamar 2013 (2)	0.11545 (0.285689)		3.7 %	0.12 [-0.44, 0.68]
Subtotal (95% CI)			**19.8 %**	**-0.18 [-0.38, 0.02]**
Heterogeneity: Tau^2 = 0.0; Chi^2 = 2.21, df = 4 (P = 0.70); I^2 =0.0%				
Test for overall effect: Z = 1.75 (P = 0.080)				
2 Multiple-dose studies				
Ahn 2017	-0.88 (0.344184)		3.2 %	-0.88 [-1.55, -0.21]
Antal 2010	-0.38 (0.673469)		1.5 %	-0.38 [-1.70, 0.94]
Ayache 2016	-0.3 (0.354592)		3.1 %	-0.30 [-0.99, 0.39]
Bae 2014	0.15 (0.556122)		1.9 %	0.15 [-0.94, 1.24]
Brietzke 2016	-0.51 (0.385204)		2.9 %	-0.51 [-1.26, 0.24]
Chang 2017	-0.45 (0.405612)		2.8 %	-0.45 [-1.24, 0.34]
Fagerlund 2015	-0.37 (0.290816)		3.6 %	-0.37 [-0.94, 0.20]
Fenton 2009	0.06593 (0.323217)		3.4 %	0.07 [-0.57, 0.70]
Fregni 2006a	-1.32 (0.568878)		1.9 %	-1.32 [-2.43, -0.21]
Fregni 2006b (3)	1.11 (0.477041)		2.3 %	1.11 [0.18, 2.04]
Fregni 2006b (4)	-0.73 (0.556122)		1.9 %	-0.73 [-1.82, 0.36]
Hagenacker 2014	-1.1137 (0.343836)		3.2 %	-1.11 [-1.79, -0.44]
Hazime 2017	-0.85 (0.308673)		3.5 %	-0.85 [-1.45, -0.25]
Jales Junior 2015	-0.87 (0.471939)		2.4 %	-0.87 [-1.79, 0.05]
Khedr 2017	-1.81 (0.403061)		2.8 %	-1.81 [-2.60, -1.02]

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Study or subgroup	Std. Mean Difference (SE)	Std. Mean Difference IV,Random,95% CI	Weight	Std. Mean Difference IV,Random,95% CI
Kim 2013 (5)	-1.76 (0.456633)		2.4 %	-1.76 [-2.65, -0.87]
Kim 2013 (6)	-0.48 (0.392587)		2.9 %	-0.48 [-1.25, 0.29]
Lagueux 2017	-0.56 (0.436224)		2.6 %	-0.56 [-1.41, 0.29]
Luedtke 2015	0.04 (0.181122)		4.5 %	0.04 [-0.31, 0.39]
Mendonca 2016	-0.3 (0.367347)		3.0 %	-0.30 [-1.02, 0.42]
Mori 2010	-1.19 (0.507653)		2.2 %	-1.19 [-2.18, -0.20]
Oliveira 2015	-0.97 (0.3775)		3.0 %	-0.97 [-1.71, -0.23]
Riberto 2011	0.02 (0.4158)		2.7 %	0.02 [-0.79, 0.83]
Sakrajai 2014	-1.58 (0.418367)		2.7 %	-1.58 [-2.40, -0.76]
Soler 2010 (7)	-0.55 (0.45663)		2.4 %	-0.55 [-1.44, 0.34]
Souto 2014	-0.67 (0.464286)		2.4 %	-0.67 [-1.58, 0.24]
Thibaut 2017	-0.06 (0.40051)		2.8 %	-0.06 [-0.84, 0.72]
Volz 2016	-0.85 (0.471939)		2.4 %	-0.85 [-1.77, 0.07]
Wrigley 2014	0.35377 (0.278353)		3.7 %	0.35 [-0.19, 0.90]
Subtotal (95% CI)			**80.2 %**	**-0.56 [-0.79, -0.32]**
Heterogeneity: Tau^2 = 0.24; Chi^2 = 75.03, df = 28 (P<0.00001); I^2 =63%				
Test for overall effect: Z = 4.69 (P < 0.00001)				
Total (95% CI)			**100.0 %**	**-0.48 [-0.67, -0.29]**
Heterogeneity: Tau^2 = 0.17; Chi^2 = 82.78, df = 33 (P<0.00001); I^2 =60%				
Test for overall effect: Z = 4.97 (P < 0.00001)				
Test for subgroup differences: Chi^2 = 5.93, df = 1 (P = 0.01), I^2 =83%				

(1) cathodal

(2) anodal

(3) DLPFC

(4) M1

(5) M1

(6) DLPFC

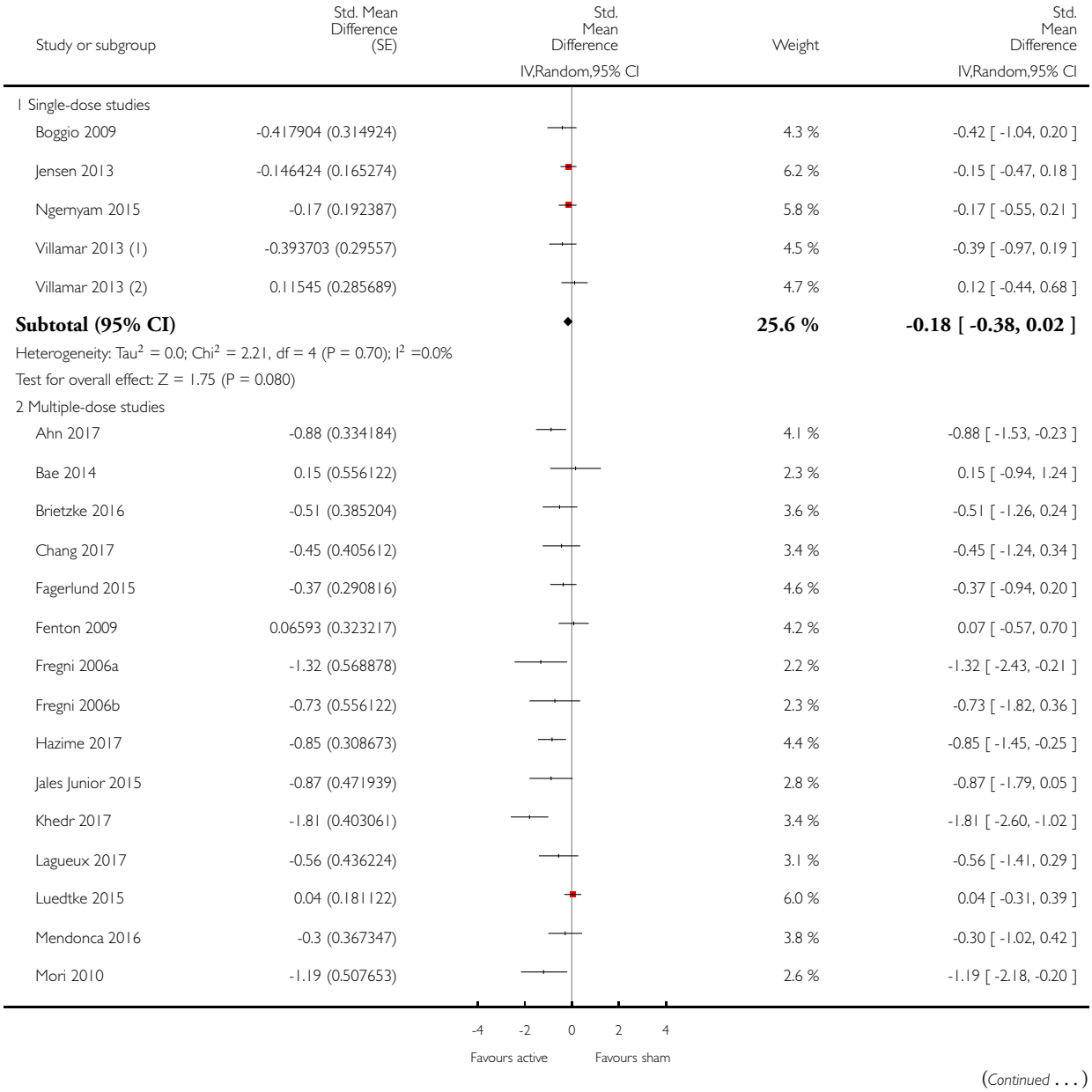
(7) tDCS+ sham illusion vs sham tDCS + sham illusion

Analysis 3.5. Comparison 3 Transcranial direct current stimulation (tDCS), Outcome 5 Pain: short-term follow-up, subgroup analysis: motor cortex studies only.

Review: Non-invasive brain stimulation techniques for chronic pain

Comparison: 3 Transcranial direct current stimulation (tDCS)

Outcome: 5 Pain: short-term follow-up, subgroup analysis: motor cortex studies only



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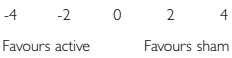
Study or subgroup	Std. Mean Difference (SE)	Std. Mean Difference IV,Random,95% CI	Weight	Std. Mean Difference IV,Random,95% CI
Oliveira 2015	-0.97 (0.3775)		3.7 %	-0.97 [-1.71, -0.23]
Riberto 2011	0.02 (0.4158)		3.3 %	0.02 [-0.79, 0.83]
Sakrajai 2014	-1.58 (0.418367)		3.3 %	-1.58 [-2.40, -0.76]
Soler 2010	-0.55 (0.45663)		3.0 %	-0.55 [-1.44, 0.34]
Volz 2016	-0.85 (0.367347)		3.8 %	-0.85 [-1.57, -0.13]
Wrigley 2014	0.35377 (0.278353)		4.8 %	0.35 [-0.19, 0.90]
Subtotal (95% CI)			**74.4 %**	**-0.58 [-0.84, -0.33]**
Heterogeneity: $Tau^2 = 0.21$; $Chi^2 = 51.60$, df = 20 (P = 0.00013); $I^2 = 61\%$				
Test for overall effect: Z = 4.45 (P < 0.00001)				
Total (95% CI)			**100.0 %**	**-0.47 [-0.67, -0.28]**
Heterogeneity: $Tau^2 = 0.14$; $Chi^2 = 58.85$, df = 25 (P = 0.00015); $I^2 = 58\%$				
Test for overall effect: Z = 4.69 (P < 0.00001)				
Test for subgroup differences: $Chi^2 = 6.01$, df = 1 (P = 0.01), $I^2 = 83\%$				



(1) cathodal

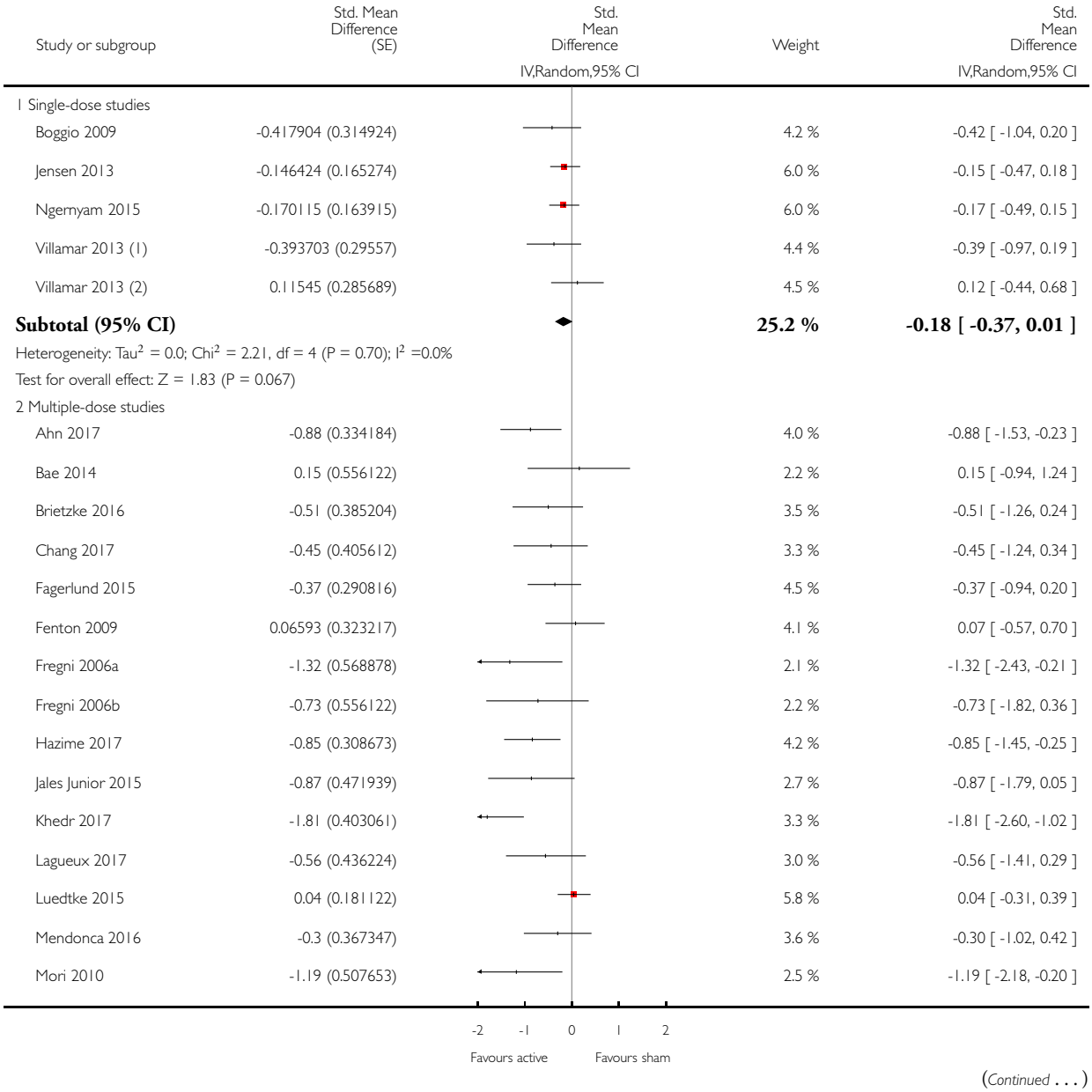
(2) anodal

Analysis 3.6. Comparison 3 Transcranial direct current stimulation (tDCS), Outcome 6 Pain: short-term follow-up, subgroup analysis: motor cortex studies only, sensitivity analysis: correlation increased.

Review: Non-invasive brain stimulation techniques for chronic pain

Comparison: 3 Transcranial direct current stimulation (tDCS)

Outcome: 6 Pain: short-term follow-up, subgroup analysis: motor cortex studies only, sensitivity analysis: correlation increased



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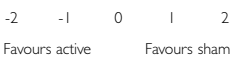
Study or subgroup	Std. Mean Difference (SE)	Std. Mean Difference IV,Random,95% CI	Weight	Std. Mean Difference IV,Random,95% CI
Oliveira 2015	-0.97 (0.3775)		3.5 %	-0.97 [-1.71, -0.23]
Riberto 2011	0.02 (0.4158)		3.2 %	0.02 [-0.79, 0.83]
Sakrajai 2014	-1.58 (0.418367)		3.2 %	-1.58 [-2.40, -0.76]
Soler 2010	-0.55 (0.45663)		2.8 %	-0.55 [-1.44, 0.34]
Thibaut 2017	-0.06 (0.40051)		3.3 %	-0.06 [-0.84, 0.72]
Volz 2016	-0.85 (0.471939)		2.7 %	-0.85 [-1.77, 0.07]
Wrigley 2014	0.35377 (0.237244)		5.1 %	0.35 [-0.11, 0.82]
Subtotal (95% CI)			**74.8 %**	**-0.55 [-0.81, -0.30]**
Heterogeneity: Tau^2 = 0.21; Chi^2 = 55.10, df = 21 (P = 0.00007); I^2 =62%				
Test for overall effect: Z = 4.28 (P = 0.000019)				
Total (95% CI)			**100.0 %**	**-0.45 [-0.64, -0.26]**
Heterogeneity: Tau^2 = 0.13; Chi^2 = 61.24, df = 26 (P = 0.00011); I^2 =58%				
Test for overall effect: Z = 4.56 (P < 0.00001)				
Test for subgroup differences: Chi^2 = 5.46, df = 1 (P = 0.02), I^2 =82%				



(1) cathodal

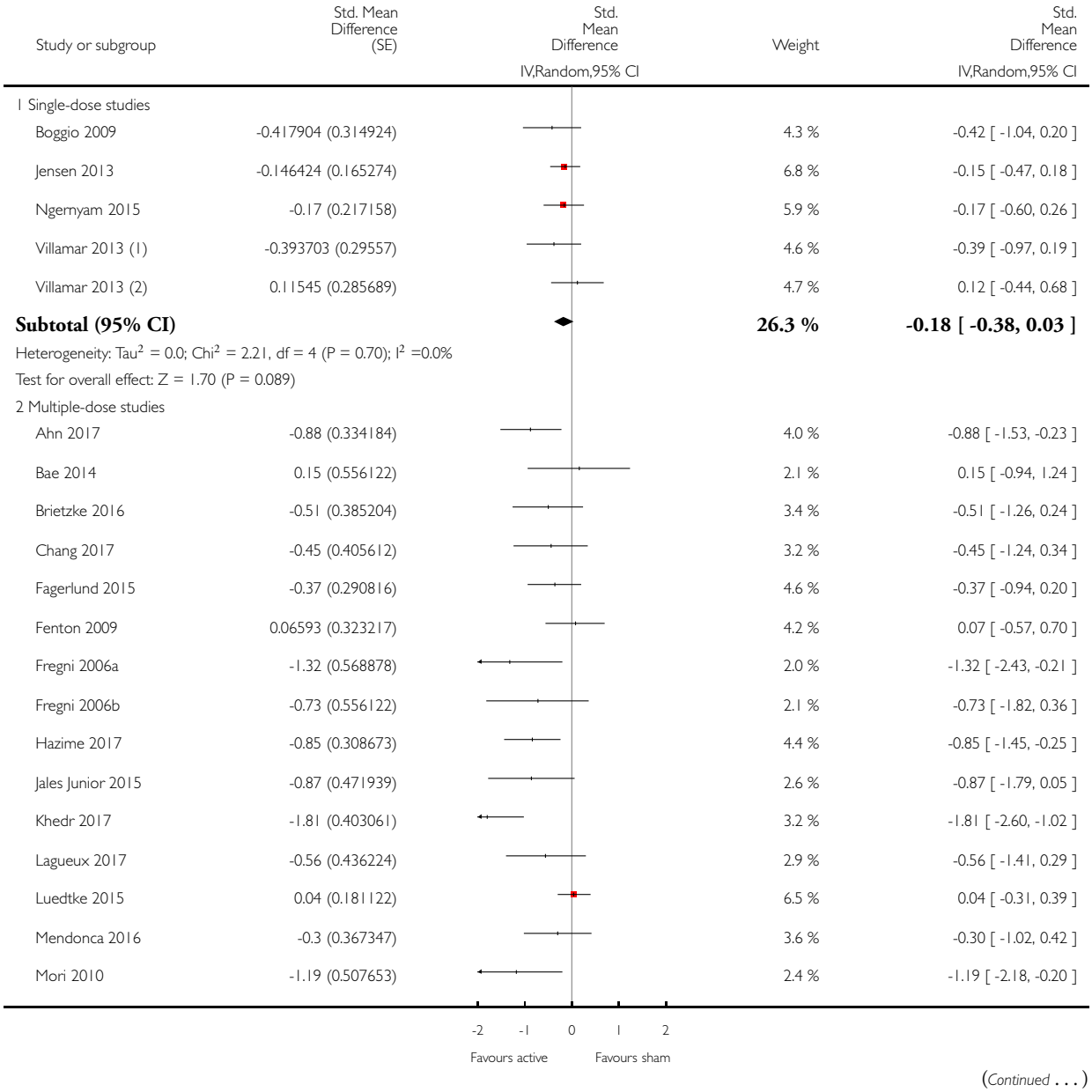
(2) anodal

Analysis 3.7. Comparison 3 Transcranial direct current stimulation (tDCS), Outcome 7 Pain: short-term follow-up, subgroup analysis: motor cortex studies only, sensitivity analysis: correlation decreased.

Review: Non-invasive brain stimulation techniques for chronic pain

Comparison: 3 Transcranial direct current stimulation (tDCS)

Outcome: 7 Pain: short-term follow-up, subgroup analysis: motor cortex studies only, sensitivity analysis: correlation decreased



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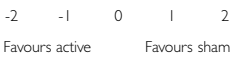
Study or subgroup	Std. Mean Difference (SE)	Std. Mean Difference IV,Random,95% CI	Weight	Std. Mean Difference IV,Random,95% CI
Oliveira 2015	-0.97 (0.3775)		3.5 %	-0.97 [-1.71, -0.23]
Riberto 2011	0.02 (0.4158)		3.1 %	0.02 [-0.79, 0.83]
Sakrajai 2014	-0.158 (0.418367)		3.1 %	-0.16 [-0.98, 0.66]
Soler 2010	-0.55 (0.45663)		2.7 %	-0.55 [-1.44, 0.34]
Thibaut 2017	-0.06 (0.40051)		3.3 %	-0.06 [-0.84, 0.72]
Volz 2016	-0.85 (0.471939)		2.6 %	-0.85 [-1.77, 0.07]
Wrigley 2014	0.35377 (0.314305)		4.3 %	0.35 [-0.26, 0.97]
Subtotal (95% CI)			**73.7 %**	**-0.49 [-0.72, -0.26]**
Heterogeneity: $Tau^2 = 0.14$; $Chi^2 = 43.20$, df = 21 (P = 0.003); $I^2 = 51\%$				
Test for overall effect: Z = 4.19 (P = 0.000028)				
Total (95% CI)			**100.0 %**	**-0.40 [-0.58, -0.22]**
Heterogeneity: $Tau^2 = 0.09$; $Chi^2 = 48.49$, df = 26 (P = 0.005); $I^2 = 46\%$				
Test for overall effect: Z = 4.44 (P < 0.00001)				
Test for subgroup differences: $Chi^2 = 3.97$, df = 1 (P = 0.05), $I^2 = 75\%$				



(1) cathodal

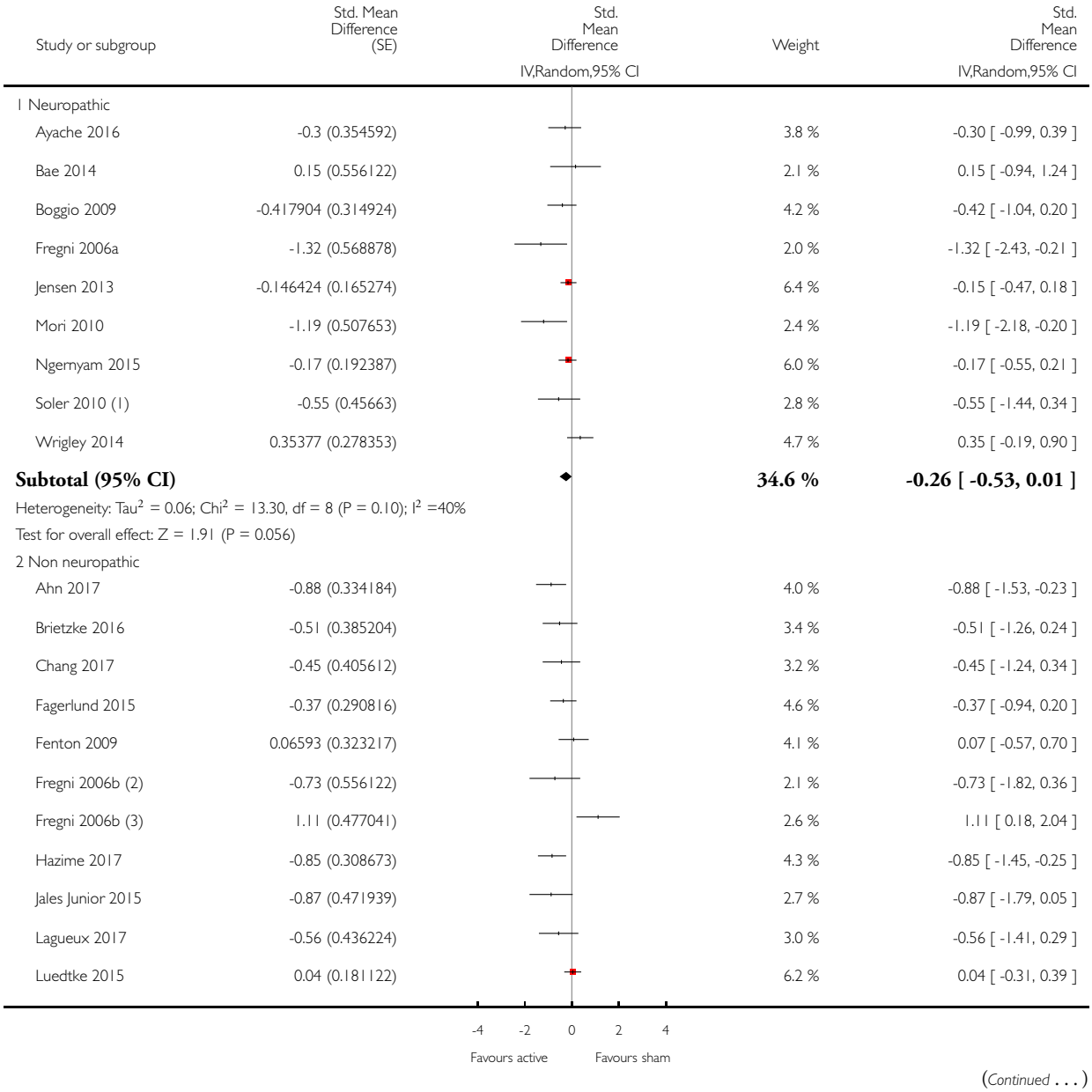
(2) anodal

Analysis 3.8. Comparison 3 Transcranial direct current stimulation (tDCS), Outcome 8 Pain: short-term follow-up, subgroup analysis, neuropathic and non neuropathic pain.

Review: Non-invasive brain stimulation techniques for chronic pain

Comparison: 3 Transcranial direct current stimulation (tDCS)

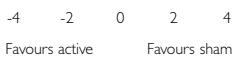
Outcome: 8 Pain: short-term follow-up, subgroup analysis, neuropathic and non neuropathic pain



(*Continued . . .*)

(. . . *Continued*)

Study or subgroup	Std. Mean Difference (SE)	Std. Mean Difference IV,Random,95% CI	Weight	Std. Mean Difference IV,Random,95% CI
Mendonca 2016	-0.3 (0.367347)		3.6 %	-0.30 [-1.02, 0.42]
Oliveira 2015	-0.97 (0.3775)		3.5 %	-0.97 [-1.71, -0.23]
Riberto 2011	0.02 (0.4158)		3.1 %	0.02 [-0.79, 0.83]
Sakrajai 2014	-1.58 (0.418367)		3.1 %	-1.58 [-2.40, -0.76]
Villamar 2013 (4)	0.11545 (0.285689)		4.6 %	0.12 [-0.44, 0.68]
Villamar 2013 (5)	-0.393703 (0.29557)		4.5 %	-0.39 [-0.97, 0.19]
Volz 2016	-0.85 (0.471939)		2.7 %	-0.85 [-1.77, 0.07]
Subtotal (95% CI)			**65.4 %**	**-0.42 [-0.67, -0.17]**
Heterogeneity: $Tau^2 = 0.15$; $Chi^2 = 38.90$, df = 17 (P = 0.002); $I^2 = 56\%$				
Test for overall effect: Z = 3.30 (P = 0.00096)				
Total (95% CI)			**100.0 %**	**-0.37 [-0.56, -0.19]**
Heterogeneity: $Tau^2 = 0.11$; $Chi^2 = 53.51$, df = 26 (P = 0.001); $I^2 = 51\%$				
Test for overall effect: Z = 3.92 (P = 0.000087)				
Test for subgroup differences: $Chi^2 = 0.68$, df = 1 (P = 0.41), $I^2 = 0.0\%$				



(1) tDCS+ sham illusion vs sham tDCS + sham illusion

(2) M1

(3) DLPFC

(4) anodal

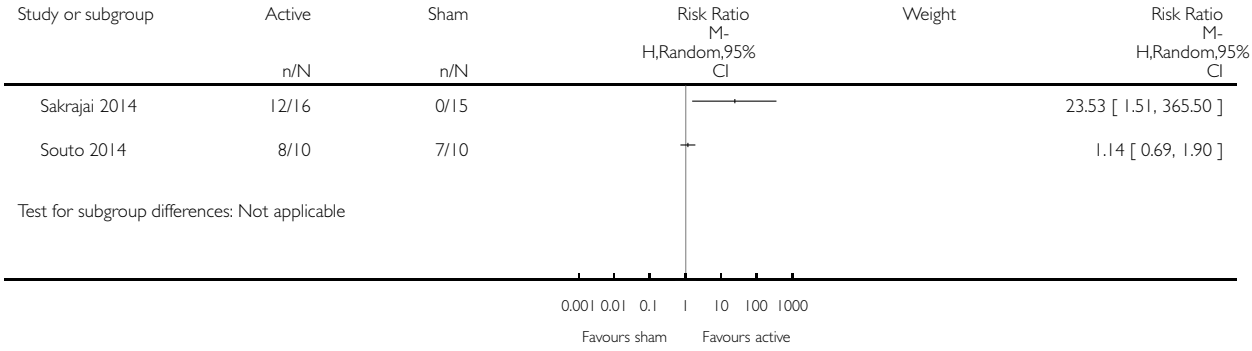
(5) cathodal

Analysis 3.9. Comparison 3 Transcranial direct current stimulation (tDCS), Outcome 9 Pain: short term follow-up responder analysis 30% pain reduction.

Review: Non-invasive brain stimulation techniques for chronic pain

Comparison: 3 Transcranial direct current stimulation (tDCS)

Outcome: 9 Pain: short term follow-up responder analysis 30% pain reduction

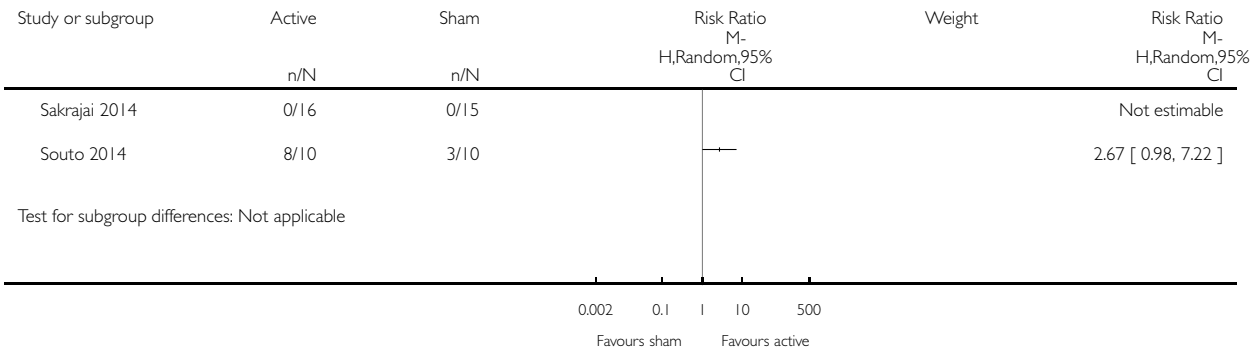


Analysis 3.10. Comparison 3 Transcranial direct current stimulation (tDCS), Outcome 10 Pain: short term follow-up responder analysis 50% pain reduction.

Review: Non-invasive brain stimulation techniques for chronic pain

Comparison: 3 Transcranial direct current stimulation (tDCS)

Outcome: 10 Pain: short term follow-up responder analysis 50% pain reduction

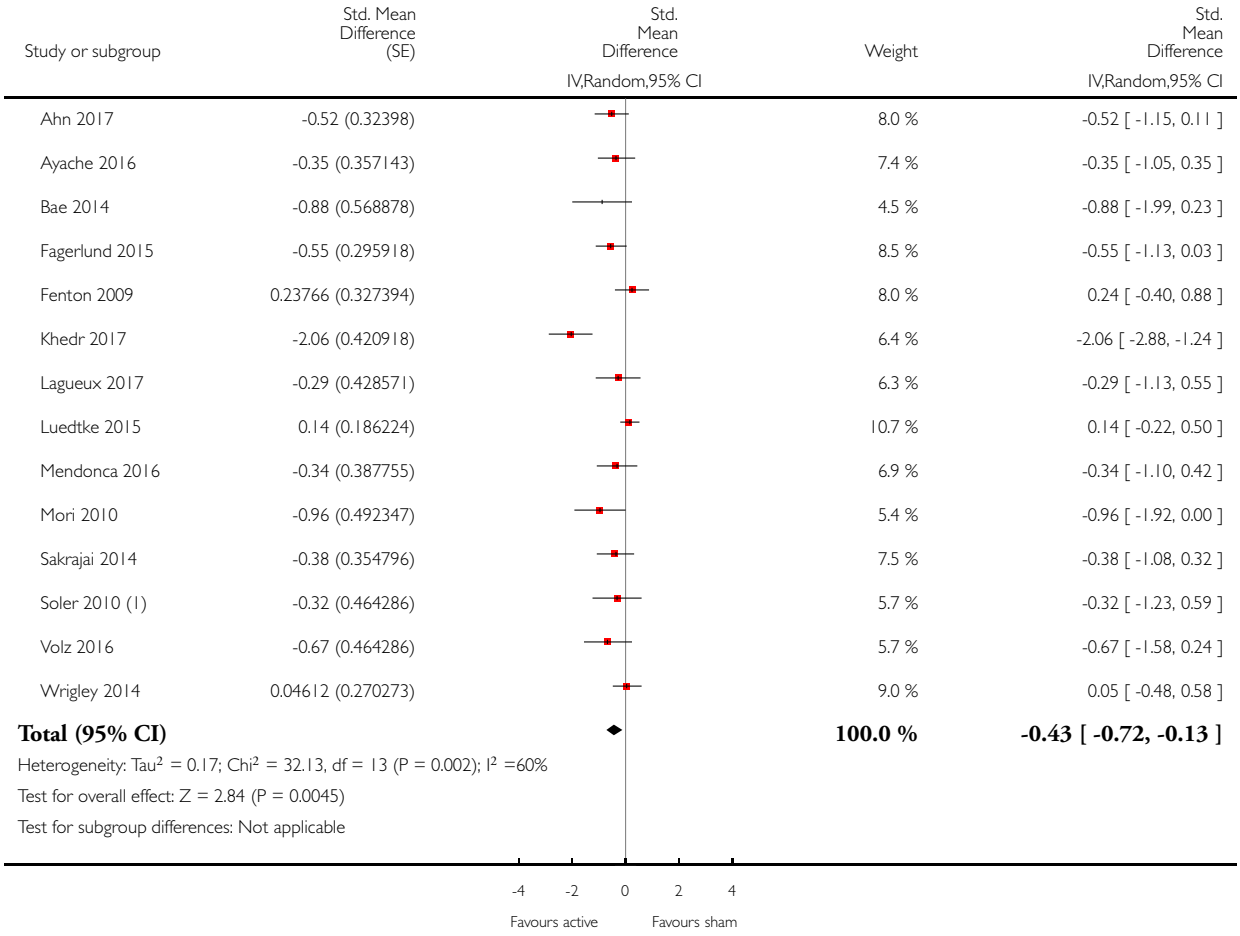


Analysis 3.11. Comparison 3 Transcranial direct current stimulation (tDCS), Outcome 11 Pain: medium-term follow-up.

Review: Non-invasive brain stimulation techniques for chronic pain

Comparison: 3 Transcranial direct current stimulation (tDCS)

Outcome: 11 Pain: medium-term follow-up



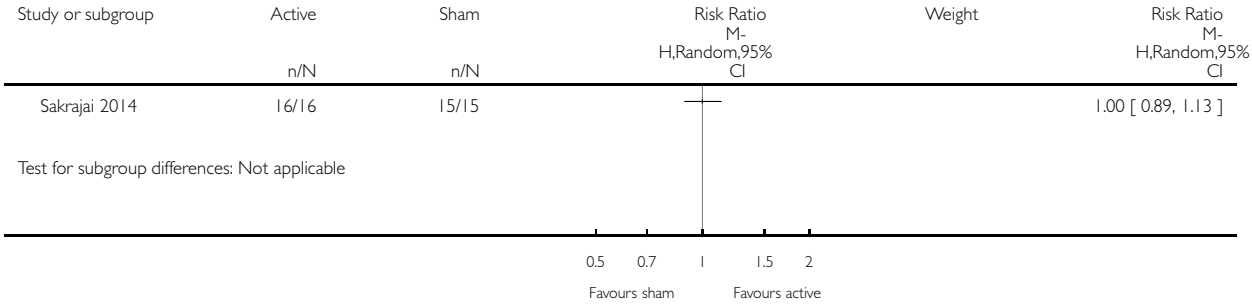
(1) tDCS+sham illusion versus sham tDCS + sham illusion

Analysis 3.12. Comparison 3 Transcranial direct current stimulation (tDCS), Outcome 12 Pain: medium term follow-up responder analysis 30% pain reduction.

Review: Non-invasive brain stimulation techniques for chronic pain

Comparison: 3 Transcranial direct current stimulation (tDCS)

Outcome: 12 Pain: medium term follow-up responder analysis 30% pain reduction

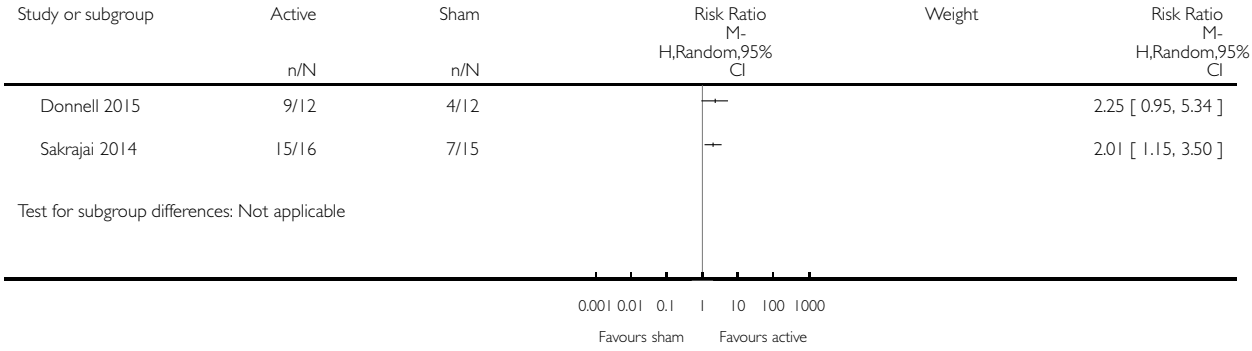


Analysis 3.13. Comparison 3 Transcranial direct current stimulation (tDCS), Outcome 13 Pain: medium term follow-up responder analysis 50% pain reduction.

Review: Non-invasive brain stimulation techniques for chronic pain

Comparison: 3 Transcranial direct current stimulation (tDCS)

Outcome: 13 Pain: medium term follow-up responder analysis 50% pain reduction

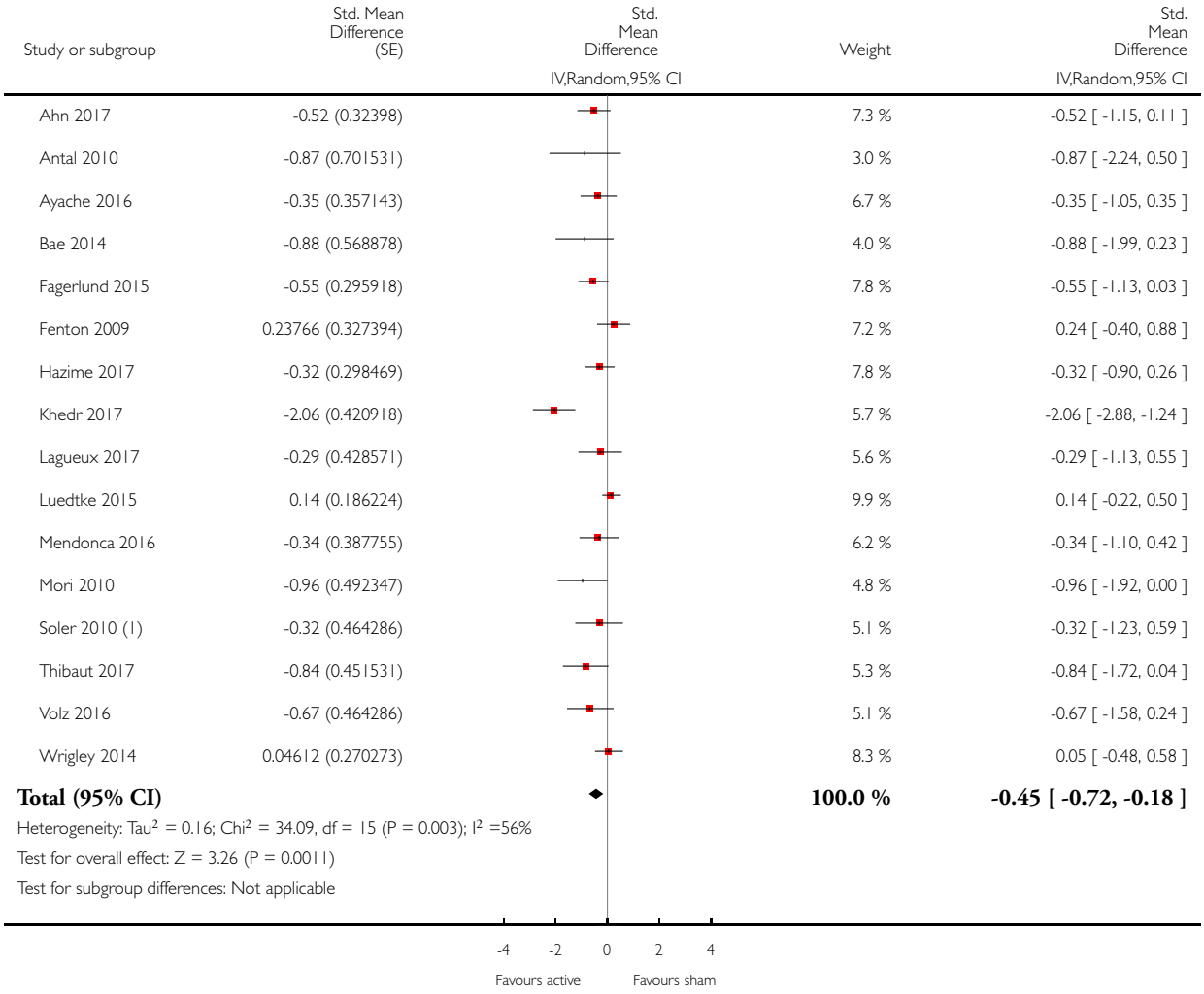


Analysis 3.14. Comparison 3 Transcranial direct current stimulation (tDCS), Outcome 14 Sensitivity analysis - inclusion of high risk of bias studies. Pain: medium-term follow-up.

Review: Non-invasive brain stimulation techniques for chronic pain

Comparison: 3 Transcranial direct current stimulation (tDCS)

Outcome: 14 Sensitivity analysis - inclusion of high risk of bias studies. Pain: medium-term follow-up



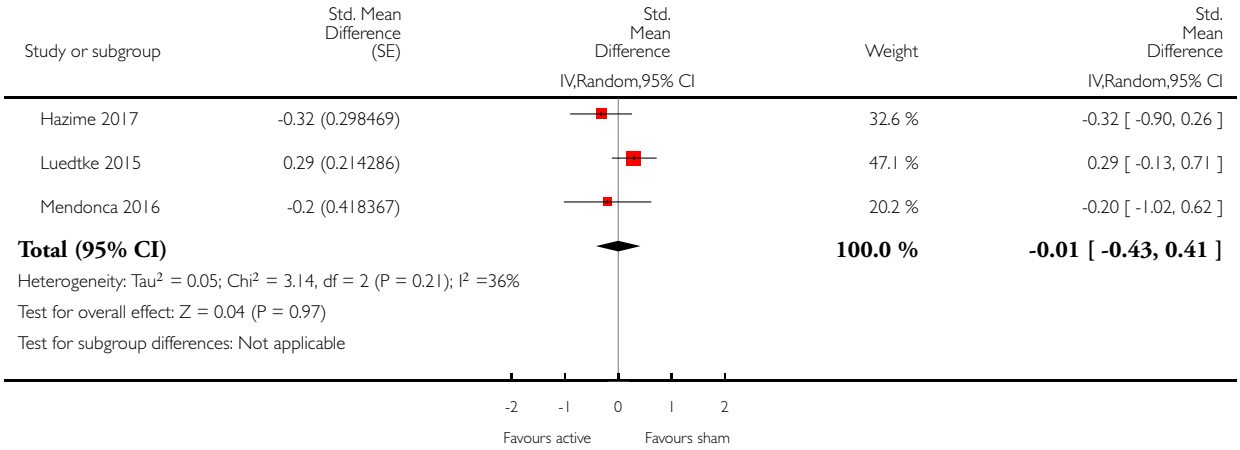
(1) tDCS+sham illusion versus sham tDCS + sham illusion

Analysis 3.15. Comparison 3 Transcranial direct current stimulation (tDCS), Outcome 15 Pain: long-term follow-up.

Review: Non-invasive brain stimulation techniques for chronic pain

Comparison: 3 Transcranial direct current stimulation (tDCS)

Outcome: 15 Pain: long-term follow-up



Analysis 3.16. Comparison 3 Transcranial direct current stimulation (tDCS), Outcome 16 Disability: short-term follow-up.

Review: Non-invasive brain stimulation techniques for chronic pain

Comparison: 3 Transcranial direct current stimulation (tDCS)

Outcome: 16 Disability: short-term follow-up

Study or subgroup	Active N	Mean(SD)	Sham N	Mean(SD)	Std. Mean Difference IV,Random,95% CI	Weight	Std. Mean Difference IV,Random,95% CI
Ahn 2017	20	-2.4 (10.4)	20	-0.1 (7.3)		18.8 %	-0.25 [-0.87, 0.37]
Chang 2017	15	26 (10.42)	15	27.8 (9.6)		14.2 %	-0.17 [-0.89, 0.54]
Luedtke 2015 (1)	61	15 (7)	61	14 (6)		57.7 %	0.15 [-0.20, 0.51]
Soler 2010 (2)	10	4 (3.4)	10	4.9 (2.8)		9.4 %	-0.28 [-1.16, 0.60]
Total (95% CI)	**106**		**106**			**100.0 %**	**-0.01 [-0.28, 0.26]**

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 1.93$, df = 3 (P = 0.59); $I^2 = 0.0\%$

Test for overall effect: Z = 0.07 (P = 0.94)

Test for subgroup differences: Not applicable

(1) Oswestry Disability Index

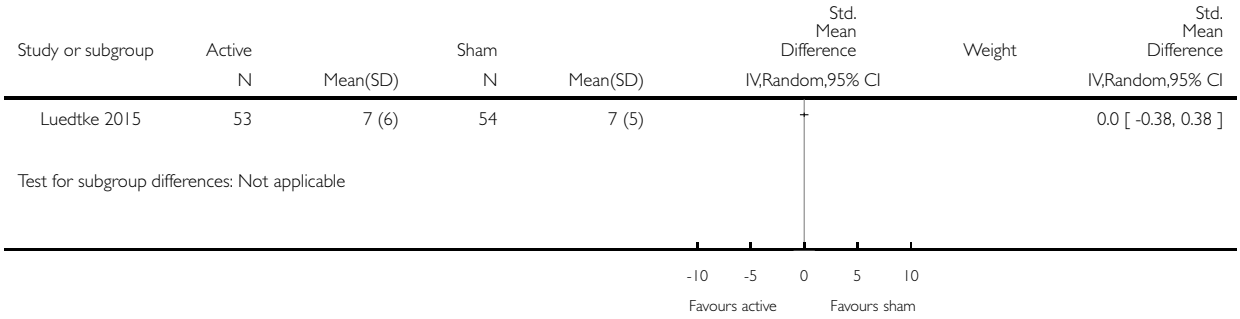
(2) BPI - interference

Analysis 3.17. Comparison 3 Transcranial direct current stimulation (tDCS), Outcome 17 Disability: medium-term follow-up.

Review: Non-invasive brain stimulation techniques for chronic pain

Comparison: 3 Transcranial direct current stimulation (tDCS)

Outcome: 17 Disability: medium-term follow-up

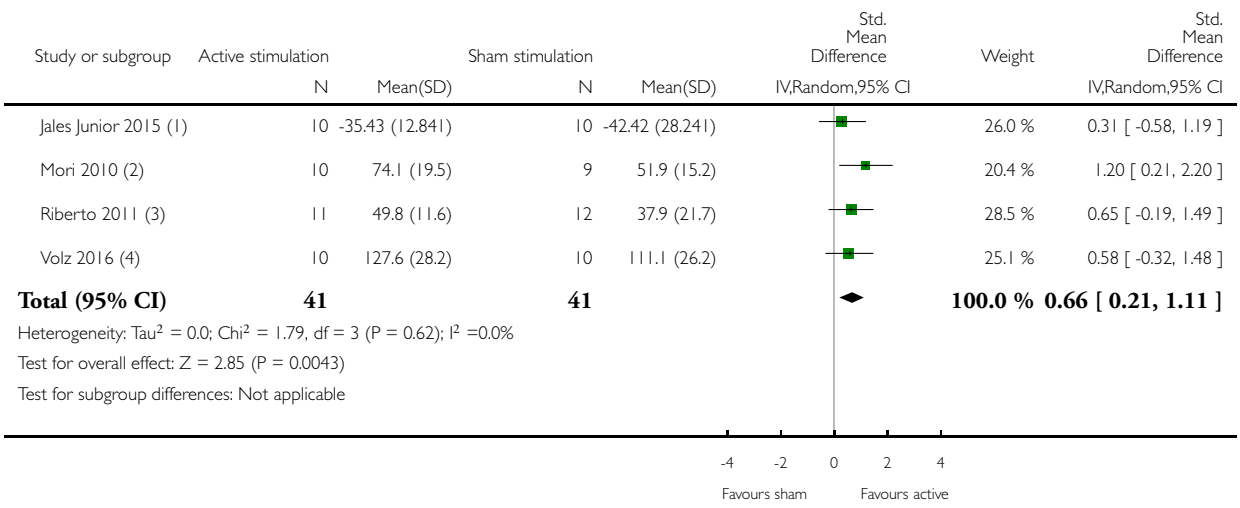


Analysis 3.18. Comparison 3 Transcranial direct current stimulation (tDCS), Outcome 18 Quality of life: short-term follow-up.

Review: Non-invasive brain stimulation techniques for chronic pain

Comparison: 3 Transcranial direct current stimulation (tDCS)

Outcome: 18 Quality of life: short-term follow-up



(1) FIQ (scales reversed)

(2) MS-QoL-54

(3) SF-36 total

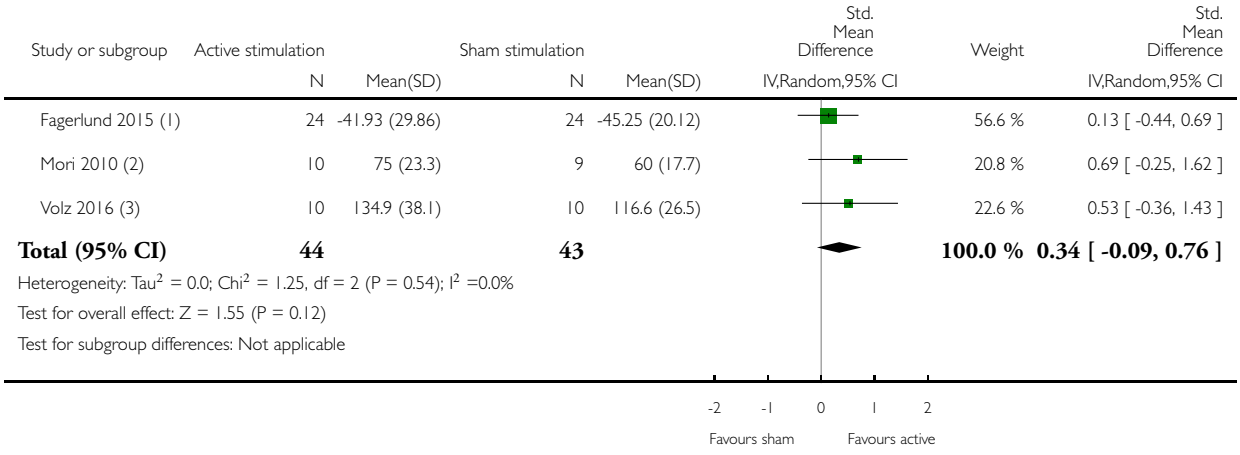
(4) IBDQ QoL

Analysis 3.19. Comparison 3 Transcranial direct current stimulation (tDCS), Outcome 19 Quality of life: medium-term follow-up.

Review: Non-invasive brain stimulation techniques for chronic pain

Comparison: 3 Transcranial direct current stimulation (tDCS)

Outcome: 19 Quality of life: medium-term follow-up



(1) FIQ (scale reversed to correct directional diference with other scales in the meta-analysis)

(2) multiple sclerosis quality of life-54 scale (MSQoL-54)

(3) Inflammatory bowel disease QoL questionnaire

Analysis 4.1. Comparison 4 Reduced impedance non-invasive cortical electrostimulation (RINCE), Outcome 1 Pain: short-term follow-up.

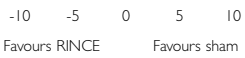
Review: Non-invasive brain stimulation techniques for chronic pain

Comparison: 4 Reduced impedance non-invasive cortical electrostimulation (RINCE)

Outcome: 1 Pain: short-term follow-up

Study or subgroup	Active		Sham		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Fixed,95% CI		IV,Fixed,95% CI
Hargrove 2012a (1)	39	4.6 (2.27)	38	6.01 (2.53)			-1.41 [-2.48, -0.34]

Test for subgroup differences: Not applicable



(1) Per protocol analysis

Analysis 4.2. Comparison 4 Reduced impedance non-invasive cortical electrostimulation (RINCE), Outcome 2 Sensitivity analysis - inclusion of high risk of bias studies. Pain: short-term follow-up.

Review: Non-invasive brain stimulation techniques for chronic pain

Comparison: 4 Reduced impedance non-invasive cortical electrostimulation (RINCE)

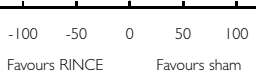
Outcome: 2 Sensitivity analysis - inclusion of high risk of bias studies. Pain: short-term follow-up

Study or subgroup	Active		Sham		Std. Mean Difference	Weight	Std. Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Random,95% CI		IV,Random,95% CI
Deering 2017 (1)	15	35.8 (22.84)	4	56 (27.15)		12.4 %	-0.82 [-1.96, 0.33]
Deering 2017 (2)	16	46.69 (25.22)	3	56 (27.15)		10.5 %	-0.35 [-1.59, 0.89]
Hargrove 2012a (3)	39	4.6 (2.27)	38	6.01 (2.53)		77.2 %	-0.58 [-1.04, -0.12]
Total (95% CI)	**70**		**45**			**100.0 %**	**-0.59 [-0.99, -0.18]**

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.30$, df = 2 (P = 0.86); $I^2 = 0.0\%$

Test for overall effect: Z = 2.86 (P = 0.0042)

Test for subgroup differences: Not applicable



(1) 12 week active intervetnion

(2) 8 week active intervention

(3) Per protocol analysis

Analysis 4.3. Comparison 4 Reduced impedance non-invasive cortical electrostimulation (RINCE), Outcome 3 Quality of Life: short term follow-up.

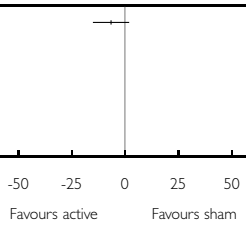
Review: Non-invasive brain stimulation techniques for chronic pain

Comparison: 4 Reduced impedance non-invasive cortical electrostimulation (RINCE)

Outcome: 3 Quality of Life: short term follow-up

Study or subgroup	Active		Sham		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Fixed,95% CI		IV,Fixed,95% CI
Hargrove 2012a	39	45.96 (20.42)	38	52.46 (18.53)			-6.50 [-15.21, 2.21]

Test for subgroup differences: Not applicable



Analysis 4.4. Comparison 4 Reduced impedance non-invasive cortical electrostimulation (RINCE), Outcome 4 Sensitivity analysis - inclusion of high risk of bias studies. Quality of life: short term follow-up.

Review: Non-invasive brain stimulation techniques for chronic pain

Comparison: 4 Reduced impedance non-invasive cortical electrostimulation (RINCE)

Outcome: 4 Sensitivity analysis - inclusion of high risk of bias studies. Quality of life: short term follow-up

Study or subgroup	Active		Sham		Std. Mean Difference	Weight	Std. Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Random,95% CI		IV,Random,95% CI
Deering 2017 (1)	16	43.43 (24.81)	3	48.43 (22.72)		13.3 %	-0.19 [-1.43, 1.04]
Deering 2017 (2)	15	25.87 (15.53)	4	48.43 (22.72)		14.2 %	-1.27 [-2.46, -0.07]
Hargrove 2012a	39	45.96 (20.42)	38	52.46 (18.53)		72.4 %	-0.33 [-0.78, 0.12]
Total (95% CI)	**70**		**45**			**100.0 %**	**-0.45 [-0.91, 0.02]**

Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 2.22$, df = 2 (P = 0.33); $I^2 = 10\%$

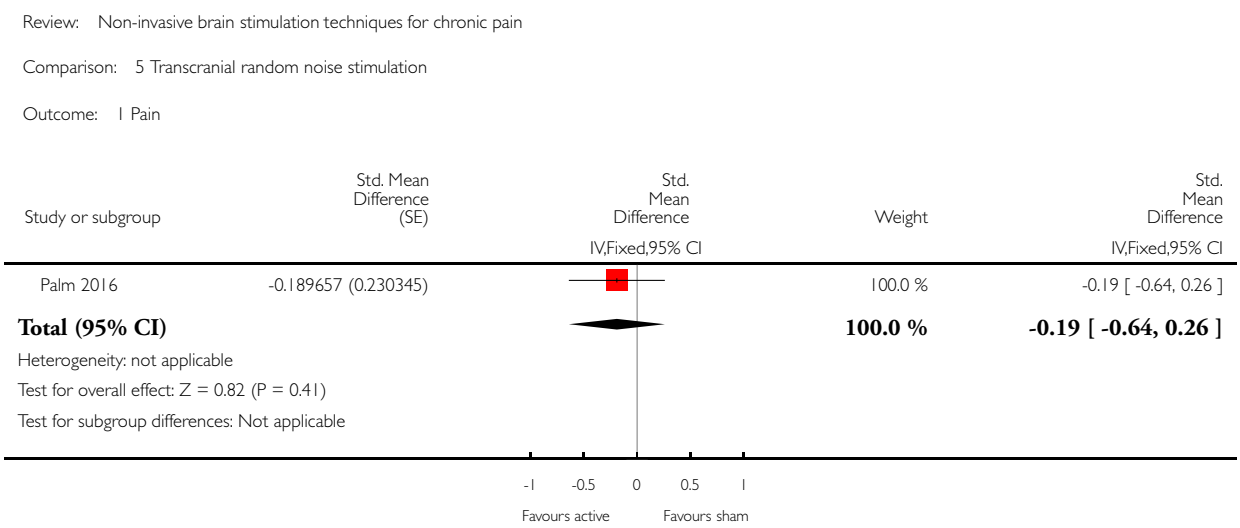
Test for overall effect: Z = 1.88 (P = 0.060)

Test for subgroup differences: Not applicable

(1) 8 week active intervention. Revised FIQ

(2) 12 week active intervention. Revised FIQ

Analysis 5.1. Comparison 5 Transcranial random noise stimulation, Outcome 1 Pain.



ADDITIONAL TABLES

Table 1. Repetitive transcranial magnetic stimulation (rTMS) studies - characteristics of stimulation

Study	Location of stimulation	Coil orientation	Frequency (Hz)	Intensity (% RMT)	Number of trains	Duration of trains	Inter-train intervals (sec)	Number of pulses per session	Treatment sessions per group
Ahmed 2011	M1 stump region	45° angle from sagittal line	20	80	10	10 sec	50	2000	5, x 1 daily
Attal 2016	M1 contralateral to painful side	Antero-posterior induced current	10	80	30	10	20	3000	3, x1 daily
André-Obadia 2006	M1 contralateral to painful side	Posteroanterior	20, 1	90	20 Hz: 20 1 Hz: 1	20 Hz: 4 sec 1 Hz: 26 min	20 Hz: 84	1600	1
André-Obadia 2008	M1 contralateral to painful side	Posteroanterior Medial-lateral	20	90	20	4 sec	84	1600	1

Table 1. Repetitive transcranial magnetic stimulation (rTMS) studies - characteristics of stimulation (*Continued*)

André-Obadia 2011	M1 hand area, not clearly reported but likely contralateral to painful side	Not specified	20	90	20	4 sec	84	1600	1
Avery 2013	Left DLPFC	Not specified	10	120	75	4	26	3000	15
Borckardt 2009	Left PFC	Not specified	10	100	40	10 sec	20	4000	3 over a 5-day period
Boyer 2014	Left M1	anteroposterior	10	90	20	10	50	2000	14, 10 sessions in 2 weeks followed by maintenance phase of 1 session at weeks 4, 6, 8, and 10
Carretero 2009	Right DLPFC	Not specified	1	110	20	60 sec	45	1200	Up to 20 on consecutive working days
Dall'Agnol 2014	Left M1	45° angle from sagittal line	10	80	16	10	26	1600	10, timescale not specified
Defrin 2007	M1 midline	Not specified	5	115	500	10 sec	30	? 500*	10, x 1 daily
de Oliveira 2014	Left DLPFC/ premotor	not specified	10	120	25	5 sec	25	1250	10, x 1 daily (working days) for 2 weeks
Fregni 2005	Left and right SII	Not specified	1 or 20	90	Not specified	Not specified	Not specified	1600	1

Table 1. Repetitive transcranial magnetic stimulation (rTMS) studies - characteristics of stimulation (*Continued*)

Fregni 2011	Right SII	Not specified	1	70% maximum stimulator output intensity (not RMT)	1	Not specified	Not specified	1600	10, x 1 daily (weekdays only)
Hirayama 2006	M1, S1, PMA, SMA	Not specified	5	90	10	10 sec	50	500	1
Hosomi 2013	M1 corresponding to painful region	Not specified	5	90	10	10 sec	50	500	10, x 1 daily (weekdays only)
Irlbacher 2006	M1 contralateral to painful side	Not specified	5, 1	95	Not specified	Not specified	Not specified	500	1
Jetté 2013	M1 hand or leg area with neuro navigation	45° postero-lateral	10	90	40	5	25	2000	1, per stimulation condition
Kang 2009	Right M1	45° postero-lateral	10	80	20	5 sec	55	1000	5, x 1 daily
Khedr 2005	M1 contralateral to painful side	Not specified	20	80	10	10 sec	50	2000	5, x 1 daily
Lee 2012	Right DLPFC (low-frequency) Left M1 (high-frequency)	Not specified	10, 1	10 Hz: 80 1 Hz: 110	10 Hz: 25 1 Hz: 2	10 Hz: 8 sec 1 Hz: 800 sec	10 Hz: 10 1 Hz: 60	10 Hz: 2000 1 Hz: 1600	10, x 1 daily (weekdays only)
Lefaucheur 2001a	M1 contralateral to painful side	Not specified	10	80	20	5 sec	55	1000	1

Table 1. Repetitive transcranial magnetic stimulation (rTMS) studies - characteristics of stimulation (*Continued*)

Lefaucheur 2001b	M1 contralateral to painful side	Posteroanterior	10, 0.5	80	10 Hz: 20 0.5 Hz: 1	10 Hz: 5 sec 0.5 Hz: 20 min	10 Hz: 55	10 Hz: 1000 0.5 Hz: 600	1
Lefaucheur 2004	M1 contralateral to painful side	Posteroanterior	10	80	20	5 sec	55	1000	1
Lefaucheur 2006	M1 contralateral to painful side	Posteroanterior	10, 1	90	10 Hz: 20 1 Hz: 1	10 Hz: 6 sec 1 Hz: 20 min	10 Hz: 54	10 Hz: 1200 1 Hz: 1200	1
Lefaucheur 2008	M1 contralateral to painful side	Posteroanterior	10, 1	90	10 Hz: 20 1 Hz: 1	10 Hz: 6 sec 1 Hz: 20 min	10 Hz: 54	10 Hz: 1200 1 Hz: 1200	1
Malavera 2013	M1 contralateral to painful side	45° angle from sagittal line	10	90	20	6	54	1200	10, x 1 daily (weekdays only)
Medeiros 2016	Left M1	45° angle from sagittal line	10	80	not reported	not reported	not reported	1600	10, x 1 daily
Mhalla 2011	Left M1	Posteroanterior	10	80	15	10 sec	50	1500	14, 5 x 1 daily (working days), then 3 x 1 weekly, then 3 x 1 fortnightly, then 3 x 1 monthly
Nardone 2017	Left PFC	Posteroanterior	10	120	25	5 sec	25	1250	10, x5 per week for 2 weeks
Nurmikko 2016	M1 hotspot contralateral to pain	Posteroanterior	10	90	20	10 sec	60	2000	5, x 3-5 times per week

Table 1. Repetitive transcranial magnetic stimulation (rTMS) studies - characteristics of stimulation (*Continued*)

	M1 in reorganised area contralateral to pain								
Onesti 2013	M1 deep central sulcus	H-coil	20	100	30	2.5 sec	30	1500	5, x 1 daily on consecutive days
Passard 2007	M1 contralateral to painful side	Posteroanterior	10	80	25	8 sec	52	2000	10, x 1 daily (working days)
Picarelli 2010	M1 contralateral to painful side	Posteroanterior	10	100	25	10 sec	60	2500	10, x 1 daily (working days)
Pleger 2004	M1 hand area	Not specified	10	110	10	1.2 sec	10	120	1
Rollnik 2002	M1 midline	Not specified	20	80	20	2 sec	Not specified	800	1
Saitoh 2007	M1 over motor representation of painful area	Not specified	10, 5, 1	90	10 Hz; 5 5 Hz: 10 1 Hz: 1	10 Hz: 10 sec 5 Hz: 10 sec 1 Hz: 500 sec	10 Hz: 50 5 Hz: 50	500	1
Short 2011	Left DLPFC	Parasagittal	10	120	80	5 sec	10 sec	4000	10, x 1 daily (working days) for 2 weeks
Tekin 2014	M1 midline	45° angle from sagittal line	10	100	30	5	12	1500	10, x 1 daily (not clear if only work days)
Tzabazis 2013	Targeted to ACC	4-coil configuration	1 Hz (10 Hz data excluded as not ran-	110	Not reported	Not reported	Not reported	1800	20, x 1 daily (working days)

Table 1. Repetitive transcranial magnetic stimulation (rTMS) studies - characteristics of stimulation (*Continued*)

			domised)						
Umezaki 2016	Left DLPFC	Not specified	10	100	10	5	10	3000	10, x1 daily (working days)
Yagci 2014	Left M1	Not specified	1	90	20	60	45	1200	10, x1 daily (working days)
Yilmaz 2014	M1 midline	Handle pointing posteriorly	10	10	30	5	25	1500	10, x1 daily (working days)

ACC: anterior cingulate cortex; **DLPFC**: dorsolateral prefrontal cortex; **M1**: primary motor cortex; **PFC**: prefrontal cortex; PMA: pre-motor area; RMT: resting motor threshold; dS1: primary somatosensory cortex; **SII**: secondary somatosensory cortex; **SMA**: supplementary motor area

*Inconsistency between stimulation parameters and reported total number of pulses in study report. See Included studies section for mored detail.

Table 2. Cranial electrotherapy stimulation (CES) studies - characteristics of stimulation

Study	Electrode placement	Frequency (Hz)	Pulse width (ms)	Waveform shape	Intensity	Duration (min)	Treatment sessions per group
Capel 2003	Ear clip electrodes	10	2	Not specified	12 μA	53	x 2 daily for 4 days
Cork 2004	Ear clip electrodes	0.5	Not specified	Modified square-wave biphasic	100 μA	60	? daily for 3 weeks
Gabis 2003	Mastoid processes and forehead	77	3.3	Biphasic asymmetric	$\leq$ 4 mA	30	x 1 daily for 8 days
Gabis 2009	Mastoid processes and forehead	77	3.3	Biphasic asymmetric	$\leq$ 4 mA	30	x 1 daily for 8 days
Katsnelson 2004	Mastoid processes and forehead	Not specified	Not specified	2 conditions: symmetric, asymmetric	11 to 15 mA	40	x 1 daily for 5 days

Table 2. Cranial electrotherapy stimulation (CES) studies - characteristics of stimulation (*Continued*)

Lichtbroun 2001	Ear clip electrodes	0.5	Not specified	Biphasic square wave	100 μA	60	x 1 daily for 30 days
Rintala 2010	Ear clip electrodes	Not specified	Not specified	Not specified	100 μA	40	x 1 daily for 6 weeks
Tan 2000	Ear clip electrodes	0.5	Not specified	Not specified	10 to 600 μA	20	12 (timing not specified)
Tan 2006	Ear clip electrodes	Not specified	Not specified	Not specified	100 to 500 μA	60	x 1 daily for 21 days
Tan 2011	Ear clip electrodes	Not specified	Not specified	Not specified	100 μA	60	x 1 daily for 21 days
Taylor 2013	Ear clip electrodes	0.5	Not specified	Modified square-wave biphasic	100 μA	60	x 1 daily for 8 weeks

Table 3. Transcranial direct current stimulation (tDCS) studies - characteristics of stimulation

Study	Location of stimulation (Anode)	Electrode pad size	Intensity (mA)	Anodal or cathodal?	Stimulus duration (min)	Treatment sessions per group
Ahn 2017	M1 contralateral to painful side	35 cm^2	2 mA	Anodal	20	5, x 1 daily
Antal 2010	M1 left hand area	35 cm^2	1 mA	Anodal	20	5, x 1 daily
Ayache 2016	Left DLPFC	25 cm^2	2mA	Anodal	20	3, x 1 daily
Bae 2014	M1 contralateral to painful side	35 cm^2	2 mA	Anodal	20	x 3 per week for 3 weeks
Boggio 2009	M1 contralateral to painful side	35 cm^2	2 mA	Anodal	30	1
Brietzke 2016	Left M1	25-35 cm^2	2 mA	Anodal	20	5, x 1 daily
Chang 2017	M1 contralateral to painful side	35 cm^2	1 mA	Anodal	20	16, x 2 weekly for 8 weeks
Donnell 2015	M1 contralateral to painful side	HD-tDCS	2 mA	Anodal	20	5, x 1 daily

Table 3. Transcranial direct current stimulation (tDCS) studies - characteristics of stimulation (*Continued*)

Fagerlund 2015	M1, side not specified	35 cm^2	2mA	Anodal	20	5, x 1 daily
Fenton 2009	M1 dominant hemisphere	35 cm^2	1 mA	Anodal	20	2
Fregni 2006a	M1 contralateral to painful side or dominant hand	35 cm^2	2 mA	Anodal	20	5, x 1 daily
Fregni 2006b	M1 and DLPFC contralateral to painful side or dominant hand	35 cm^2	2 mA	Anodal	20	5, x 1 daily
Hagenacker 2014	M1 contralateral to painful side	40 cm^2	1mA	Anodal	20	Daily, self-administered for 14 days
Harvey 2017	M1 contralateral to painful side	35 cm^2	2 mA	Anodal	20	5, x 1 daily
Hazime 2017	M1 contralateral to painful side	35 cm^2	2 mA	Anodal	20	12, x 3 per week for 4 weeks
Jales Junior 2015	Left M1	15 cm^2	1mA	Anodal	20	x 1 weekly for 10 weeks
Jensen 2013	M1 left	35cm^2	2 mA	Anodal	20	1
Khedr 2017	M1 contralateral to painful side	24 cm^2	2 mA	Anodal	20	10, x 1 daily, 5 days per week for 2 weeks
Kim 2013	M1, side not specified DLPFC	25 cm^2	2mA	Anodal	20	5, x 1 daily
Lagueux 2017	M1 contralateral to painful side	35 cm^2	2 mA	Anodal	20	14, x 5 weekly for 2 weeks, x 1 weekly for 4 weeks
Luedtke 2015	M1 left side not specified	35 cm^2	2 mA	Anodal	20	5, x 1 daily
Mendonca 2011	Group 1: anodal left M1 Group 2: catho-	35 cm^2	2 mA	Anodal or cathodal	20	1

Table 3. Transcranial direct current stimulation (tDCS) studies - characteristics of stimulation (*Continued*)

	dal left M1 Group 3: anodal supraorbital Group 4: catho-dal supraorbital Group 5: sham					
Mendonca 2016	Left M1	35 cm^2	2 mA	Anodal	20	5, x 1 daily
Mori 2010	M1 contralateral to painful side	35 cm^2	2 mA	Anodal	20	5, x 1 daily
Ngernyam 2015	M1 contralateral to painful side	35 cm^2	2 mA	Anodal	20	1
Oliveira 2015	M1 contralateral to painful side	35 cm^2	2 mA	Anodal	20	5, x 1 daily, then x 2 weekly for 3 weeks, up to 10 sessions
Portilla 2013	M1 contralateral to painful side	35 cm^2	2 mA	Anodal	20	x 1 per condition
Riberto 2011	M1 contralateral to painful side or dominant hand	35 cm^2	2 mA	Anodal	20	10, x 1 weekly
Sakrajai 2014	M1 contralateral to painful side	35 cm^2	1 mA	Anodal	20	5, x 1 daily
Soler 2010	M1 contralateral to painful side or dominant hand	35 cm^2	2 mA	Anodal	20	10, x 1 daily (weekdays only)
Souto 2014	Left M1	25 cm^2	2 mA	Anodal	20	5, x 1 daily
Thibaut 2017	M1 contralateral to painful side	35 cm^2	2 mA	Anodal	20	5, x 1 daily
Valle 2009	M1 and DLPFC contralateral to painful side or dominant hand	35 cm^2	2 mA	Anodal	20	5, x 1 daily
Villamar 2013	M1 left	HD-tDCS 4 x 1-ring montage	2 mA	Anodal or catho-dal	20	x 1 per condition

Table 3. Transcranial direct current stimulation (tDCS) studies - characteristics of stimulation (*Continued*)

Wrigley 2014	M1 contralateral to painful side or dominant hand	35 cm^2	2 mA	Anodal	20	5, x 1 daily
Volz 2016	M1 contralateral to painful side	35 cm^2	2 mA	Anodal	20	5, x 1 daily

DLPFC: dorsolateral prefrontal cortex; **HD-tDCS**: high definition tDCS; **M1**: primary motor cortex

APPENDICES

Appendix 1. Main database search strategies for current update

CENTRAL (CRSO)

#1 MESH DESCRIPTOR pain EXPLODE ALL TREES 32731

#2 (((chronic* or back or musculoskel* or intractabl* or neuropath* or phantom limb or fantom limb or neck or myofasc* or "temporomandib* joint*" or "temperomandib* joint*" or "tempromandib* joint*" or central or post*stroke or complex or regional or spinal cord) adj4 pain*)):TI,AB,KY 15073

#3 ((sciatica or back-ache or back*ache or lumbago or fibromyalg* or (trigemin* adj2 neuralg*) or (herp* adj2 neuralg*) or (diabet* adj2 neuropath*) or (reflex adj4 dystroph*) or (sudeck* adj2 atroph*) or causalg* or whip-lash or whip*lash or polymyalg* or (failed back adj4 surg*) or (failed back adj4 syndrome*))):TI,AB,KY 6757

#4 #1 OR #2 OR #3 45871

#5 MESH DESCRIPTOR Transcranial Magnetic Stimulation 974

#6 MESH DESCRIPTOR Electronarcosis 33

#7 (((brain* or cortex or cortical or transcranial* or cranial or magneti*) adj4 stimulat*)):TI,AB,KY 4072

#8 (((transcrani* or crani* or brain*) adj4 (electrostim* or electro-stim* or electrotherap* or electro-therap*))):TI,AB,KY 64

#9 (((non-invasive or non*invasive) adj4 stimulat*)):TI,AB,KY 337

#10 ((theta burst stimulat* or iTBS or cTBS)):TI,AB,KY 150

#11 ((transcranial magnetic stimulation or rTMS or transcranial direct current stimulation or tDCS or cranial electrostimulation or cranial electrotherapy)):TI,AB,KY 2912

#12 ((electrosleep or electronarco*)):TI,AB,KY 47

#13 #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 4355

#14 #4 AND #13 310

#15 31/07/2013 TO 30/09/2016:DL 264060

#16 #14 AND #15 176

MEDLINE (OVID)

1 exp Pain/ (283010)

2 ((chronic* or back or musculoskel* or intractabl* or neuropath* or phantom limb or fantom limb or neck or myofasc* or "temporomandib* joint*" or "temperomandib* joint*" or "tempromandib* joint*" or central or post*stroke or complex or regional or spinal cord) adj4 pain*).tw. (74023)

3 (sciatica or back-ache or back*ache or lumbago or fibromyalg* or (trigemin* adj2 neuralg*) or (herp* adj2 neuralg*) or (diabet* adj2 neuropath*) or (reflex adj4 dystroph*) or (sudeck* adj2 atroph*) or causalg* or whip-lash or whip*lash or polymyalg* or (failed back adj4 surg*) or (failed back adj4 syndrome*)).tw. (28679)

4 or/1-3 (325946)

5 Transcranial Magnetic Stimulation/ or Electronarcosis/ (6328)
6 ((brain* or cortex or cortical or transcranial* or cranial or magneti*) adj4 stimulat*).tw. (25872)
7 ((transcrani* or crani* or brain*) adj4 (electrostim* or electro-stim* or electrotherap* or electro-therap*)).tw. (147)
8 ((non-invasive or non*invasive) adj4 stimulat*).tw. (822)
9 (theta burst stimulat* or iTBS or cTBS).tw. (575)
10 (transcranial magnetic stimulation or rTMS or transcranial direct current stimulation or tDCS or cranial electrostimulation or cranial electrotherapy).tw. (7423)
11 (electrosleep or electronarco*).tw. (357)
12 or/5-11 (28316)
13 randomized controlled trial.pt. (337806)
14 controlled clinical trial.pt. (84996)
15 randomized.ab. (241501)
16 placebo.ab. (134421)
17 drug therapy.fs. (1571905)
18 randomly.ab. (173459)
19 trial.ab. (248492)
20 groups.ab. (1134392)
21 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 (2928552)
22 exp animals/ not humans.sh. (3751730)
23 21 not 22 (2487755)
24 4 and 12 and 23 (295)
25 (200911* or 200912* or 2010* or 2011* or 2012* or 2013*).ed. (2428299)
26 24 and 25 (112)

Embase (OVID)

1 exp Pain/ (1006798)
2 ((chronic* or back or musculoskel* or intractabl* or neuropath* or phantom limb or fantom limb or neck or myofasc* or "temporo-mandib* joint*" or "temperomandib* joint*" or "tempromandib* joint*" or central or post*stroke or complex or regional or spinal cord) adj4 pain*).tw. (158849)
3 (sciatica or back-ache or back*ache or lumbago or fibromyalg* or (trigemin* adj2 neuralg*) or (herp* adj2 neuralg*) or (diabet* adj2 neuropath*) or (reflex adj4 dystroph*) or (sudeck* adj2 atroph*) or causalg* or whip-lash or whip*lash or polymyalg* or (failed back adj4 surg*) or (failed back adj4 syndrome*)).tw. (52041)
4 or/1-3 (1044575)
5 Transcranial Magnetic Stimulation/ or Electronarcosis/ (18453)
6 ((brain* or cortex or cortical or transcranial* or cranial or magneti*) adj4 stimulat*).tw. (50617)
7 ((transcrani* or crani* or brain*) adj4 (electrostim* or electro-stim* or electrotherap* or electro-therap*)).tw. (237)
8 ((non-invasive or non*invasive) adj4 stimulat*).tw. (2843)
9 (theta burst stimulat* or iTBS or cTBS).tw. (1549)
10 (transcranial magnetic stimulation or rTMS or transcranial direct current stimulation or tDCS or cranial electrostimulation or cranial electrotherapy).tw. (17745)
11 (electrosleep or electronarco*).tw. (383)
12 or/5-11 (57298)
13 random$.tw. (1121981)
14 factorial$.tw. (28563)
15 crossover$.tw. (58949)
16 cross over$.tw. (26241)
17 cross-over$.tw. (26241)
18 placebo$.tw. (244121)
19 (doubl$ adj blind$).tw. (172110)
20 (singl$ adj blind$).tw. (18218)
21 assign$.tw. (295873)
22 allocat$.tw. (107828)
23 volunteer$.tw. (211373)
24 Crossover Procedure/ (48595)

25 double-blind procedure.tw. (236)
26 Randomized Controlled Trial/ (419274)
27 Single Blind Procedure/ (23071)
28 or/13-27 (1749640)
29 (animal/ or nonhuman/) not human/ (5110486)
30 28 not 29 (1554658)
31 4 and 12 and 30 (1112)
32 (201307* or 201308* or 201309* or 201310* or 201311* or 201312* or 2014* or 2015* or 2016*).dd. (5443542)
33 31 and 32 (527)
34 limit 33 to embase (487)

PsycINFO (OVID)

1 exp Pain/ (48364)
2 ((chronic* or back or musculoskel* or intractabl* or neuropath* or phantom limb or fantom limb or neck or myofasc* or "temporo-mandib* joint*" or "temperomandib* joint*" or "tempromandib* joint*" or central or post*stroke or complex or regional or spinal cord) adj4 pain*).tw. (25922)
3 (sciatica or back-ache or back*ache or lumbago or fibromyalg* or (trigemin* adj2 neuralg*) or (herp* adj2 neuralg*) or (diabet* adj2 neuropath*) or (reflex adj4 dystroph*) or (sudeck* adj2 atroph*) or causalg* or whip-lash or whip*lash or polymyalg* or (failed back adj4 surg*) or (failed back adj4 syndrome*)).tw. (4998)
4 or/1-3 (56650)
5 Transcranial Magnetic Stimulation/ or Electronarcosis/ (5956)
6 ((brain* or cortex or cortical or transcranial* or cranial or magneti*) adj4 stimulat*).tw. (17936)
7 ((transcrani* or crani* or brain*) adj4 (electrostim* or electro-stim* or electrotherap* or electro-therap*)).tw. (89)
8 ((non-invasive or non*invasive) adj4 stimulat*).tw. (983)
9 (theta burst stimulat* or iTBS or cTBS).tw. (791)
10 (transcranial magnetic stimulation or rTMS or transcranial direct current stimulation or tDCS or cranial electrostimulation or cranial electrotherapy).tw. (7884)
11 (electrosleep or electronarco*).tw. (139)
12 or/5-11 (18853)
13 clinical trials/ (9724)
14 (randomis* or randomiz*).tw. (62274)
15 (random$ adj3 (allocat$ or assign$)).tw. (35100)
16 ((clinic$ or control$) adj trial$).tw. (52603)
17 ((singl$ or doubl$ or trebl$ or tripl$) adj3 (blind$ or mask$)).tw. (22429)
18 (crossover$ or "cross over$").tw. (8346)
19 random sampling/ (699)
20 Experiment Controls/ (856)
21 Placebo/ (4606)
22 placebo$.tw. (35030)
23 exp program evaluation/ (18184)
24 treatment effectiveness evaluation/ (20144)
25 ((effectiveness or evaluat$) adj3 (stud$ or research$)).tw. (70971)
26 or/13-25 (221762)
27 4 and 12 and 26 (180)
28 limit 27 to yr="2013 -Current" (82)

CINAHL (EBSCO)

S26 S25 Limiters - Published Date from: 20130701-20160914
S25 S15 AND S24
S24 S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23
S23 (allocat* random*)
S22 (MH "Quantitative Studies")
S21 (MH "Placebos")
S20 placebo*
S19 (random* allocat*)

S18 (MH "Random Assignment")
S17 (Randomi?ed control* trial*)
S16 (singl* blind*) or (doubl* blind*) or (tripl* blind*) or (trebl* blind*) or (trebl* mask*) or (tripl* mask*) or (doubl* mask*) or (singl* mask*)
S15 S4 AND S14
S14 S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13
S13 TI ((electrosleep OR electronarco*)) OR AB ((electrosleep OR electronarco*))
S12 TI (("transcranial magnetic stimulation" OR rTMS OR "transcranial direct current stimulation" OR tDCS OR "cranial electrostimulation" OR "cranial electrotherapy")) OR AB (("transcranial magnetic stimulation" OR rTMS OR "transcranial direct current stimulation" OR tDCS OR "cranial electrostimulation" OR "cranial electrotherapy"))
S11 TI (("theta burst stimulat*" OR iTBS OR cTBS)) OR AB (("theta burst stimulat*" OR iTBS OR cTBS))
S10 TI ((("non-invasive brain" OR "non*invasive brain") AND stimulat*)) OR AB ((("non-invasive brain" OR "non*invasive brain") AND stimulat*))
S9 TI (((transcrani* OR crani* OR brain*) AND (electrostim* OR electro-stim* OR electrotherap* OR electro-therap*))) OR AB (((transcrani* OR crani* OR brain*) AND (electrostim* OR electro-stim* OR electrotherap* OR electro-therap*)))
S8 TI (((transcrani* OR crani* OR brain*) AND (electrostim* OR electro-stim* OR electrotherap* OR electro-therap*))) OR AB (((transcrani* OR crani* OR brain*) AND (electrostim* OR electro-stim* OR electrotherap* OR electro-therap*)))
S7 TI (((brain* OR cortex OR cortical OR transcranial* OR cranial OR magneti*) AND stimulat*)) OR AB (((brain* OR cortex OR cortical OR transcranial* OR cranial OR magneti*) AND stimulat*))
S6 (MH "Electric Stimulation")
S5 (MH "Electronarcosis")
S4 S1 OR S2 OR S3
S3 TI ((sciatica OR back-ache OR back*ache OR lumbago OR fibromyalg* OR "trigemin* neuralg*" OR "herp* neuralg*" OR "diabet* neuropath*" OR "reflex dystroph*" OR "sudeck* atroph*" OR causalg* OR whip-lash OR whip*lash OR polymyalg* OR "failed back surg*" OR "failed back syndrome*")) OR AB ((sciatica OR back-ache OR back*ache OR lumbago OR fibromyalg* OR "trigemin* neuralg*" OR "herp* neuralg*" OR "diabet* neuropath*" OR "reflex dystroph*" OR "sudeck* atroph*" OR causalg* OR whip-lash OR whip*lash OR polymyalg* OR "failed back surg*" OR "failed back syndrome*"))
S2 TI (((chronic* OR back OR musculoskel* OR intractabl* OR neuropath* OR phantom limb OR fantom limb OR neck OR myofasc* OR "temporomandib* joint*" OR "temperomandib* joint*" OR "tempromandib* joint*" OR central OR post*stroke OR complex OR regional OR spinal cord) AND pain*).) OR AB (((chronic* OR back OR musculoskel* OR intractabl* OR neuropath* OR phantom limb OR fantom limb OR neck OR myofasc* OR "temporomandib* joint*" OR "temperomandib* joint*" OR "tempromandib* joint*" OR central OR post*stroke OR complex OR regional OR spinal cord) AND pain*))
S1 (MH "Pain+")

LILACS

1. Pain$ or dolor$ or intractabl$ or neuropath$ or phantom or fantom or myofasc$ or temp$romandibular or sciatic$ or back-ache or backache or ache or lumbago or fibromyalg$ or neuralg$ or dystroph$ or atroph$ or causalgi$ or whip-lash or whiplash or polymyalg$ [Words]¬
2. ((Estimulaci$ or stimulat$) and (cerebra$ or brain$ or cortex or cortical or crania$ or transcranial$ or magneti$)) or electrostim$ or electrotherapy$ or electro-therap$ or "theta burst stimul$" or iTBS or Ctbs or "transcrani$ magnet$ stimulat$" or rTMS or "transcrani$ direct current stimulat$" or tDCS or "cranial electrostimulat$" or "cranial electrotherapy$ or electrosleep or electronarco$ [Words]¬
3. ((Pt randomized controlled trial OR Pt controlled clinical trial OR Mh randomized controlled trials OR Mh random allocation OR Mh double-blind method OR Mh single-blind method) AND NOT (Ct animal AND NOT (Ct human and Ct animal)) OR (Pt clinical trial OR Ex E05.318.760.535$ OR (Tw clin$ AND (Tw trial$ OR Tw ensa$ OR Tw estud$ OR Tw experim$ OR Tw investiga$)) OR ((Tw singl$ OR Tw simple$ OR Tw doubl$ OR Tw doble$ OR Tw duplo$ OR Tw trebl$ OR Tw trip$) AND (Tw blind$ OR Tw cego$ OR Tw ciego$ OR Tw mask$ OR Tw mascar$)) OR Mh placebos OR Tw placebo$ OR (Tw random$ OR Tw randon$ OR Tw casual$ OR Tw acaso$ OR Tw azar OR Tw aleator$) OR Mh research design) AND NOT (Ct animal AND NOT (Ct human and Ct animal)) OR (Ct comparative study OR Ex E05.337$ OR Mh follow-up studies OR Mh prospective studies OR Tw control$ OR Tw prospectiv$ OR Tw volunt$ OR Tw volunteer$) AND NOT (Ct animal AND NOT (Ct human and Ct animal))) [Words]

Appendix 2. Trials register search results for current update

Register	Date of search	Search terms	Number of records
Clinical trials.gov	20 September 2016	Field - Interventional studies CONDITION: chronic* OR back OR musculoskel* OR intractabl* OR neuropath* OR phantom limb OR fantom limb OR neck OR myofasc* OR temp?romandib joint OR central OR post*stroke OR complex OR regional OR spinal cord OR sciatica OR back-ache OR back*ache OR lumbago INTERVENTION: brain* OR cortex OR cortical OR transcranial* OR cranial OR magneti* OR direct current OR DC OR electric OR crani* OR electrostim* OR electrotherap* OR electro-therap* OR non-invasive OR non*invasive OR theta burst stimulat* OR iTBS OR Ctbs OUTCOME: pain	91
Clinical trials.gov	20 September 2016	Field - Interventional studies CONDITION: chronic* OR back OR musculoskel* OR intractabl* OR neuropath* OR phantom limb OR fantom limb OR neck OR myofasc* OR temp?romandib joint OR central OR post*stroke OR complex OR regional OR spinal cord OR sciatica OR back-ache OR back*ache OR lumbago INTERVENTION: transcranial magnetic stimulation OR rTMS OR transcranial direct current stimulation OR tDCS OR cranial electrostimulation OR cranial electrotherapy OR electrosleep OR electronarco* OUTCOME: pain	1
Clinical trials.gov	20 September 2016	Field - Interventional studies CONDITION: fibromyalg* OR trigem* neuralg* OR herp* neuralg* OR diabet* neuropath* OR reflex dystroph* OR sudeck* atroph* OR causalg* OR whiplash OR whip*lash or polymyalg* OR failed back surg* OR failed back syndrome INTERVENTION: brain* OR cortex OR cortical OR transcranial* OR cranial OR magneti* OR direct current OR DC OR electric OR crani* OR electrostim* OR	0

(*Continued*)

		electrotherap* OR electro-therap* OR non-invasive OR non*invasive OR theta burst stimulat* OR iTBS OR Ctbs OUTCOME: pain	
Clinical trials.gov	20 September 2016	Field - Interventional studies CONDITION: fibromyalg* OR trigem* neuralg* OR herp* neuralg* OR diabet* neuropath* OR reflex dystroph* OR sudeck* atroph* OR causalg* OR whiplash OR whip*lash or polymyalg* OR failed back surg* OR failed back syndrome INTERVENTION: transcranial magnetic stimulation OR rTMS OR transcranial direct current stimulation OR tDCS OR cranial electrostimulation OR cranial electrotherapy OR electrosleep OR electronarco* OUTCOME: pain	0
WHO ICTRP	20 September 2016	Field - Interventional studies CONDITION: chronic* OR back OR musculoskel* OR intractabl* OR neuropath* OR phantom limb OR fantom limb OR neck OR myofasc* OR temp?romandib joint OR central OR post*stroke OR complex OR regional OR spinal cord OR sciatica OR back-ache OR back*ache OR lumbago INTERVENTION: brain* OR cortex OR cortical OR transcranial* OR cranial OR magneti* OR direct current OR DC OR electric OR crani* OR electrostim* OR electrotherap* OR electro-therap* OR non-invasive OR non*invasive OR theta burst stimulat* OR iTBS OR Ctbs OUTCOME: pain 01/01/2009 to 07/02/2013 adult	60
WHO ICTRP	20 September 2016	Field - Interventional studies CONDITION: chronic* OR back OR musculoskel* OR intractabl* OR neuropath* OR phantom limb OR fantom limb OR neck OR myofasc* OR temp?romandib joint OR central OR post*stroke OR complex OR regional OR spinal cord OR sciatica OR back-ache OR back*ache OR lumbago	

(*Continued*)

		INTERVENTION: transcranial magnetic stimulation OR rTMS OR transcranial direct current stimulation OR tDCS OR cranial electrostimulation OR cranial electrotherapy OR electrosleep OR electronarco* OUTCOME: pain	
WHO ICTRP	20/9/16	Field - Interventional studies CONDITION: fibromyalg* OR trigem* neuralg* OR herp* neuralg* OR diabet* neuropath* OR reflex dystroph* OR sudeck* atroph* OR causalg* OR whiplash OR whip*lash or polymyalg* OR failed back surg* OR failed back syndrome INTERVENTION: brain* OR cortex OR cortical OR transcranial* OR cranial OR magneti* OR direct current OR DC OR electric OR crani* OR electrostim* OR electrotherap* OR electro-therap* OR non-invasive OR non*invasive OR theta burst stimulat* OR iTBS OR Ctbs OUTCOME: pain	2
WHO ICTRP	20 September 2016	Field - Interventional studies CONDITION: fibromyalg* OR trigem* neuralg* OR herp* neuralg* OR diabet* neuropath* OR reflex dystroph* OR sudeck* atroph* OR causalg* OR whiplash OR whip*lash or polymyalg* OR failed back surg* OR failed back syndrome INTERVENTION: transcranial magnetic stimulation OR rTMS OR transcranial direct current stimulation OR tDCS OR cranial electrostimulation OR cranial electrotherapy OR electrosleep OR electronarco* OUTCOME: pain	

Register	Date of search	Search terms	Number of records
Clinical trials.gov	18 Octoberr 2017	Field - Interventional studies CONDITION: chronic* OR back OR musculoskel* OR intractabl* OR neuropath* OR phantom limb OR fantom limb OR neck OR myofasc* OR temp*romandib	6

(*Continued*)

		joint OR central OR post*stroke OR complex OR regional OR spinal cord OR sciatica OR back-ache OR back*ache OR lumbago INTERVENTION: brain* OR cortex OR cortical OR transcranial* OR cranial OR magneti* OR direct current OR DC OR electric OR crani* OR electrostim* OR electrotherap* OR electro-therap* OR non-invasive OR non*invasive OR theta burst stimulat* OR iTBS OR Ctbs OUTCOME: pain	
Clinical trials.gov	18 Octoberr 2017	Field - Interventional studies CONDITION: chronic* OR back OR musculoskel* OR intractabl* OR neuropath* OR phantom limb OR fantom limb OR neck OR myofasc* OR temp*romandib joint OR central OR post*stroke OR complex OR regional OR spinal cord OR sciatica OR back-ache OR back*ache OR lumbago INTERVENTION: transcranial magnetic stimulation OR rTMS OR transcranial direct current stimulation OR tDCS OR cranial electrostimulation OR cranial electrotherapy OR electrosleep OR electronarco* OUTCOME: pain	3
Clinical trials.gov	18 Octoberr 2017	Field - Interventional studies CONDITION: fibromyalg* OR trigem* neuralg* OR herp* neuralg* OR diabet* neuropath* OR reflex dystroph* OR sudeck* atroph* OR causalg* OR whip-lash OR whip*lash or polymyalg* OR failed back surg* OR failed back syndrome INTERVENTION: brain* OR cortex OR cortical OR transcranial* OR cranial OR magneti* OR direct current OR DC OR electric OR crani* OR electrostim* OR electrotherap* OR electro-therap* OR non-invasive OR non*invasive OR theta burst stimulat* OR iTBS OR Ctbs OUTCOME: pain	3
Clinical trials.gov	18 Octoberr 2017	Field - Interventional studies CONDITION: fibromyalg* OR trigem* neuralg* OR herp* neuralg* OR diabet* neuropath* OR reflex dystroph* OR sudeck* atroph* OR causalg* OR whip-lash OR	0

(*Continued*)

		whip*lash or polymyalg* OR failed back surg* OR failed back syndrome INTERVENTION: transcranial magnetic stimulation OR rTMS OR transcranial direct current stimulation OR tDCS OR cranial electrostimulation OR cranial electrotherapy OR electrosleep OR electronarco* OUTCOME: pain	
WHO ICTRP	18 Octoberr 2017	Field - Interventional studies CONDITION: chronic* OR back OR musculoskel* OR intractabl* OR neuropath* OR phantom limb OR fantom limb OR neck OR myofasc* OR temp*romandib joint OR central OR post*stroke OR complex OR regional OR spinal cord OR sciatica OR back-ache OR back*ache OR lumbago INTERVENTION: brain* OR cortex OR cortical OR transcranial* OR cranial OR magneti* OR direct current OR DC OR electric OR crani* OR electrostim* OR electrotherap* OR electro-therap* OR non-invasive OR non*invasive OR theta burst stimulat* OR iTBS OR Ctbs OUTCOME: pain 01/01/2009 to 07/02/2013 adult	36
WHO ICTRP	18 Octoberr 2017	Field - Interventional studies CONDITION: chronic* OR back OR musculoskel* OR intractabl* OR neuropath* OR phantom limb OR fantom limb OR neck OR myofasc* OR temp*romandib joint OR central OR post*stroke OR complex OR regional OR spinal cord OR sciatica OR back-ache OR back*ache OR lumbago INTERVENTION: transcranial magnetic stimulation OR rTMS OR transcranial direct current stimulation OR tDCS OR cranial electrostimulation OR cranial electrotherapy OR electrosleep OR electronarco* OUTCOME: pain	8
WHO ICTRP	18 Octoberr 2017	Field - Interventional studies CONDITION: fibromyalg* OR trigem* neuralg* OR herp* neuralg* OR diabet* neuropath* OR reflex dystroph* OR sudeck*	0

(*Continued*)

		atroph* OR causalg* OR whip-lash OR whip*lash or polymyalg* OR failed back surg* OR failed back syndrome INTERVENTION: brain* OR cortex OR cortical OR transcranial* OR cranial OR magneti* OR direct current OR DC OR electric OR crani* OR electrostim* OR electrotherap* OR electro-therap* OR non-invasive OR non*invasive OR theta burst stimulat* OR iTBS OR Ctbs OUTCOME: pain	
WHO ICTRP	18 Octoberr 2017	Field - Interventional studies CONDITION: fibromyalg* OR trigem* neuralg* OR herp* neuralg* OR diabet* neuropath* OR reflex dystroph* OR sudeck* atroph* OR causalg* OR whip-lash OR whip*lash or polymyalg* OR failed back surg* OR failed back syndrome INTERVENTION: transcranial magnetic stimulation OR rTMS OR transcranial direct current stimulation OR tDCS OR cranial electrostimulation OR cranial electrotherapy OR electrosleep OR electronarco* OUTCOME: pain	0

Appendix 3. Search results summary table for current update

Database searched	Date last searched	Number of results
CENTRAL (CRSO) 31/07/2013 TO 30/09/2016	11/10/17	243
MEDLINE (OVID) July 2013 to Aug week 5 2016	11/10/17	217
Embase (OVID) July 2013 to 2016 week 37	11/10/17	595
PsycINFO (OVID) 2013 to July week 4 2016	11/10/17	117
CINAHL (EBSCO) July 2013 to Sept 2016	11/10/17	42

(*Continued*)

LILACS (Birme) 2013 to Sept 2016	11/10/17	42
Total		1256

Appendix 4. Main database search strategies for 2014 update

CENTRAL (years 2009 to 2013 searched)

#1 MeSH descriptor: [Pain] explode all trees
#2 (chronic* or back or musculoskel* or intractabl* or neuropath* or phantom limb or fantom limb or neck or myofasc* or "temporomandib* joint" or "temperomandib* joint" or "tempromandib* joint" or central or (post next stroke) or complex or regional or "spinal cord") near/4 pain*:ti,ab,kw (Word variations have been searched)
#3 (sciatica or back-ache or back*ache or lumbago or fibromyalg* or (trigemin* near/2 neuralg*) or (herp* near/2 neuralg*) or (diabet* near/2 neuropath*) or (reflex near/4 dystroph*) or (sudeck* near/2 atroph*) or causalg* or whip-lash or whip*lash or polymyalg* or (failed back near/4 surg*) or (failed back near/4 syndrome*)):ti,ab,kw (Word variations have been searched)
#4 #1 or #2 or #3
#5 MeSH descriptor: [Transcranial Magnetic Stimulation] this term only
#6 MeSH descriptor: [Electronarcosis] explode all trees
#7 (brain* or cortex or cortical or transcranial* or cranial or magneti*) near/4 stimulat*:ti,ab,kw (Word variations have been searched)
#8 (transcrani* or crani* or brain*) near/4 (electrostim* or electro-stim* or electrotherap* or electro-therap*):ti,ab,kw (Word variations have been searched)
#9 (non-invasive or non*invasive) near/4 stimulat*:ti,ab,kw (Word variations have been searched)
#10 "theta burst stimulat*" or iTBS or cTBS:ti,ab,kw (Word variations have been searched)
#11 "transcranial magnetic stimulation" or rTMS or "transcranial direct current stimulat*" or tDCS or "cranial electrostimulation" or "cranial electrotherap*":ti,ab,kw (Word variations have been searched)
#12 (electrosleep* or electronarco*):ti,ab,kw (Word variations have been searched)
#13 #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12
#14 #4 and #13 from 2009 to 2013

MEDLINE and MEDLINE IN PROCESS (OVID)

1 exp Pain/ (283010)
2 ((chronic* or back or musculoskel* or intractabl* or neuropath* or phantom limb or fantom limb or neck or myofasc* or "temporomandib* joint*" or "temperomandib* joint*" or "tempromandib* joint*" or central or post*stroke or complex or regional or spinal cord) adj4 pain*).tw. (74023)
3 (sciatica or back-ache or back*ache or lumbago or fibromyalg* or (trigemin* adj2 neuralg*) or (herp* adj2 neuralg*) or (diabet* adj2 neuropath*) or (reflex adj4 dystroph*) or (sudeck* adj2 atroph*) or causalg* or whip-lash or whip*lash or polymyalg* or (failed back adj4 surg*) or (failed back adj4 syndrome*)).tw. (28679)
4 or/1-3 (325946)
5 Transcranial Magnetic Stimulation/ or Electronarcosis/ (6328)
6 ((brain* or cortex or cortical or transcranial* or cranial or magneti*) adj4 stimulat*).tw. (25872)
7 ((transcrani* or crani* or brain*) adj4 (electrostim* or electro-stim* or electrotherap* or electro-therap*)).tw. (147)
8 ((non-invasive or non*invasive) adj4 stimulat*).tw. (822)
9 (theta burst stimulat* or iTBS or cTBS).tw. (575)
10 (transcranial magnetic stimulation or rTMS or transcranial direct current stimulation or tDCS or cranial electrostimulation or cranial electrotherapy).tw. (7423)
11 (electrosleep or electronarco*).tw. (357)

12 or/5-11 (28316)
13 randomized controlled trial.pt. (337806)
14 controlled clinical trial.pt. (84996)
15 randomized.ab. (241501)
16 placebo.ab. (134421)
17 drug therapy.fs. (1571905)
18 randomly.ab. (173459)
19 trial.ab. (248492)
20 groups.ab. (1134392)
21 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 (2928552)
22 exp animals/ not humans.sh. (3751730)
23 21 not 22 (2487755)
24 4 and 12 and 23 (295)
25 (200911* or 200912* or 2010* or 2011* or 2012* or 2013*).ed. (2428299)
26 24 and 25 (112)

Embase (OVID)

1 exp Pain/ (729490)
2 ((chronic* or back or musculoskel* or intractabl* or neuropath* or phantom limb or fantom limb or neck or myofasc* or "temporomandib* joint*" or "temperomandib* joint*" or "tempromandib* joint*" or central or post*stroke or complex or regional or spinal cord) adj4 pain*).tw. (112128)
3 (sciatica or back-ache or back*ache or lumbago or fibromyalg* or (trigemin* adj2 neuralg*) or (herp* adj2 neuralg*) or (diabet* adj2 neuropath*) or (reflex adj4 dystroph*) or (sudeck* adj2 atroph*) or causalg* or whip-lash or whip*lash or polymyalg* or (failed back adj4 surg*) or (failed back adj4 syndrome*)).tw. (41462)
4 or/1-3 (759765)
5 Transcranial Magnetic Stimulation/ or Electronarcosis/ (11875)
6 ((brain* or cortex or cortical or transcranial* or cranial or magneti*) adj4 stimulat*).tw. (35587)
7 ((transcrani* or crani* or brain*) adj4 (electrostim* or electro-stim* or electrotherap* or electro-therap*)).tw. (194)
8 ((non-invasive or non*invasive) adj4 stimulat*).tw. (1314)
9 (theta burst stimulat* or iTBS or cTBS).tw. (770)
10 (transcranial magnetic stimulation or rTMS or transcranial direct current stimulation or tDCS or cranial electrostimulation or cranial electrotherapy).tw. (10413)
11 (electrosleep or electronarco*).tw. (375)
12 or/5-11 (39959)
13 4 and 12 (3078)
14 random$.tw. (793677)
15 factorial$.tw. (20700)
16 crossover$.tw. (46383)
17 cross over$.tw. (21096)
18 cross-over$.tw. (21096)
19 placebo$.tw. (189884)
20 (doubl$ adj blind$).tw. (140353)
21 (singl$ adj blind$).tw. (13272)
22 assign$.tw. (220119)
23 allocat$.tw. (74677)
24 volunteer$.tw. (170305)
25 Crossover Procedure/ (36109)
26 double-blind procedure.tw. (224)
27 Randomized Controlled Trial/ (338884)
28 Single Blind Procedure/ (16955)
29 or/14-28 (1300700)
30 (animal/ or nonhuman/) not human/ (4566449)

31 29 not 30 (1146950)
32 13 and 31 (574)
33 (200911* or 200912* or 2010* or 2011* or 2012* or 2013*).dd. (4384183)
34 32 and 33 (303)

PsycINFO (OVID)

1 exp Pain/ (33859)
2 ((chronic* or back or musculoskel* or intractabl* or neuropath* or phantom limb or fantom limb or neck or myofasc* or "temporomandib* joint*" or "temperomandib* joint*" or "tempromandib* joint*" or central or post*stroke or complex or regional or spinal cord) adj4 pain*).tw. (17914)
3 (sciatica or back-ache or back*ache or lumbago or fibromyalg* or (trigemin* adj2 neuralg*) or (herp* adj2 neuralg*) or (diabet* adj2 neuropath*) or (reflex adj4 dystroph*) or (sudeck* adj2 atroph*) or causalg* or whip-lash or whip*lash or polymyalg* or (failed back adj4 surg*) or (failed back adj4 syndrome*)).tw. (3654)
4 or/1-3 (39372)
5 Transcranial Magnetic Stimulation/ or Electronarcosis/ (3412)
6 ((brain* or cortex or cortical or transcranial* or cranial or magneti*) adj4 stimulat*).tw. (9508)
7 ((transcrani* or crani* or brain*) adj4 (electrostim* or electro-stim* or electrotherap* or electro-therap*)).tw. (55)
8 ((non-invasive or non*invasive) adj4 stimulat*).tw. (401)
9 (theta burst stimulat* or iTBS or cTBS).tw. (441)
10 (transcranial magnetic stimulation or rTMS or transcranial direct current stimulation or tDCS or cranial electrostimulation or cranial electrotherapy).tw. (4745)
11 (electrosleep or electronarco*).tw. (6)
12 or/5-11 (9914)
13 4 and 12 (481)
14 clinical trials/ (6486)
15 (randomis* or randomiz*).tw. (39676)
16 (random$ adj3 (allocat$ or assign$)).tw. (22629)
17 ((clinic$ or control$) adj trial$).tw. (33763)
18 ((singl$ or doubl$ or trebl$ or tripl$) adj3 (blind$ or mask$)).tw. (15332)
19 (crossover$ or "cross over$").tw. (5478)
20 random sampling/ (445)
21 Experiment Controls/ (435)
22 Placebo/ (2892)
23 placebo$.tw. (23869)
24 exp program evaluation/ (12521)
25 treatment effectiveness evaluation/ (11860)
26 ((effectiveness or evaluat$) adj3 (stud$ or research$)).tw. (45199)
27 or/14-26 (142131)
28 13 and 27 (95)
29 limit 28 to yr="2009 -Current" (60)

CINAHL (EBSCO)

S26 S25 Limiters - Published Date from: 20091101-20130231
S25 S15 AND S24
S24 S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23
S23 (allocat* random*)
S22 (MH "Quantitative Studies")
S21 (MH "Placebos")
S20 placebo*
S19 (random* allocat*)
S18 (MH "Random Assignment")

S17 (Randomi?ed control* trial*)
S16 (singl* blind*) or (doubl* blind*) or (tripl* blind*) or (trebl* blind*) or (trebl* mask*) or (tripl* mask*) or (doubl* mask*) or (singl* mask*)
S15 S4 AND S14
S14 S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13
S13 TI ((electrosleep OR electronarco*)) OR AB ((electrosleep OR electronarco*))
S12 TI (("transcranial magnetic stimulation" OR rTMS OR "transcranial direct current stimulation" OR tDCS OR "cranial electrostimulation" OR "cranial electrotherapy")) OR AB (("transcranial magnetic stimulation" OR rTMS OR "transcranial direct current stimulation" OR tDCS OR "cranial electrostimulation" OR "cranial electrotherapy"))
S11 TI (("theta burst stimulat*" OR iTBS OR cTBS)) OR AB (("theta burst stimulat*" OR iTBS OR cTBS))
S10 TI ((("non-invasive brain" OR "non*invasive brain") AND stimulat*)) OR AB ((("non-invasive brain" OR "non*invasive brain") AND stimulat*))
S9 TI (((transcrani* OR crani* OR brain*) AND (electrostim* OR electro-stim* OR electrotherap* OR electro-therap*))) OR AB (((transcrani* OR crani* OR brain*) AND (electrostim* OR electro-stim* OR electrotherap* OR electro-therap*)))
S8 TI (((transcrani* OR crani* OR brain*) AND (electrostim* OR electro-stim* OR electrotherap* OR electro-therap*))) OR AB (((transcrani* OR crani* OR brain*) AND (electrostim* OR electro-stim* OR electrotherap* OR electro-therap*)))
S7 TI (((brain* OR cortex OR cortical OR transcranial* OR cranial OR magneti*) AND stimulat*)) OR AB (((brain* OR cortex OR cortical OR transcranial* OR cranial OR magneti*) AND stimulat*))
S6 (MH "Electric Stimulation")
S5 (MH "Electronarcosis")
S4 S1 OR S2 OR S3
S3 TI ((sciatica OR back-ache OR back*ache OR lumbago OR fibromyalg* OR "trigemin* neuralg*" OR "herp* neuralg*" OR "diabet* neuropath*" OR "reflex dystroph*" OR "sudeck* atroph*" OR causalg* OR whip-lash OR whip*lash OR polymyalg* OR "failed back surg*" OR "failed back syndrome*")) OR AB ((sciatica OR back-ache OR back*ache OR lumbago OR fibromyalg* OR "trigemin* neuralg*" OR "herp* neuralg*" OR "diabet* neuropath*" OR "reflex dystroph*" OR "sudeck* atroph*" OR causalg* OR whip-lash OR whip*lash OR polymyalg* OR "failed back surg*" OR "failed back syndrome*"))
S2 TI (((chronic* OR back OR musculoskel* OR intractabl* OR neuropath* OR phantom limb OR fantom limb OR neck OR myofasc* OR "temporomandib* joint*" OR "temperomandib* joint*" OR "tempromandib* joint*" OR central OR post*stroke OR complex OR regional OR spinal cord) AND pain*).) OR AB (((chronic* OR back OR musculoskel* OR intractabl* OR neuropath* OR phantom limb OR fantom limb OR neck OR myofasc* OR "temporomandib* joint*" OR "temperomandib* joint*" OR "tempromandib* joint*" OR central OR post*stroke OR complex OR regional OR spinal cord) AND pain*))
S1 (MH "Pain+")

LILACS (7 February 2013)

1. (chronic$ or back or musculoskel$ or intractabl$ or neuropath$ or phantom limb or fantom limb or neck or myofasc$ or temporomandib$ or temperomandib$ or tempromandib$ or central or (post stroke) or complex or regional or spinal cord sciatica or back-ache or back ache or lumbago or fibromyalg$ or trigemin$ neuralg$ or herp$ neuralg$ or diabet$ neuropath$ or reflex dystroph$ or sudeck$ atrophy$ or causalg$ or whip-lash or whip$lash or polymyalg$ or failed back) 69863
2. (brain$ or cortex or cortical or transcrani$ or cranial or magneti$ stimulat$ or electrostim$ or electro-stim$ or electrotherapy$ or electro-therap$ or non-invasive or non invasive or stimul$ or theta burst stimulat$ or iTBS or cTBS or transcranial magnetic stimulat$ or rTMS or transcranial direct current stimulat$ or tDCS or cranial electrostimulation or cranial electrotherapy$ or electrosleep$ or electronarco$) 24787
3. 1&2 5559
4. (randomized controlled trial or controlled clinical trial or placebo or sham or randomly or trial or groups) 31227
5. 3&4 545
6. REMOVE ANY PRE 2009 (removed 292) 253

Appendix 5. Trials register search results for 2014 update

Register	Date of search	Search terms	Number of records	Number of relevant records
NRR archive	7 February 2013	(chronic* or back or musculoskel* or intractabl* or neuropath* or phantom limb or fantom limb or neck or myofasc* or temp*romandib joint or central or post*stroke or complex or regional or spinal cord or sciatica or back-ache or back*ache or lumbago or fibromyalg* or trigem* neuralg* or herp* neuralg* or diabet* neuropath* or reflex dystroph* or sudeck* atroph* or causalg* or whip-lash or whip*lash or polymyalg* or failed back surg* or failed back syndrome) AND (brain* or cortex or cortical or transcranial* or cranial or magneti* or direct current or DC or electric or crani* or electrostim* or electrotherap* or electro-therap* or non-invasive or non*invasive or theta burst stimulat* or iTBS or Ctbs or transcranial magnetic stimulation or rTMS or transcranial direct current stimulation or tDCS or cranial electrostimulation or cranial electrotherapy or electrosleep or electronarco*) al fields AND (2009 OR 2010 OR 2011 OR 2012 OR 2013) date started	2	0
Clinical trials.gov	7 February 2013	Field - Interventional studies CONDITION: chronic* OR back OR musculoskel* OR intractabl* OR	89	10

(*Continued*)

		neuropath* OR phantom limb OR fantom limb OR neck OR myofasc* OR temp?romandib joint OR central OR post*stroke OR complex OR regional OR spinal cord OR sciatica OR back-ache OR back*ache OR lumbago INTERVENTION: brain* OR cortex OR cortical OR transcranial* OR cranial OR magneti* OR direct current OR DC OR electric OR crani* OR electrostim* OR electrotherap* OR electro-therap* OR non-invasive OR non*invasive OR theta burst stimulat* OR iTBS OR Ctbs OUTCOME: pain 01/01/2009 to 07/02/2013 adult		
Clinical trials.gov	7 February 2013	Field - Interventional studies CONDITION: chronic* OR back OR musculoskel* OR intractabl* OR neuropath* OR phantom limb OR fantom limb OR neck OR myofasc* OR temp?romandib joint OR central OR post*stroke OR complex OR regional OR spinal cord OR sciatica OR back-ache OR back*ache OR lumbago INTERVENTION: transcranial magnetic stimulation OR rTMS OR transcranial direct current	20	

(*Continued*)

		stimulation OR tDCS OR cranial electrostimulation OR cranial electrotherapy OR electrosleep OR electronarco* OUTCOME: pain		
Clinical trials.gov	7 February 2013	Field - Interventional studies CONDITION: fibromyalg* OR trigem* neuralg* OR herp* neuralg* OR diabet* neuropath* OR reflex dystroph* OR sudeck* atroph* OR causalg* OR whip-lash OR whip*lash or polymyalg* OR failed back surg* OR failed back syndrome INTERVENTION: brain* OR cortex OR cortical OR transcranial* OR cranial OR magneti* OR direct current OR DC OR electric OR crani* OR electrostim* OR electrotherap* OR electro-therap* OR non-invasive OR non*invasive OR theta burst stimulat* OR iTBS OR Ctbs OUTCOME: pain	2	
Clinical trials.gov	7 February 2013	Field - Interventional studies CONDITION: fibromyalg* OR trigem* neuralg* OR herp* neuralg* OR diabet* neuropath* OR reflex dys-	0	

(*Continued*)

		troph* OR sudeck* atroph* OR causalg* OR whip-lash OR whip*lash or polymyalg* OR failed back surg* OR failed back syndrome INTERVENTION: transcranial magnetic stimulation OR rTMS OR transcranial direct current stimulation OR tDCS OR cranial electrostimulation OR cranial electrotherapy OR electrosleep OR electronarco* OUTCOME: pain		
HSRProj	11 February 2013	((chronic* or back or musculoskel* or intractabl* or neuropath* or phantom limb or fantom limb or neck or myofasc* or temp? romandib joint or central or post*stroke or complex or regional or spinal cord or sciatica or back-ache or back*ache or lumbago or fibromyalg* or trigem* neuralg* or herp* neuralg* or diabet* neuropath* or reflex dystroph* or sudeck* atroph* or causalg* or whip-lash or whip*lash or polymyalg* or failed back surg* or failed back syndrome) AND (brain* or cortex or cortical or transcranial* or cranial or magneti* or direct current or DC or electric or crani* or electrostim* or electrotherap* or electro-therap* or non-invasive or non*invasive or theta burst stimulat* or iTBS or Ctbs or transcra-	152	0

(*Continued*)

		nial magnetic stimulation or rTMS or transcranial direct current stimulation or tDCS or cranial electrostimulation or cranial electrotherapy or electrosleep or electronarco*))		
Current controlled trials (excl clinicatrials.gov)	11 February 2013	(sudeck* atroph* OR causalg* OR whip-lash OR whip*lash OR polymyalg* OR failed back surg* OR failed back syndrome) AND (cranial electrotherapy OR electrosleep OR electronarco*)	0	1
Current controlled trials (excl clinicatrials.gov)	11 February 2013	(sudeck* atroph* OR causalg* OR whip-lash OR whip*lash OR polymyalg* OR failed back surg* OR failed back syndrome) AND (Ctbs OR transcranial magnetic stimulation OR rTMS OR transcranial direct current stimulation OR tDCS OR cranial electrostimulation)	0	
Current controlled trials (excl clinicatrials.gov)	25 February 2013	TRANSCRANIAL and PAIN	1	
Current controlled trials (excl clinicatrials.gov)	25 February 2013	CRANIAL AND PAIN	4	
Current controlled trials (excl clinicatrials.gov)	25/2/13	STIMULATION AND PAIN	75	
Current controlled trials (excl clinicatrials.gov)	25 February 2013	(Cortex or cortical) and pain	8	
Current controlled trials (excl clinicatrials.gov)	25 February 2013	Brain and pain	33	
Current controlled trials (excl clinicatrials.gov)	25 February 2013	(Electro or electrical) and pain	46	
Total current controlled trials	25 February 2013		167	

(*Continued*)

Total relevant trial records, all databases	11

Appendix 6. Search results summary table for 2014 update

Database searched	Date searched	Number of results
CENTRAL Issue 6 of 12, 2013 (*The Cochrane Library*)	24 July 2013	2
MEDLINE (OVID) June 2013 to 19/7/2013 MEDLINE In Process (OVID) - current week	24 July 2013 24 July 2013	5 19
Embase (OVID) June 2013 to 2013 week 29	24 July 2013	8
PsycINFO (OVID) June 2013 to July week 3 2013	24 July 2013	1
CINAHL (EBSCO) June 2013 to July 2013	24 July 2013	4
Total		**39**
After de-duplication		**35**
After title abstract screening		**0**
After expert checking		**2**

Appendix 7. Full list of searches and results for 2009 version of review

1. Cochrane PaPaS Group Specialised Register, saved search: 177 results

"electric* stimulat* therap*" or "brain* stimulat*" or "cort* stimulat*" or "transcranial* stimulat*" or "cranial stimulat*" or "magneti* stimulat*" or "direct current stimulat*" or "electric* stimulat*" or electrostim* or electrotherapy* or electro-therap* or "theta burst stimulat*" or "transcran* magnet* stimulat*" or iTBS or cTBS or rTMS or "transcran* direct current stimulat*" or tDCS or electrosleep or electronarco*

2. CENTRAL in The Cochrane Library

#1	MeSH descriptor Pain explode all trees	25049
#2	(chronic* or back or musculoskel* or intractabl* or neuropath* or phantom limb or fantom limb or neck or myofasc* or "temporomandib* joint" or "temperomandib* joint" or "tempromandib* joint" or central or (post NEXT stroke) or complex or regional or "spinal cord") near/4 pain*:ti,ab,kw	7785
#3	(sciatica or back-ache or back*ache or lumbago or fibromyalg* or (trigemin* near/2 neuralg*) or (herp* near/2 neuralg*) or (diabet* near/2 neuropath*) or (reflex near/4 dystroph*) or (sudeck* near/2 atroph*) or causalg* or whip-lash or whip*lash or polymyalg* or (failed back near/4 surg*) or (failed back near/4 syndrome*)):ti,ab,kw	3040
#4	(#1 OR #2 OR #3)	30353
#5	MeSH descriptor Transcranial Magnetic Stimulation explode all trees	328
#6	MeSH descriptor Electronarcosis explode all trees	34
#7	(brain* or cortex or cortical or transcranial* or cranial or magneti*) near/4 stimulat*:ti,ab,kw	1388
#8	(transcrani* or crani* or brain*) near/4 (electrostim* or electro-stim* or electrotherap* or electro-therap*):ti,ab,kw	45
#9	(non-invasive or non*invasive) near/4 stimulat*:ti,ab,kw	55
#10	"theta burst stimulat*" or iTBS or cTBS:ti,ab,kw	9
#11	"transcranial magnetic stimulation" or rTMS or "transcranial direct current stimulat*" or tDCS or "cranial electrostimulation" or "cranial electrotherap*":ti,ab,kw	747
#12	(electrosleep* or electronarco*):ti,ab,kw	45
#13	(#5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12)	1505
#14	(#4 AND #13)	106

3a. MEDLINE

Database: Ovid MEDLINE(R) <1950 to November Week 3 2009>

1 exp Pain/ (252061)

2 ((chronic* or back or musculoskel* or intractabl* or neuropath* or phantom limb or fantom limb or neck or myofasc* or "temporomandib* joint*" or "temperomandib* joint*" or "tempromandib* joint*" or central or post*stroke or complex or regional or spinal cord) adj4 pain*).ab,ti. (61945)
3 (sciatica or back-ache or back*ache or lumbago or fibromyalg* or (trigemin* adj2 neuralg*) or (herp* adj2 neuralg*) or (diabet* adj2 neuropath*) or (reflex adj4 dystroph*) or (sudeck* adj2 atroph*) or causalg* or whip-lash or whip*lash or polymyalg* or (failed back adj4 surg*) or (failed back adj4 syndrome*)).ab,ti. (25802)
4 1 or 3 or 2 (288507)
5 Transcranial Magnetic Stimulation/ or Electronarcosis/ (4240)
6 ((brain* or cortex or cortical or transcranial* or cranial or magneti*) adj4 stimulat*).ab,ti. (21248)
7 ((transcrani* or crani* or brain*) adj4 (electrostim* or electro-stim* or electrotherap* or electro-therap*)).ab,ti. (116)
8 ((non-invasive or non*invasive) adj4 stimulat*).ab,ti. (526)
9 (theta burst stimulat* or iTBS or cTBS).ab,ti. (359)
10 (transcranial magnetic stimulation or rTMS or transcranial direct current stimulation or tDCS or cranial electrostimulation or cranial electrotherapy).ab,ti. (5306)
11 (electrosleep or electronarco*).ab,ti. (357)
12 8 or 6 or 11 or 7 or 10 or 9 or 5 (23212)
13 4 and 12 (1069)
14 randomised controlled trial.pt. (291031)
15 controlled clinical trial.pt. (82962)
16 randomized.ab. (196258)
17 (placebo or sham).ab,ti. (164609)
18 drug therapy.fs. (1385685)
19 randomly.ab. (141449)
20 trial.ab. (203139)
21 groups.ab. (961704)
22 or/14-21 (2562312)
23 exp animals/ not humans.sh. (3518581)
24 22 not 23 (2157467)
25 24 and 13 (219)

3b. Database: Ovid MEDLINE(R) In-process & Other non-indexed citations

<25 November 2009>

1 exp Pain/ (6)
2 ((chronic* or back or musculoskel* or intractabl* or neuropath* or phantom limb or fantom limb or neck or myofasc* or "temporomandib* joint*" or "temperomandib* joint*" or "tempromandib* joint*" or central or post*stroke or complex or regional or spinal cord) adj4 pain*).ab,ti. (4772)
3 (sciatica or back-ache or back*ache or lumbago or fibromyalg* or (trigemin* adj2 neuralg*) or (herp* adj2 neuralg*) or (diabet* adj2 neuropath*) or (reflex adj4 dystroph*) or (sudeck* adj2 atroph*) or causalg* or whip-lash or whip*lash or polymyalg* or (failed back adj4 surg*) or (failed back adj4 syndrome*)).ab,ti. (1251)
4 1 or 3 or 2 (5661)
5 Transcranial Magnetic Stimulation/ or Electronarcosis/ (0)
6 ((brain* or cortex or cortical or transcranial* or cranial or magneti*) adj4 stimulat*).ab,ti. (1057)
7 ((transcrani* or crani* or brain*) adj4 (electrostim* or electro-stim* or electrotherap* or electro-therap*)).ab,ti. (5)
8 ((non-invasive or non*invasive) adj4 stimulat*).ab,ti. (42)
9 (theta burst stimulat* or iTBS or cTBS).ab,ti. (38)
10 (transcranial magnetic stimulation or rTMS or transcranial direct current stimulation or tDCS or cranial electrostimulation or cranial electrotherapy).ab,ti. (375)
11 (electrosleep or electronarco*).ab,ti. (0)
12 8 or 6 or 11 or 7 or 10 or 9 or 5 (1113)
13 4 and 12 (39)

4. Database: Embase

<1980 to 2009 Week 47>

1 exp Pain/ (394924)
2 ((chronic* or back or musculoskel* or intractabl* or neuropath* or phantom limb or fantom limb or neck or myofasc* or "temporomandib* joint*" or "temperomandib* joint*" or "tempromandib* joint*" or central or post*stroke or complex or regional or spinal cord) adj4 pain*).ab,ti. (57196)
3 (sciatica or back-ache or back*ache or lumbago or fibromyalg* or (trigemin* adj2 neuralg*) or (herp* adj2 neuralg*) or (diabet* adj2 neuropath*) or (reflex adj4 dystroph*) or (sudeck* adj2 atroph*) or causalg* or whip-lash or whip*lash or polymyalg* or (failed back adj4 surg*) or (failed back adj4 syndrome*)).ab,ti. (21356)
4 1 or 3 or 2 (410258)
5 Transcranial Magnetic Stimulation/ or Electronarcosis/ (5841)
6 ((brain* or cortex or cortical or transcranial* or cranial or magneti*) adj4 stimulat*).ab,ti. (18227)
7 ((transcrani* or crani* or brain*) adj4 (electrostim* or electro-stim* or electrotherap* or electro-therap*)).ab,ti. (74)
8 ((non-invasive or non*invasive) adj4 stimulat*).ab,ti. (498)
9 (theta burst stimulat* or iTBS or cTBS).ab,ti. (330)
10 (transcranial magnetic stimulation or rTMS or transcranial direct current stimulation or tDCS or cranial electrostimulation or cranial electrotherapy).ab,ti. (5259)
11 (electrosleep or electronarco*).ab,ti. (20)
12 8 or 6 or 11 or 7 or 10 or 9 or 5 (19954)
13 4 and 12 (1331)
14 random*.ti,ab. (415216)
15 factorial*.ti,ab. (8708)
16 (crossover* or cross over* or cross-over*).ti,ab. (40788)
17 placebo*.ti,ab. (114266)
18 (doubl* adj blind*).ti,ab. (87525)
19 (singl* adj blind*).ti,ab. (7775)
20 assign*.ti,ab. (113729)
21 allocat*.ti,ab. (36179)
22 volunteer*.ti,ab. (102464)
23 CROSSOVER PROCEDURE.sh. (21985)
24 DOUBLE-BLIND PROCEDURE.sh. (74829)
25 RANDOMIZED CONTROLLED TRIAL.sh. (176320)
26 SINGLE BLIND PROCEDURE.sh. (8721)
27 or/14-26 (691134)
28 ANIMAL/ or NONHUMAN/ or ANIMAL EXPERIMENT/ (3551150)
29 HUMAN/ (6702208)
30 28 and 29 (569432)
31 28 not 30 (2981718)
32 27 not 31 (601828)
33 32 and 13 (234)

5. Database: PsycINFO

<1806 to November Week 4 2009>

1 exp Pain/ (26560)
2 ((chronic* or back or musculoskel* or intractabl* or neuropath* or phantom limb or fantom limb or neck or myofasc* or temp? romandib* joint or central or post*stroke or complex or regional or spinal cord) adj4 pain*).ab,ti. (14094)
3 (sciatica or back-ache or back*ache or lumbago or fibromyalg* or (trigemin* adj2 neuralg*) or (herp* adj2 neuralg*) or (diabet* adj2 neuropath*) or (reflex adj4 dystroph*) or (sudeck* adj2 atroph*) or causalg* or whip-lash or whip*lash or polymyalg* or (failed back adj4 surg*) or (failed back adj4 syndrome*)).ab,ti. (2649)
4 1 or 3 or 2 (30822)
5 Transcranial Magnetic Stimulation/ or Electrosleep treatment/ (1830)
6 ((brain* or cortex or cortical or transcranial* or cranial or magneti*) adj4 stimulat*).ab,ti. (7832)

7 ((transcrani* or crani* or brain*) adj4 (electrostim* or electro-stim* or electrotherap* or electro-therap*)).ab,ti. (47)
8 ((non-invasive or non*invasive) adj4 stimulat*).ab,ti. (144)
9 (theta burst stimulat* or iTBS or cTBS).ab,ti. (259)
10 (transcranial magnetic stimulation or rTMS or transcranial direct current stimulation or tDCS or cranial electrostimulation or cranial electrotherapy).ab,ti. (2652)
11 (electrosleep or electronarco*).ab,ti. (140)
12 8 or 6 or 11 or 7 or 10 or 9 or 5 (8307)
13 4 and 12 (277)
14 (random* or placebo* or sham or trial or groups).ti,ab. (391590)
15 13 and 14 (64)

6. CINAHL

<Search run 11 January 2010>

1	exp PAIN/	64959
2	((chronic* OR back OR musculoskel* OR intractabl* OR neuropath* OR phantom limb OR fantom limb OR neck OR myofasc* OR "temporomandib* joint*" OR "tempero-mandib* joint*" OR "tempromandib* joint*" OR central OR post*stroke OR complex OR regional OR spinal cord) AND pain*).ti,ab	25127
3	(sciatica OR back-ache OR back*ache OR lumbago OR fi-bromyalg* OR "trigemin* neuralg*" OR "herp* neuralg*" OR "diabet* neuropath*" OR "reflex dystroph*" OR "sudeck* atroph*" OR causalg* OR whip-lash OR whip*lash OR polymyalg* OR "failed back surg*" OR "failed back syn-drome*").ti,ab	4111
4	1 OR 2 OR 3	75018
5	ELECTRONARCOSIS/	1
6	ELECTRIC STIMULATION/	3829
7	((brain* OR cortex OR cortical OR transcranial* OR cranial OR "magneti*) AND stimulat*).ti,ab	545
8	((transcrani* OR crani* OR brain*) AND (electrostim* OR electro-stim* OR electrotherap* OR electro-therap*)).ti,ab	26
9	(("non-invasive brain" OR "non*invasive brain") AND stimu-lat*).ti,ab	12
10	("theta burst stimulat*" OR iTBS OR cTBS).ti,ab	16

(*Continued*)

11	("transcranial magnetic stimulation" OR rTMS OR "transcranial direct current stimulation" OR tDCS OR "cranial electrostimulation" OR "cranial electrotherapy").ti,ab	437
12	(electrosleep OR electronarco*).ti,ab	1
13	5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12	4387
14	4 AND 13	836
15	exp CLINICAL TRIALS/	79642
16	(clinical AND trial*).af	148411
17	((singl* OR doubl* OR trebl* OR tripl*) AND (blind* OR mask*)).ti,ab	11736
18	(Randomi?ed AND control* AND trial*).af	65515
19	RANDOM ASSIGNMENT/	22506
20	(Random* AND allocat*).ti,ab	3666
21	placebo*.af	34556
22	PLACEBOS/	5386
23	QUANTITATIVE STUDIES/	5131
24	15 OR 16 OR17 OR 18 OR 19 OR 20 OR 21 OR 22 OR 23	176918
25	14 AND 24	226

7. SCOPUS

We did not search this database as it includes all of MEDLINE, all of Embase and some of CINAHL, which have been searched separately.

8. Search strategy for LILACS

http://bases.bireme.br/cgi-bin/wxislind.exe/iah/online/

1. Pain$ or dolor$ or intractabl$ or neuropath$ or phantom or fantom or myofasc$ or temp$romandibular or sciatic$ or back-ache or backache or ache or lumbago or fibromyalg$ or neuralg$ or dystroph$ or atroph$ or causalgi$ or whip-lash or whiplash or polymyalg$ [Words]

2. ((Estimulaci$ or stimulat$) and (cerebra$ or brain$ or cortex or cortical or crania$ or transcranial$ or magneti$)) or electrostim$ or electrotherapy$ or electro-therap$ or "theta burst stimul$" or iTBS or Ctbs or "transcrani$ magnet$ stimulat$" or rTMS or "transcrani$ direct current stimulat$" or tDCS or "cranial electrostimulat$" or "cranial electrotherapy$ or electrosleep or electronarco$ [Words]

3. ((Pt randomized controlled trial OR Pt controlled clinical trial OR Mh randomized controlled trials OR Mh random allocation OR Mh double-blind method OR Mh single-blind method) AND NOT (Ct animal AND NOT (Ct human and Ct animal)) OR (Pt clinical trial OR Ex E05.318.760.535$ OR (Tw clin$ AND (Tw trial$ OR Tw ensa$ OR Tw estud$ OR Tw experim$ OR Tw investiga$)) OR ((Tw singl$ OR Tw simple$ OR Tw doubl$ OR Tw doble$ OR Tw duplo$ OR Tw trebl$ OR Tw trip$) AND (Tw blind$ OR Tw cego$ OR Tw ciego$ OR Tw mask$ OR Tw mascar$)) OR Mh placebos OR Tw placebo$ OR (Tw random$ OR Tw randon$ OR Tw casual$ OR Tw acaso$ OR Tw azar OR Tw aleator$) OR Mh research design) AND NOT (Ct animal AND NOT (Ct human and Ct animal)) OR (Ct comparative study OR Ex E05.337$ OR Mh follow-up studies OR Mh prospective studies OR Tw control$ OR Tw prospectiv$ OR Tw volunt$ OR Tw volunteer$) AND NOT (Ct animal AND NOT (Ct human and Ct animal))) [Words]
4. 1 and 2 and 3 (68)

Appendix 8. Trials register search results for 2009 version of review

Database	Date of search	Search strategy	No. hits	Agreed potential studies
National Research Register (NRR) Archive (NIHR)	23 October 2009	(chronic* or back or musculoskel* or intractabl* or neuropath* or phantom limb or fantom limb or neck or myofasc* or temp?romandib joint or central or post*stroke or complex or regional or spinal cord or sciatica or backache or back*ache or lumbago or fibromyalg* or trigem* neuralg* or herp* neuralg* or diabet* neuropath* or reflex dystroph* or sudeck* atroph* or causalg* or whip-lash or whip*lash or polymyalg* or failed back surg* or failed back syndrome) AND (brain* or cortex or cortical or transcranial* or cranial or magneti* or direct current or DC or electric or crani* or electrostim* or electrotherap* or electrotherap* or non-invasive or non*invasive or theta burst stimulat* or iTBS or Ctbs or transcranial magnetic stimulation or	366	**2**

(*Continued*)

		rTMS or transcranial direct current stimulation or tDCS or cranial electrostimulation or cranial electrotherapy or electrosleep or electronarco*) IN "TITLE" Field		
Clinicaltrials.gov	23 October 2009 Search 1	**Field - Interventional studies** **CONDITION:** chronic* OR back OR musculoskel* OR intractabl* OR neuropath* OR phantom limb OR fantom limb OR neck OR myofasc* OR temp? romandib joint OR central OR post*stroke OR complex OR regional OR spinal cord OR sciatica OR back-ache OR back*ache OR lumbago **INTERVENTION:** brain* OR cortex OR cortical OR transcranial* OR cranial OR magneti* OR direct current OR DC OR electric OR crani* OR electrostim* OR electrotherap* OR electrotherap* OR non-invasive OR non*invasive OR theta burst stimulat* OR iTBS OR Ctbs **OUTCOME:** pain	62	
Clinicaltrials.gov	23 October 2009 Search 2	**Field - Interventional studies** **CONDITION:** chronic* OR back OR musculoskel* OR intractabl* OR neuropath* OR phantom limb OR fantom limb OR neck OR myofasc* OR temp? romandib joint OR cen-	8 (all also picked up in search 1)	

(*Continued*)

		tral OR post*stroke OR complex OR regional OR spinal cord OR sciatica OR back-ache OR back*ache OR lumbago **INTERVENTION:** transcranial magnetic stimulation OR rTMS OR transcranial direct current stimulation OR tDCS OR cranial electrostimulation OR cranial electrotherapy OR electrosleep OR electronarco* **OUTCOME:** pain		
Clinicaltrials.gov	23 October 2009 Search 3	**Field - Interventional studies** **CONDITION:** fibromyalg* OR trigem* neuralg* OR herp* neuralg* OR diabet* neuropath* OR reflex dystroph* OR sudeck* atroph* OR causalg* OR whip-lash OR whip*lash or polymyalg* OR failed back surg* OR failed back syndrome **INTERVENTION:** brain* OR cortex OR cortical OR transcranial* OR cranial OR magneti* OR direct current OR DC OR electric OR crani* OR electrostim* OR electrotherap* OR electrotherap* OR non-invasive OR non*invasive OR theta burst stimulat* OR iTBS OR Ctbs **OUTCOME:** pain	0	
Clinicaltrials.gov	23 October 2009 Search 4	**Field - Interventional studies** **CONDITION:** fibromyalg* OR trigem*	0	

(*Continued*)

		neuralg* OR herp* neuralg* OR diabet* neuropath* OR reflex dystroph* OR sudeck* atroph* OR causalg* OR whip-lash OR whip*lash or polymyalg* OR failed back surg* OR failed back syndrome **INTERVENTION:** transcranial magnetic stimulation OR rTMS OR transcranial direct current stimulation OR tDCS OR cranial electrostimulation OR cranial electrotherapy OR electrosleep OR electronarco* **OUTCOME:** pain		
		TOTAL UNIQUE RESULTS FOR CLINICAL TRIALS.GOV	**62**	7
HSRProj (Health Services Research Projects in Progress)	23 October 2009	(chronic* or back or musculoskel* or intractabl* or neuropath* or phantom limb or fantom limb or neck or myofasc* or temp?romandib joint or central or post*stroke or complex or regional or spinal cord or sciatica or backache or back*ache or lumbago or fibromyalg* or trigem* neuralg* or herp* neuralg* or diabet* neuropath* or reflex dystroph* or sudeck* atroph* or causalg* or whip-lash or whip*lash or polymyalg* or failed back surg* or failed back syndrome) AND (brain* or cortex or cortical or transcranial* or cranial or	77	**0**

(*Continued*)

		magneti* or direct current or DC or electric or crani* or electrostim* or electrotherap* or electrotherap* or non-invasive or non*invasive or theta burst stimulat* or iTBS or Ctbs or transcranial magnetic stimulation or rTMS or transcranial direct current stimulation or tDCS or cranial electrostimulation or cranial electrotherapy or electrosleep or electronarco*)		
Current Controlled Trials	23 October 2009 Search 1	(sudeck* atroph* OR causalg* OR whiplash OR whip*lash OR polymyalg* OR failed back surg* OR failed back syndrome) AND (cranial electrotherapy OR electrosleep OR electronarco*)	0	
Current Controlled Trials	23 October 2009 Search 2	(sudeck* atroph* OR causalg* OR whiplash OR whip*lash OR polymyalg* OR failed back surg* OR failed back syndrome) AND (Ctbs OR transcranial magnetic stimulation OR rTMS OR transcranial direct current stimulation OR tDCS OR cranial electrostimulation)	0	
Current Controlled Trials	23 October 2009 Search 3	(sudeck* atroph* OR causalg* OR whiplash OR whip*lash OR polymyalg* OR failed back surg* OR failed back syndrome) AND (crani* OR electrostim* OR electrotherap* OR elec-	4	

(*Continued*)

		tro-therap* OR non-invasive OR non*invasive OR theta burst stimulat* OR iTBS)		
Current Controlled Trials	23 October 2009 Search 4	(sudeck* atroph* OR causalg* OR whiplash OR whip*lash OR polymyalg* OR failed back surg* OR failed back syndrome) AND (brain* OR cortex OR cortical OR transcranial* OR cranial OR magneti* OR direct current OR DC)	13	
Current Controlled Trials	23 October 2009 Search 5	(back-ache OR back*ache OR lumbago OR fibromyalg* OR trigem* neuralg* OR herp* neuralg* OR diabet* neuropath* OR reflex dystroph*) AND (cranial electrostimulation OR cranial electrotherapy OR electrosleep OR electronarco*)	0	
Current Controlled Trials	23 October 2009 Search 6	(back-ache OR back*ache OR lumbago OR fibromyalg* OR trigem* neuralg* OR herp* neuralg* OR diabet* neuropath* OR reflex dystroph*) AND (Ctbs OR transcranial magnetic stimulation OR rTMS OR transcranial direct current stimulation OR tDCS)	9	
Current Controlled Trials	3 November 2009 Search 7	(back-ache OR back*ache OR lumbago OR fibromyalg* OR trigem* neuralg* OR herp* neuralg* OR diabet* neuropath* OR	36	

(*Continued*)

		reflex dystroph*) AND (crani* OR electrostim* OR electrotherap* OR electro-therap*)		
Current Controlled Trials	23 October 2009 Search 8	(backache OR back*ache OR lumbago OR fibromyalg* OR trigem* neuralg* OR herp* neuralg* OR diabet* neuropath* OR reflex dystroph*) AND (non-invasive OR non*invasive OR theta burst stimulat* OR iTBS)	53	
Current Controlled Trials	3 November 2009 Search 9	(back-ache OR back*ache OR lumbago OR fibromyalg* OR trigem* neuralg* OR herp* neuralg* OR diabet* neuropath* OR reflex dystroph*) AND (cranial OR magneti* OR direct current OR DC)	52	
Current Controlled Trials	3 November 2009 Search 10	(back-ache OR back*ache OR lumbago OR fibromyalg* OR trigem* neuralg* OR herp* neuralg* OR diabet* neuropath* OR reflex dystroph*) AND (brain* OR cortex OR cortical OR transcranial*)	63	
Current Controlled Trials	3 November 2009 Search 11	(temp? romandib joint OR central OR post*stroke OR complex OR regional OR spinal cord OR sciatica) AND (cranial electrostimulation OR cranial electrotherapy OR electrosleep OR electronarco*)	0	

(*Continued*)

Current Controlled Trials	3 November 2009 Search 12	(temp? romandib joint OR central OR post*stroke OR complex OR regional OR spinal cord OR sciatica) AND (transcranial direct current stimulation OR tDCS)	11	
Current Controlled Trials	3 November 2009 Search 13	(central OR post*stroke OR complex OR regional OR spinal cord OR sciatica) AND (iTBS OR cTBS OR transcranial magnetic stimulation OR rTMS)	48	
Current Controlled Trials	3 November 2009 Search 14	(central OR post*stroke OR complex OR regional OR spinal cord OR sciatica) AND (electrotherap* OR electrotherap* OR non-invasive OR non*invasive OR theta burst stimulat*)	199	
Current Controlled Trials	3 November 2009 Search 15	(central OR post*stroke OR complex OR regional OR spinal cord OR sciatica) AND (brain* OR cortex OR cortical OR transcranial* OR cranial OR magneti* OR direct current OR DC OR crani* OR electrostim*)	1905	
Current Controlled Trials	3 November 2009 Search 16	(temp?romandib joint) AND (brain* OR cortex OR cortical OR transcranial* OR cranial OR magneti* OR direct current OR DC OR electric OR crani* OR electrostim* OR electrotherap* OR electro-therap*)	0	

(*Continued*)

Current Controlled Trials	3 November 2009 Search 17	(temp?romandib joint) AND (iTBS OR cTBS OR transcranial magnetic stimulation OR rTMS)	0	
Current Controlled Trials	3 November 2009 Search 18	(temp?romandib joint) AND (non-invasive OR non*invasive OR theta burst stimulat*)	0	
Current Controlled Trials	3 November 2009 Search 19	(chronic* OR back OR musculoskel* OR intractabl* OR neuropath* OR phantom limb OR fantom limb OR neck) AND (transcranial direct current stimulation OR tDCS OR cranial electrostimulation OR cranial electrotherapy OR electrosleep OR electronarco*)	16	
Current Controlled Trials	3 November 2009 Search 20	(chronic* OR back OR musculoskel* OR intractabl* OR neuropath* OR phantom limb OR fantom limb OR neck) AND (Ctbs OR transcranial magnetic stimulation OR Rtms)	55	
Current Controlled Trials	3 November 2009 Search 21	(chronic* OR back OR musculoskel* OR intractabl* OR neuropath* OR phantom limb OR fantom limb OR neck) AND (crani* OR electrostim* OR electrotherap* OR electro-therap* OR non-invasive OR non*invasive OR theta burst stimulat* OR iTBS)	557	

(*Continued*)

Current Controlled Trials	3 November 2009 Search 22	(chronic* OR back OR musculoskel* OR intractabl* OR neuropath* OR phantom limb OR fantom limb OR neck) AND (brain* OR cortex OR cortical OR transcranial* OR cranial OR magneti* OR direct current OR DC)	2385	
Current Controlled Trials	3 November 2009 Search 23	(temp*romandibular joint) AND (brain* OR cortex OR cortical OR transcranial* OR cranial OR magneti* OR direct current OR DC OR electric OR crani* OR electrostim* OR electrotherap*)	8	
Current Controlled Trials	3 November 2009 Search 24	(temp*romandibular joint) AND (electro-therap* OR non-invasive OR non*invasive OR theta burst stimulat* OR iTBS OR Ctbs OR transcranial magnetic stimulation)	1	
Current Controlled Trials	3 November 2009 Search 25	(temp*romandibular joint) AND (rTMS OR transcranial direct current stimulation OR tDCS OR cranial electrostimulation OR cranial electrotherapy OR electrosleep OR electronarco*)	0	
		TOTAL RESULTS FOR CURRENT CONTROLLED TRIALS	**5415**	**14**
		TOTAL RESULTS FROM ALL DATABASES		**23**

(*Continued*)

		DUPLICATES BETWEEN DATABASES		7
		FINAL TOTAL FROM TRIALS REGISTERS SEARCHES		**16**

WHAT'S NEW

Last assessed as up-to-date: 11 October 2017.

Date	Event	Description
12 April 2018	Amended	Review to be published with Gold Open Access.
12 April 2018	New citation required but conclusions have not changed	Review to be published with Gold Open Access.

HISTORY

Protocol first published: Issue 1, 2010

Review first published: Issue 9, 2010

Date	Event	Description
7 November 2017	New citation required but conclusions have not changed	We have updated all analyses and GRADE quality assessments for all core comparisons. The addition of data has not substantially altered our conclusions that there remains substantial uncertainty regarding the effectiveness of non invasive brain stimulation techniques for chronic pain
11 October 2017	New search has been performed	We have performed a full update of the searches (October 2017). This involved the inclusion of 38 new trials with an additional 1225 participants
11 February 2013	New search has been performed	For this update we have altered the 'Risk of bias' assessment to reflect new evidence regarding the adequacy of blinding of studies of tDCS and we have included the following new 'Risk of bias' criteria: sample size and study duration. Details of this can be found in the sections: Assessment of risk of bias in included studies

(*Continued*)

		and Description of the intervention. We have also applied the GRADE approach to assessing the quality of evidence
13 September 2010	Amended	We amended the 'Risk of bias' tables so that the criterion "allocation concealment" is not assessed for studies with cross-over designs and the criterion "free from carry-over effects?" is not assessed for studies with parallel designs. These changes are now reflected in Figure 2, where those criteria now appear as empty boxes for the appropriate studies. This is in line with the original review protocol and the changes are necessary due to a copy-editing error rather than any change to the review methods

CONTRIBUTIONS OF AUTHORS

For this update

NOC: co-implemented the search strategy alongside the Cochrane PaPaS Group Information Specialist, applied eligibility criteria, assessed studies, extracted and analysed data, and led the write-up of the review.
BW: acted as the second review author, applied eligibility criteria, assessed studies, extracted data and assisted with the write-up of the review.
LM: provided statistical advice and support throughout the review.
LDS: acted as a third review author for conflicts in applying eligibility criteria and assessing included studies.
SS: aupported the implementation and reporting of the review throughout.
All review authors read and commented upon the systematic review and commented on and approved the final manuscript.

For previous versions of this review

NOC: conceived and designed the review protocol, co-implemented the search strategy alongside the Cochrane PaPaS Group Information Specialist, applied eligibility criteria, assessed studies, extracted and analysed data, and led the write-up of the review.
BW: closely informed the protocol design and acted as the second review author, applied eligibility criteria, assessed studies, extracted data and assisted with the write-up of the review.
LM: provided statistical advice and support throughout the review and contributed to the design of the protocol.
LDS: was involved in the conception and design of the review and acted as a third review author for conflicts in applying eligibility criteria and assessing included studies.
SS: informed the design of the protocol and has supported the implementation and reporting of the review throughout.
All review authors read and commented upon the systematic review and commented on and approved the final manuscript.

DECLARATIONS OF INTEREST

NOC: none known

LM: none known

SS: none known

LHD: none known

BW: none known

SOURCES OF SUPPORT

Internal sources

- Brunel University London, UK.

Salary for authors NOC, LDS

- Edge Hill University, UK.

Salary for author SS

- University College London, UK.

Salary for author LM

- University of Notre Dame Australia, Australia.

Salary for author BMW

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

For this update

For this update we searched ClinialTrials.gov and the World Health Organization International Clinical Trials Registry Platform, as these searches offer superior coverage to those outlined in our original protocol, and because the meta-register of controlled trials is no longer operational. We assessed the quality of the body of evidence using GRADE and added three 'Summary of findings' tables.

For the 2014 update

We did not search the database Scopus in the 2014 update or this update as the other searches had covered the full scope of this database. In compliance with new author guidelines from Cochrane Pain, Palliative and Supportive Care and the recommendations of Moore 2010 we added two criteria, 'study size' and 'study duration', to our 'Risk of bias' assessment using the thresholds for judgement suggested by Moore 2010:

- **size** (we rated studies with fewer than 50 participants per arm as being at high risk of bias, those with between 50 and 199 participants per arm at unclear risk of bias, and 200 or more participants per arm at low risk of bias);
- **duration** (we rated studies with follow-up of less than two weeks as being at high risk of bias, two to seven weeks at unclear risk of bias and eight weeks or longer at low risk of bias).

For the 2010 update

As described in detail in Unit of analysis issues, on advice from a Cochrane statistician we meta-analysed parallel and cross-over studies using the generic inverse variance method rather than combining them without this statistical adjustment as was specified in the protocol. Subsequently the planned sensitivity analysis investigating the influence of study design was not deemed necessary. However on advice from a Cochrane statistician we performed a sensitivity analysis to assess the impact of our approach to imputation of standard errors for cross-over studies.

In order to meet our second objective of considering the influence of varying stimulation parameters, we included studies regardless of the number of stimulation sessions delivered, including single-dose studies.

The following decision was taken on encountering multiple outcomes within the same time period: for short-term outcomes where more than one data point was available, we used the first post-stimulation measure; where multiple treatments were given, we took the first outcome at the end of the treatment period. For medium-term outcomes where more than one data point was available we used the measure that was closest to the mid-point of this time period. We decided to pool data from studies with a low or unclear risk of bias as we felt that the analysis specified in the protocol (including only those studies with an overall low risk of bias) was too stringent and would not allow any statistical assessment of the data.

We did not use overall risk of bias in sensitivity analyses as we found that it lacked sensitivity. Instead we considered individual criteria in the 'Risk of bias' assessment for sensitivity analyses. However, we excluded studies with a 'high' risk of bias for any criterion from the meta-analysis except study size and study duration.

For this update we have altered the 'Risk of bias' assessment to reflect new evidence regarding the adequacy of blinding of studies of tDCS. Details of this can be found in Assessment of risk of bias in included studies and Description of the intervention.

INDEX TERMS

Medical Subject Headings (MeSH)

Brain [*physiology]; Chronic Pain [*therapy]; Electric Stimulation Therapy [adverse effects; *methods]; Pain Management [*methods]; Randomized Controlled Trials as Topic; Transcranial Magnetic Stimulation [adverse effects; *methods]

MeSH check words

Humans