Non-invasive brain stimulation techniques for chronic pain (Review)

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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. 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) and reduced impedance non-invasive cortical electrostimulation (RINCE).

Objectives

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

Search methods

We searched CENTRAL (2013, Issue 6), MEDLINE, EMBASE, CINAHL, PsycINFO, LILACS and clinical trials registers. The original search for the review was run in November 2009 and searched all databases from their inception. To identify studies for inclusion in this update we searched from 2009 to July 2013.

Selection criteria

Randomised and quasi-randomised studies of rTMS, CES, tDCS or RINCE if they employed a sham stimulation control group, recruited patients over the age of 18 with pain of three months duration or more and measured pain as a primary outcome.

Data collection and analysis

Two authors independently extracted and verified data. Where possible we entered data into meta-analyses. We excluded studies judged as being at high risk of bias from the analysis. We used the GRADE system to summarise the quality of evidence for core comparisons.

Main results

We included an additional 23 trials (involving 773 participants randomised) in this update, making a total of 56 trials in the review (involving 1710 participants randomised). This update included a total of 30 rTMS studies, 11 CES, 14 tDCS and one study of RINCE(the original review included 19 rTMS, eight CES and six tDCS studies). We judged only three studies as being at low risk of bias across all criteria.

Meta-analysis of studies of rTMS (involving 528 participants) demonstrated significant heterogeneity. Pre-specified subgroup analyses suggest that low-frequency stimulation is ineffective (low-quality evidence) and that rTMS applied to the dorsolateral prefrontal cortex is ineffective (very low-quality evidence). We found a short-term effect on pain of active high-frequency stimulation of the motor cortex in single-dose studies (low-quality evidence, standardised mean difference (SMD) 0.39 (95% confidence interval (CI) -0.27 to -0.51 P < 0.01)). This equates to a 12% (95% CI 8% to 15%) reduction in pain, which does not exceed the pre-established criteria for a minimal clinically important difference (≥ 15%). Evidence for multiple-dose studies was heterogenous but did not demonstrate a significant effect (very low-quality evidence).

For CES (six studies, 270 participants) no statistically significant difference was found between active stimulation and sham (low-quality evidence).

Analysis of tDCS studies (11 studies, 193 people) demonstrated significant heterogeneity and did not find a significant difference between active and sham stimulation (very low-quality evidence). Pre-specified subgroup analysis of tDCS applied to the motor cortex (n = 183) did not demonstrate a statistically significant effect and this lack of effect was consistent for subgroups of single or multiple-dose studies.

One small study (n = 91) at unclear risk of bias suggested a positive effect of RINCE over sham stimulation on pain (very low-quality evidence).

Non-invasive brain stimulation appears to be frequently associated with minor and transient side effects, though there were two reported incidences of seizure related to active rTMS in the included studies.

Authors' conclusions

Single doses of high-frequency rTMS of the motor cortex may have small short-term effects on chronic pain. It is likely that multiple sources of bias may exaggerate this observed effect. The effects do not meet the predetermined threshold of minimal clinical significance and multiple-dose studies do not consistently demonstrate effectiveness. The available evidence suggests that low-frequency rTMS, rTMS applied to the pre-frontal cortex, CES and tDCS are not effective in the treatment of chronic pain. While the broad conclusions for rTMS and CES have not changed substantially, the addition of this new evidence and the application of the GRADE system has modified some of our interpretation and the conclusion regarding the effectiveness of tDCS has changed. We recommend that previous readers should re-read this update. There is a need for larger, rigorously designed studies, particularly of longer courses of stimulation. It is likely that future evidence may substantially impact upon the presented results.

PLAIN LANGUAGE SUMMARY

Stimulating the brain without surgery in the management of chronic pain

Various devices are available that can electrically stimulate the brain without the need for surgery or any invasive treatment in order to manage chronic pain. There are four 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) and reduced impedance non-invasive cortical electrostimulation (RINCE) 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, but the efficacy of these treatments is uncertain.

This review update included 56 studies: 30 of rTMS, 11 of CES, 14 of tDCS and one of RINCE. We judged only three studies as having a low risk of bias. Low or very low-quality evidence suggests that low-frequency rTMS and rTMS applied to pre-frontal areas of the brain are not effective but that a single dose of high-frequency stimulation of the motor cortex area of the brain provides short-term pain relief. This effect appears to be small and may be exaggerated by a number of sources of bias. Studies that gave a course of multiple treatments of rTMS produced conflicting results with no overall effect seen when we pooled the results of these studies. Most studies of rTMS are small and there is substantial variation between studies in terms of the treatment methods used. Low-quality evidence does not suggest that CES or tDCS are effective treatments for chronic pain. A single small study of RINCE provided very low-quality evidence of a short-term effect on pain. For all forms of stimulation the evidence is not conclusive and uncertainty remains.

The reporting of side effects varied across the studies. 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 after real and sham stimulation. There were two reports of seizure following real rTMS.

While the broad conclusions for rTMS and CES have not changed substantially, the addition of this new evidence and the application of the GRADE system has modified some of our interpretation. Previous readers should re-read this update.

More studies of rigorous design and adequate size are required to evaluate accurately all forms of non-invasive brain stimulation for the treatment of chronic pain.

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

Repetitive transcranial magnetic stimulation (rTMS) compared with sham for chronic pain				
Intervention: active rTMS **Comparison: sham rTMS**				
Outcomes: pain (VAS or NRS)				
Comparison	**No of participants (studies)**	**Effect size (SMD, 95% CIs)**	**Relative effect (average % improvement (reduction) in pain (95% CIs) in relation to post-treatment score from sham group)*** *statistically significant outcomes with low heterogeneity only	**Quality of the evidence (GRADE)**
Pain: short-term follow-up **Subgroup analysis: low-frequency rTMS**	81 (6)	Ineffective 0.15 (-0.01 to 0.31) P = 0.07		⊕⊕◯◯ **low**
Pain: short-term follow-up **subgroup analysis: high-frequency rTMS**	447 (20)	Effective -0.27 (-0.35 to -0.20) P <0.01		⊕⊕◯◯ **low**
Pain: short-term follow-up **Subgroup analysis: motor cortex studies only, low-frequency studies excluded, single-dose studies**	233 (12)	Effective -0.39 (-0.51 to -0.27) P <0.01	12% (8% to 15%)	⊕⊕◯◯ **low**
Pain: short-term follow-up **Subgroup analysis: motor cortex studies only, low-frequency studies excluded, multiple-dose studies**	157 (5)	Ineffective -0.07 (-0.41 to 0.26) P = 0.68		⊕◯◯◯ **very low**
Pain: short-term follow-up **Subgroup analysis: prefrontal cortex studies only**	68 (5)	Ineffective -0.47 (-1.48 to 0.11) P = 0.36		⊕◯◯◯ **very low**

Pain: medium-term follow-up rTMS all studies	184 (8)	Ineffective -0.18 (-0.43 to 0.06) P = 0.15	⊕◯◯◯ **very low**
Pain: long-term follow-up rTMS all studies	59 (3)	Ineffective -0.12 (-0.46 to 0.21) P = 0.47	⊕⊕◯◯ **low**
CES compared with sham for chronic pain			
Intervention: active CES Comparison: sham CES			
Outcomes: pain (VAS or NRS)			
Pain: short-term follow-up CES all studies	270 (5)	Ineffective -0.24 (-0.48 to 0.01) P = 0.06	⊕⊕◯◯ **low**
tDCS compared with sham for chronic pain			
Intervention: active tDCS Comparison: sham tDCS			
Outcomes: pain (VAS or NRS)			
Pain: short-term follow-up tDCS all studies	183 (10)	Ineffective -0.18 (-0.56 to 0.09) P = 0.19	⊕◯◯◯ **very low**
Pain: short-term follow-up Subgroup analysis: motor cortex studies only (single and multiple-dose studies)	172 (10)	Ineffective -0.23 (-0.48 to 0.01) P = 0.06	⊕⊕◯◯ **low**
Pain: short-term follow-up Subgroup analysis: motor cortex studies only (multiple-dose studies only)	119 (7)	Ineffective -0.35 (-0.79 to 0.09) P = 0.12	⊕◯◯◯ **very low**
Pain: medium-term follow-up tDCS	77 (4)	Ineffective -0.20 (-0.63 to 0.24) P = 0.37	⊕⊕◯◯ **low**
RINCE compared with sham for chronic pain			

Intervention: active RINCE **Comparison: sham RINCE**			
Outcomes: pain (VAS or NRS)			
Pain: short-term follow-up **tDCS all studies**	91 (1)	Effective -1.41 (-2.48 to -0.34) P = 0.01	⊕◯◯◯ **very low**

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.
CES: cranial electrotherapy stimulation; CI: confidence interval; NRS: numerical rating scale; RINCE: reduced impedance non-invasive cortical electrostimulation; rTMS: repetitive transcranial magnetic stimulation; tDCS: transcranial direct current stimulation; VAS: visual analogue scale

For full details of the GRADE judgements for each comparison see Appendix 6.

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).

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). 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). Chronic pain is a heterogenous phenomenon that results from a wide variety of pathologies including chronic somatic tissue injury such as arthritis, peripheral nerve injury and central nervous system injury, as well as a range of chronic pain syndromes such as fibromyalgia. It is likely that different mechanisms of pain production underpin these different causes of chronic pain (Ossipov 2006).

Description of the intervention

Brain stimulation techniques have been used to address a variety of pathological pain conditions including fibromyalgia, chronic post-stroke pain and complex regional pain syndrome (Cruccu 2007; Fregni 2007; Gilula 2007), and clinical studies of both invasive and non-invasive techniques have produced preliminary data showing reductions in pain (Cruccu 2007; 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 2007). 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 damage to the 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) and cranial electrotherapy stimulation (CES) involve the safe and painless application of low-intensity (commonly ≤ 2 mA) electrical current to the cerebral cortex of the brain (Fregni 2007; Gilula 2007; Hargrove 2012). 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). Recent 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). 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 2012).

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 (≤ 1 Hz) results in lowered cortical excitability at the site of stimulation, whereas high-frequency stimulation (≥ 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). Modulation of activity in brain networks is also proposed as the mechanism of action of CES and RINCE 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 patient blinding, particularly in cross-over design studies. Lisanby 2001 and Loo 2000 suggest that an ideal sham condition for rTMS should:

1. not stimulate the cortex;
2. be the same as active stimulation in visual terms and in terms of its position on the scalp; and
3. 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. Recent 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 review all randomised and quasi-randomised studies of non-invasive cortical stimulation techniques in the treatment of chronic pain. The key aims of the review were:

1. to critically evaluate the efficacy of non-invasive cortical stimulation techniques compared to sham controls for chronic pain; and

2. to critically evaluate the influence of altered treatment parameters (i.e. stimulation method, parameters, dosage, site) on the efficacy of non-invasive cortical stimulation for chronic pain.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs) and quasi-randomised trials (e.g. by order of entry or date of birth) that utilise a sham control group were included. 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 are 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 or RINCE). 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. 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, were also not included. 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 self reported pain 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 included 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 (Higgins 2011). We have slightly adapted this filter to include the term 'sham' in the title or abstract. The search strategies 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

We ran the original search for the review in November 2009 and searched all databases from their inception. To identify studies for inclusion in this update we searched the following electronic

databases from 2009 to July 2013 to identify additional published articles:

- the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2013, Issue 6);
- OVID MEDLINE & MEDLINE in Process to 23 July 2013;
- OVID EMBASE to 2013 week 29;
- PsycINFO to July week 3 2013;
- CINAHL to July 2013;
- LILACS to January 2013;

For full details of the search parameters including dates for this update see Appendix 1; Appendix 2; Appendix 3.

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

We searched the National Research Register (NRR) Archive, Health Services Research Projects in Progress (HSRProj), Current Controlled Trials register (incorporating the meta-register of controlled trials and the International Standard Randomised Controlled Trial Number (ISRCTN)) to January 2013 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 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 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 post-intervention 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 2011).
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.
For this update, in compliance with new author guidelines from the Cochrane Pain, Palliative and Supportive Care review group 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 partici-

pants 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 sub-optimal (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 previous 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 sub-optimal 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 100 mm VAS format on the basis of the mean standard deviation from trials using 0 to 100 mm 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 < 15% as no important change, ≥ 15% as a minimally important change, ≥ 30% as a moderately important change and ≥ 50% 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 2011). We imputed the post-treatment between-condition correlation coefficient from an included cross-over study that presented individual patient 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 times data from that trial were entered in the meta-analysis. We calculated the SMD(SE) for parallel studies in RevMan. 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.

Data synthesis

We performed pooling of results where adequate data supported this using RevMan 5 software (version 5.2) (RevMan 2012), 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 and RINCE) and for short-term (0 to < 1 week post-intervention), mid-term (≥ 1 to 6 weeks post-intervention) and long-term (≥ 6 weeks post-intervention) outcomes where adequate data were identified.

Where more than one data point was available for short-term outcomes, we used the first post-stimulation 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'.

For this update we utilised the GRADE approach to assessing the quality of a body of evidence (Guyatt 2008). 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 'Risk of bias' criteria.
- Inconsistency: downgrade once if heterogeneity is statistically significant 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 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.

While we had planned to use GRADE in our initial protocol we introduced these criteria specifically for this update.

Subgroup analysis and investigation of heterogeneity

We assessed heterogeneity using the Chi^2 test to investigate its statistical significance and the I^2 statistic to estimate the amount. Where significant heterogeneity ($P < 0.1$) was present we explored subgroup analysis. Pre-planned comparisons included site of stimulation, frequency of TMS stimulation (low $\leq$ 1 Hz, high $\geq$ 5 Hz), multiple 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.

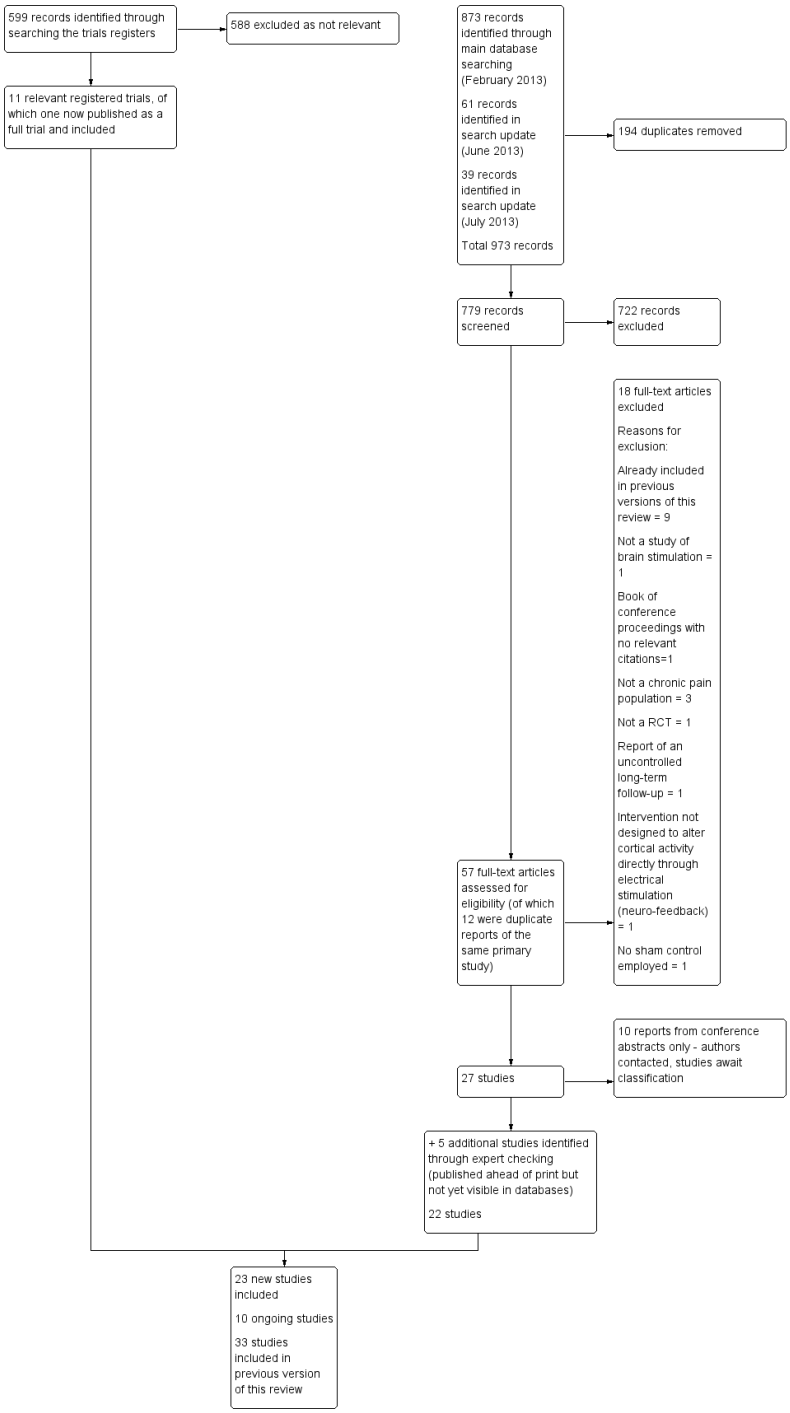
Results of the search

Published data

In our original review the search strategy identified 1148 citations, including 305 duplicates. See Appendix 4 and Appendix 5 for full details of the search results from the original review. Screening of the 843 unique citations by title and abstract identified 39 as potentially eligible for the review. Three studies were identified from handsearching of the reference lists of included studies of which two were not retrievable in abstract or full manuscript form. The level of agreement between review authors, calculated using the kappa statistic for study eligibility based on title and abstract alone, was 0.77. We identified three more papers that were not picked up from the search strategy. We also deemed these to be potentially eligible for the review. One of the experts contacted to review the search results for possible omissions identified one additional study. The full-text screening of the 44 citations identified 33 eligible studies (19 of rTMS, 422 participants randomised; six of tDCS, 124 participants randomised; eight of CES, 391 participants randomised) (André-Obadia 2006; André-Obadia 2008; Boggio 2009; Borckardt 2009; Capel 2003; Carretero 2009; Cork 2004; Defrin 2007; Fenton 2009; Fregni 2005; Fregni 2006a; Fregni 2006b; Gabis 2003; Gabis 2009; Hirayama 2006; Irlbacher 2006; Kang 2009; Katsnelson 2004; Khedr 2005; Lefaucheur 2001a; Lefaucheur 2001b; Lefaucheur 2004; Lefaucheur 2006; Lefaucheur 2008; Lichtbroun 2001; Mori 2010; Passard 2007; Pleger 2004; Rollnik 2002; Saitoh 2007; Tan 2000; Tan 2006; Valle 2009). The kappa level of agreement between authors for eligibility from full-text screening was 0.87.

In this update we conducted a full search in February 2013 and updated the search of the main databases on 12 June 2013 and again on 24 July 2013. We included a further 23 completed studies with 773 participants randomised (range of n = 3 to 105, see Figure 2 for a flow chart of the search process). Of these, 11 studies (324 participants randomised) investigated rTMS (Ahmed 2011; André-Obadia 2011; Avery 2013, Fregni 2011; Hosomi 2013; Jensen 2013; Lee 2012; Mhalla 2011; Picarelli 2010; Short 2011; Tzabazis 2013), eight studies (177 participants randomised) investigated tDCS (Antal 2010; Jensen 2013; Mendonca 2011; Portilla 2013; Riberto 2011; Soler 2010; Villamar 2013; Wrigley 2014), three studies (181 participants randomised) investigated CES (Rintala 2010; Tan 2011; Taylor 2013), and one study investigated a novel form of stimulation (reduced impedance non-invasive cortical electrostimulation (RINCE)) that did not fit neatly into any of the three broad categories (Hargrove 2012, 91 participants)). Overall this updated review included 56 studies (1710 participants randomised), with 30 trials of rTMS (746 participants randomised), 14 trials of tDCS (301 participants randomised), 11 studies of CES (572 participants randomised) and one study of RINCE stimulation (91 participants randomised).

Figure 2. Study flow diagram for updated search.



We identified an additional 11 conference abstracts that were not related to full published studies (Acler 2012; Albu 2011; Ansari 2013; Fricova 2009; Fricova 2011; Klirova 2010; Klirova 2011; Knotkova 2011; Pellaprat 2012; Schneider 2012; Yağ ci 2013). We contacted the authors of these abstracts to try to ascertain whether they were unique studies or duplicates and to acquire full study reports. Where we were unable to obtain this information we placed these records in Studies awaiting classification. For two of these abstracts the authors confirmed that they referred to studies that are either in the analysis/write-up stage or under review for publication, and as such were unavailable for this review update (Knotkova 2011; Schneider 2012). For the remaining abstracts identified in this update our attempts to contact the authors were not successful (Acler 2012; Albu 2011; Ansari 2013 Fricova 2009; Fricova 2011; Klirova 2010; Klirova 2011; Pellaprat 2012; Yağ ci 2013). We sent requests by email where possible in February 2013, with a follow-up email in April and June 2013, for those identified in the first search of this update, and in June 2013 for those identified by the second round of searching.

Unpublished data

In our original review the search strategy identified 5920 registered studies. Screening of the studies by the register records identified 23 studies that might potentially produce relevant data. Of these, seven were duplicated across trials registers, leaving 16 unique registered studies. We contacted the contact author for each of these studies by post or email with a request for any relevant data that might inform the review. No data were available from any of these studies for inclusion in this review.

In this update our search of the trials registers identified 599 records from which 11 relevant ongoing trials were identified. In addition to the two ongoing studies remaining from the last update (NCT00947622; NCT00815932); this makes a total of 13 ongoing studies identified. We contacted the contact author for each of these studies by post or email with a request for any relevant data that might inform the review. No data were available from any of these studies for inclusion in this review. We sent initial request emails for this update in April, and where no response was received also in May and in June 2013. Unpublished data and a full study report was provided for one study of rTMS identified from the trials registers search of the last update of this review (reference was Wajdik 2009, now Avery 2013).

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, Egypt, Europe (France, Germany, Italy, Spain and the UK), Israel, Japan, Russia, South Korea and the USA. Most studies were based in a laboratory or outpatient pain clinic setting.

Type of stimulation, application and use

In total 30 studies investigated rTMS (Ahmed 2011; André-Obadia 2006; André-Obadia 2008; André-Obadia 2011; Avery 2013; Borckardt 2009; Carretero 2009; Defrin 2007; Fregni 2005; Fregni 2011; Hirayama 2006; Hosomi 2013; Irlbacher 2006; Kang 2009; Khedr 2005; Lee 2012; Lefaucheur 2001a; Lefaucheur 2001b; Lefaucheur 2004; Lefaucheur 2006; Lefaucheur 2008; Mhalla 2011; Onesti 2013; Passard 2007; Picarelli 2010; Pleger 2004; Rollnik 2002; Saitoh 2007; Short 2011; Tzabazis 2013). 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), 14 studies investigated tDCS (Antal 2010; Boggio 2009; Fenton 2009; Fregni 2006a; Fregni 2006b; Jensen 2013; Mendonca 2011; Mori 2010; Portilla 2013; Riberto 2011; Soler 2010; Valle 2009; Villamar 2013; Wrigley 2014), and one study investigated RINCE stimulation (Hargrove 2012). We had not been aware of RINCE therapy until it was identified in this search update. While it bears similarities with CES the author of the included trial suggested that due to the specific unique stimulation parameters that differ from conventional forms of CES, it represents a novel form of cortical stimulation (Hargrove 2012).

Study designs

There were a mixture of parallel and cross-over study designs. For rTMS there were 12 parallel studies (Ahmed 2011; Avery 2013; Carretero 2009; Defrin 2007; Fregni 2011; Khedr 2005; Lee 2012; Mhalla 2011; Passard 2007; Picarelli 2010; Short 2011; Tzabazis 2013), and 18 cross-over studies (André-Obadia 2006; André-Obadia 2008; André-Obadia 2011, Borckardt 2009; Fregni 2005; Hirayama 2006; Hosomi 2013; Irlbacher 2006; Kang 2009; Lefaucheur 2001a; Lefaucheur 2001b; Lefaucheur 2004; Lefaucheur 2006; Lefaucheur 2008; 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 seven parallel studies (Fregni 2006a; Fregni 2006b; Mendonca

2011; Mori 2010; Riberto 2011; Soler 2010; Valle 2009), and seven cross-over studies (Antal 2010; Boggio 2009; Fenton 2009; Jensen 2013; 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).

Study participants

The included studies were published between 2000 and 2013. 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 41 participants and the single RINCE study recruited 91 participants. Studies included a variety of chronic pain conditions. Nine rTMS studies included participants with neuropathic pain of mixed origin; of these seven included a mix of central, peripheral and facial neuropathic pain patients (André-Obadia 2006; André-Obadia 2008; André-Obadia 2011; Hirayama 2006; Hosomi 2013, Lefaucheur 2004; Lefaucheur 2008), two included a mix of central and peripheral neuropathic pain patients (Lefaucheur 2006; Saitoh 2007), of which one study included a patient with phantom limb pain (Saitoh 2007). One study included a mix of central neuropathic pain and phantom limb pain patients (Irlbacher 2006). One study included a mix of central and facial neuropathic pain patients (Lefaucheur 2001a), two rTMS studies included only central neuropathic pain patients (Defrin 2007; Kang 2009), one included only peripheral neuropathic pain patients (Borckardt 2009), and nine studies included non-neuropathic chronic pain including fibromyalgia (Carretero 2009; Lee 2012; Mhalla 2011; Passard 2007; Short 2011; Tzabazis 2013), chronic widespread pain (Avery 2013), chronic pancreatitis pain (Fregni 2005; Fregni 2011), and complex regional pain syndrome type I (CRPSI) (Picarelli 2010; Pleger 2004). One study included only phantom limb pain (Ahmed 2011). 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 (17) 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; Onesti 2013; Picarelli 2010; Rollnik 2002; Saitoh 2007). This inclusion criterion was varyingly described as intractable, resistant to medical intervention or 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), one study included participants with neuropathic pain secondary to multiple sclerosis (Mori 2010), three included participants with central neuropathic pain following spinal cord injury (Fregni 2006a; Soler 2010; Wrigley 2014), one with neuropathic or non-neuropathic pain following spinal cord injury (Jensen 2013), and six studies included non-neuropathic pain, specifically chronic pelvic pain (Fenton 2009), and fibromyalgia (Fregni 2006b; Mendonca 2011; Riberto 2011; Villamar 2013), or a mixed group (Antal 2010). One study included participants with neuropathic pain following burn injury (Portilla 2013). Four studies of tDCS specified recruiting participants with pain that was refractory to medical management (Antal 2010; Boggio 2009; Fenton 2009; Fregni 2006a). The study relating to RINCE stimulation included participants with fibromyalgia (Hargrove 2012). Most studies included both male and female participants except the studies of Fenton 2009 (chronic pelvic pain) and Fregni 2006b, Valle 2009, Riberto 2011 and Mhalla 2011; Lee 2012 (fibromyalgia), which recruited females only and Fregni 2006a (post-spinal cord injury pain), which recruited only males. Two studies did not present data specifying the gender distribution of participants (Capel 2003; Katsnelson 2004).

Outcomes

Primary outcomes

All included studies assessed pain using self reported pain visual analogue or numerical rating scales. 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. Twenty-three studies reported collecting medium-term outcome data (≥ 1 to 6 weeks post-treatment) (Ahmed 2011; André-Obadia 2008; Antal 2010; Borckardt 2009; Carretero 2009; Defrin 2007; Fenton 2009; Fregni 2006a; Fregni 2006b; Fregni 2011; Gabis 2009; Kang 2009; Khedr 2005; Lee 2012; Lefaucheur 2001a; Mori 2010; Passard 2007; Picarelli 2010;

Short 2011; Soler 2010; Tzabazis 2013; Valle 2009; Wrigley 2014). Only three studies collected controlled outcome data on long-term (> 6 weeks post-treatment) follow-up (Avery 2013; Kang 2009; Passard 2007).

Secondary outcomes

We only considered secondary outcomes that distinctly measured self reported disability or quality of life for extraction and inclusion in the Characteristics of included studies table. Nine studies used measures of disability or pain interference (Avery 2013; Cork 2004; Kang 2009; Mhalla 2011; Passard 2007; Short 2011; Soler 2010; Tan 2000; Tan 2006), and 14 studies collected measures of quality of life (Avery 2013; Fregni 2006b; Lee 2012; Lichtbroun 2001; Mhalla 2011; Mori 2010; Passard 2007; Picarelli 2010; Riberto 2011; Short 2011; Tan 2011; Taylor 2013; Tzabazis 2013; Valle 2009).

Adverse event reporting

Seventeen studies did not report any information regarding adverse events (Ahmed 2011; André-Obadia 2011; Borckardt 2009; Cork 2004; Defrin 2007; Gabis 2009; Jensen 2013; Kang 2009; Katsnelson 2004; Khedr 2005; Lefaucheur 2006; Lefaucheur 2008; Lichtbroun 2001; Pleger 2004; Riberto 2011; Tan 2000; Tan 2006).

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; Defrin 2007; Hirayama 2006; Hosomi 2013; Irlbacher 2006; Kang 2009; Khedr 2005; Lee 2012, Lefaucheur 2001a; Lefaucheur 2001b; Lefaucheur 2004; Lefaucheur 2006; Lefaucheur 2008; Mhalla 2011; Onesti 2013; Passard 2007; Picarelli 2010; Pleger 2004; Rollnik 2002; Saitoh 2007). Of these, one study specified stimulation of the right hemisphere (Kang 2009), one study specified the left hemisphere (Mhalla 2011), and two studies specified stimulation over the midline (Defrin 2007; Pleger 2004). 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). Two studies stimulated the dorsolateral pre-frontal cortex (DLPFC), with two studies stimulating the left hemisphere (Borckardt 2009; Short 2011), 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

Eleven 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). 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. Twenty-seven studies investigated high-frequency (≥ 5 Hz) rTMS (Ahmed 2011; André-Obadia 2006; André-Obadia 2008; André-Obadia 2011; Avery 2013; Borckardt 2009; Defrin 2007; Fregni 2005; Hirayama 2006; Hosomi 2013; Irlbacher 2006; Kang 2009; Khedr 2005; Lee 2012; Lefaucheur 2001a; Lefaucheur 2001b; Lefaucheur 2004; Lefaucheur 2006; Lefaucheur 2008; Mhalla 2011; Onesti 2013; Passard 2007; Picarelli 2010; Pleger 2004; Rollnik 2002; Saitoh 2007; Short 2011). 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. The study by 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. Eight studies specified a posteroanterior or parasagittal orientation of the stimulating coil (André-Obadia 2006; Lefaucheur 2001b; Lefaucheur 2004; Lefaucheur 2006; Lefaucheur 2008; Passard 2007; Picarelli 2010; Short 2011), two studies specified a coil orientation 45º to the midline (Ahmed 2011; Kang 2009), 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 11 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), 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). The remaining studies utilised sham coils. Of these, eight studies specified that the sham coil made similar or identical sounds to those elicited during active stimulation (André-Obadia 2011; Borckardt 2009; Defrin 2007; Irlbacher 2006; Mhalla 2011; Passard 2007; Picarelli 2010; Tzabazis 2013), and five specified that the sham coil made similar sounds, looked the same and elicited similar scalp sensations as the real coil (Avery 2013; Fregni 2011; Hosomi 2013; Onesti 2013; Short 2011). Six studies did not specify whether the sham coil controlled for the auditory characteristics of active stimulation (Fregni 2005; Lefaucheur 2001a; Lefaucheur 2001b; Lefaucheur 2004; Lefaucheur 2006; Lefaucheur 2008).

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 patient'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 patient blinding. Similarly, Katsnelson 2004 utilised a visually indistinguishable sham device that delivered brief pulses of current of < 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

Two studies of tDCS stimulated the dorsolateral prefrontal cortex in one treatment group (Fregni 2006b; Valle 2009). Thirteen studies stimulated the motor cortex (Antal 2010; Boggio 2009; Fenton 2009; Fregni 2006a; Fregni 2006b; Jensen 2013; Mori 2010; Portilla 2013; Riberto 2011; Soler 2010; Valle 2009; Villamar 2013; Wrigley 2014). Of these, nine stimulated the cortex contralateral to the side of worst pain (Boggio 2009; Fregni 2006a; Fregni 2006b; Mori 2010; Portilla 2013; Riberto 2011; Soler 2010; Villamar 2013; 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). Three studies stimulated the left hemisphere for all participants (Antal 2010; 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 applied anodal or cathodal stimulation to the left motor cortex or to the right supraorbital area (Mendonca 2011).

Six studies delivered a current intensity of 2 mA for 20 minutes once a day for five days (Antal 2010; Fregni 2006a; Fregni 2006b; Mori 2010; Valle 2009; Wrigley 2014). One study applied a current intensity of 1 mA once a day for two days (Fenton 2009), and four studies applied one treatment per stimulation condition at an intensity of 2 mA for 20 minutes (Boggio 2009; Mendonca 2011; Jensen 2013; Villamar 2013). One study delivered 10 stimulation sessions of 20 minutes at 2 mA once weekly for 10 weeks (Riberto 2011), and another delivered 10 sessions once a day, with a visual illusion condition or a sham visual illusion condition for 10 consecutive weekdays (Soler 2010).

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 our original review we excluded 11 studies after consideration of the full study report. Of these, one was not a study of brain stimulation (Frentzel 1989), two did not assess self reported pain as an outcome (Belci 2004; Johnson 2006), four were not restricted to participants with chronic pain (Evtiukhin 1998; Katz 1991; Longobardi 1989; Pujol 1998), one study was unclear on the duration of participants' symptoms (Avery 2007), 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), and one did not employ a sham control (Evtiukhin 1998).

For this update we excluded a further 17 reports, after consideration of the full study report. Nine reports referred to studies which had already been included in the previous version of this review, one was not a study of brain stimulation (Carraro 2010), two were not clearly in a chronic pain population (Choi 2012a; Choi 2012b), one was not a randomised controlled trial (O'Connell 2013), one reported uncontrolled long-term follow-up data from an included study (Hargrove 2012a), 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). Finally one citation referred to a booklet of conference proceedings which contained no relevant citations.

Risk of bias in included studies

Risk of bias varied across studies for all of the assessment criteria. For a summary of 'Risk of bias' assessment across studies see Figure 1.

Sequence generation

For the criterion 'adequate sequence generation' we awarded crossover 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 14 trials as having an unclear risk of bias (Antal 2010; Carretero 2009; Cork 2004; Defrin 2007; Hargrove 2012; Katsnelson 2004; Lee 2012; Mendonca 2011; Picarelli 2010; Riberto 2011; Rintala 2010; Tan 2006; Taylor 2013; Tzabazis 2013), 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 patients were allocated depending on the day of the week on which they were recruited, which we did not judge as being genuinely random.

Allocation concealment

We only considered for the criterion 'Adequate concealment of allocation' studies with parallel designs or from which only data from the first phase of the study were included (i.e. we them considered as parallel studies). Seventeen studies did not report concealment of allocation and we judged them as 'unclear' (Antal 2010; Carretero 2009; Cork 2004; Defrin 2007; Fregni 2011; Hargrove 2012; Katsnelson 2004; Lee 2012; Mendonca 2011; Passard 2007; Picarelli 2010; Riberto 2011; Rintala 2010; Soler 2010; Tan 2006; Taylor 2013; Tzabazis 2013), 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 concealment of allocation (Ahmed 2011; Khedr 2005).

Blinding

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. As such, where blinding of assessors was not clearly stated we made a judgement of 'unclear' for this criterion.

Sixteen studies did not specify whether they blinded outcome assessors (André-Obadia 2011; Borckardt 2009; Hirayama 2006; Irlbacher 2006; Lee 2012; Lefaucheur 2001a; Lefaucheur 2001b; Lefaucheur 2004; Lefaucheur 2006; Onesti 2013; Picarelli 2010; Pleger 2004; Rollnik 2002; Saitoh 2007; Tan 2000; Tzabazis 2013), while we judged the majority of studies of tDCS at unclear risk of bias on this criterion (Boggio 2009; Fregni 2006a; Fregni

2006b; Jensen 2013; Mori 2010; Portilla 2013; Riberto 2011; Soler 2010; Valle 2009; Villamar 2013; Wrigley 2014), since there is evidence that assessor blinding may be compromised at the stimulation intensities used (O'Connell 2012).

Blinding of participants

rTMS studies

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 angulated or angulated 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 angulating 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 sub-optimal sham control conditions and we therefore assessed them as having an 'unclear' risk of bias. Four rTMS studies included in this update utilised modern sham coils that are visually indistinguishable, emit the same noise during stimulation and elicit similar scalp sensations (Avery 2013; Fregni 2011; Onesti 2013; Short 2011). 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 (Boggio 2009; Fregni 2006a; Fregni 2006b; Jensen 2013; Mori 2010; Portilla 2013; Riberto 2011; Soler 2010; Valle 2009; Villamar 2013; Wrigley 2014).

We assessed all studies of CES as having a low risk of bias for this criterion.

Incomplete outcome data

We assessed 11 studies as having an unclear risk of bias for this criterion (Ahmed 2011; André-Obadia 2006; André-Obadia 2011; Boggio 2009; Cork 2004; Fregni 2011; Hargrove 2012; Katsnelson 2004; Lefaucheur 2006; Lichtbroun 2001; Tzabazis 2013). Ahmed 2011 and Fregni 2011 did not report the level of drop-out from their studies. 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. Five studies did not clearly report levels of drop-out (Cork 2004; Katsnelson 2004; Lefaucheur 2006; Lichtbroun 2001; Tzabazis 2013), of which one 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 (Schneider 2012). We assessed three studies as having a high risk of bias for this criterion (Antal 2010; Irlbacher 2006; Tan 2000). In the Antal 2010 study, of 23 participants recruited only 12 completed the full cross-over. In the study by Irlbacher 2006, only 13 of the initial 27 participants completed all of the treatment conditions. In the studies of 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. We considered this level of withdrawal unsustainable.

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, and these data were not made available upon request. We assessed 11 studies as having a high risk of bias for this criterion (Capel 2003; Cork 2004; Fregni 2005; Fregni 2011; Katsnelson 2004; Lichtbroun 2001; Mendonca 2011; Onesti 2013; Portilla 2013; Tzabazis 2013; Valle 2009). We judged two studies as being at unclear risk of bias (Fregni 2006a; Fregni 2006b). In the reports of these studies 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. We assessed the remaining studies as having a low risk of bias for this criterion. For this update, we first made requests for data (by email where possible) in February 2013, with repeat emails sent where necessary in March, April and June 2013. For studies identified in the second round of searches we made requests in June 2013 and we made the final round of requests on 1 August 2013. If these data are made available in time for future updates then we can revise judgements on this criterion accordingly.

Study size

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

Study duration

We rated seven studies at low risk of bias on this criterion (Ahmed 2011; Avery 2013; Gabis 2009; Mhalla 2011; Passard 2007; Picarelli 2010; Valle 2009), 19 studies at unclear risk of bias (André-Obadia 2008; André-Obadia 2011; Antal 2010; Borckardt 2009; Carretero 2009; Defrin 2007; Fenton 2009;

Fregni 2006a; Fregni 2006b; Fregni 2011; Hosomi 2013; Kang 2009; Khedr 2005; Lee 2012; Mori 2010; Onesti 2013; Soler 2010; Tzabazis 2013; Wrigley 2014), and the remaining studies at high risk of bias (André-Obadia 2006; Boggio 2009; Capel 2003; Cork 2004; Fregni 2005; Gabis 2003; Hargrove 2012; Hirayama 2006; Irlbacher 2006; Jensen 2013; Katsnelson 2004; Lefaucheur 2001a; Lefaucheur 2001b; Lefaucheur 2004; Lefaucheur 2006; Lefaucheur 2008; Lichtbroun 2001; Mendonca 2011; Pleger 2004; Portilla 2013; Riberto 2011; Rintala 2010; Rollnik 2002; Saitoh 2007; Short 2011; Tan 2000; Tan 2006; Tan 2011; Taylor 2013; Villamar 2013) .

Other potential sources of bias

Carry-over effects in cross-over trials

We judged one study as unclear on this criterion as no pre-stimulation data were provided and no investigation of carry-over effects was discussed in the study report (Fenton 2009). 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 significant difference (P > 0.1) and we judged this study as having a low risk of bias for carry-over effects. We judged another study at unclear risk of bias on this criterion as the necessary data were not available in the study report from which to make a judgement (Portilla 2013).

Other sources of bias

Two studies did not present baseline data for key outcome variables and we judged them as 'unclear' (Fregni 2011; Tzabazis 2013). Three studies demonstrated baseline imbalances: one study on pain intensity levels (Defrin 2007), one study on Brief Pain Inventory pain interference, SF-36 pain sub-scale and coping strategies (Tan 2011) and one study on duration of pain, education, age and economic activity (Riberto 2011). We judged these studies at unclear risk of bias for these reasons. One study of CES did not clearly present relevant baseline group characteristics of the included participants and we judged it as being at high risk of bias for this criterion (Katsnelson 2004). 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 judged one study at high risk of bias on this criterion due to imbalances between the groups at baseline on the duration of pain, education, age and economic activity (Riberto 2011).

Effects of interventions

See: **Summary of findings for the main comparison**
For a summary of all core findings see Summary of findings for the main comparison.

Primary outcome: pain

Repetitive transcranial magnetic stimulation (rTMS) for short-term relief of chronic pain

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 (n = 528), including cross-over and parallel designs, using the generic inverse variance method (André-Obadia 2006; André-Obadia 2008; André-Obadia 2011; Borckardt 2009; Carretero 2009; Defrin 2007; Hirayama 2006; Hosomi 2013; Kang 2009; Lefaucheur 2001a; Lefaucheur 2001b; Lefaucheur 2004; Lefaucheur 2006; Lefaucheur 2008; Mhalla 2011; Passard 2007; Pleger 2004; Pleger 2004; Rollnik 2002; Saitoh 2007; Short 2011). We excluded the studies by Ahmed 2011, Khedr 2005, Irlbacher 2006 and Lee 2012, as we classified them as having a high risk of bias on at least one criterion. We were unable to include data from five studies (Fregni 2005; Fregni 2011; Onesti 2013; Picarelli 2010; Tzabazis 2013 combined n = 86), as the necessary data were not available in the study report or upon request by the submission date of this update. 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 entered into the meta-analysis. For parallel studies we calculated the standard error of the mean (SEM) from the 95% confidence intervals 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.
We observed substantial heterogeneity (I^2 = 67%, P < 0.01) and investigated this using pre-planned subgroup analysis. Categorising studies by high (≥ 5 Hz) or low (< 5 Hz) frequency rTMS demonstrated a significant difference between subgroups (P < 0.01) and reduced heterogeneity in the low-frequency group (n = 81, I^2 = 0%). In this group there was no evidence of an effect of low-frequency rTMS for short-term relief of chronic pain (SMD 0.15, 95% confidence interval (CI) -0.01 to 0.3, P = 0.07). While high-

frequency stimulation demonstrated a significant effect (SMD -0.27, 95% CI -0.35 to -0.20, P < 0.01), we observed substantial heterogeneity in this (n = 447, I^2 = 64%). 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 = 225, I^2 = 75%) or single-dose studies (n = 303, I^2 = 61%) (Analysis 1.2).

There were insufficient data to support the planned 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 excluding Carretero 2009; Mhalla 2011; Passard 2007; Pleger 2004; Rollnik 2002; Short 2011), there was little impact on heterogeneity (I^2 = 71% P < 0.01). In the subgroup of non-neuropathic pain studies overall heterogeneity remained significant and high (I^2 = 56%, P = 0.04) (Analysis 1.4).

rTMS motor cortex

Restricting the analysis to single-dose studies of high-frequency stimulation of the motor cortex (n = 233) reduced heterogeneity (I^2 = 31%, P = 0.13) (Analysis 1.5). In this group the pooled SMD was -0.39 (95% confidence interval (CI) -0.51 to -0.27, P < 0.01). We back-transformed the SMD to a mean difference using the mean standard deviation of the post-treatment sham group score of the studies included in this analysis (1.87). We then used this to estimate the real percentage change on a 0 to 100 mm visual analogue scale (VAS) of active stimulation compared with the mean post-stimulation score from the sham groups of the included studies (6.2). This equated to a reduction of 7.3 mm (95% CI 5 mm to 9.5 mm), or a percentage change of 12% (95% CI 8% to 15%) 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). 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 statistically significant difference between sham and active stimulation although the SMD reduced to -0.31 (95% CI -0.49 to -0.13). This equates to a percentage change of 9% (95% CI 4% to 15%) in comparison with sham stimulation. For multiple-dose studies of high-frequency motor cortex stimulation heterogeneity was high (n = 157, I^2 = 71%, P < 0.01), but the pooled effect was not significant (SMD -0.07, 95% CI -0.41 to 0.26, P = 0.68).

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; Rollnik 2002), there was little effect on the pooled estimate (SMD -0.43, 95% CI -0.57 to -0.30) or heterogeneity (I^2 = 31%, not significant). When we applied the same process to multiple-dose studies of high-frequency motor cortex stimulation (excluding data from Passard 2007) heterogeneity remained high (I^2 = 62%, P = 0.03) with no significant pooled effect.

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). The same process was applied 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 of this subgroup.

To assess the impact of excluding the studies of Ahmed 2011, Irlbacher 2006, Khedr 2005 and Lee 2012, 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 69% to 74%. Inclusion of Ahmed 2011, Khedr 2005 and Lee 2012 to the multiple-dose studies of high-frequency motor cortex stimulation subgroup increased heterogeneity (I^2 = 88%, P < 0.01), though the subgroup demonstrated an effect that approached statistical significance (SMD -0.50, 95% CI -0.99 to -0.01, P = 0.05) (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 -0.36, 95% CI -0.48 to -0.24) with no impact on heterogeneity.

Small study effects/publication bias

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 dorsolateral pre-frontal cortex (DLPFC) included four studies (n = 68) (Avery 2013; Borckardt 2009; Carretero 2009; Short 2011) (Analysis 1.12). We excluded the study by Lee 2012 due to its high risk of bias. The pooled effect was non-significant (P = 0.36) with substantial heterogeneity (I^2 = 82%, P < 0.01). Restricting the analysis to high-frequency studies (Avery 2013; Borckardt 2009; Short 2011), the effect remained non-significant (P = 0.33) with high heterogeneity (I^2 = 85%, P < 0.01). The only remaining low-frequency study (Carretero 2009, n = 26) was not suggestive of a significant effect (SMD 0.16, 95% CI -0.29 to 0.61). It is worthy of note that the only study in the analysis which individually demonstrated a significant effect was very small (n = 4) and its removal

from the analysis makes heterogeneity non-significant (Borckardt 2009).

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 = 0.27) with high heterogeneity (I^2 = 76%, P < 0.01). Restricting this to low-frequency studies (Carretero 2009; Lee 2012) brought heterogeneity down to a non-significant level (I^2 = 16%, P = 0.28), though the effect remained non-significant. Restricting the analysis to high-frequency studies (Borckardt 2009; Lee 2012; Short 2011), the effect remained non-significant (P = 0.25) though heterogeneity remained high (I^2 = 74%, P < 0.01). Restricting the analysis to low-frequency studies (Carretero 2009; Lee 2012), the effect remained non-significant (P = 0.92) with no heterogeneity (I^2 = 16%, P = 0.28).

rTMS for medium-term relief of chronic pain (< 6 weeks post-treatment)

Seven studies provided data on medium-term pain outcomes (Avery 2013; Carretero 2009; Hosomi 2013; Lefaucheur 2001a; Kang 2009; Passard 2007; Short 2011). We excluded the studies by Ahmed 2011, Khedr 2005 and Lee 2012 as we classified them as having a high risk of bias. The analysis included 184 participants (Analysis 1.14). Overall heterogeneity was high (I^2 = 57%, P = 0.02) and no significant effect was observed (SMD -0.18, 95% CI -0.43 to 0.06, P = 0.15). Restricting the analysis to studies of prefrontal cortex stimulation (Avery 2013; Carretero 2009; Short 2011) demonstrated no significant effect (SMD -0.03, 95% CI -0.52 to 0.35). Studies of motor cortex stimulation also demonstrated no significant effect (SMD -0.22, 95% CI -0.52 to 0.07, P = 0.14) although heterogeneity was high (I^2 = 72%, P < 0.01). We performed sensitivity analysis to assess the impact of excluding the studies by Ahmed 2011, Khedr 2005 and Lee 2012 on the basis of risk of bias (Analysis 1.15). Including these studies increased heterogeneity (I^2 = 76%, P < 0.01) though the effect reached significance overall (SMD -0.43, 95% CI -0.76 to -0.10) and specifically for high-frequency studies (SMD -0.48, 95% CI -0.83 to -0.13) (I^2 = 79%, P < 0.01).

rTMS for long-term relief of chronic pain (≥ 6 weeks post-treatment)

Three studies provided data for long-term pain relief (Avery 2013; Kang 2009; Passard 2007) (Analysis 1.16). The analysis included 59 participants. There was no heterogeneity (I^2 = 0%, P = 0.95). The analysis demonstrated no significant effect (SMD -0.12, 95% CI -0.46 to 0.21, P = 0.47). Sensitivity analysis to assess the impact of excluding the study of Ahmed 2011 due to its high risk of bias continued to demonstrate no significant effect, though heterogeneity was introduced (Analysis 1.17, I^2 = 68%, P = 0.03).

Cranial electrotherapy stimulation (CES) for short-term pain relief

Six studies provided data for this analysis (Gabis 2003; Gabis 2009; Rintala 2010; 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 differ 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 demonstrates superiority of active stimulation over sham and the results of the meta-analysis do not demonstrate statistical significance (SMD -0.24, 95% CI -0.48 to 0.01, P = 0.06). 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).

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

Transcranial direct current stimulation (tDCS) for short-term pain relief

Adequate data were available from 11 studies (Antal 2010; Boggio 2009; Fenton 2009; Fregni 2006a; Fregni 2006b; Jensen 2013; Mori 2010; Riberto 2011; Soler 2010; Villamar 2013; Wrigley 2014) for this analysis (n = 193). We were unable to include data from Mendonca 2011 and Valle 2009 (combined n = 71) as the necessary data were not reported in the study report or available upon request to the authors. We only included first-stage data from the study of Antal 2010 (n = 12) due to the unsustainable level of attrition following this stage. 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). Combining the treatment conditions was considered 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. The overall meta-analysis did not demonstrate a significant effect of active stimulation (SMD -0.18, 95% CI -0.46 to 0.09, P = 0.19) (Analysis 3.1), but heterogeneity was significant (I^2 = 49%, P = 0.02). Subgrouping studies by

multiple or single dose did not demonstrate a significant subgroup difference (test for subgroup differences P = 0.89) and decreased heterogeneity in the single-dose subgroup (I^2 = 0%, P = 0.53) but increased heterogeneity in the multiple-dose subgroup (I^2 = 62%, P < 0.01). Analysis restricted to comparisons of active motor cortex stimulation (single and multiple-dose studies (n = 183, Analysis 3.2) reduced heterogeneity substantially (I^2 = 33%, P = 0.13) but did not demonstrate a statistically significant effect (SMD -0.23, 95% CI -0.48 to 0.01, P = 0.06). This lack of effect was consistent for the subgroups of single-dose studies (SMD -0.18, 95% CI -0.41 to 0.05, P = 0.13) and multiple-dose studies (SMD -0.35, 95% CI -0.79 to 0.09, P = 0.12).

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 3.3; Analysis 3.4; Analysis 3.5; Analysis 3.6). When the correlation was decreased the analysis including both single and multiple-dose studies of motor cortex tDCS stimulation only approached, but did not reach, statistical significance (SMD -0.24, 95% CI -0.48 to 0.00, P = 0.05).

Small study effects/publication bias

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

tDCS for medium-term pain relief (1 to < 6 weeks post-treatment)

Five studies provided adequate data for this analysis (Antal 2010; Fenton 2009; Mori 2010; Soler 2010, Wrigley 2014, pooled n = 87) (Analysis 3.7). There was no significant heterogeneity (I^2 = 31%, P = 0.21) and the pooled effect was not statistically significant (SMD -0.20, 95% CI -0.63 to 0.24, P = 0.37).

Reduced impedance non-invasive cortical electrostimulation (RINCE) for short-term pain relief

The one study that investigated RINCE stimulation demonstrated a positive effect on pain (mean difference (0 to 10 pain scale) -1.41, 95% CI -2.48 to -0.34, P < 0.01) (Analysis 4.1; Hargrove 2012).

Secondary outcomes: disability and quality of life

rTMS for disability/pain interference: short-term follow-up

Five studies provided data on disability/pain interference at short-term follow-up (Avery 2013; Kang 2009; Mhalla 2011; Passard 2007; Short 2011). Pooling of these studies (Analysis 1.18; n = 119) demonstrated no significant effect on pain interference (SMD -0.29, 95% CI -0.87 to 0.29, P = 0.33) with substantial heterogeneity (I^2 = 71%, P < 0.01). All of these studies delivered multiple doses of high-frequency stimulation. 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.

rTMS for disability/pain interference: medium-term follow-up (1 to < 6 weeks post-treatment)

Four studies provided data on disability/pain interference at medium-term follow-up (Avery 2013; Kang 2009; Mhalla 2011; Passard 2007). Pooling of these studies (Analysis 1.19; n = 99) demonstrated no significant effect (SMD -0.37, 95% CI -1.07 to 0.33, P = 0.3) with significant heterogeneity (I^2 = 78%, P < 0.01). 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 < 0.01).

rTMS for disability/pain interference: long-term follow-up (≥ 6 weeks post-treatment)

Three studies provided data on disability/pain interference at long-term follow-up (Avery 2013; Kang 2009; Passard 2007). Pooling of these studies demonstrated no significant effect (SMD -0.23, 95% CI -0.62 to 0.16, P = 0.24) without significant heterogeneity (I^2 = 15%, P = 0.31) (Analysis 1.20).

rTMS for quality of life: short-term follow-up

Three studies provided data on quality of life at short-term follow-up (Mhalla 2011; Passard 2007; Short 2011). 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 so we were able to use the mean difference as the measure of effect. Pooling data from these studies (Analysis 1.21; n = 80) demonstrated a significant effect (mean difference (MD) -10.38, 95% CI -14.89 to -5.87, P < 0.01) with no heterogeneity (I^2 = 0%, P = 0.99). Expressed as a percentage of the mean post-stimulation score in the sham groups from the included studies (58.3) this equates to a 18% (95% CI 10% to 26%) reduction in fibromyalgia impact.

rTMS for quality of life: medium-term follow-up (1 to < 6 weeks post-treatment)

The same three studies provided data on quality of life at medium-term follow-up (Mhalla 2011; Passard 2007; Short 2011). All studies used the Fibromyalgia Impact Questionnaire so we were able to use the mean difference as the measure of effect. Pooling data

from these studies (Analysis 1.22; n = 80) demonstrated a significant effect (MD -11.49, 95% CI -17.04 to -5.95, P < 0.01) with no heterogeneity (I^2 = 0%, P = 0.63). Expressed as a percentage of the mean post-stimulation score in the sham groups from the included studies (57.8) this equates to a 20% (95% CI 10% to 29%) reduction in fibromyalgia impact.

rTMS for quality of life: long-term follow-up (≥ 6 weeks post-treatment)

Data were only available from one study (Passard 2007, n = 30) for quality of life at long-term follow-up. This study demonstrated no significant effect (MD -0.61, 95% CI -1.34 to 0.12) (Analysis 1.23).

CES for quality of life: short-term follow-up

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 Fibromyalgia Impact Questionnaire. However, one study demonstrated a baseline imbalance of the SF-12 that exceeded in size any pre-post stimulation 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 (SMD -1.25, 95% CI -1.98 to -0.53) (Analysis 2.3).

tDCS for quality of life

Two studies provided adequate data for this analysis (Mori 2010; Riberto 2011, pooled n = 32). Of these, Mori 2010 used the Multiple Sclerosis Quality of Life 54 scale (MS-QoL-54) and Riberto 2011 used the SF-36 (total score). The pooled effect was significant (SMD 0.88, 95% CI 0.24 to 1.53, P < 0.01) with no heterogeneity (I^2 = 0%, P = 0.41) (Analysis 3.9). At medium-term follow-up only Mori 2010 (n = 19) provided data and the effect of tDCS on quality of life was not significant.

RINCE for quality of life

The one study of RINCE therapy demonstrated no significant effect on quality of life (Fibromyalgia Impact Questionnaire) (Analysis 4.2) .

Adverse events

rTMS

Minor

Of the rTMS studies that reported adverse events, nine studies reported none (André-Obadia 2006; André-Obadia 2008; Fregni 2005; Hirayama 2006; Lefaucheur 2001a; Lefaucheur 2001b; Lefaucheur 2004; Onesti 2013; Saitoh 2007). 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. 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). Rollnik 2002 reported that one participant experienced headache, but it is unclear in the report whether this was following active or sham stimulation. 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. Mhalla 2011 reported that nine patients (five following active stimulation and four following sham stimulation) reported transient headache, and one participant reported transient dizziness after active stimulation. 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. Short 2011 reported that there were few side effects and Hosomi 2013 reported no difference between real and sham rTMS for minor adverse events. 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. 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 verus 11% following sham) were more common with active stimulation.

Major

Both Lee 2012 and Picarelli 2010 reported one incidence of seizure following high-frequency active stimulation.

CES

Four studies of CES reported the incidence of adverse events (Capel 2003; Gabis 2003; Rintala 2010; Tan 2011). In these studies no adverse events were reported. Rintala 2010 reported no major adverse events. In the active stimulation group they reported

incidences of pulsing, tingling, tickling in ears (three participants), tender ears (one participant) and pins and needles feeling near 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

Most studies of tDCS reported the incidence of adverse events. Of these, four studies reported none (Fregni 2006a; Mendonca 2011; Mori 2010; Portilla 2013). Boggio 2009 reported that one participant experienced headache with active stimulation. 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. Soler 2010 recorded three reports of headache, all following active stimulation. 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 where equally distributed between active and sham 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. Wrigley 2014 reported only "mild to moderate" side effects with no significant difference between active and sham over the 24-hour post-stimulation 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. Jensen 2013 and Riberto 2011 did not consider adverse events in their study reports.

RINCE

Hargrove 2012 reported a low incidence of side effects from RINCE stimulation 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).

GRADE judgements

GRADE judgements for all core comparisons of the primary outcome can be found in Table 4. For all comparisons the highest rating of the quality of evidence was 'low'.

DISCUSSION

Summary of main results

This update has included a substantial number of new studies. Despite this, for rTMS and CES our findings have not altered substantially from the previous version of this review. However, for tDCS the inclusion of these new data have altered the outcome of our analyses, which no longer suggest a statistically significant effect of tDCS over sham. We recommend that previous readers should re-read this update.

Repetitive transcranial magnetic stimulation (rTMS) for chronic pain

Meta-analysis of all rTMS studies in chronic pain demonstrated significant 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 significance. 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 pre-frontal 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 suggest a significant effect of rTMS in the medium term. The limited evidence at long-term follow-up consistently suggests no effect of rTMS.

Cranial electrotherapy stimulation (CES) for chronic pain

The evidence from trials where it is possible to extract data is not suggestive of a significant 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.

Transcranial direct current stimulation (tDCS) for chronic pain

Meta-analysis of all tDCS studies in chronic pain demonstrated significant heterogeneity. Predetermined subgroup analyses did not demonstrate a statistically significant effect of tDCS on chronic pain despite many of the studies included in this review being at unclear risk of bias for participant and assessor blinding. The evidence available at medium-term follow-up does not suggest a significant effect of tDCS.

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

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

Adverse effects

rTMS, CES, tDCS 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.

Secondary outcome measures

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

Limited evidence suggests that rTMS and tDCS have positive effects on quality of life. This finding in rTMS is difficult to interpret as it arises from multiple-dose studies which together do not demonstrate an effect on pain intensity levels. Any hypothesised effects of non-invasive brain stimulation techniques on quality of life would presumably be through the reduction of pain. Given this inconsistency between outcomes for rTMS and the limited amount of data available to these analyses, we would recommend that this finding should be interpreted with caution.

Overall completeness and applicability of evidence

For rTMS we were unable to include data from five full published studies (Fregni 2005; Fregni 2011, Onesti 2013; Picarelli 2010; Tzabazis 2013, combined n = 86). In addition, we identified six 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, assuming that some reports refer to the same study, is 243.

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 two studies of tDCS (Mendonca 2011; Valle 2009), and these data were not made available upon request to the study authors. These data would have significantly contributed to the power of the meta-analysis by the introduction of a further 71 participants and may have altered our conclusions. In addition, we identified three studies of tDCS (Acler 2012; Albu 2011; Knotkova 2011, combined n = 87) published in abstract format, one of which is currently being re-analysed by the study authors and as such the data were not available (Knotkova 2011), and for two of which we were unsuccessful in our efforts to contact the authors (Acler 2012; Albu 2011).

For both rTMS and tDCS there are a number of ongoing studies identified through the trials registers searches. Of these, two registered trials that were identified in the original version of this review have not yet been published and our attempts to contact the authors were unsuccessful (NCT00947622; NCT00815932). 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-quality. In large part this is due to issues of blinding and of precision and to a degree it reflects the early stage of research development that these technique are at. The majority of studies of rTMS were at unclear risk of bias. The predominant reason for this was the use of sub-optimal 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. 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. However the combined evidence from studies of rTMS that delivered multiple doses (excluding studies judged as being at high risk of bias), while demonstrating substantial heterogeneity, does not indicate a significant effect on pain.

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 last version of this review which 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 (O'Connell 2012). Meta-epidemiological evidence demonstrates that incomplete blinding in controlled trials that measure subjective outcomes may exaggerate the observed effect size by around 25% (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. The non-significant trend towards a positive effect of CES and tDCS over sham should be considered in this light.

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 stimulation 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 publication or small study bias, wherein there is a propensity for negative studies to not reach full publication. There is evidence that this might lead to an overly positive picture for some interventions (Dechartres 2013; Moore 2012; 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 a recent Cochrane review of amitriptyline neuropathic pain and fibromyalgia (Moore 2012), smaller studies were associated with substantially lower numbers needed to treat (NNTs) 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. We did not downgrade any of the GRADE judgements on the basis of publication bias as there was no direct evidence. However, it is accepted that existing approaches to detecting publication bias are unsatisfactory. To an extent our GRADE judgements reflect this risk through the assessment of imprecision and the limitations of included studies. It should 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.

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 significantly reduced this heterogeneity.

The majority of 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 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 af-

fected 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 visual analogue 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 treatments has been found to display a bimodal distribution (Moore 2013). More plainly, some participants demonstrate a substantial response to pain therapies while many demonstrate little or no response with few individual participants demonstrating a response 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 analysis based on predetermined cut-offs for a clinically important response (≥ 30% reduction in pain for a moderate benefit, ≥ 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 statistically significant 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 a small number of participants.

Agreements and disagreements with other studies or reviews

The European Federation of Neurological Societies (EFNS) published guidelines on the use of neurostimulation therapy for chronic neuropathic pain in 2007 (Cruccu 2007), following a review of the existing literature. Using a narrative synthesis of the evidence they similarly concluded that there was moderate evidence (two randomised controlled trials) that high-frequency rTMS (≥ 5 Hz) of the motor cortex induces significant pain relief in central post-stroke pain and several other neuropathic conditions, but that the effect is modest and short-lived. They did not recommend its use as a sole clinical treatment but suggested that it might be considered in the treatment of short-lasting pain.

Leung 2009 performed a meta-analysis of individual patient 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 participants' pain (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 authors also performed an analysis of the influence of the neuroanatomical origins of pain 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 pain, 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 (≥ 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 significantly higher following active stimulation compared with sham (risk ratio 2.64, 95% confidence interval (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 published since that review (André-Obadia 2008; Defrin 2007; Kang 2009; Lefaucheur 2006; Lefaucheur 2008; Passard 2007; Saitoh 2007). 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, significant 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 recent 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 significant 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 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 drop-out. The results of their meta-analysis are broadly consistent with those presented in the last iteration of this review and similarly 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. However, the inclusion of new studies in this update has rendered these analyses non-significant.

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 do not suggest a statistically or 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.

AUTHORS' CONCLUSIONS

Implications for practice

Low or very low-quality evidence suggests that low-frequency repetitive transcranial magnetic stimulation (rTMS), or rTMS applied to the prefrontal cortex, are not effective for the treatment of chronic pain. Subgroup analysis suggests that single doses of high-frequency rTMS of the motor cortex 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 is heterogenous but does not demonstrate a significant effect (very low-quality evidence). As such it is not currently clear whether rTMS represents a useful clinical tool. Very low-quality evidence suggests that transcranial direct current stimulation (tDCS) is not effective for treating chronic pain and low-quality evidence suggests that tDCS applied to the motor cortex is not effective. Low-quality evidence suggests that cranial electrotherapy stimulation (CES) is not effective. Due to various biases and limitations within the evidence base it is likely that future studies may have a substantial impact upon the estimates of effects presented. Due to this uncertainty, any clinical application of non-invasive brain stimulation techniques would be most appropriate within a clinical research setting rather than in routine clinical care.

Implications for research

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. All studies of non-invasive brain stimulation techniques should measure, record and clearly report adverse events from both active and sham stimulation. 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).

In rTMS the evidence base is dominated by studies of intractable neuropathic pain and there is little evidence from which to draw conclusions regarding other types of chronic pain. Most of the included rTMS studies are affected by the use of sub-optimal sham conditions that may adversely impact upon blinding. 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 reliable and valid sham

controls. We have recently recommended that while there remains a case for exploring alternative stimulation targets and parameters, there is a more urgent need to examine robustly the more promising findings within the existing data through large, rigorous, adequately blinded trials that deliver a reasonable dose and investigate effects over a meaningful timescale (O'Connell 2011). A data-led approach suggests that high-frequency stimulation of the motor cortex is a logical focus for this effort. Until a body of this type of research is generated there will be continued uncertainty as to whether rTMS has genuine clinical utility for chronic pain.

Future studies of tDCS should give consideration to the integrity of participant blinding, particularly when utilising stimulation intensities that exceed 1 mA and should possess adequate sample sizes to reduce uncertainty.

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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-randomised controlled trial
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), sham group 53.3 (13.3) 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, no. of trains 10; duration of trains 10 sec; ITI 50 sec; total no. 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: post-stimulation session 1 and 5 and at 1 month and 2 months post-treatment Secondary: none relevant
Notes	Adverse events: not reported Conflict of interest: 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
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: levels of drop-out not reported
Selective reporting (reporting bias)	Low risk	Comment: primary outcomes presented in full

Ahmed 2011 (*Continued*)

Other bias	Low risk	Comment: no other bias detected
Adequate blinding of assessors?	Low risk	Quote: "The second author evaluated these measures blindly, without knowing the type of TMS"
Adequate blinding of participants?	Unclear risk	Comment: sham credibility assessment - sub-optimal. Coil angled away from scalp. Does not control for sensory characteristics of active stimulation and is visually distinguishable
Study Size	High risk	Comment: < 50 participants per treatment arm
Study duration	Low risk	> 8 weeks follow-up

André-Obadia 2006

Methods	Cross-over randomised controlled trial; 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 to 66; 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; no. of trains 20; duration of trains 4 sec; ITI 84 sec; total no. pulses 1600 Condition 2: frequency 1 Hz; coil orientation lateromedial; no. of trains 1; duration of trains 26 min, total no. pulses 1600 Condition 3: sham - same as for condition 2 with coil angled away perpendicular to scalp Stimulation location: motor cortex contralateral to painful side Number of treatments: 1 for each condition
Outcomes	Primary: VAS 0 to 10 cm, anchors "no pain" to "unbearable pain" When taken: immediately post-stimulation then daily for 1 week Secondary: none
Notes	Data requested from authors and received
Risk of bias	

André-Obadia 2006 (*Continued*)

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."
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
Other bias	Low risk	Comment: no significant other bias detected
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."
Adequate blinding of participants?	Unclear risk	Comment: sham credibility assessment "sub optimal". Coil angled away from scalp and not in contact in sham condition. Does not control for sensory characteristics of active stimulation and is visually distinguishable
Free from carry-over effects?	Low risk	Comment: a 2-week wash-out 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

André-Obadia 2008

Methods	Cross-over randomised controlled trial; 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 to 72, 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; no. of trains 20; duration of trains 4 sec; ITI 84 sec; total no. pulses 1600 Condition 2: frequency 20 Hz, coil orientation lateromedial; no. of trains 20; duration of trains 4 sec; ITI 84 sec; total no. pulses 1600 Condition 3: sham - same as for active conditions with coil angled away perpendicular to scalp Stimulation location: motor cortex contralateral to painful side Number of treatments: 1 for each condition
Outcomes	Primary: 0 to 10 NRS (anchors "no pain" to "unbearable pain") When taken: daily for 2 weeks post-stimulation Secondary: none
Notes	Data requested from authors

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "the order of sessions was randomised (by computerized random-number generation)"
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 authors on request
Other bias	Low risk	Comment: no significant other bias detected

André-Obadia 2008 (*Continued*)

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."
Adequate blinding of participants?	Unclear risk	Comments: sham credibility assessment - sub-optimal. Coil angled away from scalp and not in contact in sham condition. Does not control for sensory characteristics of active stimulation and is visually distinguishable
Free from carry-over effects?	Low risk	Comment: a 2-week wash-out 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

André-Obadia 2011

Methods	Cross-over randomised controlled trial
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 to 72 (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, no. of trains 20; duration of trains 4 sec; ITI 84 sec; total no. 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

André-Obadia 2011 (*Continued*)

Notes	Adverse events: not reported Funding source: charity-funded Conflict of interest: 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"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: no mention of drop-out/withdrawal
Selective reporting (reporting bias)	Low risk	Comment: primary outcomes reported for all groups and further data made available upon request to authors
Other bias	Low risk	Comment: no other biases detected
Adequate blinding of assessors?	Unclear risk	Comment: no mention of blinded assessors
Adequate blinding of participants?	Unclear risk	Comment: the 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
Free from carry-over effects?	Low risk	Comment: 2-week wash-out period observed
Study Size	High risk	Comment: < 50 participants per treatment arm
Study duration	Unclear risk	Comment: ≥ 2 weeks but < 8 weeks follow-up

Antal 2010

Methods	Cross-over randomised controlled trial
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 to 70, sham only group 50 to 70, cross-over group 41 to 70 Duration of symptoms: chronic 1.5 to 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 minutes Stimulation location: anode - left M1 hand area, cathode right supraorbital Number of treatments: x 5, daily Control type: sham tDCS
Outcomes	Primary: pain VAS 0 to 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 Conflicts of interest: 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
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: the high level of drop-out 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 are used - first-phase data 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

Antal 2010 (*Continued*)

Other bias	Low risk	Comment: no other sources of bias detected
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"
Adequate blinding of participants?	Low risk	Comment: see above
Free from carry-over effects?	Low risk	Comment: patients 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

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), sham 51.09 (10.02) Duration of symptoms (months mean (SD)): 15.64 (6.93) Gender distribution: all female
Interventions	Stimulation type: rTMS Stimulation parameters: frequency 10 Hz; coil orientation not specified; 120% RMT; no. of trains 75; duration of trains 4 sec; ITI 26 sec; total no. pulses 3000 Stimulation location: left 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 to 10 anchors not reported When taken: end of treatment period, 1 month following and 3 months following Secondary: pain interference BPI Adverse events: multiple minor; no clear difference in incidence between active and sham stimulation

Notes	Government-funded study, manufacturer loaned stimulator	
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)	Low 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"
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 drop-outs from the TMS group, 1 was excluded (reasons given)
Selective reporting (reporting bias)	Low risk	Comment: all outcomes presented in full in study report
Other bias	Low risk	No other bias detected
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

Avery 2013 (*Continued*)

		raters were separate from this process
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 subject 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
Study Size	High risk	Comment: < 50 participants per treatment arm
Study duration	Low risk	Comment: > 8 weeks follow-up

Boggio 2009

Methods	Cross-over randomised controlled trial; 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 to 82; mean 63.3 (SD 5.6) Duration of symptoms: 1 to 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 minutes Condition 1: active tDCS/active TENS Condition 2: active tDCS/sham TENS Condition 3: sham tDCS/sham TENS Stimulation location: motor cortex contralateral to painful side Number of treatments: 1 for each condition Control type: sham tDCS (switched off after 30 seconds stimulation)
Outcomes	Primary: VAS 0 to 10 anchors "no pain" to "worst possible pain" When taken: pre and post each stimulation Secondary: none
Notes	

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)."
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 are 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
Other bias	Low risk	Comment: no significant other bias detected
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)
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)
Free from carry-over effects?	Low risk	Comment: a 48-hour wash-out 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

Boggio 2009 (*Continued*)

Study duration	High risk	Comment: < 2 weeks follow-up

Borckardt 2009

Methods	Cross-over randomised controlled trial; 2 conditions
Participants	Country of study: USA Setting: laboratory Condition: peripheral neuropathic pain Prior management details: not specified n = 4 Age: 33 to 58; mean 46 (SD 11) Duration of symptoms: 5 to 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; no. of trains 40; duration of trains 10 sec; ITI 20 sec; total no. pulses 4000 Stimulation location: L pre-frontal cortex Number of treatments: 3 over a 5-day period Control type: neuronetics sham coil (looks and sounds identical)
Outcomes	Primary: average daily pain 0 to 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 post-stimulation Secondary: none
Notes	Adverse events: not reported

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
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: no drop-out
Selective reporting (reporting bias)	Low risk	Comment: all results reported clearly and in full
Other bias	Low risk	Comment: no significant other bias detected

Borckardt 2009 (*Continued*)

Adequate blinding of assessors?	Unclear risk	Comment: not specified
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 - sub-optimal. Sham coil controls for auditory cues and is visually indistinguishable from active stimulation but does not control for sensory characteristics of active stimulation
Free from carry-over effects?	Low risk	Comment: a 3-week wash-out period was observed. Presented average pain values are 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

Capel 2003

Methods	Partial cross-over randomised controlled trial. NB: only first-phase results were considered therefore the trial was considered as having a parallel design
Participants	Country of study: UK Setting: residential educational centre Condition: post-SCI pain (unclear whether this is 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 msec; intensity 1 2μA; 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

Capel 2003 (*Continued*)

Outcomes	Primary: 0 to 10 VAS "level of pain", anchors not specified When taken: daily during the treatment period Secondary: none
Notes	

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
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: 3 subjects withdrew (not voluntarily) and while the data are not clearly accounted for in the data analysis this constitutes 10% of the overall cohort and is 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 are not provided for any time point
Other bias	Low risk	Comment: no significant other bias detected
Adequate blinding of assessors?	Low risk	Quote: "neither the administrators nor the recipients of the treatment could distinguish between the devices."

Capel 2003 (*Continued*)

Adequate blinding of participants?	Low risk	Quote: "neither the administrators nor the recipients of the treatment could distinguish between the devices."
Study Size	High risk	Comment: < 50 participants per treatment arm
Study duration	High risk	Comment: < 2 weeks follow-up

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), sham group 54.9 (SD 4.9) 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; no. of trains 20; duration of trains 60 sec; ITI 45 sec; no. of pulses 1200 Stimulation location: R dorsolateral prefrontal cortex Number of treatments: up to 20 on consecutive working days Control type: coil angled 45º from the scalp
Outcomes	Primary: Likert pain scale 0 to 10, anchors "no pain" to "extreme pain" When taken: 2 weeks, 4 weeks and 8 weeks from commencement of study Secondary: none
Notes	

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
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

Carretero 2009 (*Continued*)

Selective reporting (reporting bias)	Low risk	Comment: outcomes presented clearly and in full
Other bias	Low risk	Comment: no significant other bias detected
Adequate blinding of assessors?	Low risk	Quote: patients and raters (but not the treating physician) were blind to the procedure
Adequate blinding of participants?	Unclear risk	Comments: sham credibility assessment - sub-optimal. Coil angled 45º away from scalp. Does not control for sensory characteristics of active stimulation and is visually distinguishable
Study Size	High risk	Comment: < 50 participants per treatment arm
Study duration	Unclear risk	Comment: ≥ 2 weeks but < 8 weeks follow-up

Cork 2004

Methods	Cross-over randomised controlled trial (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 to 75; mean 53 Duration of symptoms: 1 to 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
Outcomes	Primary: 0 to 5 numerical pain intensity scale, 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	Adverse events: not reported
Risk of bias	

Cork 2004 (*Continued*)

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
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: drop-out rate not reported
Selective reporting (reporting bias)	High risk	Comment: pain score numerical values are not provided clearly with measures of variance for any time point
Other bias	Low risk	Comment: no significant other bias detected
Adequate blinding of assessors?	Low risk	Quote: "All staff, the physicians, and the patient were blind to the treatment conditions."
Adequate blinding of participants?	Low risk	Quote: "All staff, the physicians, and the patient were blind to the treatment conditions."
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

Defrin 2007

Methods	Parallel randomised controlled trial
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 to 60; mean 54 (SD 6) Duration of symptoms: > 12 months Gender distribution: 7 M, 4 F

Defrin 2007 (*Continued*)

Interventions	Stimulation type: rTMS, figure of 8 coil Stimulation parameters: frequency 5 Hz; coil orientation not specified; 115% RMT; no. of trains 500; duration of trains 10 sec; ITI 30 sec; total no. pulses 500 reported, likely to have been 25,000 judging by these parameters Stimulation location: motor cortex - 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 to 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	Adverse events: not reported

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
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: only one participant withdrew for "logistic reasons". Unlikely to have strongly influenced the findings
Selective reporting (reporting bias)	Low risk	Comment: while group means/SD are not presented in the study report, the study authors have provided the requested data
Other bias	Unclear risk	Comment: baseline differences observed in pain intensity levels (higher in active group)
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."
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 - sub-optimal. Sham coil controls for auditory cues and is visually indistinguishable from active stimulation,

Defrin 2007 (*Continued*)

		but does 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
Study Size	High risk	Comment: < 50 participants per treatment arm
Study duration	Unclear risk	Comment: ≥ 2 weeks but < 8 weeks follow-up

Fenton 2009

Methods	Cross-over randomised controlled trial
Participants	Country of study: USA Setting: unclear Condition: chronic pelvic pain Prior management details: refractory to treatment n = 7 Age: mean 38 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 minutes Stimulation location: M1 dominant hemisphere Number of treatments: 2 Control type: sham tDCS (switched off after 30 seconds 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	

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
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: no drop-out reported
Selective reporting (reporting bias)	Low risk	Comment: variance measures not presented for group means post-stimulation but data

Fenton 2009 (*Continued*)

		provided by author on request
Other bias	Low risk	Comment: no significant other bias detected
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."
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."
Free from carry-over effects?	Unclear risk	Comments: pre-stimulation data are not presented and no formal investigation for carry-over effects is discussed
Study Size	High risk	Comment: < 50 participants per treatment arm
Study duration	Unclear risk	Comment: < 2 weeks follow-up

Fregni 2005

Methods	Cross-over randomised controlled trial
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; coil orientation not specified; 90% RMT; no. of trains not specified; duration of trains not specified; ITI not specified; total no. pulses 1600 Stimulation location: left and right secondary somatosensory area (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

Fregni 2005 (*Continued*)

Notes		
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "The order of stimulation was randomised and counterbalanced across patients using a Latin square design."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: no drop-out reported
Selective reporting (reporting bias)	High risk	Comment: pain score numerical values are not provided clearly with measures of variance for any time point for the sham condition
Other bias	Low risk	Comment: no significant other bias detected
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."
Adequate blinding of participants?	Unclear risk	Comment: sham credibility assessment "unclear". Type of sham coil not specified
Free from carry-over effects?	Low risk	Quote: "Importantly, baseline pain scores were not significantly different across the six conditions of stimulation... speaking against carry-over effect."
Study Size	High risk	Comment: < 50 participants per treatment arm
Study duration	High risk	Comment: < 2 weeks follow-up

Fregni 2006a

Methods	Parallel randomised controlled trial
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)

Fregni 2006a (*Continued*)

	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 minutes Stimulation location: motor cortex (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 seconds stimulation)
Outcomes	Primary: pain VAS 0 to 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	

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
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 are 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
Other bias	Low risk	Comment: no significant other bias detected

Fregni 2006a (*Continued*)

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)
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)
Study Size	High risk	Comment: < 50 participants per treatment arm
Study duration	Unclear risk	Comment: ≥ 2 weeks but < 8 weeks follow-up

Fregni 2006b

Methods	Parallel randomised controlled trial; 3 conditions
Participants	Country of study: Brazil Setting: laboratory Condition: fibromyalgia Prior management details: unclear n = 32 Age: 53.4 (SD 8.9) 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: 0 M, 32 F
Interventions	Stimulation type: tDCS Stimulation parameters: intensity 2 mA, 35 cm^2 electrodes, duration 20 minutes Stimulation location: condition 1: dorsolateral prefrontal cortex; condition 2: motor cortex; condition 3: sham motor cortex. 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 seconds stimulation)
Outcomes	Primary: pain VAS 0 to 10 cm, anchors not specified When taken: at the end of the stimulation period and at 21-day follow-up Secondary: quality of life: Fibromyalgia Impact Questionnaire
Notes	

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
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 are 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
Other bias	Low risk	Comment: no significant other bias detected
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)
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)
Study Size	High risk	Comment: < 50 participants per treatment arm
Study duration	Unclear risk	Comment: ≥ 2 weeks but < 8 weeks follow-up

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), sham group 46.71 (13.03) Duration of symptoms: > 2 years Gender distribution: 14 F, 3 M
Interventions	Stimulation type: rTMS Stimulation parameters:frequency 1 Hz; coil orientation not specified, no. of trains 1; duration of trains not specified; intensity 70% maximum stimulator output, total no. 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	

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
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: drop-out/withdrawal not reported
Selective reporting (reporting bias)	High risk	Comment: reporting of pain scores is incomplete across all time points
Other bias	Unclear risk	Comment: baseline values not presented by group for key outcome variables
Adequate blinding of assessors?	Low risk	Quote: "The pain evaluation was carried out by a blinded assessor"

Fregni 2011 (*Continued*)

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
Study Size	High risk	Comment: < 50 participants per treatment arm
Study duration	Unclear risk	Comment: ≥ 2 weeks but < 8 weeks follow-up

Gabis 2003

Methods	Parallel randomised controlled trial
Participants	Country of study: USA Setting: pain clinic Condition: chronic back and neck pain Prior management details: unclear n = 20 Age: 20 to 77 Duration of symptoms: 0.5 to 40 years Gender distribution: 9 M, 11 F
Interventions	Stimulation type: CES Stimulation parameters: frequency 77 Hz; pulse width 3.3 msec; 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 Secondary: none
Notes	

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."

Gabis 2003 (*Continued*)

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."
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 are not provided clearly with measures of variance for most time points in the study report the study authors have provided the requested data
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)
Adequate blinding of assessors?	Low risk	Quote: "The active placebo device was indistinguishable to the patient and medical team."
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"
Study Size	High risk	Comment: < 50 participants per treatment arm
Study duration	High risk	Comment: < 2 weeks follow-up

Gabis 2009

Methods	Parallel randomised controlled trial
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, range 22 to 82 Duration of symptoms: 0.5 to 40 years Gender distribution: 35 M, 40 F

Gabis 2009 (*Continued*)

Interventions	Stimulation type: CES Stimulation parameters: frequency 77 Hz; pulse width 3.3 msec; 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	Adverse events: not reported

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."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: no drop-out is indicated, comparing the results with the number enrolled
Selective reporting (reporting bias)	Low risk	Comment: results for primary outcomes are reported clearly and in full
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)
Adequate blinding of assessors?	Low risk	Quote: "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"
Study Size	High risk	Comment: < 50 participants per treatment arm

Gabis 2009 (*Continued*)

Study duration	Low risk	Comment: > 8 weeks follow-up

Hargrove 2012

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 to 54.7, sham group 51 to 57 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 (reduced impedance non-invasive cortical electrostimulation) Stimulation parameters: current density 0.3 mA/cm^2, stimulation duration 11 minutes, frequency 10 kHz carrier signal delivered at 40Hz Stimulation location: parietal region (international 10/20 site PZ), ground leads fixed to earlobes Number of treatments: x 2 weekly for 11 weeks 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 declares 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
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: per protocol analysis used, drop-out 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
Other bias	Low risk	Comment: no other biases detected

Hargrove 2012 (*Continued*)

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."
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"
Study Size	High risk	Comment: < 50 participants per treatment arm
Study duration	High risk	Comment: < 2 weeks follow-up

Hirayama 2006

Methods	Cross-over randomised controlled trial; 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 to 72 years Duration of symptoms: 1.5 to 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; no. of trains 10; duration of trains 10 sec; ITI 50 sec; total no. pulses 500 Stimulation location: condition 1: motor cortex; 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 minutes post-stimulation Secondary: none	
Notes		
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
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 are not provided clearly with measures of variance for any time point but data provided upon request
Other bias	Low risk	Comment: no significant other bias detected
Adequate blinding of assessors?	Unclear risk	Comment: blinding of assessors not reported
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 - sub-optimal. Sensory and auditory aspects are controlled for but angulation of coil away from the scalp may be visually distinguishable
Free from carry-over effects?	Low risk	Comment: 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

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 which 64 analysed Age mean (SD): 60.7 (10.6) Duration of symptoms: 58.2 (10.6) Gender distribution: 40 M, 24 F
Interventions	Stimulation type: rTMS Stimulation parameters: frequency 5 Hz; coil orientation para-sagittal, no. of trains 10; duration of trains 10 sec; ITI 50 sec, intensity 90% RMT, total no. 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 to 100 VAS (anchors not reported), SF McGill Adverse events
Notes	

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."

Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: drop-out 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 are not reported for all time points all data were made available upon request to the study authors
Other bias	Low risk	Comment: no other bias detected
Adequate blinding of assessors?	Low risk	Quote: "Patients and assessors were blind to group assignment until the study was completed."
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, 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
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

Irlbacher 2006

Methods	Cross-over randomised controlled trial; 3 conditions
Participants	Country of study: Germany Setting: laboratory Condition: phantom limb pain (PLP) and central neuropathic pain (CNP) Prior management details: unclear n = 27 Age: (median) PLP 46.6, CNP 51.1 Duration of symptoms: mean PLP 15.2 (SD 14.8), CNP 3.9 (SD 4.1) 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; no. of trains not specified; duration of trains not specified; ITI not specified; total no. pulses 500 Condition 2: frequency 5 Hz; coil orientation not specified; 95% RMT; no. of trains not specified; duration of trains not specified; ITI not specified; total no. pulses 500 Condition 3: sham frequency 2 Hz; coil orientation not specified; no. of trains not specified; duration of trains not specified; ITI not specified; total no. pulses 500 Stimulation location: motor cortex, 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 to 100 mm VAS pain intensity, anchors "no pain" and "most intense pain imaginable" When taken: pre- and post-stimulation Secondary: none
Notes	

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
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: 13 of 27 participants did not complete all treatment conditions and this drop-out is not clearly accounted for in the analysis
Selective reporting (reporting bias)	Low risk	Comment: primary outcome data presented clearly and in full
Other bias	Low risk	Comment: no significant other bias detected

Irlbacher 2006 (*Continued*)

Adequate blinding of assessors?	Unclear risk	Comment: blinding of assessors is not reported
Adequate blinding of participants?	Unclear risk	Sham credibility assessment - sub-optimal. Sham coil controls for auditory cues and is visually indistinguishable from active stimulation but does not control for sensory characteristics of active stimulation
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

Jensen 2013

Methods	Cross-over RCT
Participants	Country of study: USA Setting: laboratory Condition: post-spinal cord injury pain (neuropathic and non-neuropathic) Prior management details: not reported n = 31 randomised Age: 22 to 77 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 minutes Stimulation location: M1 contralateral to painful side or on left where pain bilateral Number of treatments: 1 Control type: sham tDCS (switched off after 30 seconds stimulation)
Outcomes	Primary: 0 to 10 NRS; 0 = no pain, 10 = most intense pain sensation imaginable. An average of current, least, worst and average pain scores When taken: post-stimulation Secondary: none relevant
Notes	Adverse events not reported Government-funded

Risk of bias

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

Jensen 2013 (*Continued*)

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."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: of 31 randomised there are data from 28 following active tDCS and 27 following sham
Selective reporting (reporting bias)	Low risk	Comment: outcomes adequately reported
Other bias	Low risk	Comment: no other bias detected
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)
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)
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

Kang 2009

Methods	Cross-over randomised controlled trial
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 to 75, 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; no. of trains 20; duration of trains 5 sec; ITI 55 sec; total no. pulses 1000 Stimulation location: R motor cortex, hand area Number of treatments: 5, x 1 daily Control type: coil elevated and angled away from the scalp

Kang 2009 (*Continued*)

Outcomes	Primary: NRS average pain over last 24 hours, 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	Adverse events: not reported

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
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 are reported clearly and in full
Other bias	Low risk	Comment: no significant other bias detected
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)"
Adequate blinding of participants?	Unclear risk	Comments: sham credibility assessment - suboptimal. Coil angled away from scalp and not in contact in sham condition. Does not control for sensory characteristics of active stimulation and is visually distinguishable
Free from carry-over effects?	Low risk	Comment: a 12-week wash-out 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

Katsnelson 2004

Methods	Parallel randomised controlled trial; 3 conditions
Participants	Country of study: Russia Setting: unclear Condition: hip and knee osteoarthritis 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 to 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 to 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	Adverse events: not reported

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
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: drop-out level not specified
Selective reporting (reporting bias)	High risk	Comment: it is unclear in the report which time points are reported for primary outcomes
Other bias	High risk	Comment: the reporting of baseline group characteristics is insufficient

Katsnelson 2004 (*Continued*)

Adequate blinding of assessors?	Low risk	Quote: "The physicians, like all other participants in the study, were unaware of which treatment each subject received."
Adequate blinding of participants?	Low risk	Quote: "The physicians, like all other participants in the study, were unaware of which treatment each subject received."
Study Size	High risk	Comment: < 50 participants per treatment arm
Study duration	High risk	Comment: < 2 weeks follow-up

Khedr 2005

Methods	Parallel randomised controlled trial
Participants	Country of study: Egypt Setting: university hospital neurology department Condition: neuropathic pain, mixed central (post-stroke) and facial (trigeminal neuralgia) pain Prior management details: refractory to drug management n = 48 Age: post-stroke 52.3 (SD 10.3), trigeminal neuralgia 51.5 (SD 10.7) Duration of symptoms: post-stroke 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; no. of trains 10; duration of trains 10 sec; ITI 50 sec; total no. pulses 2000 Stimulation location: motor cortex 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	Adverse events: not reported

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
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."

Khedr 2005 (*Continued*)

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

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), high-frequency group 53 (4.2), sham group 51.3 (6.2) 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 female
Interventions	Stimulation type: rTMS Stimulation parameters: Low-frequency group: frequency 1 Hz; coil orientation not specified, no. of trains 2; duration of trains 800 sec; ITI 60 sec; total no. pulses 1600

Lee 2012 (*Continued*)

	High-frequency group: frequency 10 Hz; coil orientation not specified, no. of trains 25; duration of trains 8 sec; ITI 10 sec; total no. pulses 2000 Stimulation location: right DLPFC (low-frequency), left 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 to 100 mm pain VAS; 0 = none, 100 = an extreme amount of pain When taken: post-treatment and at 1 month follow-up Secondary: Fibromyalgia Impact Questionnaire
Notes	Comment: no information on adverse events given relating to those participants who did not complete all sessions

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
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: no intention-to-treat 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
Other bias	Low risk	Comment: no other biases detected
Adequate blinding of assessors?	Unclear risk	Comment: blinding of assessors not specified
Adequate blinding of participants?	Unclear risk	Comment: sham credibility assessment - sub-optimal. Coil angled away from scalp. Does not control for sensory characteristics of active stimulation and is visually distinguishable
Study Size	High risk	Comment: < 50 participants per treatment arm
Study duration	Unclear risk	Comment: ≥ 2 weeks but < 8 weeks follow-up

Lefaucheur 2001a

Methods	Cross-over randomised controlled trial
Participants	Country of study: France Setting: laboratory Condition: intractable neuropathic pain (mixed central and facial) Prior management details: refractory to drug management

Lefaucheur 2001a (*Continued*)

	n = 14 Age: 34 to 80, 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; no. of trains 20; duration of trains 5 sec; ITI 55 sec; total no. pulses 1000 Stimulation location: motor cortex, contralateral to painful side Number of treatments: x 1 for each condition Control type: sham coil used (? inert)
Outcomes	Primary: 0 to 10 VAS, anchors not specified When taken: daily for 12 days post-stimulation Secondary: none
Notes	

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
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: no drop-out is apparent from the data presented
Selective reporting (reporting bias)	Low risk	Comment: pain score numerical values are not provided clearly with measures of variance for any time point in the report but were provided by authors on request
Other bias	Low risk	Comment: no significant other bias detected
Adequate blinding of assessors?	Unclear risk	Comment: blinding of assessors is not reported
Adequate blinding of participants?	Unclear risk	Comments: sham credibility assessment - suboptimal. This study uses the same sham coil as that used in Lefaucheur 2004, which in that paper is stated as not meeting the criteria for an ideal sham
Free from carry-over effects?	Low risk	Comment: 3/52 wash-out period makes carry-over effects unlikely

Lefaucheur 2001a (*Continued*)

Study Size	High risk	Comment: < 50 participants per treatment arm
Study duration	High risk	Comment: < 2 weeks follow-up

Lefaucheur 2001b

Methods	Cross-over randomised controlled trial
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 to 75, mean 54.7 Duration of symptoms: not specified "chronic" Gender distribution: 11 M, 7 F
Interventions	Stimulation type: rTMS, figure of 8 coil Stimulation parameters: Condition 1: frequency 10 Hz; coil orientation posteroanterior; 80% RMT; no. of trains 20; duration of trains 5 sec; ITI 55 sec; total no. pulses 1000 Condition 2: frequency 0.5 Hz; coil orientation posteroanterior; no. of trains 1; duration of trains 20 minutes; total no. pulses 600 Condition 3: sham - same as for condition 1 with sham coil Stimulation location: motor cortex contralateral to painful side Number of treatments: x 1 for each condition
Outcomes	Primary: 0 to 10 VAS pain, anchors not specified When taken: 5 to 10 minutes post-stimulation Secondary: none
Notes	

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
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: no drop-out is apparent from the data presented

Lefaucheur 2001b (*Continued*)

Selective reporting (reporting bias)	Low risk	Comment: results for primary outcomes are reported clearly and in full
Other bias	Unclear risk	Comment: the results of some of the planned data analysis (ANOVA of group differences after each condition) are not reported. However, adequate data are available for inclusion in the meta-analysis
Adequate blinding of assessors?	Unclear risk	Comment: blinding of assessors is not reported
Adequate blinding of participants?	Unclear risk	Comments: sham credibility assessment - suboptimal. This study uses the same sham coil as that used in Lefaucheur 2004, which in that paper is stated as not meeting the criteria for an ideal sham
Free from carry-over effects?	Low risk	Comment: 3-week wash-out 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 2004

Methods	Cross-over randomised controlled trial
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 to 79, 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; no. of trains 20; duration of trains 5 sec; ITI 55 sec; total no. pulses 1000 Stimulation location: motor cortex contralateral to painful side Number of treatments: x 1 for each condition Control type: sham coil

Lefaucheur 2004 (*Continued*)

Outcomes	Primary: 0 to 10 VAS pain, anchors not specified When taken: 5 minutes post-stimulation Secondary: none	
Notes		

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
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: no drop-out is apparent from the data presented
Selective reporting (reporting bias)	Low risk	Comment: results for primary outcomes are reported clearly and in full
Other bias	Low risk	Comment: no significant other bias detected
Adequate blinding of assessors?	Unclear risk	Comment: blinding of assessors is not reported
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." Comments: sham credibility assessment - suboptimal
Free from carry-over effects?	Low risk	Comment: 3-week wash-out 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

Lefaucheur 2006

Methods	Cross-over randomised controlled trial, 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 to 75, mean 56.5 (SD 2.9) Duration of symptoms: 2 to 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; no. of trains 20; duration of trains 6 sec; ITI 54 sec; total no. pulses 1200 Condition 2: frequency 1 Hz; coil orientation posteroanterior; 90% RMT; no. of trains 1; duration of trains 20 minutes; total no. pulses 1200 Condition 3: sham coil Stimulation location: motor cortex contralateral to painful side Number of treatments: x 1 for each condition
Outcomes	Primary: 0 to 10 VAS pain, anchors not specified When taken: pre and post-stimulation Secondary: none
Notes	Adverse events: not reported

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
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: level of drop-out not reported and unclear from the data presented
Selective reporting (reporting bias)	Low risk	Comment: pain score numerical values are not provided clearly with measures of variance for any time point in the study report but were provided by the authors on request
Other bias	Low risk	Comment: no significant other bias detected

Lefaucheur 2006 (*Continued*)

Adequate blinding of assessors?	Unclear risk	Comment: blinding of assessors is only reported for measures of cortical excitability
Adequate blinding of participants?	Unclear risk	Comments: sham credibility assessment - sub-optimal. This study uses the same sham as Lefaucheur 2004, which in that paper is stated as not meeting the criteria for an ideal sham
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

Lefaucheur 2008

Methods	Cross-over randomised controlled trial, 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 to 79, mean 54.2 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; no. of trains 20; duration of trains 6 sec; ITI 54 sec; total no. pulses 1200 Condition 2: frequency 1 Hz; coil orientation posteroanterior; 90% RMT; no. of trains 1; duration of trains 20 minutes; total no. pulses 1200 Condition 3: sham coil Stimulation location: motor cortex contralateral to painful side Number of treatments: x 1 for each condition
Outcomes	Primary: 0 to 10 VAS, anchors not specified When taken: pre- and post-stimulation Secondary: none
Notes	Adverse events: not reported

Lefaucheur 2008 (*Continued*)

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
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 are reported clearly and in full
Other bias	Low risk	Comment: no significant other bias detected
Adequate blinding of assessors?	Low risk	Quote: "In all cases, the examiner was blinded to the type of rTMS administered. "
Adequate blinding of participants?	Unclear risk	Comments: sham credibility assessment - sub-optimal. This study uses the same sham coil as that used in Lefaucheur 2004, which in that paper is stated as not meeting the criteria for an ideal sham
Free from carry-over effects?	Low risk	Comment: 3-week wash-out 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

Lichtbroun 2001

Methods	Parallel randomised controlled study
Participants	Country of study: USA Setting: outpatient fibromyalgia clinic Condition: fibromyalgia Prior management details: unclear n = 60

Lichtbroun 2001 (*Continued*)

	Age: 23 to 82, mean 50 Duration of symptoms: 1 to 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: post-stimulation (not precisely defined) Secondary: quality of life - 0 to 10 VAS scale (data not reported)
Notes	Adverse events: not reported

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

Mendonca 2011

Methods	Parallel randomised controlled trial
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) Duration of symptoms: not reported Gender distribution: 28 F, 2 M
Interventions	Stimulation type: tDCS Stimulation parameters: simulation intensity 2 mA, 20 minutes 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 seconds stimulation)
Outcomes	Primary: pain VAS; 0 = no pain, 10 = worst possible pain When taken: immediately post-stimulation Secondary: none relevant
Notes	

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
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: no drop-outs occurred
Selective reporting (reporting bias)	High risk	No numerical data are provided for any post-treatment clinical outcome. Data not provided upon request to authors
Other bias	Low risk	No other bias detected
Adequate blinding of assessors?	Unclear risk	Comment: 2 mA intensity used - empirical evidence that assessor blinding may be sub-optimal at this intensity
Adequate blinding of participants?	Unclear risk	Comment: 2 mA intensity used - empirical evidence that participant blinding may be sub-optimal at this intensity

Study Size	High risk	Comment: < 50 participants per treatment arm
Study duration	High risk	Comment: < 2 weeks follow-up

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), sham group 49.6 (10) Duration of symptoms (mean (SD) years): active group 13 (12.9), sham group 14.1 (11.9) Gender distribution: all female
Interventions	Stimulation type: rTMS Stimulation parameters: frequency 10 Hz; coil orientation posteroanterior, no. of trains 15; duration of trains 10 sec; ITI 50 sec, intensity 80% RMT, total no. pulses 1500 Stimulation location: left M1 Number of treatments: 14, x 1 daily for 5 days, x 1 weekly for 3 weeks, x 1 fortnightly for 6 weeks, x 1 monthly for 3 months Control type: sham coil, does 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, Fibromyalgia Impact Questionnaire
Notes	

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
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: 25% drop-out at long-term follow-up but intention-to-treat analysis used with BOCF imputation

Mhalla 2011 (*Continued*)

Selective reporting (reporting bias)	Low risk	Comment: no numeric point measures provided for the primary outcome but provided upon request to the authors
Other bias	Low risk	Comment: no other biases detected
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."
Adequate blinding of participants?	Unclear risk	Comment: sham credibility assessment - sham coil controls for sound and appearance but not the skin sensation of stimulation
Study Size	High risk	Comment: < 50 participants per treatment arm
Study duration	Low risk	Comment: > 8 weeks follow-up

Mori 2010

Methods	Parallel randomised controlled trial
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 to 69, mean 44.8 (SD 27.5) Duration of symptoms: 1 to 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 minutes Stimulation location: motor cortex, contralateral to painful side Number of treatments: 5, x 1 daily on consecutive days Control type: sham tDCS (switched off after 30 seconds stimulation)
Outcomes	Primary: 0 to 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: quality of life, multiple sclerosis quality of life-54 scale (MSQoL-54) When taken: as for primary outcome
Notes	Adverse events: none

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
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: no drop-outs observed Quote: "... none of the patients enrolled discontinued the study."
Selective reporting (reporting bias)	Low risk	Comment: between-group means are not presented clearly to allow meta-analysis but data provided on request
Other bias	Low risk	Comment: no significant other bias detected
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)
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)
Study Size	High risk	Comment: < 50 participants per treatment arm
Study duration	Unclear risk	Comment: ≥ 2 weeks but < 8 weeks follow-up

Onesti 2013

Methods	Randomised cross-over trial
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) Duration of symptoms (months mean (SD)): not reported Gender distribution: 9 F 14 M
Interventions	Stimulation type: rTMS using H-coil Stimulation parameters: frequency 20 Hz; coil orientation H coil, no. of trains 30; duration of trains 2.5 sec; ITI 30 sec, intensity 100% RMT, total no. pulses 1500 Stimulation location: M1 lower limb (deep in central sulcus) Number of treatments: 5 per condition on consecutive days

Onesti 2013 (*Continued*)

	Control type: sham coil, controls for scalp sensory, auditory and visual cues	
Outcomes	Primary: pain VAS 0 to 100, no pain to worst possible pain When taken: immediately post-stimulation, 3 weeks post-stimulation Secondary: none relevant	
Notes	COI: 2 authors have links to the manufacturer of the H-coil	
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."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: only 2 patients lost to follow-up
Selective reporting (reporting bias)	High risk	Comment: data are not presented by stimulation condition - rather they are grouped by the order in which interventions were delivered. No SDs presented. Data requested
Other bias	Low risk	Comment: no other bias detected
Adequate blinding of assessors?	Unclear risk	Comment: while study is described as "double blind" there is no specific mention of blinding assessors
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: controls for visual auditory and sensory aspects of stimulation
Free from carry-over effects?	Low risk	Comment: 5-week wash-out period observed with no difference at T3
Study Size	High risk	Comment: < 50 participants per treatment arm
Study duration	Unclear risk	Comment: ≥ 2 weeks but < 8 weeks follow-up

Passard 2007

Methods	Parallel randomised controlled trial
Participants	Country of study: France Setting: laboratory Condition: fibromyalgia Prior management details: unclear n = 30 Age: active group: 52.6 (SD 7.8), sham group 55.3 (SD 8.9) 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; no. of trains 25; duration of trains 8 sec; ITI 52 sec; total no. pulses 2000 Stimulation location: motor cortex 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 to 10 NRS of average pain intensity over last 24 hours, 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: Fibromyalgia Impact Questionnaire When taken: as for primary outcome
Notes	

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, according to a computer-generated list, to two groups"
Allocation concealment (selection bias)	Unclear risk	Comment: allocation concealment not specified
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: equal drop-out 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."

Passard 2007 (*Continued*)

Selective reporting (reporting bias)	Low risk	Comment: while pain score numerical values are not provided clearly with measures of variance for all time points in the study report, the study authors have provided the requested data
Other bias	Low risk	Comment: no significant other bias detected
Adequate blinding of assessors?	Low risk	Quote: "... investigators were blind to treatment group."
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 - sub-optimal. Sham coil controls for auditory cues and is visually indistinguishable from active stimulation but does not control for sensory characteristics of active stimulation over the scalp
Study Size	High risk	Comment: < 50 participants per treatment arm
Study duration	Low risk	Comment: ≥ 8 weeks follow-up

Picarelli 2010

Methods	Parallel randomised controlled trial
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), sham group 40.6 (9.9) Duration of symptoms (months mean (SD)): active group 82.33 (34.5), sham group 79.27 (32.1) Gender distribution: 14 F, 9 M
Interventions	Stimulation type: rTMS Stimulation parameters: frequency 10Hz; coil orientation posteroanterior, no. of trains 25; duration of trains 10 sec; ITI 60 sec, intensity 100% RMT, total no. pulses 2500 Stimulation location: M1 contralateral to painful limb Number of treatments: 10, x 1 daily on consecutive weekdays Control type: sham coil - does 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: quality of life SF-36, not reported

Picarelli 2010 (*Continued*)

Notes		
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: while states "randomized" the method of randomisation is not reported
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not 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 is not adequate for meta-analysis is does not really constitute selectivity. No response received to request for full data access
Other bias	Low risk	Comment: no other biases detected
Adequate blinding of assessors?	Unclear risk	Comment: study described as "double-blinded" but assessor blinding not specifically reported
Adequate blinding of participants?	Unclear risk	Comment: sham sub-optimal as it does not control for scalp sensation. Study reported that number who guessed the condition correctly was similar but no formal data or analysis is reported
Study Size	High risk	Comment: < 50 participants per treatment arm
Study duration	Low risk	Comment: ≥ 8 weeks follow-up

Pleger 2004

Methods	Cross-over randomised controlled trial
Participants	Country of study: Germany Setting: laboratory Condition: complex regional pain syndrome type I Prior management details: drug management ceased for 48 hours prior to study n = 10 Age: 29 to 72, mean 51 Duration of symptoms: 24 to 72 months, mean 35 Gender distribution: 3 M, 7 F

Pleger 2004 (*Continued*)

Interventions	Stimulation type: rTMS Stimulation parameters: frequency 10 Hz; coil orientation unspecified; 110% RMT; no. of trains 10; duration of trains 1.2 sec; ITI 10 sec; total no. pulses 120 Stimulation location: motor cortex hand area Number of treatments: 1 for each condition Control type: coil angled 45º away from scalp
Outcomes	Primary: 0 to 10 VAS current pain intensity, anchors "no pain" to "most extreme pain" When taken: 30 sec, 15, 45 and 90 min post-stimulation Secondary: none When taken: 30 seconds, 15, 45 and 90 minutes post-stimulation
Notes	Adverse events: not reported

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"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: no drop-out is 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 have provided the requested data
Other bias	Low risk	Comment: no significant other bias detected
Adequate blinding of assessors?	Unclear risk	Comment: blinding of assessors not reported
Adequate blinding of participants?	Unclear risk	Comments: sham credibility assessment - suboptimal. Coil angled 45º away from scalp. Does not control for sensory characteristics of active stimulation and is visually distinguishable
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)."

Pleger 2004 (*Continued*)

Study Size	High risk	Comment: < 50 participants per treatment arm
Study duration	High risk	Comment: < 2 weeks follow-up

Portilla 2013

Methods	Randomised cross-over study
Participants	Country of study: USA Setting: laboratory Condition: post-burn neuropathic pain Prior management details: varied n = 3 Age range: 34 to 52 Duration of symptoms: > 6 months Gender distribution: 2 F 1 M
Interventions	Stimulation type: tDCS Stimulation parameters: intensity 2 mA, duration 20 minutes Stimulation location: M1 contralateral to most painful side Number of treatments: 1 per condition Control type: sham tDCS (switched off after 30 seconds stimulation)
Outcomes	Primary: pain VAS; 0 = "no pain", 10 = "worst pain ever felt" When taken: before and after stimulation Secondary: none relevant
Notes	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
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: all 3 patients completed study
Selective reporting (reporting bias)	High risk	Comment: no numeric data provided for pain outcomes
Other bias	Low risk	Comment: no other bias detected

Portilla 2013 (*Continued*)

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)
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)
Free from carry-over effects?	Unclear risk	Comment: 1-week wash-out 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

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), sham group 52.4 (11.5) Duration of symptoms, months (mean (SD)): active group 9.9 (11.8), sham group 6.4 (10.3) Gender distribution: all female
Interventions	Stimulation type: tDCS Stimulation parameters: intensity 2 mA, duration 20 minutes 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 seconds 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: quality of life SF36, Fibromyalgia Impact Questionnaire
Notes	Adverse events: not reported

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: states simple randomisation method but method not described

Riberto 2011 (*Continued*)

Allocation concealment (selection bias)	Unclear risk	Comment: allocation concealment not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: no drop-outs
Selective reporting (reporting bias)	Low risk	Comment: while numeric data on the primary outcome not reported in study report the authors have made it available upon request
Other bias	Unclear risk	Comment: there are group imbalances at baseline on the duration of pain, education, age and economic activity
Adequate blinding of assessors?	Unclear risk	Comment: 2 mA intensity used - empirical evidence that assessor blinding may be sub-optimal at this intensity
Adequate blinding of participants?	Unclear risk	Comment: 2 mA used, which may threaten assessor blinding, though formal analysis of blinding appears acceptable
Study Size	High risk	Comment: < 50 participants per treatment arm
Study duration	High risk	Comment: < 2 weeks follow-up

Rintala 2010

Methods	Parallel RCT
Participants	Country of study: USA Setting: outpatient clinic, patients take device home Condition: pain related to Parkinson's disease Prior management details: not reported n = 19 (reduced to 13 through drop-out) Age mean (SD): active group 74.7 (7.8), sham group 74.4 (8.3) 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 minutes 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 to 10, anchors not reported When taken: at the end of the treatment period Secondary: none
Notes	Comments: equipment provided by CES manufacturer as an "unrestricted gift"

Rintala 2010 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: states randomised but method of randomisation not reported
Allocation concealment (selection bias)	Unclear risk	Comment: allocation concealment not reported
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: > 30% drop-out
Selective reporting (reporting bias)	Low risk	Comment: mean (SD) pain scores reported for both groups pre- and post-stimulation
Other bias	Low risk	Comment: no other bias detected
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
Adequate blinding of participants?	Low risk	Comment: see above comment
Study Size	High risk	Comment: < 50 participants per treatment arm
Study duration	High risk	Comment: < 2 weeks follow-up

Rollnik 2002

Methods	Cross-over randomised controlled trial
Participants	Country of study: Germany Setting: pain clinic Condition: chronic pain (mixed musculoskeletal and neuropathic) Prior management details: "intractable" n = 12 Age: 33 to 67, 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; no. of trains 20; duration of trains 2 sec; ITI not specified; total no. pulses 800; treatment duration 20 minutes Stimulation location: motor cortex (midline) Number of treatments: x 1 for each condition

	Control type: coil angled 45º away from the scalp	
Outcomes	Primary: 0 to 100 mm VAS pain intensity, anchors "no pain" to "unbearable pain" When taken: 0, 5, 10 and 20 minutes post-stimulation Secondary: none	
Notes		

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
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: only 1 participant withdrew due to "headaches". Unlikely to have strongly influenced the findings
Selective reporting (reporting bias)	Low risk	Comment: while pain score numerical values are not provided clearly with measures of variance for all time points in the study report, the study authors have provided the requested data
Other bias	Low risk	Comment: no significant other bias detected
Adequate blinding of assessors?	Unclear risk	Comment: blinding of assessors is not reported
Adequate blinding of participants?	Unclear risk	Comments: sham credibility assessment - suboptimal. Coil angled 45º away from scalp. Does not control for sensory characteristics of active stimulation over the scalp and is visually distinguishable. Given that stimulation was delivered at 110% RMT active stimulation, but not sham, is likely to have elicited muscle twitches in peripheral muscles
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

Saitoh 2007

Methods	Cross-over randomised controlled trial, 4 conditions
Participants	Country of study: Japan Setting: laboratory Condition: neuropathic pain (mixed central and peripheral) Prior management details: intractable n = 13 Age: 29 to 76, mean 59.4 Duration of symptoms: 2 to 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; no. of trains 5; duration of trains 10 sec; ITI 50 sec; total no. pulses 500 Condition 2: frequency 5 Hz; coil orientation not specified; 90% RMT; no. of trains 10; duration of trains 10 sec; ITI 50 sec; total no. pulses 500 Condition 3: frequency 1 Hz; coil orientation not specified; 90% RMT; no. of trains 1; duration of trains 500 sec; total no. pulses 500 Condition 4: sham, coil angled 45º from scalp with synchronised electrical scalp stimulations to mask sensation Stimulation location: motor cortex 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 post-stimulation Secondary: none
Notes	

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
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "All 13 patients participated in all planned sessions of navigation-guided rTMS"

Saitoh 2007 (*Continued*)

		Comment: no drop-outs observed
Selective reporting (reporting bias)	Low risk	Comment: while pain score numerical values are not provided clearly with measures of variance for all time points in the study report, the study authors have provided the requested data
Other bias	Low risk	Comment: no significant other bias detected
Adequate blinding of assessors?	Unclear risk	Comment: blinding of assessors not reported
Adequate blinding of participants?	Unclear risk	Comment: sham credibility assessment - sub-optimal. Sensory and auditory aspects are controlled for but angulation of coil away from the scalp may be visually distinguishable
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

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) sham group 51.67 (18.19) Duration of symptoms, years mean (SD): active group 12.1 (7.75), sham group 10.10 (12.81) Gender distribution: 84% female
Interventions	Stimulation type: rTMS Stimulation parameters: frequency 10 Hz; coil orientation para-sagittal, no. of trains 80; duration of trains 5 sec; ITI 10 sec, intensity 120% RMT, total no. pulses per session 4000

	Stimulation location: left 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 post-treatment Secondary: Fibromyalgia Impact Questionnaire, Brief Pain Inventory function scale
Notes	Adverse events: no data provided. COI: 1 researcher has received research grants from the device manufacturer and holds patents for TMS technology

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

Soler 2010

Methods	Parallel randomised controlled trial
Participants	Country of study: Spain Setting: laboratory Condition: post-spinal cord injury 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) Duration of symptoms: not reported Gender distribution: 30 M, 9 F
Interventions	Stimulation type: tDCS Stimulation parameters: intensity 2 mA, duration 20 minutes 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 hours When taken: end of treatment period, 12 and 24 days post-treatment Secondary: BPI pain interference scale
Notes	

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
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: only 3 drop-outs, 1 in each group
Selective reporting (reporting bias)	Low risk	Comment: all main outcomes reported
Other bias	Low risk	Comment: no other biases detected
Adequate blinding of assessors?	Unclear risk	Comment: 2 mA intensity used - empirical evidence that assessor blinding may be sub-optimal at this intensity
Adequate blinding of participants?	Unclear risk	Comment: 2 mA may threaten blinding but assessment of blinding seemed OK
Study Size	High risk	Comment: < 50 participants per treatment arm

Study duration	Unclear risk	Comment: ≥ 2 weeks but < 8 weeks follow-up

Tan 2000

Methods	Cross-over randomised controlled trial
Participants	Country of study: USA Setting: tertiary care teaching hospital Condition: neuromuscular pain (excluding fibromyalgia) Prior management details: unclear n = 28 Age: 45 to 65, mean 55.6 Duration of symptoms: 4 to 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 to 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 to 5 pain intensity When taken: pre and post each treatment Secondary: life interference scale, sickness impact profile - Roland Scale When taken: not specified
Notes	Adverse events: not reported

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
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: only 17 participants completed the study and this drop-out (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*)

Other bias	Unclear risk	Comment: participants also received local stimulation to the painful area that may have elicited a therapeutic effect
Adequate blinding of assessors?	Unclear risk	Comment: blinding of assessors not reported
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
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

Tan 2006

Methods	Parallel randomised controlled trial
Participants	Country of study: USA Setting: medical centre Condition: post-SCI pain (not clearly neuropathic) Prior management details: unclear n = 40 Age: 38 to 82 Duration of symptoms: chronic > 6 months Gender distribution: all male
Interventions	Stimulation type: CES Stimulation parameters: frequency not specified; pulse width not specified; intensity 100 to 500 μA; waveform shape not specified; duration 1 hour 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: Brief Pain Inventory (0 to 10 NRS), anchors "no pain" to "pain as bad as you can imagine" When taken: post-treatment period Secondary: pain interference sub-scale of BPI When taken: as for primary outcome
Notes	Adverse events: not reported

Tan 2006 (*Continued*)

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
Allocation concealment (selection bias)	Unclear risk	Comment: allocation concealment not specified
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: only 2 (5%) patients 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
Other bias	Low risk	Comment: no significant other bias detected
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."
Adequate blinding of participants?	Low risk	Comment: see quote above
Study Size	High risk	Comment: < 50 participants per treatment arm
Study duration	High risk	Comment: < 2 weeks follow-up

Tan 2011

Methods	Parallel randomised controlled trial
Participants	Country of study: USA Setting: 4 veterans affairs medical centres and 1 private rehabilitation clinic Condition: post-spinal cord injury neuropathic pain Prior management details: not reported n = 105 Age mean (SD): active group 52.1 (10.5), sham group 52.5 (11.7) 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 hour per session Stimulation location: earlobe clips Number of treatments: 21, x 1 daily

	Control type: sham CES unit indistinguishable from active unit
Outcomes	Primary: Brief Pain Inventory pain intensity VAS 0 to 100, anchors not reported When taken: at end of treatment period Secondary: quality of life SF-12 physical and mental component sub-scales
Notes	

Risk of bias

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 appears to avoid a systematic bias
Allocation concealment (selection bias)	Low risk	Comment: see quote/comment above
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
Other bias	Unclear risk	Comment: baseline between-group imbalances on BPI pain interference, SF-36 pain sub-scale and coping strategies
Adequate blinding of assessors?	Low risk	Comment: stimulation sub-sensory and units indistinguishable
Adequate blinding of participants?	Low risk	Comment: Stimulation sub sensory and units indistinguishable
Study Size	Unclear risk	Comment: > 50 but < 200 participants per treatment condition
Study duration	High risk	Comment: < 2 weeks follow-up

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 drop-out) Age mean (SD): active group 51(10.6) sham group 51.5 (10.9), usual care group 48.6 (9.8) Duration of symptoms: not reported Gender distribution: 43 F, 3 M (data reported on completers)
Interventions	Stimulation type: CES Stimulation parameters: frequency 0.5 Hz; pulse width not specified; intensity 100 μA; waveform shape square wave biphasic, duration 1 hour 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: Fibromyalgia Impact Questionnaire
Notes	

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
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: of 57, 11 did not complete - unclear if ITT analysis employed. However, only 2 to 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
Other bias	Low risk	Comment: no other source of bias detected
Adequate blinding of assessors?	Low risk	Comment: participants self rated at home
Adequate blinding of participants?	Low risk	Comment: identical devices given to sham and active group with sub-sensory stimulation parameters

Taylor 2013 (*Continued*)

Study Size	High risk	Comment: < 50 participants per treatment arm
Study duration	High risk	Comment: < 2 weeks follow-up

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) states 45, but full paper states 16 Age mean (SD): 53.2 (8.9) Duration of symptoms, years mean (SD): not reported Gender distribution: 14 female, 2 male
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 no. 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: Brief Pain Inventory average pain last 24 hours NRS, anchors not reported When taken: end of treatment, 4 weeks post-treatment Secondary: Fibromyalgia Impact Questionnaire
Notes	COI: 3 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

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
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: no mention of the degree of drop-out or how it was managed. However, 45 participants with fibromyalgia reported

Tzabazis 2013 (*Continued*)

		in the abstract of the same study (Schneider 2012), 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
Other bias	Unclear risk	Comment: baseline and demographic data not presented for clinical group
Adequate blinding of assessors?	Unclear risk	Comment: no description or mention of blinding assessors for clinical part of study
Adequate blinding of participants?	Unclear risk	Comment: no description of blinding of participants for clinical part of study. Sham coil controls for auditory cues and is visually indistinguishable from active stimulation but does not control for sensory characteristics of active stimulation over the scalp
Study Size	High risk	Comment: < 50 participants per treatment arm
Study duration	Unclear risk	Comment: ≥ 2 weeks but < 8 weeks follow-up

Valle 2009

Methods	Parallel randomised controlled trial, 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 minutes Stimulation location: condition 1: left dorsolateral prefrontal cortex; condition 2: left motor cortex, condition 3; sham left motor cortex Number of treatments: 10, x 1 daily on consecutive working days Control type: sham tDCS (switched off after 30 seconds stimulation)

Outcomes	Primary: pain VAS 0 to 10 cm, anchors not specified When taken: immediately post-treatment, averaged over 3 days post-treatment, 30 and 60 days post-treatment Secondary: quality of life; Fibromyalgia Impact Questionnaire
Notes	

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"
Allocation concealment (selection bias)	Low risk	Comment: the use of a pre-generated randomisation list should have adequately ensured this
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: no drop-out occurred
Selective reporting (reporting bias)	High risk	Comment: pain score numerical values are not provided clearly with measures of variance for any post-treatment time point in the study report
Other bias	Low risk	Comment: no significant other bias detected
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)
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)
Study Size	High risk	Comment: < 50 participants per treatment arm
Study duration	Low risk	Comment: ≥ 8 weeks follow-up

Villamar 2013

Methods	Randomised cross-over trial
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) 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 minutes, anodal/cathodal/sham 4 x 1-ring configuration Stimulation location: left motor cortex Number of treatments: x 1 per condition Control type: sham tDCS
Outcomes	Primary: pain visual numerical scale; 0 = complete absence of pain, 10 = worst pain imaginable When taken: baseline, immediately post-stimulation, 30 minutes post-stimulation Secondary: adapted quality if life scale for persons with chronic illness (7 points: 1 = terrible, 7 = delighted)
Notes	

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
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
Other bias	Low risk	Comment: no other bias detected
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)
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)

Villamar 2013 (*Continued*)

Free from carry-over effects?	Low risk	Comment: 7 day wash-out 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

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) Duration of symptoms: 15.8 (11.3) years Gender distribution: 8M 2F
Interventions	Stimulation type: tDCS Stimulation parameters: intensity 2 mA, duration 20 minutes 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 seconds 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	

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."
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

Other bias	Low risk	Comment: no other bias detected
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)
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)
Free from carry-over effects?	Low risk	Comment: 4-week wash-out 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

AE: adverse event
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
CRPS: complex regional pain syndrome
DLPFC: dorsolateral pre-frontal 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
M: male
MCS: motor cortex stimulation (MCS)
NIH: National Institutes of Health
NRS: numerical rating scale
PLP: phantom limb pain
R: right
RCT: randomised controlled trial
RMT: resting motor threshold
rTMS: repetitive transcranial magnetic stimulation
SCI: spinal cord injury
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

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
Carraro 2010	Not a study of electrical brain stimulation
Choi 2012b	Study of acute pain
Choi 2012a	Study of acute pain
Evtiukhin 1998	A study of postoperative pain. No sham control employed
Frentzel 1989	Not a study of brain stimulation
Hargrove 2012a	Uncontrolled long-term follow-up data from Hargrove 2012
Johnson 2006	Self reported pain is not measured
Katz 1991	Study not confined to chronic pain
Longobardi 1989	Not clearly studying chronic pain
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
Sichinava 2012	No sham control employed for tDCS
Silva 2007	A single case report
Zaghi 2009	Single case report

NIBS: non-invasive brain stimulation
RCT: randomised controlled trial
tDCS: transcranial direct current stimulation

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 minutes, daily for 5 days
Outcomes	Pain, quality of life
Notes	Published as conference abstract only. Attempts to contact authors currently unsuccessful

Albu 2011

Methods	Sham controlled study, unclear whether randomised
Participants	Post-spinal cord injury 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 authors currently unsuccessful

Ansari 2013

Methods	Parallel RCT
Participants	Fibromyalgia, n = 118
Interventions	rTMS right DLPFC, low-frequency, 20 sessions
Outcomes	Unclear whether self reported pain scores were collected
Notes	Published as conference abstract only. Attempts to contact 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

Fricova 2009 (*Continued*)

Notes	Published as conference abstract only. Attempts to contact 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. Published as conference abstract only. Likely to be a duplicate report of Fricova 2009. Attempts to contact authors 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 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	Complex regional pain syndrome type I, n = 25
Interventions	tDCS, motor cortex, 2 mA, 20 minutes per session, daily for 5 days
Outcomes	Pain, quality of life, physical activity
Notes	Currently published as conference abstract only. Correspondence with authors - data unavailable as currently being re-analysed

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 authors currently unsuccessful

Shklar 1997

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

Vatashsky 1997

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

Yağci 2013

Methods	Parallel RCT
Participants	Fibromyalgia, n = 25
Interventions	rTMS motor cortex, 1 Hz, 90% RMT, 10 sessions daily
Outcomes	Pain VAS, FIQ
Notes	Published as conference abstract only. Attempts to contact authors currently unsuccessful

DLPFC: dorsolateral pre-frontal cortex
FIQ: Fibromyalgia Impact Questionnaire
RCT: randomised controlled trial
tDCS: transcranial direct current stimulation
VAS: visual analogue scale

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

ISRCTN89874874

Trial name or title	Effectiveness of anodal transcranial direct current stimulation (tDCS) in patients with chronic low back pain: a randomised controlled trial
Methods	Parallel RCT
Participants	Chronic low back pain, n = 135
Interventions	tDCS 2 mA, 20 minutes, daily for 5 consecutive days
Outcomes	Pain VAS, disability (Oswestry Disability Index), patient perceived satisfactory improvement, quality of life (SF-36)
Starting date	20 February 2011
Contact information	Kerstin Luedtke, Matinistr. 52, Hamburg, Germany, 20246
Notes	Correspondence with authors - trial currently ongoing

NCT00697398

Trial name or title	Repetitive Trans-Cranial Magnetic Stimulation of the Motor Cortex in Fibromylagia: A Study Evaluating the Clinical Efficiency and the Metabolic Correlate in 18FDG-PET
Methods	Parallel RCT

NCT00697398 (*Continued*)

Participants	Fibromyalgia
Interventions	rTMS motor cortex, parameters not specified
Outcomes	Analgesic efficiency at 36-month follow-up, quality of life
Starting date	October 2008
Contact information	Dr Eric Guedj, eric.guedj@ap-hm.fr
Notes	Correspondence with authors: Study complete and currently under peer review for publication

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 minutes, x 1 session, location not specified
Outcomes	Pain intensity
Starting date	February 2009
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

NCT00947622 (*Continued*)

Notes	Attempts to contact 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 spinal cord injury, proposed n = 60
Interventions	tDCS 2 mA, 10 sessions
Outcomes	Pain VAS, quality of life
Starting date	April 2010
Contact information	Dr Felipe Fregni, ffregni@neuromodulationlab.org, Kayleen Weaver, kmweaver@partners.org
Notes	Contact with 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 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 spinal cord injury, n = 60

NCT01402960 (*Continued*)

Interventions	tDCS or sham, 2 mA, motor cortex, 20 minutes, 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 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 osteoarthritis pain, n = 30
Interventions	tDCS or sham, 20 minutes, 2 mA, motor cortex, 5 sessions
Outcomes	Pain
Starting date	January 2011
Contact information	Dr Felipe Fregni, ffregni@partners.org; Kayleen Weaver, kmweaver@partners.org
Notes	Contact with 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 author - study at "to be analysed and reported" stage

NCT01599767

Trial name or title	Spaulding-Harvard model system: Effects of transcranial direct current stimulation on chronic pain in spinal cord injury
Methods	Parallel RCT
Participants	Moderate to severe sub-lesional pain post-spinal cord injury
Interventions	Anodal tDCS 15 sessions x 1 daily, parameters not reported
Outcomes	Pain
Starting date	December 2011
Contact information	Dr Felipe Fregni, ffregni@partners.org; Kayleen Weaver, kmweaver@partners.org
Notes	Contact with author - study at "to be analysed and reported" stage

NCT01608321

Trial name or title	rTMS for the treatment of chronic pain in GW1 veterans
Methods	Parallel RCT
Participants	Chronic pain related to Gulf War illness that meets diagnostic criteria for fibromyalgia, n = 206
Interventions	rTMS 20 sessions, stimulation parameters unclear
Outcomes	McGill pain questionnaire
Starting date	August 2012
Contact information	Dr Ansgar Furst, Dr John Ashford, ansgar.furst@va.gov, wes.ashford@va.gov
Notes	Correspondence with authors: recruiting due to commence Spring 2013

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

NCT01746355 (*Continued*)

Starting date	March 2011
Contact information	Ricardo Galhardoni
Notes	Correspondence with 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 osteoarthritis 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 authors: study ongoing

CRPS: complex regional pain syndrome
DLPFC: dorsolateral pre-frontal cortex
FIQ: Fibromyalgia Impact Questionnaire
RCT: randomised controlled trial
rTMS: repetitive transcranial magnetic stimulation
tDCS: transcranial direct current stimulation
VAS: visual analogue scale
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	21		Std. Mean Difference (Fixed, 95% CI)	-0.20 [-0.26, -0.13]
1.1 Low-frequency ≤ 1 Hz	6		Std. Mean Difference (Fixed, 95% CI)	0.15 [-0.01, 0.31]
1.2 High-frequency ≥ 5 Hz	20		Std. Mean Difference (Fixed, 95% CI)	-0.27 [-0.35, -0.20]
2 Pain: short-term follow-up, subgroup analysis: multiple-dose vs single-dose studies	21		Std. Mean Difference (Random, 95% CI)	-0.19 [-0.33, -0.06]
2.1 Single-dose studies	12		Std. Mean Difference (Random, 95% CI)	-0.23 [-0.37, -0.09]
2.2 Multiple-dose studies	9		Std. Mean Difference (Random, 95% CI)	-0.12 [-0.47, 0.23]
3 Pain: short-term follow-up, subgroup analysis, neuropathic pain participants only	14		Std. Mean Difference (Fixed, 95% CI)	-0.20 [-0.27, -0.12]
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	14		Std. Mean Difference (Fixed, 95% CI)	-0.27 [-0.35, -0.19]
4 Pain: short-term follow-up, subgroup analysis, non-neuropathic pain participants only	6		Std. Mean Difference (Fixed, 95% CI)	-0.19 [-0.44, 0.05]
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	5		Std. Mean Difference (Fixed, 95% CI)	-0.34 [-0.63, -0.05]
5 Pain: short-term follow-up, subgroup analysis: motor cortex studies only, low-frequency studies excluded	17		Std. Mean Difference (Random, 95% CI)	-0.32 [-0.46, -0.17]
5.1 Single-dose studies	12		Std. Mean Difference (Random, 95% CI)	-0.39 [-0.51, -0.27]
5.2 Multiple-dose studies	5		Std. Mean Difference (Random, 95% CI)	-0.07 [-0.41, 0.26]
6 Sensitivity analysis - imputed correlation coefficient increased. Pain: short-term follow-up	23		Std. Mean Difference (Random, 95% CI)	-0.21 [-0.34, -0.08]
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	22		Std. Mean Difference (Random, 95% CI)	-0.30 [-0.44, -0.16]
7 Sensitivity analysis - imputed correlation coefficient decreased. Pain: short-term follow-up	22		Std. Mean Difference (Random, 95% CI)	-0.20 [-0.34, -0.06]
7.1 Low-frequency ≤ 1 Hz	6		Std. Mean Difference (Random, 95% CI)	0.17 [-0.03, 0.37]
7.2 High-frequency ≥ 5 Hz	21		Std. Mean Difference (Random, 95% CI)	-0.28 [-0.42, -0.13]

8 Sensitivity analysis - imputed correlation increased. Pain: short-term follow-up, subgroup analysis: motor cortex studies only, low-frequency studies excluded	17	Std. Mean Difference (Random, 95% CI)	-0.33 [-0.47, -0.20]
8.1 Single-dose studies	12	Std. Mean Difference (Random, 95% CI)	-0.41 [-0.53, -0.29]
8.2 Multiple-dose studies	5	Std. Mean Difference (Random, 95% CI)	-0.08 [-0.39, 0.23]
9 Sensitivity analysis - imputed correlation decreased. Pain: short-term follow-up, subgroup analysis: motor cortex studies only, low-frequency studies excluded	17	Std. Mean Difference (Random, 95% CI)	-0.31 [-0.46, -0.17]
9.1 Single-dose studies	12	Std. Mean Difference (Random, 95% CI)	-0.38 [-0.49, -0.27]
9.2 Multiple-dose studies	5	Std. Mean Difference (Random, 95% CI)	-0.11 [-0.48, 0.25]
10 Sensitivity analysis - inclusion of high risk of bias studies. Pain: short-term follow-up	25	Std. Mean Difference (Fixed, 95% CI)	-0.23 [-0.31, -0.16]
10.1 Low-frequency ≤ 1 Hz	9	Std. Mean Difference (Fixed, 95% CI)	0.09 [-0.05, 0.24]
10.2 High-frequency ≥ 5 Hz	23	Std. Mean Difference (Fixed, 95% CI)	-0.34 [-0.42, -0.26]
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	21	Std. Mean Difference (Random, 95% CI)	-0.39 [-0.56, -0.23]
11.1 Single-dose studies	14	Std. Mean Difference (Random, 95% CI)	-0.36 [-0.48, -0.24]
11.2 Multiple-dose studies	8	Std. Mean Difference (Random, 95% CI)	-0.50 [-0.99, -0.01]
12 Pain: short-term follow-up, subgroup analysis: prefrontal cortex studies only	4	Std. Mean Difference (Random, 95% CI)	-0.47 [-1.48, 0.54]
12.1 Multiple-dose studies	4	Std. Mean Difference (Random, 95% CI)	-0.47 [-1.48, 0.54]
13 Sensitivity analysis - inclusion of high risk of bias studies. Pain: short-term follow-up, subgroup analysis: prefrontal cortex studies only	5	Std. Mean Difference (Random, 95% CI)	-0.48 [-1.32, 0.37]
13.1 Multiple-dose studies	5	Std. Mean Difference (Random, 95% CI)	-0.48 [-1.32, 0.37]
14 Pain: medium-term follow-up	7	Std. Mean Difference (Random, 95% CI)	-0.18 [-0.43, 0.06]
14.1 Low-frequency ≤ 1 Hz	1	Std. Mean Difference (Random, 95% CI)	0.36 [-0.41, 1.13]
14.2 High-frequency ≥ 5 Hz	6	Std. Mean Difference (Random, 95% CI)	-0.23 [-0.48, 0.03]
15 Sensitivity analysis - inclusion of high risk of bias studies. Pain: medium-term follow-up	10	Std. Mean Difference (Random, 95% CI)	-0.43 [-0.76, -0.10]
15.1 Low-frequency ≤ 1 Hz	2	Std. Mean Difference (Random, 95% CI)	-0.08 [-1.26, 1.10]
15.2 High-frequency ≥ 5 Hz	9	Std. Mean Difference (Random, 95% CI)	-0.48 [-0.83, -0.13]
16 Pain: long-term follow-up	3	Std. Mean Difference (Random, 95% CI)	-0.12 [-0.46, 0.21]
17 Sensitivity analysis - inclusion of high risk of bias studies. Pain: long-term follow-up	4	Std. Mean Difference (Random, 95% CI)	-0.46 [-1.10, 0.17]

18 Disability/pain interference: short-term follow-up	5		Std. Mean Difference (Random, 95% CI)	-0.29 [-0.87, 0.29]
19 Disability/pain interference: medium-term follow-up	4		Std. Mean Difference (Random, 95% CI)	-0.37 [-1.07, 0.33]
20 Disability/pain interference: long-term follow-up	3		Std. Mean Difference (Random, 95% CI)	-0.23 [-0.62, 0.16]
21 Quality of life: short-term follow-up (Fibromyalgia Impact Questionnaire)	3	80	Mean Difference (IV, Random, 95% CI)	-10.38 [-14.89, -5.87]
22 Quality of life: medium-term follow-up (Fibromyalgia Impact Questionnaire)	3	80	Mean Difference (IV, Fixed, 95% CI)	-11.49 [-17.04, -5.95]
23 Quality of life: long-term follow-up	1		Std. Mean Difference (Random, 95% CI)	Totals not selected

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 Disability/function/pain interference	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
3 Quality of life	1		Std. 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	11		Std. Mean Difference (Random, 95% CI)	-0.18 [-0.46, 0.09]
1.1 Single-dose studies	3		Std. Mean Difference (Random, 95% CI)	-0.18 [-0.41, 0.05]
1.2 Multiple-dose studies	8		Std. Mean Difference (Random, 95% CI)	-0.22 [-0.69, 0.25]
2 Pain: short-term follow-up, subgroup analysis: motor cortex studies only	11		Std. Mean Difference (Random, 95% CI)	-0.23 [-0.48, 0.01]
2.1 Single-dose studies	3		Std. Mean Difference (Random, 95% CI)	-0.18 [-0.41, 0.05]
2.2 Multiple-dose studies	8		Std. Mean Difference (Random, 95% CI)	-0.35 [-0.79, 0.09]
3 Pain: short-term sensitivity analysis: correlation increased	11		Std. Mean Difference (Random, 95% CI)	-0.20 [-0.47, 0.06]
4 Pain: short-term sensitivity analysis: correlation decreased	11		Std. Mean Difference (Random, 95% CI)	-0.23 [-0.51, 0.06]
5 Pain: short-term follow-up, subgroup analysis: motor cortex studies only, sensitivity analysis: correlation increased	11		Std. Mean Difference (Random, 95% CI)	-0.23 [-0.48, 0.02]
5.1 Single-dose studies	3		Std. Mean Difference (Random, 95% CI)	-0.18 [-0.41, 0.05]

5.2 Multiple-dose studies	8		Std. Mean Difference (Random, 95% CI)	-0.35 [-0.79, 0.10]
6 Pain: short-term follow-up, subgroup analysis: motor cortex studies only, sensitivity analysis: correlation decreased	11		Std. Mean Difference (Random, 95% CI)	-0.24 [-0.48, -0.00]
6.1 Single-dose studies	3		Std. Mean Difference (Random, 95% CI)	-0.18 [-0.41, 0.05]
6.2 Multiple-dose studies	8		Std. Mean Difference (Random, 95% CI)	-0.36 [-0.79, 0.07]
7 Pain: medium-term follow-up	5		Std. Mean Difference (Random, 95% CI)	-0.20 [-0.63, 0.24]
8 Disability (pain interference): short-term follow-up	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
9 Quality of life: short-term follow-up	2	42	Std. Mean Difference (IV, Random, 95% CI)	0.88 [0.24, 1.53]
10 Quality of life: medium-term follow-up	1		Std. Mean Difference (IV, Random, 95% CI)	Totals not selected
11 Pain: short-term follow-up, subgroup analysis: motor cortex studies only	11		Std. Mean Difference (Random, 95% CI)	-0.26 [-0.49, -0.03]
11.1 Single-dose studies	3		Std. Mean Difference (Random, 95% CI)	-0.18 [-0.41, 0.05]
11.2 Multiple-dose studies	8		Std. Mean Difference (Random, 95% CI)	-0.38 [-0.80, 0.03]

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 Fibromyalgia Impact Questionnaire total score	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only

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)	Weight	Std. Mean Difference IV,Fixed,95% CI
1 Low-frequency ≤ 1 Hz			
Andr -Obadia 2006	-0.016296 (0.259415)	1.8 %	-0.02 [-0.52, 0.49]
Carretero 2009	0.15649 (0.230164)	2.3 %	0.16 [-0.29, 0.61]
Lefaucheur 2001b	0.156 (0.162229)	4.6 %	0.16 [-0.16, 0.47]
Lefaucheur 2006 (1)	0.37847 (0.21421)	2.6 %	0.38 [-0.04, 0.80]
Lefaucheur 2008	0.14778 (0.140854)	6.1 %	0.15 [-0.13, 0.42]
Saitoh 2007	-0.169857 (0.332186)	1.1 %	-0.17 [-0.82, 0.48]
Subtotal (95% CI)		**18.6 %**	**0.15 [-0.01, 0.31]**
Heterogeneity: Chi² = 2.48, df = 5 (P = 0.78); I² =0.0%			
Test for overall effect: Z = 1.84 (P = 0.065)			
2 High-frequency ≥ 5 Hz			
Andr -Obadia 2006	-0.066506 (0.259685)	1.8 %	-0.07 [-0.58, 0.44]
Andr -Obadia 2008 (2)	-0.41092 (0.191008)	3.3 %	-0.41 [-0.79, -0.04]
Andr -Obadia 2008 (3)	-0.287518 (0.187174)	3.5 %	-0.29 [-0.65, 0.08]
Andr -Obadia 2011	-0.383319 (0.105999)	10.8 %	-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]
Defrin 2007 (4)	1.12 (0.642857)	0.3 %	1.12 [-0.14, 2.38]
Hirayama 2006 (5)	0.18872 (0.309645)	1.3 %	0.19 [-0.42, 0.80]
Hirayama 2006 (6)	0.23554 (0.311152)	1.3 %	0.24 [-0.37, 0.85]
Hirayama 2006 (7)	0.19336 (0.309779)	1.3 %	0.19 [-0.41, 0.80]
Hirayama 2006 (8)	-0.38726 (0.318223)	1.2 %	-0.39 [-1.01, 0.24]
Hosomi 2013 (9)	-0.11985 (0.116422)	9.0 %	-0.12 [-0.35, 0.11]
Hosomi 2013 (10)	-0.057109 (0.127547)	7.5 %	-0.06 [-0.31, 0.19]
Kang 2009	0.43402 (0.216454)	2.6 %	0.43 [0.01, 0.86]

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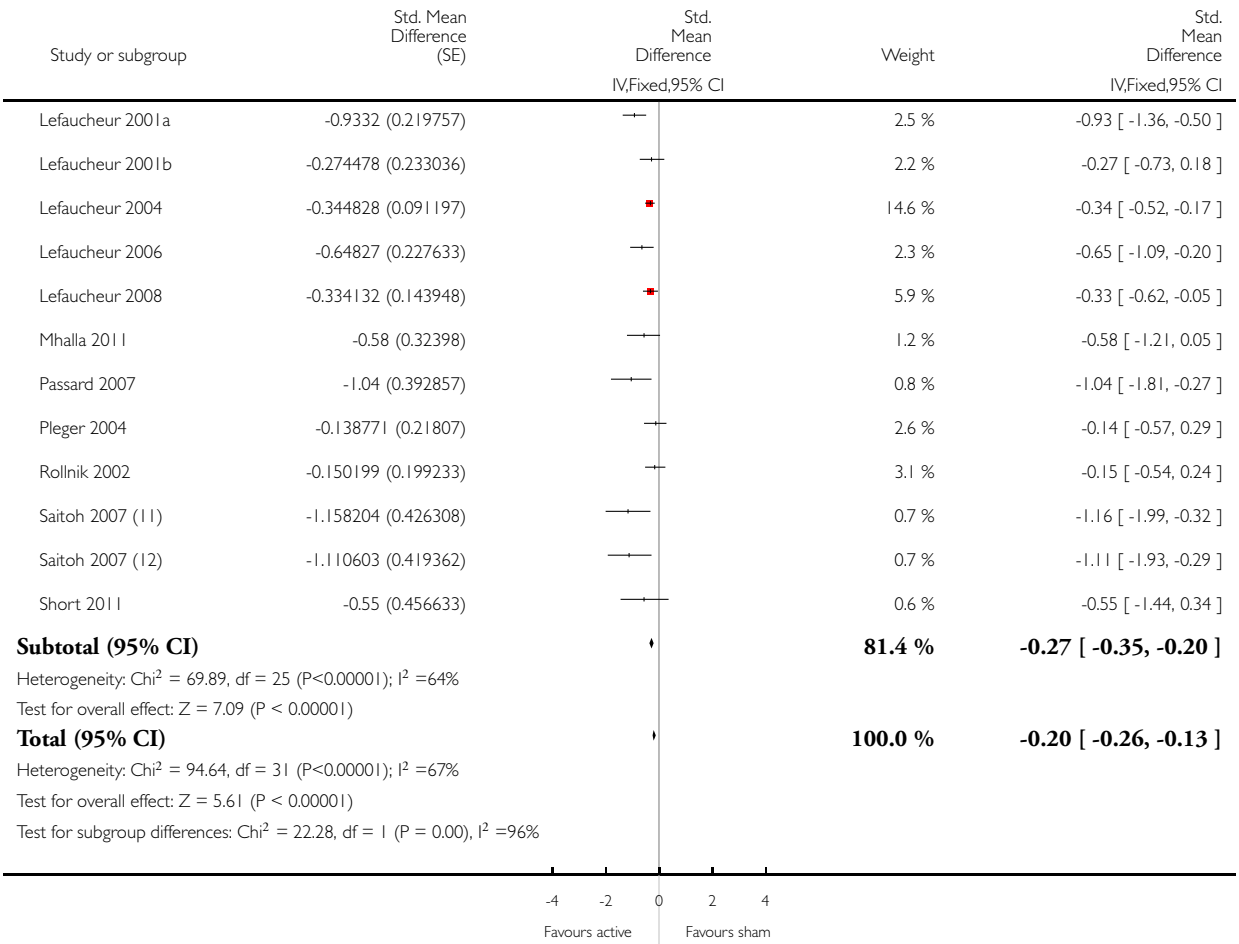


(1) 1Hz

(2) antero-posterior coil orientation

(3) medial-lateral coil orientation

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

(5) SMA

(6) S1

(7) PMA

(8) M1

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

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

(11) 5Hz

(12) 10 Hz

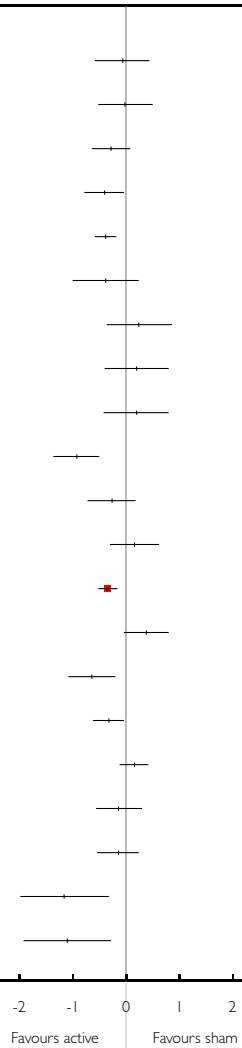
Analysis 1.2. Comparison 1 Repetitive transcranial magnetic stimulation (rTMS), Outcome 2 Pain: short-term follow-up, subgroup analysis: multiple-dose vs single-dose studies.

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)	-0.066506 (0.259685)		3.2 %	-0.07 [-0.58, 0.44]
Andr -Obadia 2006 (2)	-0.016296 (0.259415)		3.2 %	-0.02 [-0.52, 0.49]
Andr -Obadia 2008 (3)	-0.287518 (0.187174)		4.0 %	-0.29 [-0.65, 0.08]
Andr -Obadia 2008 (4)	-0.41092 (0.191008)		3.9 %	-0.41 [-0.79, -0.04]
Andr -Obadia 2011	-0.383319 (0.105999)		5.0 %	-0.38 [-0.59, -0.18]
Hirayama 2006 (5)	-0.38726 (0.318223)		2.6 %	-0.39 [-1.01, 0.24]
Hirayama 2006 (6)	0.23554 (0.311152)		2.7 %	0.24 [-0.37, 0.85]
Hirayama 2006 (7)	0.19336 (0.309779)		2.7 %	0.19 [-0.41, 0.80]
Hirayama 2006 (8)	0.18872 (0.309645)		2.7 %	0.19 [-0.42, 0.80]
Lefaucheur 2001a	-0.9332 (0.219757)		3.6 %	-0.93 [-1.36, -0.50]
Lefaucheur 2001b (9)	-0.274478 (0.233036)		3.5 %	-0.27 [-0.73, 0.18]
Lefaucheur 2001b (10)	0.156 (0.230164)		3.5 %	0.16 [-0.30, 0.61]
Lefaucheur 2004	-0.344828 (0.091197)		5.1 %	-0.34 [-0.52, -0.17]
Lefaucheur 2006 (11)	0.37847 (0.21421)		3.7 %	0.38 [-0.04, 0.80]
Lefaucheur 2006 (12)	-0.64827 (0.227633)		3.5 %	-0.65 [-1.09, -0.20]
Lefaucheur 2008 (13)	-0.334132 (0.143948)		4.5 %	-0.33 [-0.62, -0.05]
Lefaucheur 2008 (14)	0.14778 (0.140854)		4.6 %	0.15 [-0.13, 0.42]
Pleger 2004	-0.138771 (0.21807)		3.6 %	-0.14 [-0.57, 0.29]
Rollnik 2002	-0.150199 (0.199233)		3.9 %	-0.15 [-0.54, 0.24]
Saitoh 2007 (15)	-1.158204 (0.426308)		1.8 %	-1.16 [-1.99, -0.32]
Saitoh 2007 (16)	-1.110603 (0.419362)		1.9 %	-1.11 [-1.93, -0.29]



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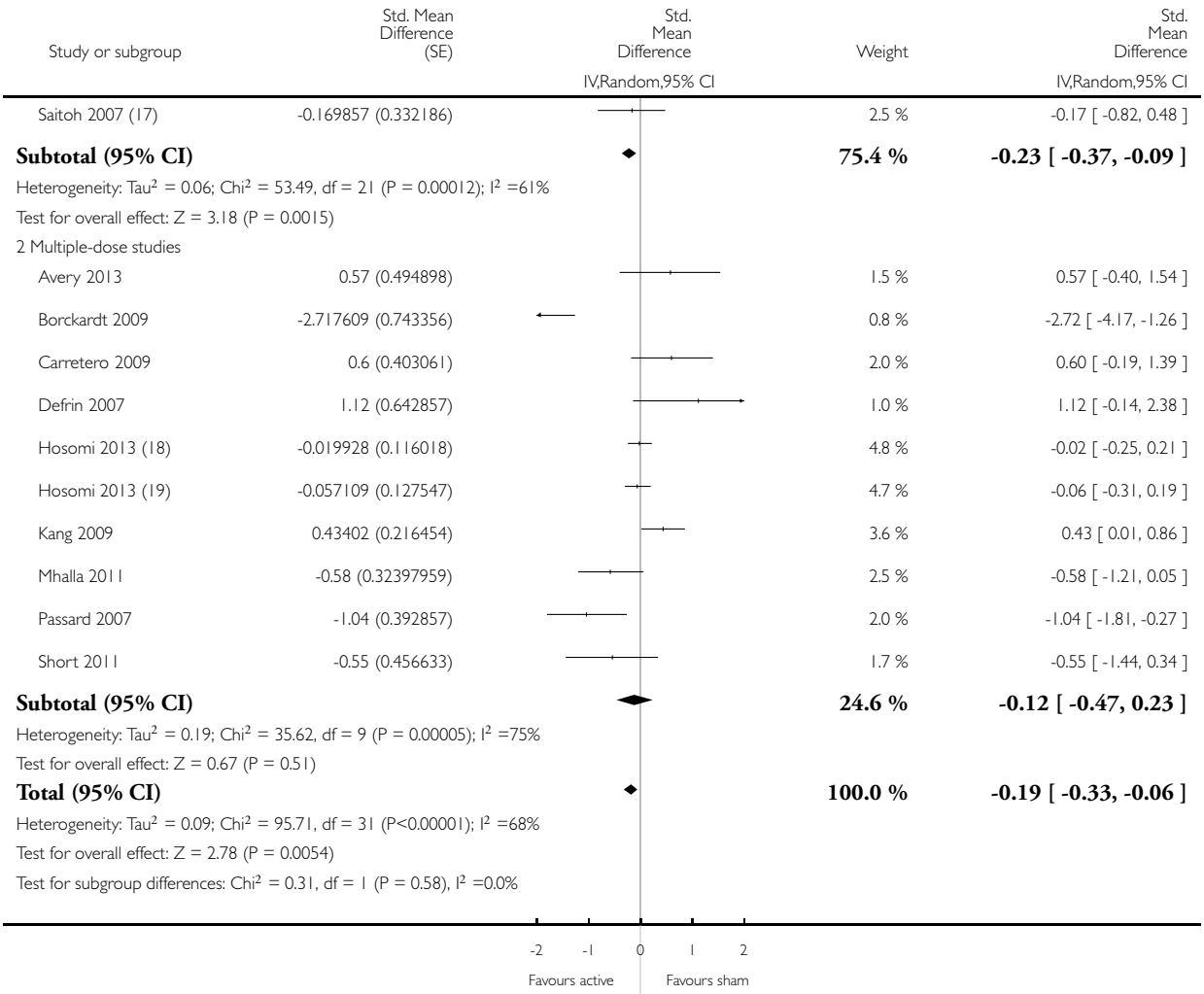

(1) 20Hz

(2) 1Hz

(3) 20 Hz medial-lateral coil orientation

(4) 20Hz antero-posterior coil orientation

(5) M1

(6) S1

(7) PMA

(8) SMA

(9) 10Hz

(10) 0.5 Hz

(11) 1Hz

(12) 10Hz

(13) 10 Hz

(14) 1Hz

(15) 5Hz

(16) 10Hz

(17) 1Hz

(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)	Weight	Std. Mean Difference IV,Fixed,95% CI
1 Low-frequency ≤ 1 Hz			
Andr -Obadia 2006	-0.016296 (0.259415)	2.0 %	-0.02 [-0.52, 0.49]
Lefaucheur 2001b	0.156 (0.162229)	5.2 %	0.16 [-0.16, 0.47]
Lefaucheur 2006 (1)	0.37847 (0.21421)	3.0 %	0.38 [-0.04, 0.80]
Lefaucheur 2008	0.14778 (0.140854)	6.9 %	0.15 [-0.13, 0.42]
Saitoh 2007	-0.169857 (0.332186)	1.2 %	-0.17 [-0.82, 0.48]
Subtotal (95% CI)		**18.3 %**	**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)	2.0 %	-0.07 [-0.58, 0.44]
Andr -Obadia 2008 (2)	-0.41092 (0.191008)	3.7 %	-0.41 [-0.79, -0.04]
Andr -Obadia 2008 (3)	-0.287518 (0.187174)	3.9 %	-0.29 [-0.65, 0.08]
Andr -Obadia 2011	-0.383319 (0.105999)	12.1 %	-0.38 [-0.59, -0.18]
Borckardt 2009	-2.717609 (0.743356)	0.2 %	-2.72 [-4.17, -1.26]
Defrin 2007 (4)	1.12 (0.642857)	0.3 %	1.12 [-0.14, 2.38]
Hirayama 2006 (5)	0.19336 (0.309779)	1.4 %	0.19 [-0.41, 0.80]
Hirayama 2006 (6)	0.23554 (0.311152)	1.4 %	0.24 [-0.37, 0.85]
Hirayama 2006 (7)	-0.38726 (0.318223)	1.3 %	-0.39 [-1.01, 0.24]
Hirayama 2006 (8)	0.18872 (0.309645)	1.4 %	0.19 [-0.42, 0.80]
Hosomi 2013 (9)	-0.11985 (0.116422)	10.1 %	-0.12 [-0.35, 0.11]
Hosomi 2013 (10)	-0.057109 (0.127547)	8.4 %	-0.06 [-0.31, 0.19]
Kang 2009	0.43402 (0.216454)	2.9 %	0.43 [0.01, 0.86]
Lefaucheur 2001a	-0.9332 (0.219757)	2.8 %	-0.93 [-1.36, -0.50]
Lefaucheur 2001b	-0.274478 (0.233036)	2.5 %	-0.27 [-0.73, 0.18]

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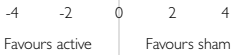
Study or subgroup	Std. Mean Difference (SE)	Std. Mean Difference IV,Fixed,95% CI	Weight	Std. Mean Difference IV,Fixed,95% CI
Lefaucheur 2004	-0.344828 (0.091197)		16.4 %	-0.34 [-0.52, -0.17]
Lefaucheur 2006	-0.64827 (0.227633)		2.6 %	-0.65 [-1.09, -0.20]
Lefaucheur 2008	-0.334132 (0.143948)		6.6 %	-0.33 [-0.62, -0.05]
Saitoh 2007 (11)	-1.110603 (0.419362)		0.8 %	-1.11 [-1.93, -0.29]
Saitoh 2007 (12)	-1.158204 (0.426308)		0.7 %	-1.16 [-1.99, -0.32]
Subtotal (95% CI)			**81.7 %**	**-0.27 [-0.35, -0.19]**
Heterogeneity: Chi^2 = 61.15, df = 19 (P<0.00001); I^2 =69%				
Test for overall effect: Z = 6.71 (P < 0.00001)				
Total (95% CI)			**100.0 %**	**-0.20 [-0.27, -0.12]**
Heterogeneity: Chi^2 = 83.16, df = 24 (P<0.00001); I^2 =71%				
Test for overall effect: Z = 5.34 (P < 0.00001)				
Test for subgroup differences: Chi^2 = 19.53, 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) PMA

(6) S1

(7) M1

(8) SMA

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

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

(11) 10 Hz

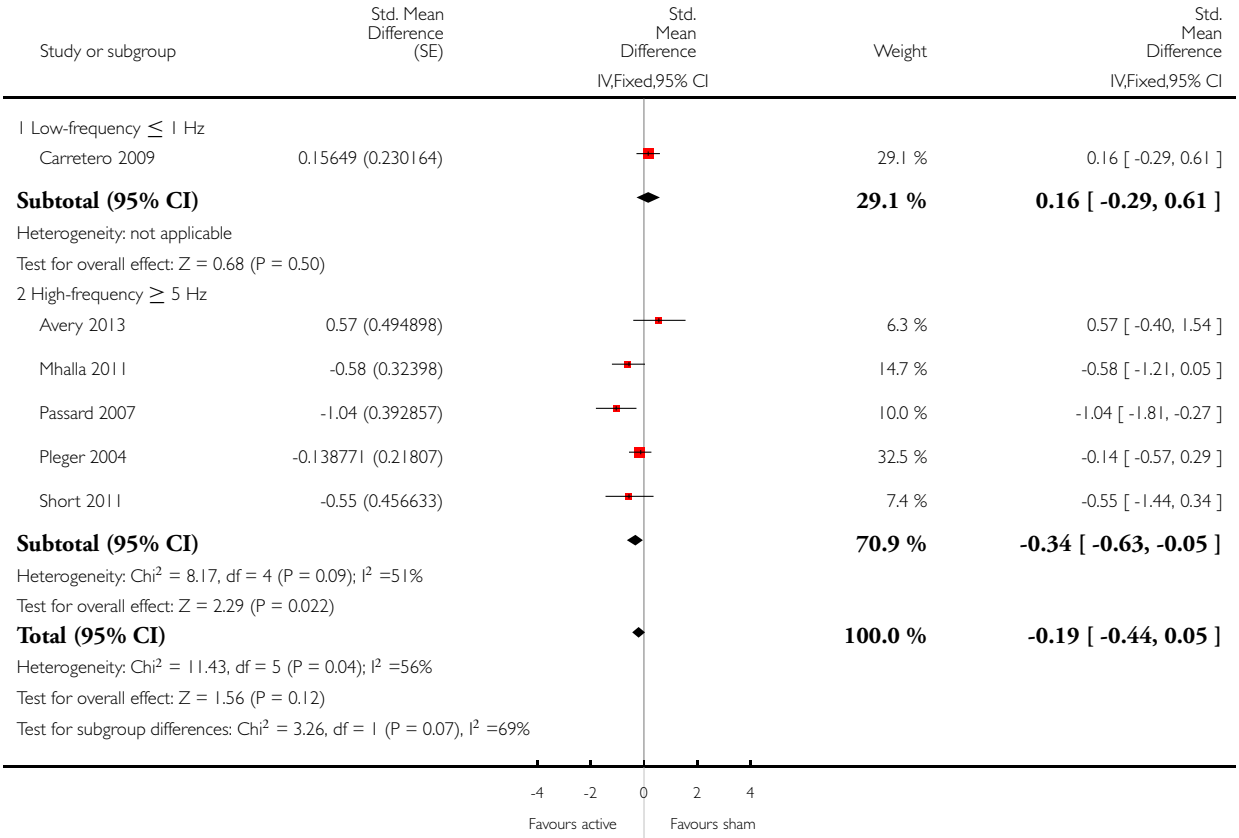
(12) 5Hz

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

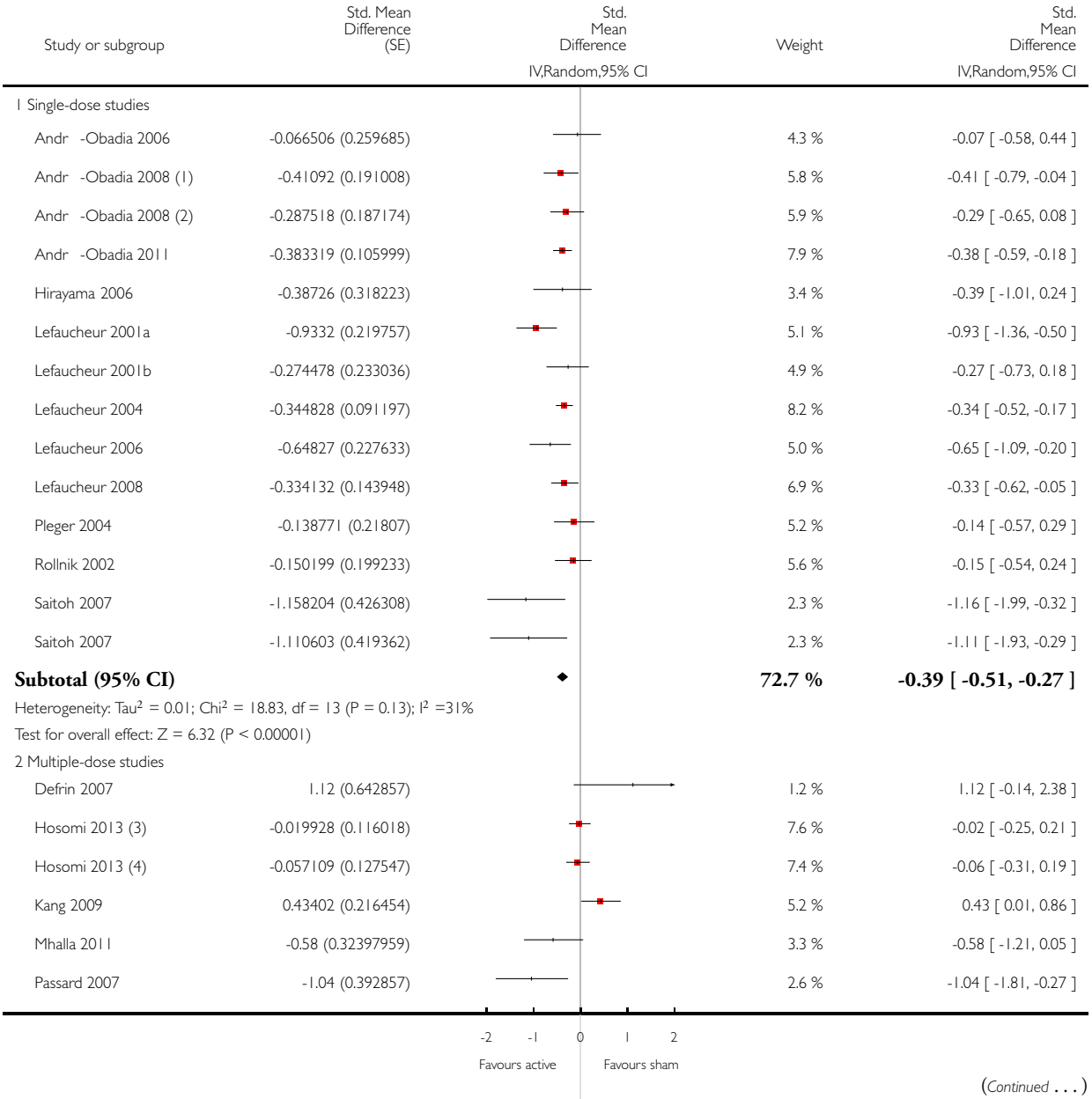


Analysis 1.5. Comparison 1 Repetitive transcranial magnetic stimulation (rTMS), Outcome 5 Pain: short-term follow-up, subgroup analysis: motor cortex studies only, low-frequency studies excluded.

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



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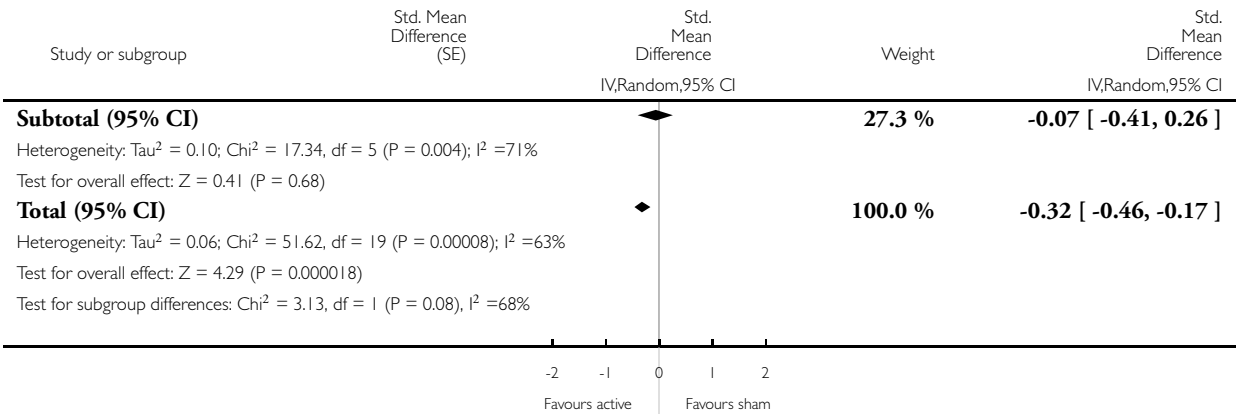

(1) antero-posterior coil orientation

(2) medial-lateral coil orientation

(3) Group A real followed by sham

(4) Group B sham followed by real

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)	3.3 %	-0.02 [-0.41, 0.38]
Carretero 2009	0.6 (0.403061)	1.7 %	0.60 [-0.19, 1.39]
Lee 2012	-0.59 (0.760204)	0.7 %	-0.59 [-2.08, 0.90]
Lefaucheur 2001b	0.15649 (0.17746)	3.5 %	0.16 [-0.19, 0.50]
Lefaucheur 2006 (1)	0.37847 (0.165159)	3.7 %	0.38 [0.05, 0.70]
Lefaucheur 2008	0.14778 (0.097135)	4.3 %	0.15 [-0.04, 0.34]
Saitoh 2007	-0.169857 (0.256121)	2.8 %	-0.17 [-0.67, 0.33]
Subtotal (95% CI)		**20.0 %**	**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)	3.3 %	-0.07 [-0.46, 0.33]
Andr -Obadia 2008 (2)	-0.41092 (0.14727)	3.8 %	-0.41 [-0.70, -0.12]
Andr -Obadia 2008 (3)	-0.287518 (0.144314)	3.9 %	-0.29 [-0.57, 0.00]
Andr -Obadia 2011	-0.383319 (0.081727)	4.4 %	-0.38 [-0.54, -0.22]
Avery 2013	0.57 (0.494898)	1.3 %	0.57 [-0.40, 1.54]
Borckardt 2009	-2.717609 (0.57314)	1.0 %	-2.72 [-3.84, -1.59]
Defrin 2007	1.12 (0.642857)	0.9 %	1.12 [-0.14, 2.38]
Fregni 2005	0 (0)		Not estimable
Hirayama 2006 (4)	0.18872 (0.238741)	2.9 %	0.19 [-0.28, 0.66]
Hirayama 2006 (5)	-0.38726 (0.245355)	2.9 %	-0.39 [-0.87, 0.09]
Hirayama 2006 (6)	0.23554 (0.239903)	2.9 %	0.24 [-0.23, 0.71]
Hirayama 2006 (7)	0.19336 (0.238845)	2.9 %	0.19 [-0.27, 0.66]
Hosomi 2013 (8)	-0.11985 (0.089763)	4.4 %	-0.12 [-0.30, 0.06]

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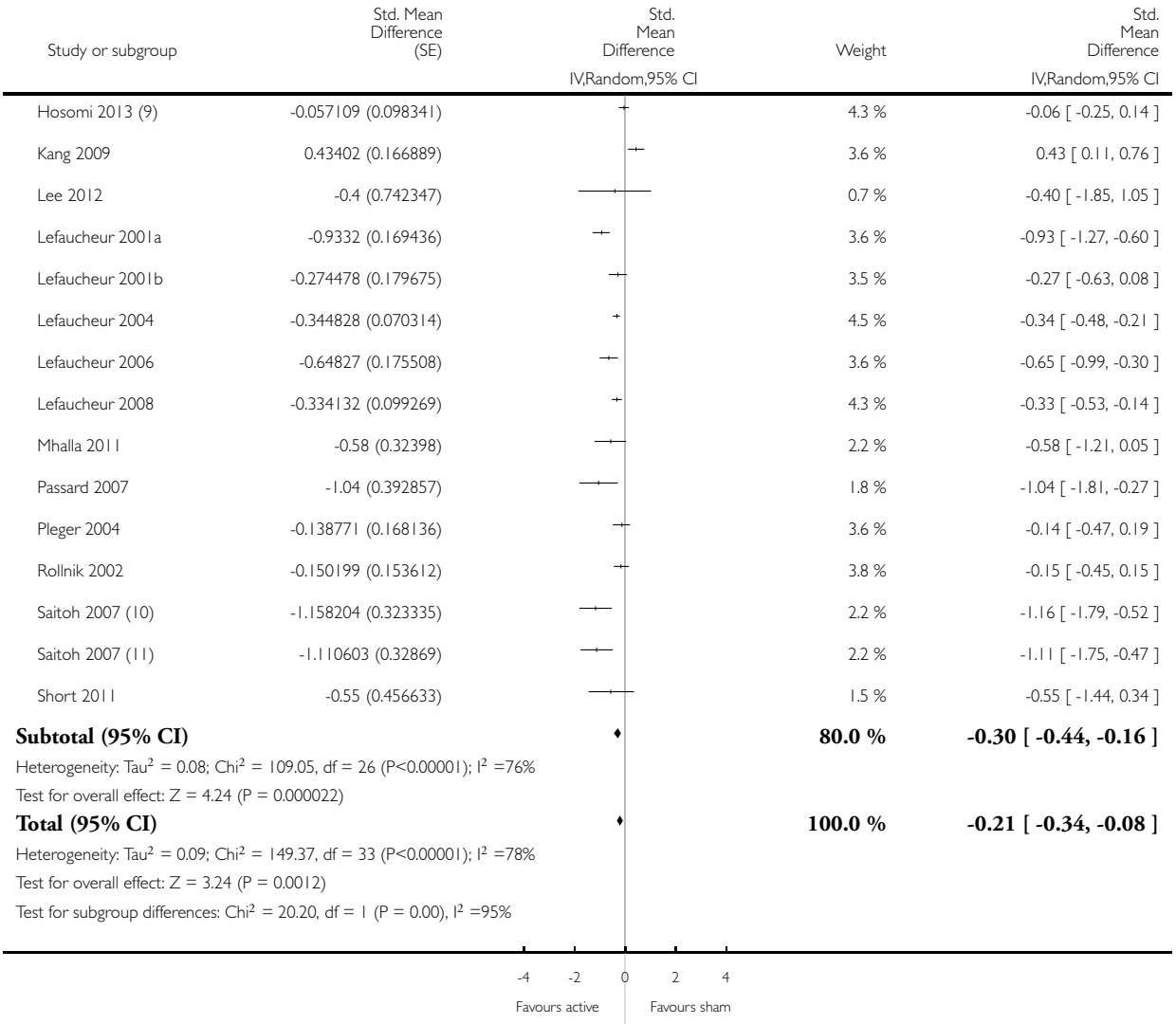


(1) 1Hz

(2) antero-posterior coil orientation

(3) medial-lateral coil orientation

(4) SMA

(5) M1

(6) S1

(7) PMA

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

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

(10) 10 Hz

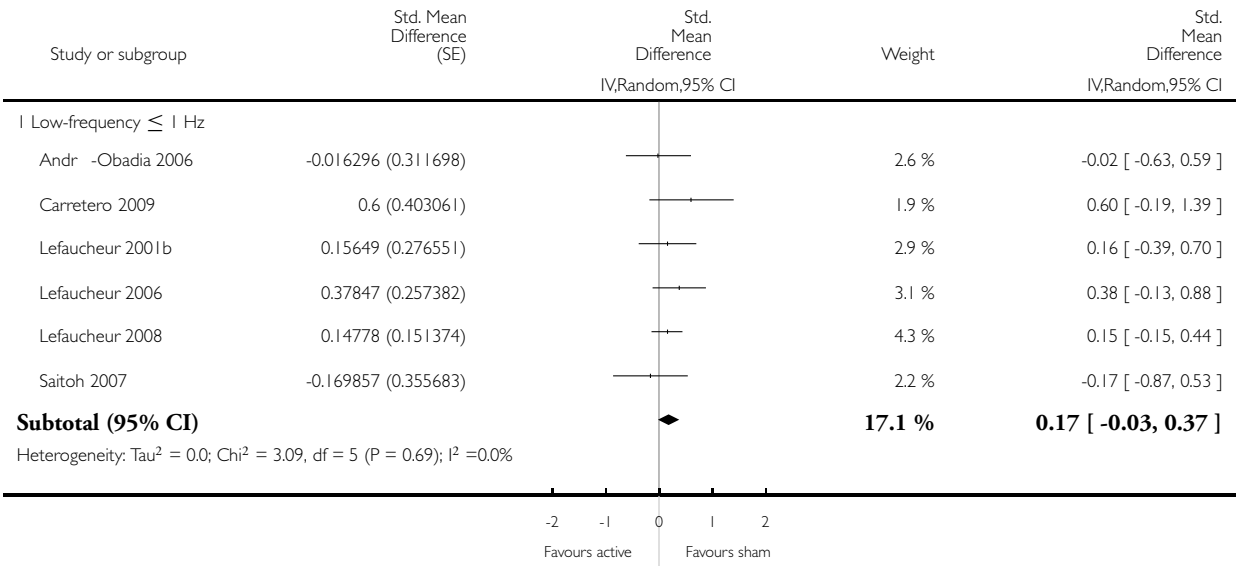
(11) 5Hz

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



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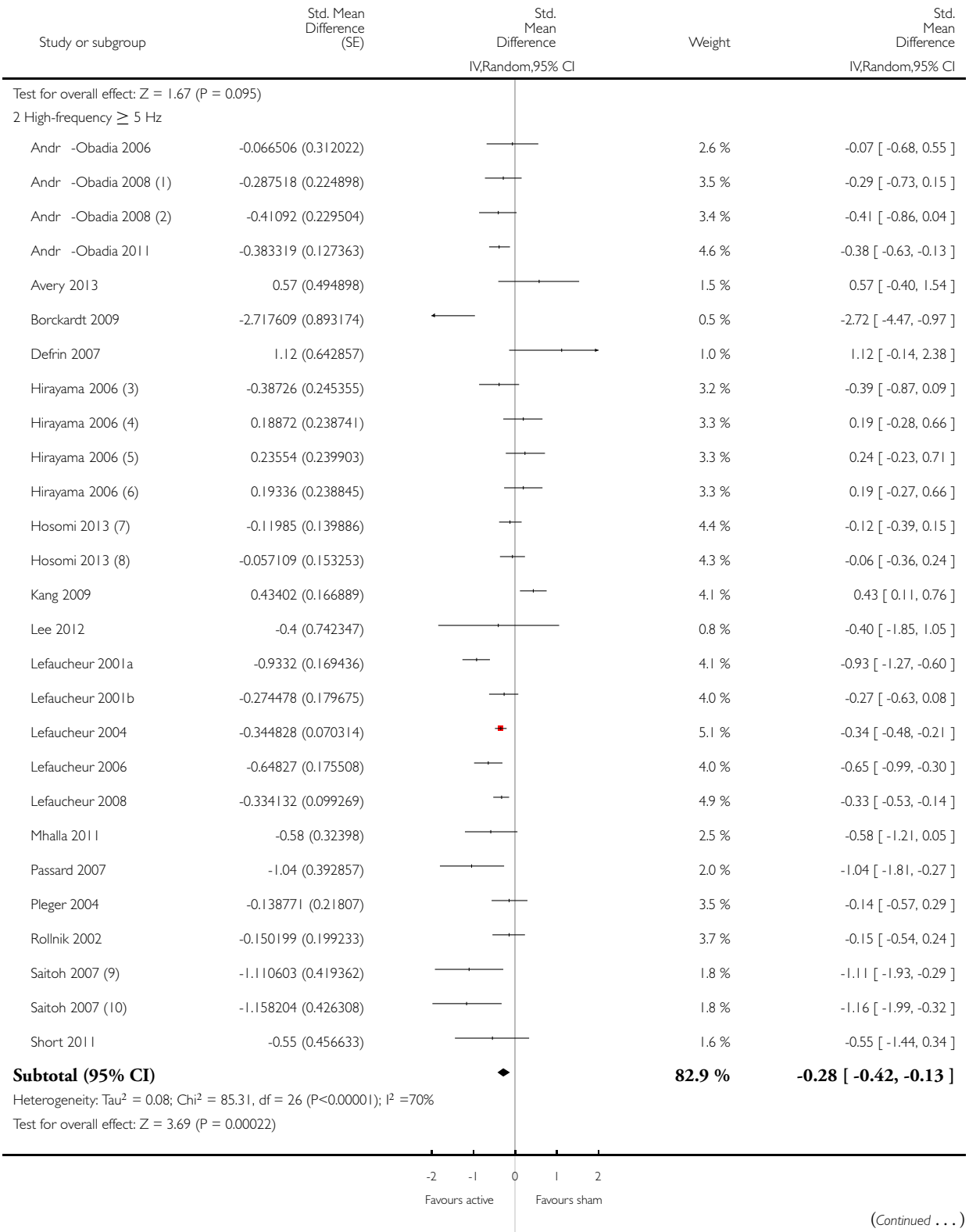

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Study or subgroup	Std. Mean Difference (SE)	Std. Mean Difference IV,Random,95% CI	Weight	Std. Mean Difference IV,Random,95% CI
Total (95% CI)		◆	**100.0 %**	**-0.20 [-0.34, -0.06]**
Heterogeneity: Tau² = 0.09; Chi² = 105.99, df = 32 (P<0.00001); I² =70%				
Test for overall effect: Z = 2.85 (P = 0.0044)				
Test for subgroup differences: Chi² = 12.45, df = 1 (P = 0.00), I² =92%				

(1) medial-lateral coil orientatioin

(2) antero-posterior coil orientation

(3) M1

(4) SMA

(5) S1

(6) PMA

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

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

(9) 10 Hz

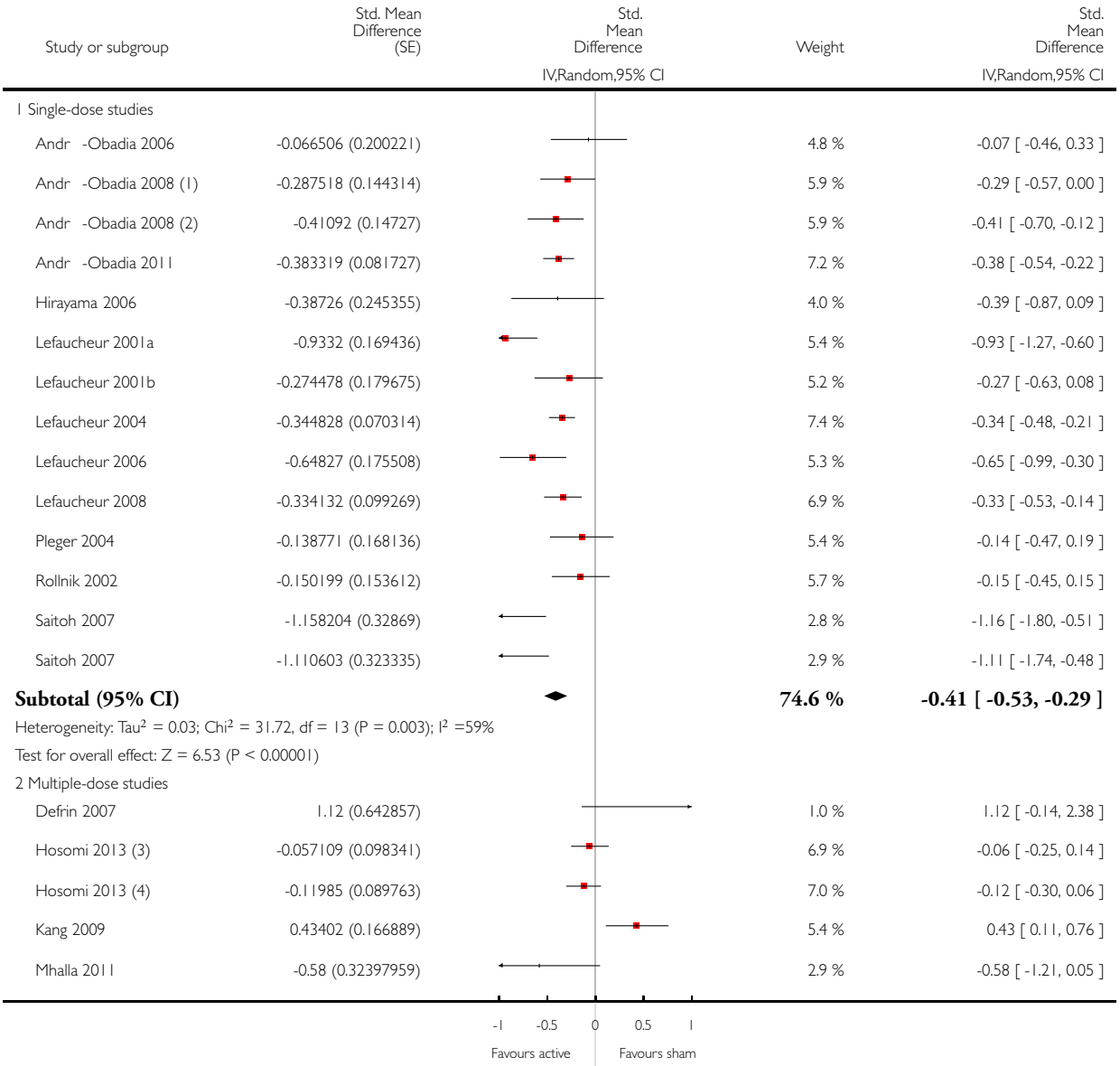
(10) 5Hz

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



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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
Passard 2007	-1.08 (0.393857)		2.2 %	-1.08 [-1.85, -0.31]
Subtotal (95% CI)			**25.4 %**	**-0.08 [-0.39, 0.23]**
Heterogeneity: Tau^2 = 0.09; Chi^2 = 21.85, df = 5 (P = 0.00056); I^2 =77%				
Test for overall effect: Z = 0.52 (P = 0.61)				
Total (95% CI)			**100.0 %**	**-0.33 [-0.47, -0.20]**
Heterogeneity: Tau^2 = 0.06; Chi^2 = 75.48, df = 19 (P<0.00001); I^2 =75%				
Test for overall effect: Z = 4.85 (P < 0.00001)				
Test for subgroup differences: Chi^2 = 3.62, df = 1 (P = 0.06), I^2 =72%				

(1) medial-lateral coil orientation

(2) antero-posterior coil orientation

(3) Group A (real followed by sham)

(4) Group B (sham followed by real)

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)		3.8 %	-0.07 [-0.68, 0.55]
Andr -Obadia 2008 (1)	-0.287518 (0.224898)		5.7 %	-0.29 [-0.73, 0.15]
Andr -Obadia 2008 (2)	-0.41092 (0.229504)		5.6 %	-0.41 [-0.86, 0.04]
Andr -Obadia 2011	-0.383319 (0.127363)		9.0 %	-0.38 [-0.63, -0.13]
Hirayama 2006	-0.38726 (0.382358)		2.8 %	-0.39 [-1.14, 0.36]
Lefaucheur 2001a	-0.9332 (0.264047)		4.7 %	-0.93 [-1.45, -0.42]
Lefaucheur 2001b	-0.274478 (0.280003)		4.4 %	-0.27 [-0.82, 0.27]
Lefaucheur 2004	-0.344828 (0.109577)		9.7 %	-0.34 [-0.56, -0.13]
Lefaucheur 2006	-0.64827 (0.312022)		3.8 %	-0.65 [-1.26, -0.04]
Lefaucheur 2008	-0.334132 (0.1547)		8.0 %	-0.33 [-0.64, -0.03]
Pleger 2004	-0.138771 (0.262021)		4.8 %	-0.14 [-0.65, 0.37]
Rollnik 2002	-0.150199 (0.239386)		5.3 %	-0.15 [-0.62, 0.32]
Saitoh 2007	-1.110603 (0.503881)		1.8 %	-1.11 [-2.10, -0.12]
Saitoh 2007	-1.158204 (0.512227)		1.7 %	-1.16 [-2.16, -0.15]
Subtotal (95% CI)			**71.1 %**	**-0.38 [-0.49, -0.27]**
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 12.83$, df = 13 (P = 0.46); $I^2 = 0.0\%$				
Test for overall effect: Z = 6.72 (P < 0.00001)				
2 Multiple-dose studies				
Defrin 2007	1.12 (0.642857)		1.2 %	1.12 [-0.14, 2.38]
Hosomi 2013 (3)	-0.11985 (0.139886)		8.5 %	-0.12 [-0.39, 0.15]
Hosomi 2013 (4)	-0.057109 (0.153253)		8.0 %	-0.06 [-0.36, 0.24]
Kang 2009	0.43402 (0.260078)		4.8 %	0.43 [-0.08, 0.94]
Mhalla 2011	-0.58 (0.32397959)		3.6 %	-0.58 [-1.21, 0.05]

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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
Passard 2007	-1.08 (0.392857)		2.7 %	-1.08 [-1.85, -0.31]
Subtotal (95% CI)			**28.9 %**	**-0.11 [-0.48, 0.25]**
Heterogeneity: Tau^2 = 0.13; Chi^2 = 16.33, df = 5 (P = 0.01); I^2 =69%				
Test for overall effect: Z = 0.61 (P = 0.54)				
Total (95% CI)			**100.0 %**	**-0.31 [-0.46, -0.17]**
Heterogeneity: Tau^2 = 0.04; Chi^2 = 36.36, df = 19 (P = 0.01); I^2 =48%				
Test for overall effect: Z = 4.30 (P = 0.000017)				
Test for subgroup differences: Chi^2 = 1.78, df = 1 (P = 0.18), I^2 =44%				

(1) medial-lateral coil orientation

(2) antero-posterior coil orientation

(3) Group A (sham followed by real)

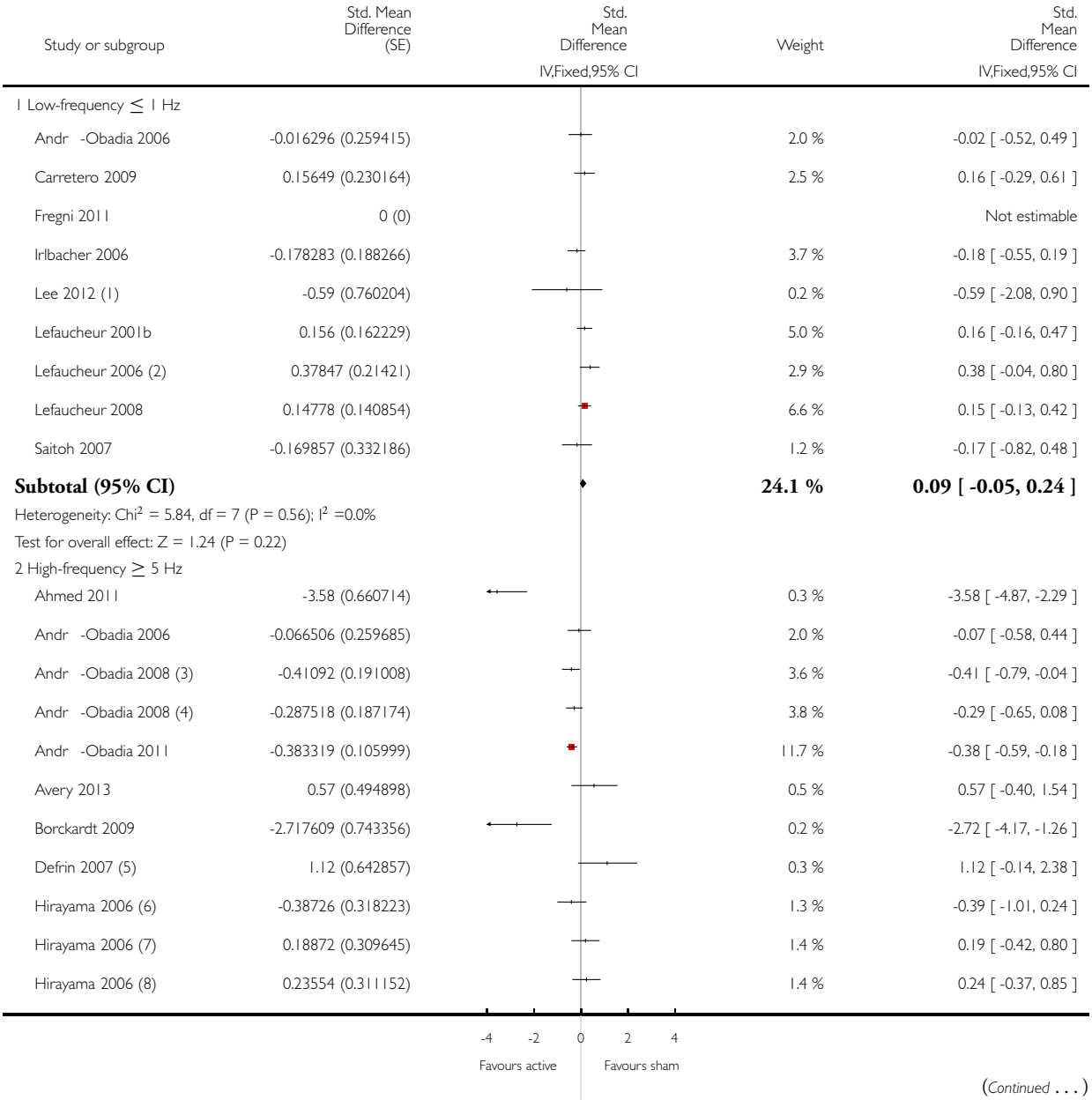
(4) Group A (real followed by sham)

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



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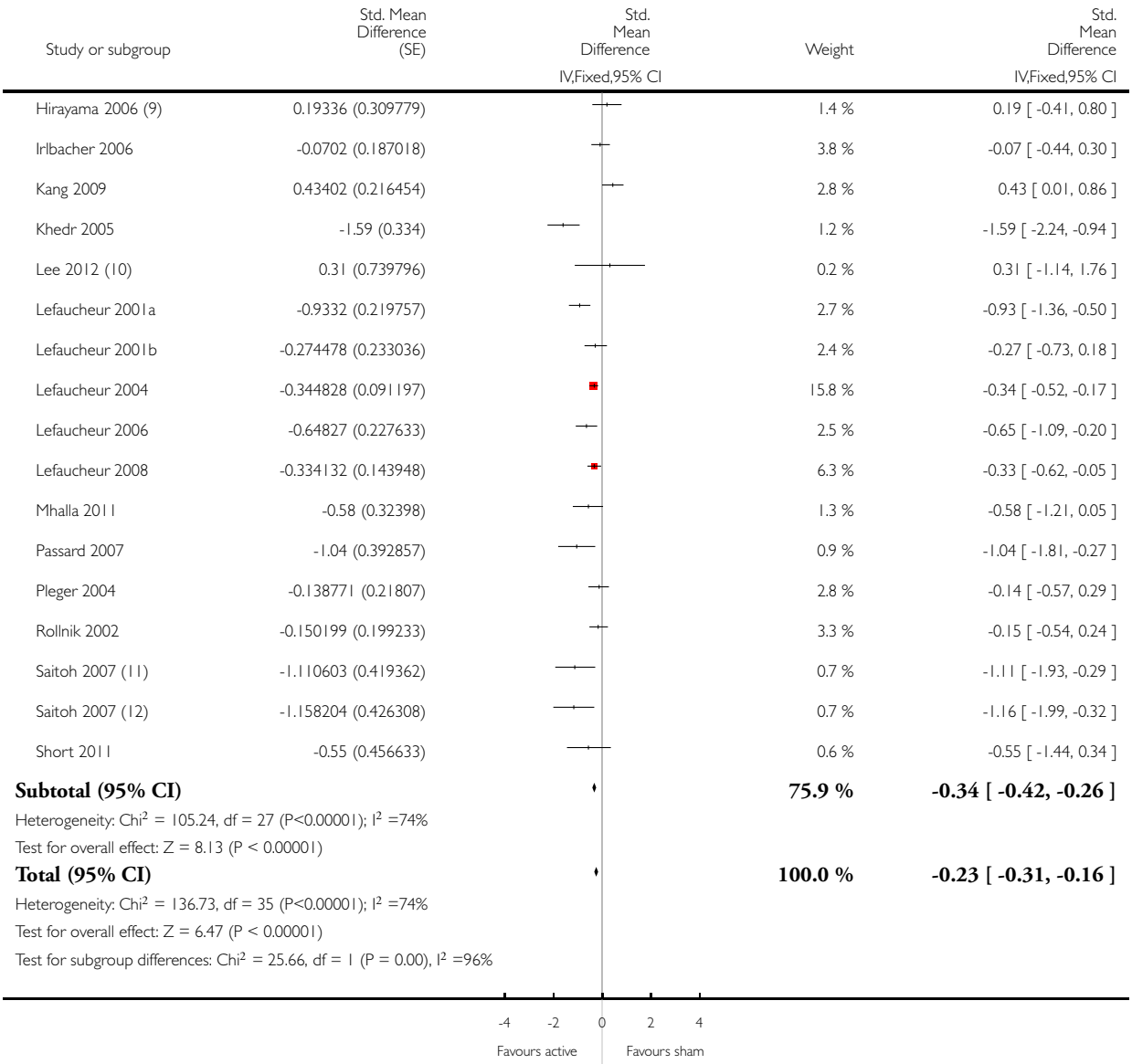

(1) right DLPFC

(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) SMA

(8) S1

(9) PMA

(10) left M1

(11) 10 Hz

(12) 5Hz

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)		4.1 %	-0.07 [-0.58, 0.44]
Andr -Obadia 2008 (1)	-0.41092 (0.191008)		4.9 %	-0.41 [-0.79, -0.04]
Andr -Obadia 2008 (2)	-0.287518 (0.187174)		5.0 %	-0.29 [-0.65, 0.08]
Andr -Obadia 2011	-0.383319 (0.149906)		5.4 %	-0.38 [-0.68, -0.09]
Hirayama 2006	-0.38726 (0.318223)		3.4 %	-0.39 [-1.01, 0.24]
Irlbacher 2006	-0.0702 (0.187018)		5.0 %	-0.07 [-0.44, 0.30]
Lefaucheur 2001a	-0.9332 (0.219757)		4.5 %	-0.93 [-1.36, -0.50]
Lefaucheur 2001b	-0.274478 (0.233036)		4.4 %	-0.27 [-0.73, 0.18]
Lefaucheur 2004	-0.344828 (0.091197)		6.0 %	-0.34 [-0.52, -0.17]
Lefaucheur 2006	-0.64827 (0.227633)		4.4 %	-0.65 [-1.09, -0.20]
Lefaucheur 2008	-0.334132 (0.143948)		5.5 %	-0.33 [-0.62, -0.05]
Mhalla 2011	-0.21 (0.316327)		3.4 %	-0.21 [-0.83, 0.41]
Pleger 2004	-0.138771 (0.21807)		4.6 %	-0.14 [-0.57, 0.29]
Rollnik 2002	-0.150199 (0.199233)		4.8 %	-0.15 [-0.54, 0.24]
Saitoh 2007	-1.158204 (0.426308)		2.5 %	-1.16 [-1.99, -0.32]
Saitoh 2007	-1.110603 (0.419362)		2.5 %	-1.11 [-1.93, -0.29]
Subtotal (95% CI)			**70.4 %**	**-0.36 [-0.48, -0.24]**
Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 21.60$, df = 15 (P = 0.12); $I^2 = 31\%$				
Test for overall effect: Z = 5.95 (P < 0.00001)				
2 Multiple-dose studies				
Ahmed 2011	-3.58 (0.660714)		1.3 %	-3.58 [-4.87, -2.29]
Defrin 2007	1.12 (0.642857)		1.4 %	1.12 [-0.14, 2.38]
Hosomi 2013 (3)	-0.11985 (0.116422)		5.8 %	-0.12 [-0.35, 0.11]

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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 (0.127547)		5.7 %	-0.06 [-0.31, 0.19]
Kang 2009	0.43402 (0.216454)		4.6 %	0.43 [0.01, 0.86]
Khedr 2005	-1.59 (0.334)		3.3 %	-1.59 [-2.24, -0.94]
Lee 2012	0.26 (0.635204)		1.4 %	0.26 [-0.98, 1.50]
Mhalla 2011	-0.58 (0.32397959)		3.4 %	-0.58 [-1.21, 0.05]
Passard 2007	-1.04 (0.392857)		2.7 %	-1.04 [-1.81, -0.27]
Subtotal (95% CI)			**29.6 %**	**-0.50 [-0.99, -0.01]**
Heterogeneity: Tau^2 = 0.41; Chi^2 = 64.43, df = 8 (P<0.00001); I^2 =88%				
Test for overall effect: Z = 1.99 (P = 0.046)				
Total (95% CI)			**100.0 %**	**-0.39 [-0.56, -0.23]**
Heterogeneity: Tau^2 = 0.11; Chi^2 = 90.00, df = 24 (P<0.00001); I^2 =73%				
Test for overall effect: Z = 4.59 (P < 0.00001)				
Test for subgroup differences: Chi^2 = 0.27, df = 1 (P = 0.60), I^2 =0.0%				

(1) antero-posterior coil orientation

(2) medial-lateral coil orientation

(3) Group A (sham followed by real)

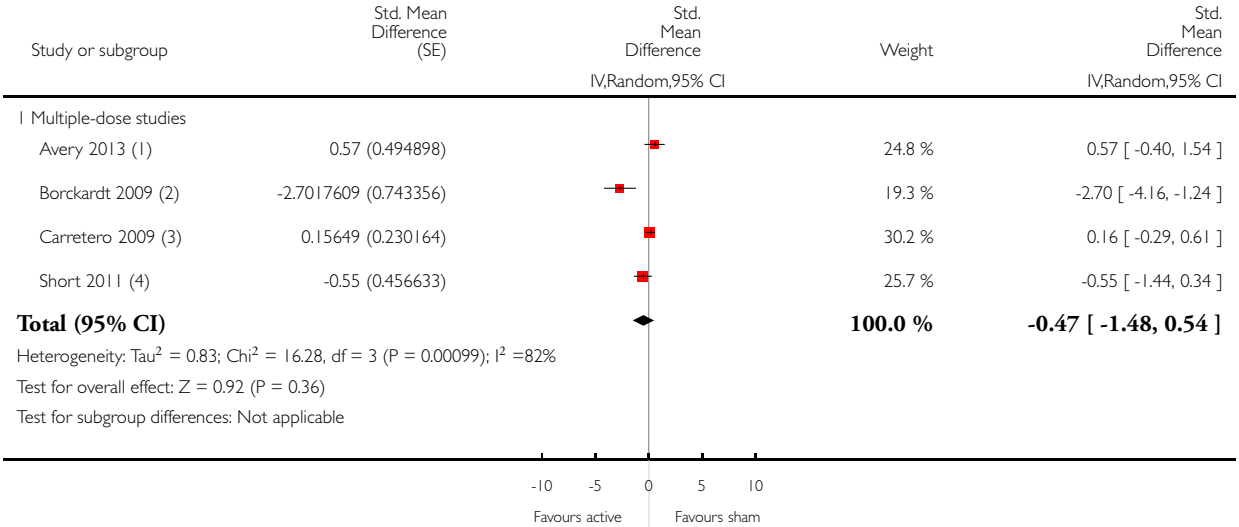
(4) Group B (real followed by sham)

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) 1 Hz

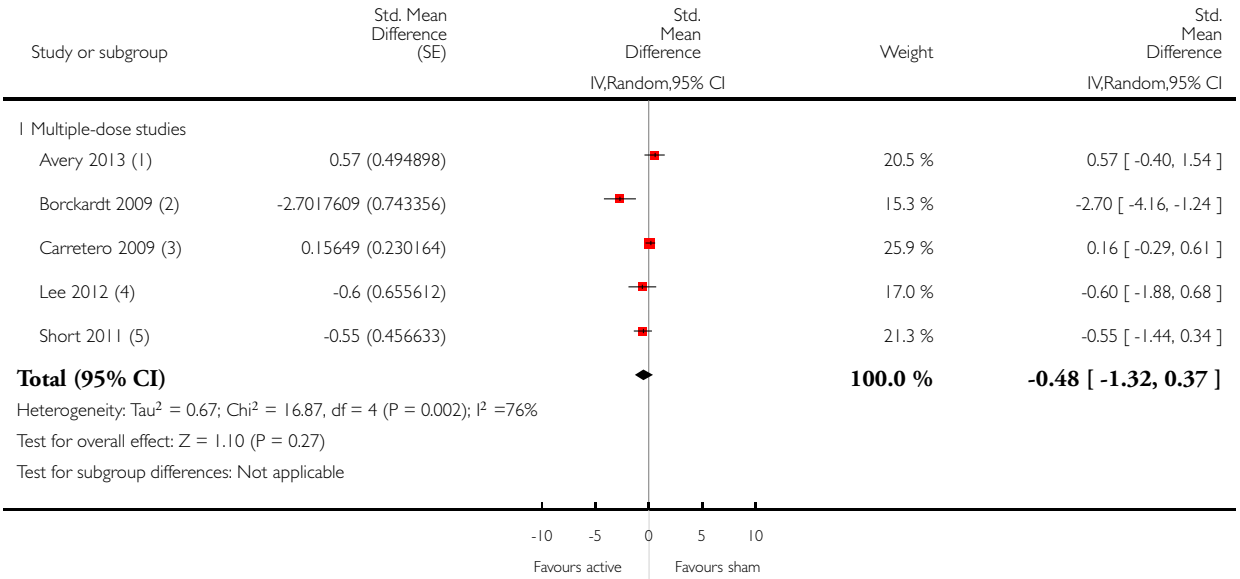
(4) 10Hz

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

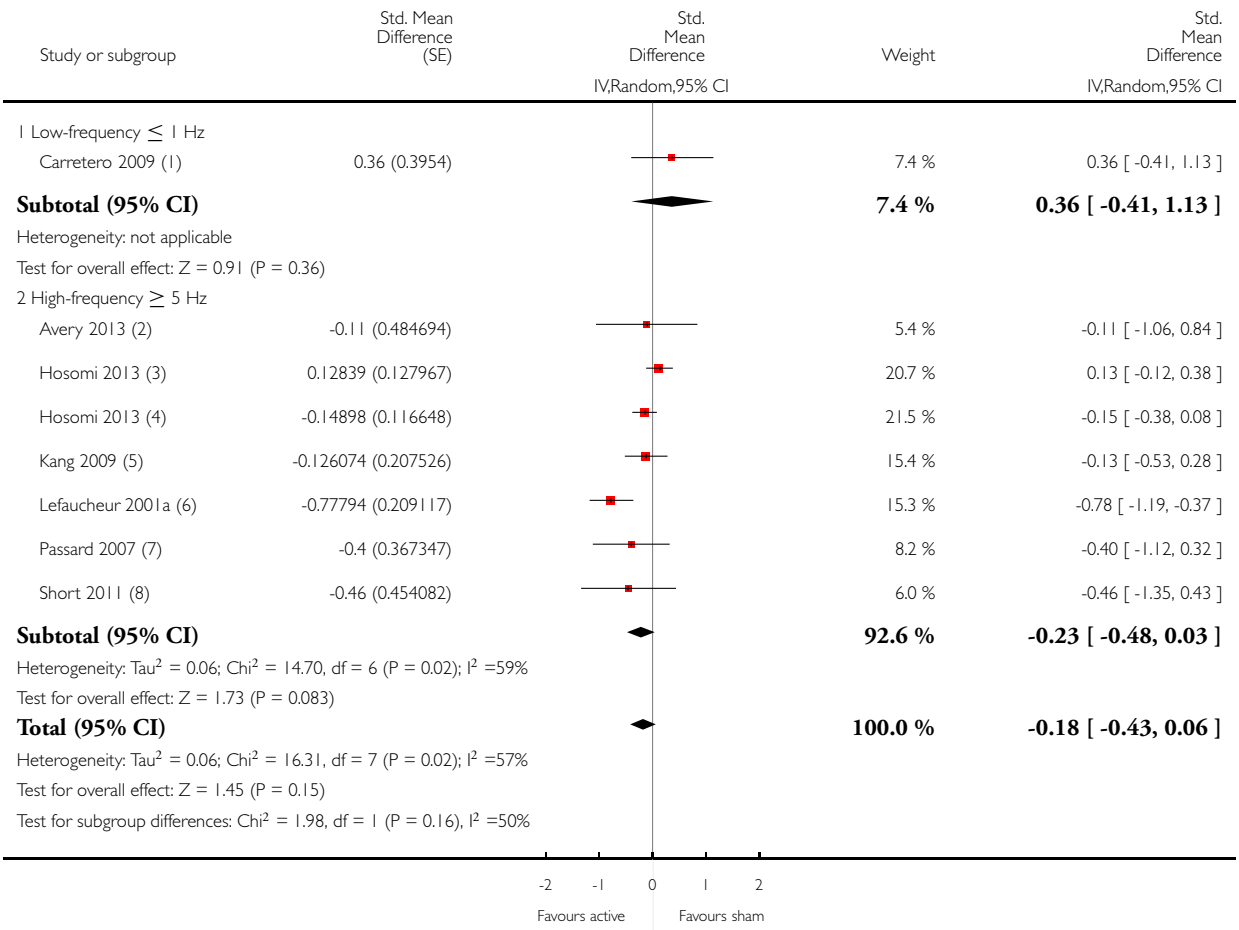
(5) 10Hz

Analysis 1.14. Comparison 1 Repetitive transcranial magnetic stimulation (rTMS), Outcome 14 Pain: medium-term follow-up.

Review: Non-invasive brain stimulation techniques for chronic pain

Comparison: 1 Repetitive transcranial magnetic stimulation (rTMS)

Outcome: 14 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)

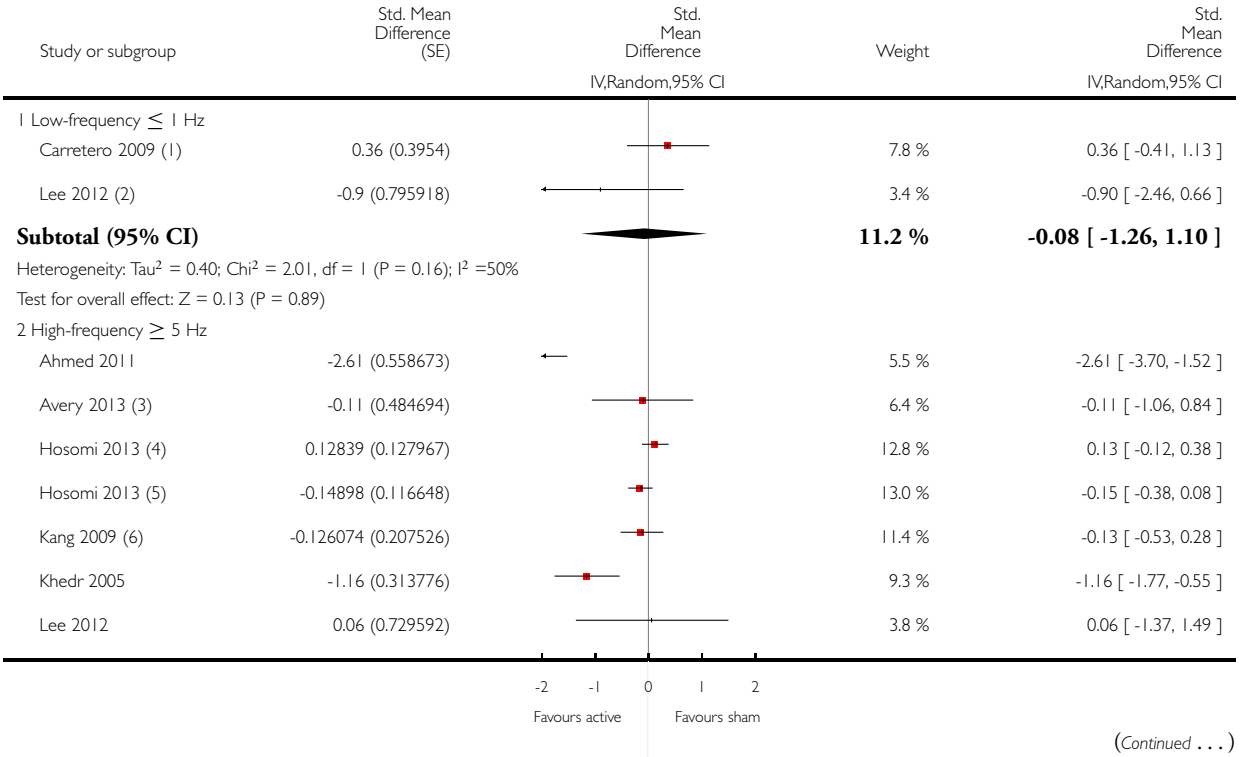
(8) DLPFC,10Hz, 2 weeks post treatment

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



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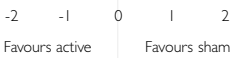
Study or subgroup	Std. Mean Difference (SE)	Std. Mean Difference IV,Random,95% CI	Weight	Std. Mean Difference IV,Random,95% CI
Lefaucheur 2001a (7)	-0.77794 (0.209117)		11.4 %	-0.78 [-1.19, -0.37]
Passard 2007 (8)	-0.4 (0.367347)		8.3 %	-0.40 [-1.12, 0.32]
Short 2011 (9)	-0.46 (0.454082)		6.9 %	-0.46 [-1.35, 0.43]
Subtotal (95% CI)			**88.8 %**	**-0.48 [-0.83, -0.13]**
Heterogeneity: Tau^2 = 0.21; Chi^2 = 43.06, df = 9 (P<0.00001); I^2 =79%				
Test for overall effect: Z = 2.68 (P = 0.0074)				
Total (95% CI)			**100.0 %**	**-0.43 [-0.76, -0.10]**
Heterogeneity: Tau^2 = 0.20; Chi^2 = 45.98, df = 11 (P<0.00001); I^2 =76%				
Test for overall effect: Z = 2.56 (P = 0.011)				
Test for subgroup differences: Chi^2 = 0.41, df = 1 (P = 0.52), I^2 =0.0%				



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

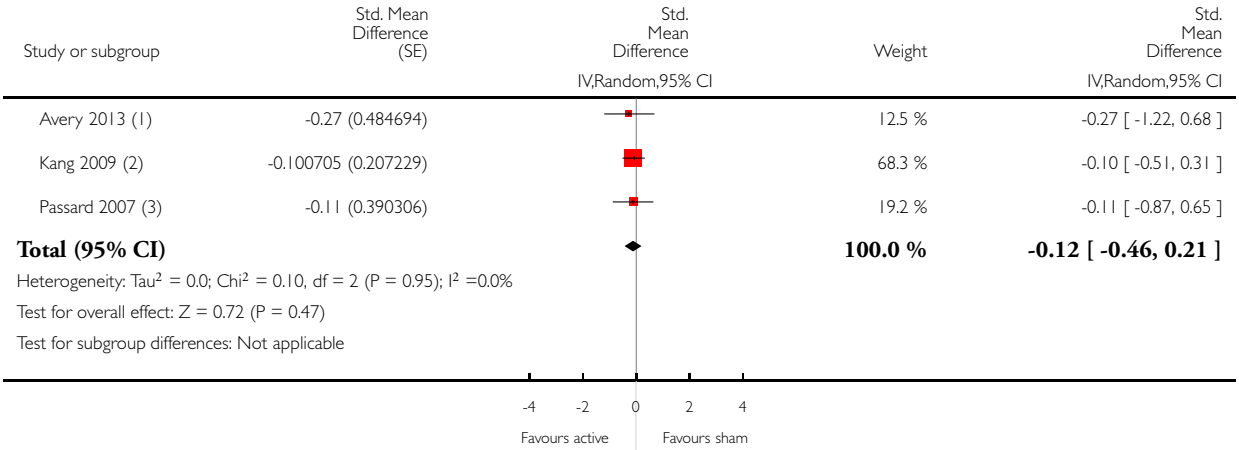
(9) DLPFC 2 weeks post treatment

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

Review: Non-invasive brain stimulation techniques for chronic pain

Comparison: 1 Repetitive transcranial magnetic stimulation (rTMS)

Outcome: 16 Pain: long-term follow-up



(1) 3 month follow up

(2) 7 week follow up

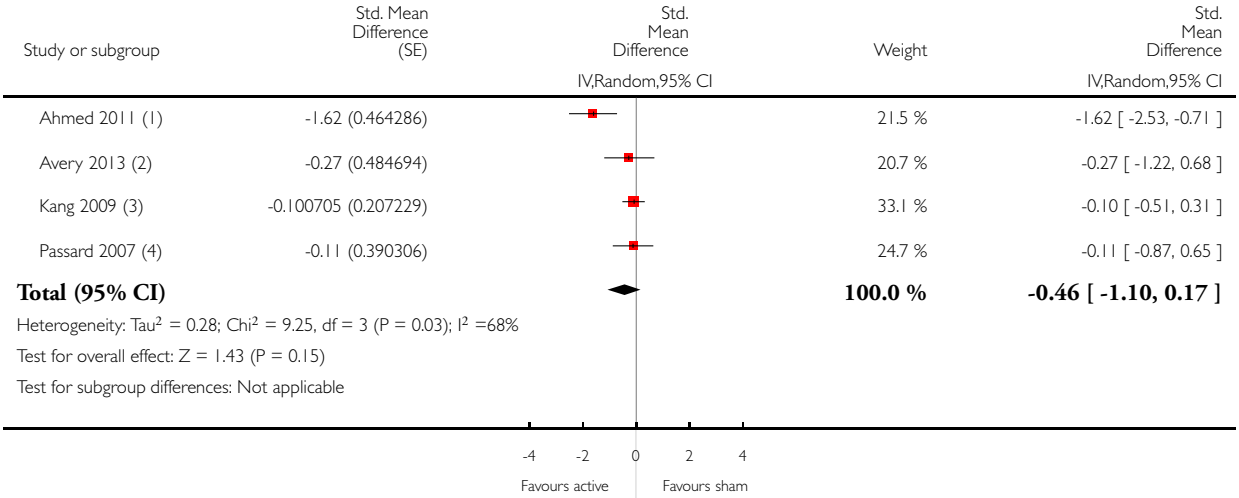
(3) 60 day follow up

Analysis 1.17. Comparison 1 Repetitive transcranial magnetic stimulation (rTMS), Outcome 17 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: 17 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

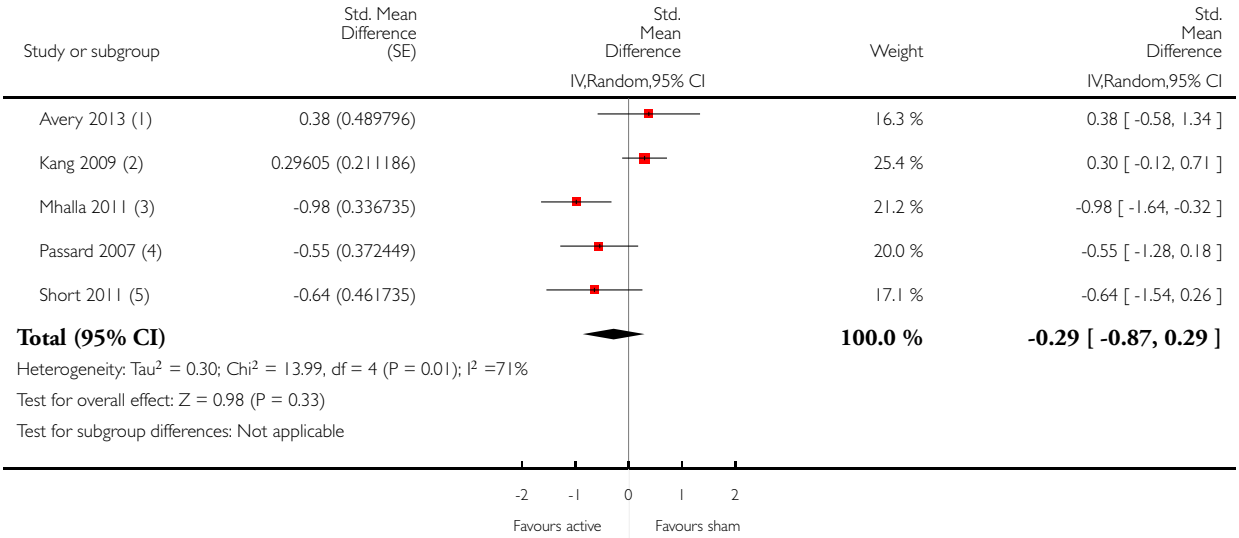
(4) 10Hz, M1, 60 day follow up

Analysis 1.18. Comparison 1 Repetitive transcranial magnetic stimulation (rTMS), Outcome 18 Disability/pain interference: short-term follow-up.

Review: Non-invasive brain stimulation techniques for chronic pain

Comparison: 1 Repetitive transcranial magnetic stimulation (rTMS)

Outcome: 18 Disability/pain interference: 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

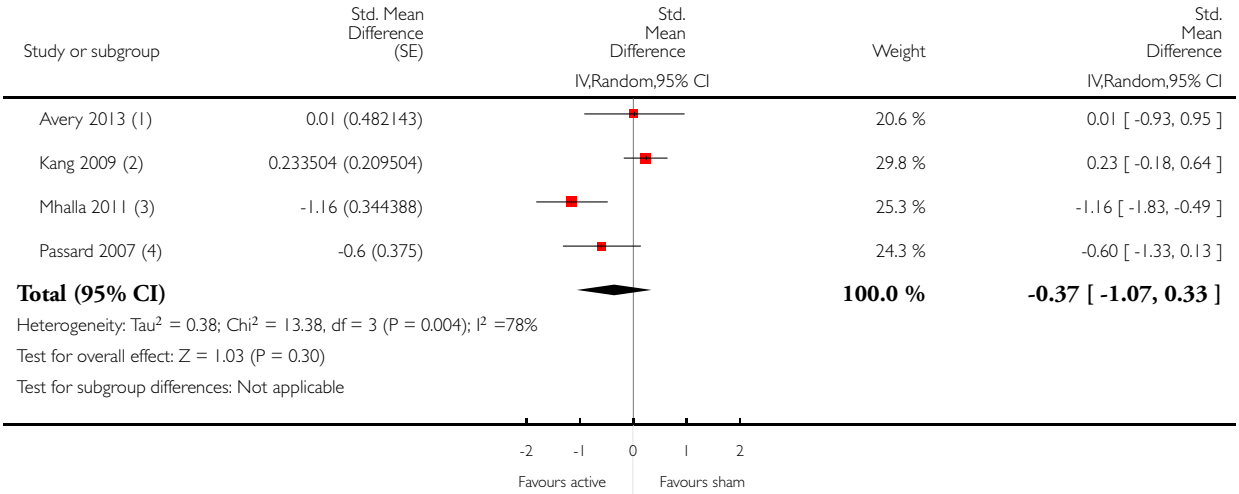
(5) BPI functional impairment end of 2 week treatment period

Analysis 1.19. Comparison 1 Repetitive transcranial magnetic stimulation (rTMS), Outcome 19 Disability/pain interference: medium-term follow-up.

Review: Non-invasive brain stimulation techniques for chronic pain

Comparison: 1 Repetitive transcranial magnetic stimulation (rTMS)

Outcome: 19 Disability/pain interference: 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

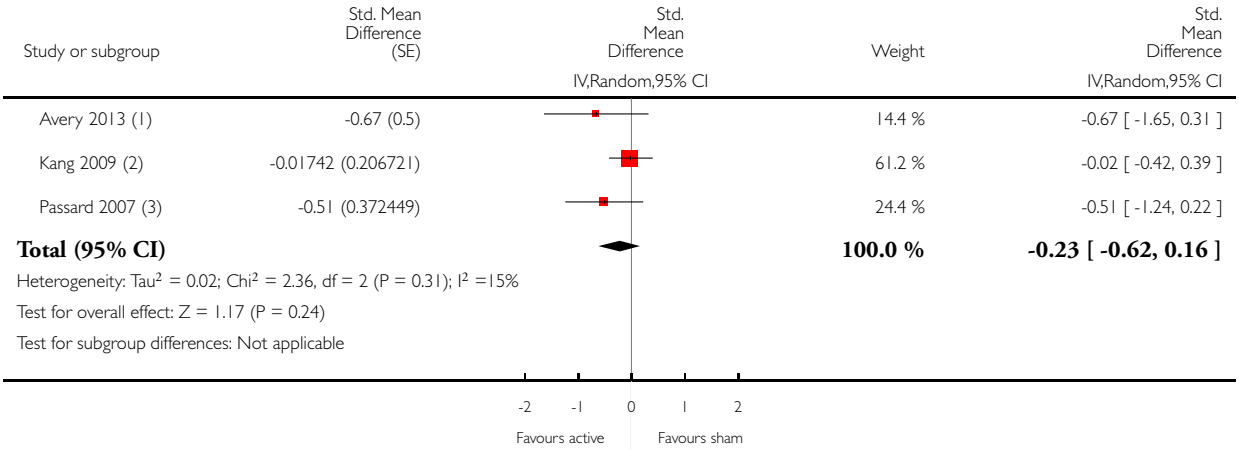
(4) BPI general activity subscale. 16 days post stim period

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

Review: Non-invasive brain stimulation techniques for chronic pain

Comparison: 1 Repetitive transcranial magnetic stimulation (rTMS)

Outcome: 20 Disability/pain interference: 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 1.21. Comparison 1 Repetitive transcranial magnetic stimulation (rTMS), Outcome 21 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)

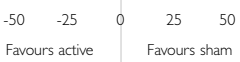
Outcome: 21 Quality of life: short-term follow-up (Fibromyalgia Impact Questionnaire)

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)		20.5 %	-10.70 [-20.67, -0.73]
Passard 2007 (2)	15	47.4 (8.1)	15	57.8 (6.8)		71.1 %	-10.40 [-15.75, -5.05]
Short 2011 (3)	10	42.07 (18.13)	10	51.5 (17.32)		8.4 %	-9.43 [-24.97, 6.11]
Total (95% CI)	**41**		**39**			**100.0 %**	**-10.38 [-14.89, -5.87]**

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.02$, df = 2 (P = 0.99); $I^2 = 0.0\%$

Test for overall effect: Z = 4.51 (P < 0.00001)

Test for subgroup differences: Not applicable



(1) M1, 10Hz

(2) M1, 10Hz

(3) DLPFC, 10Hz

Analysis 1.22. Comparison 1 Repetitive transcranial magnetic stimulation (rTMS), Outcome 22 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: 22 Quality of life: medium-term follow-up (Fibromyalgia Impact Questionnaire)

Study or subgroup	Active stimulation N	Mean(SD)	Sham stimulation N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Mhalla 2011 (1)	16	56 (17.7)	14	63.3 (15)		22.5 %	-7.30 [-19.00, 4.40]
Passard 2007 (2)	15	48.7 (10.4)	15	62.2 (8.9)		64.1 %	-13.50 [-20.43, -6.57]
Short 2011 (3)	10	38.99 (19.44)	10	47.93 (14.7)		13.5 %	-8.94 [-24.05, 6.17]
Total (95% CI)	**41**		**39**			**100.0 %**	**-11.49 [-17.04, -5.95]**

Heterogeneity: $Chi^2 = 0.93$, df = 2 (P = 0.63); $I^2 = 0.0\%$

Test for overall effect: Z = 4.06 (P = 0.000049)

Test for subgroup differences: Not applicable

(1) M1, 10Hz

(2) M1, 10Hz

(3) DLPFC, 10Hz

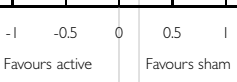
Analysis 1.23. Comparison 1 Repetitive transcranial magnetic stimulation (rTMS), Outcome 23 Quality of life: long-term follow-up.

Review: Non-invasive brain stimulation techniques for chronic pain

Comparison: 1 Repetitive transcranial magnetic stimulation (rTMS)

Outcome: 23 Quality of life: long-term follow-up

Study or subgroup	Std. Mean Difference (SE)	Std. Mean Difference IV,Random,95% CI	Std. Mean Difference IV,Random,95% CI
Passard 2007 (1)	-0.61 (0.375)		-0.61 [-1.34, 0.12]



(1) 46 days post stimulation. Fibromyalgia impact questionnaire (total score)

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 Disability/function/pain interference.

Review: Non-invasive brain stimulation techniques for chronic pain

Comparison: 2 Cranial electrotherapy stimulation (CES)

Outcome: 2 Disability/function/pain interference

Study or subgroup	Active stimulation N	Mean(SD)	Sham stimulation N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Tan 2011 (1)	45	39.5 (24.3)	55	32.2 (23.8)			7.30 [-2.19, 16.79]
Subtotal (95% CI)	**0**		**0**				**0.0 [0.0, 0.0]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.0 (P < 0.00001)							
Test for subgroup differences: Not applicable							

(1) Baseline imbalances on this outcome

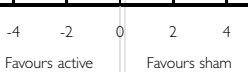
Analysis 2.3. Comparison 2 Cranial electrotherapy stimulation (CES), Outcome 3 Quality of life.

Review: Non-invasive brain stimulation techniques for chronic pain

Comparison: 2 Cranial electrotherapy stimulation (CES)

Outcome: 3 Quality of life

Study or subgroup	Active stimulation N	Mean(SD)	Sham stimulation N	Mean(SD)	Std. Mean Difference IV,Random,95% CI	Weight	Std. Mean Difference IV,Random,95% CI
Taylor 2013 (1)	18	45.05 (16.27)	18	70.1 (22.34)			-1.25 [-1.98, -0.53]
Subtotal (95% CI)	**0**		**0**				**0.0 [0.0, 0.0]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.0 (P < 0.00001)							
Test for subgroup differences: Not applicable							



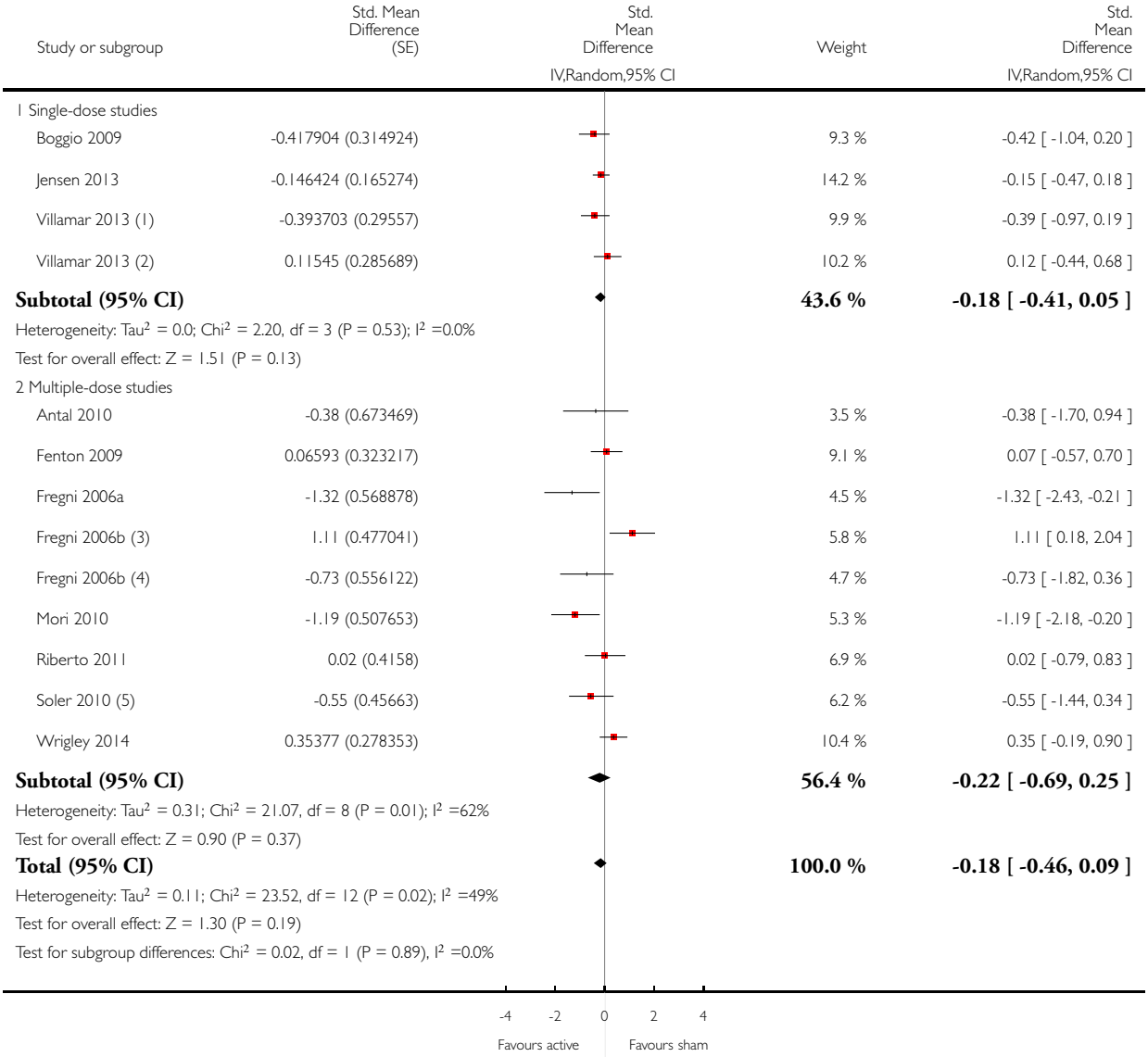
(1) Fibromyalgia Impact Questionnaire

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



(1) cathodal

(2) anodal

(3) DLPFC

(4) M1

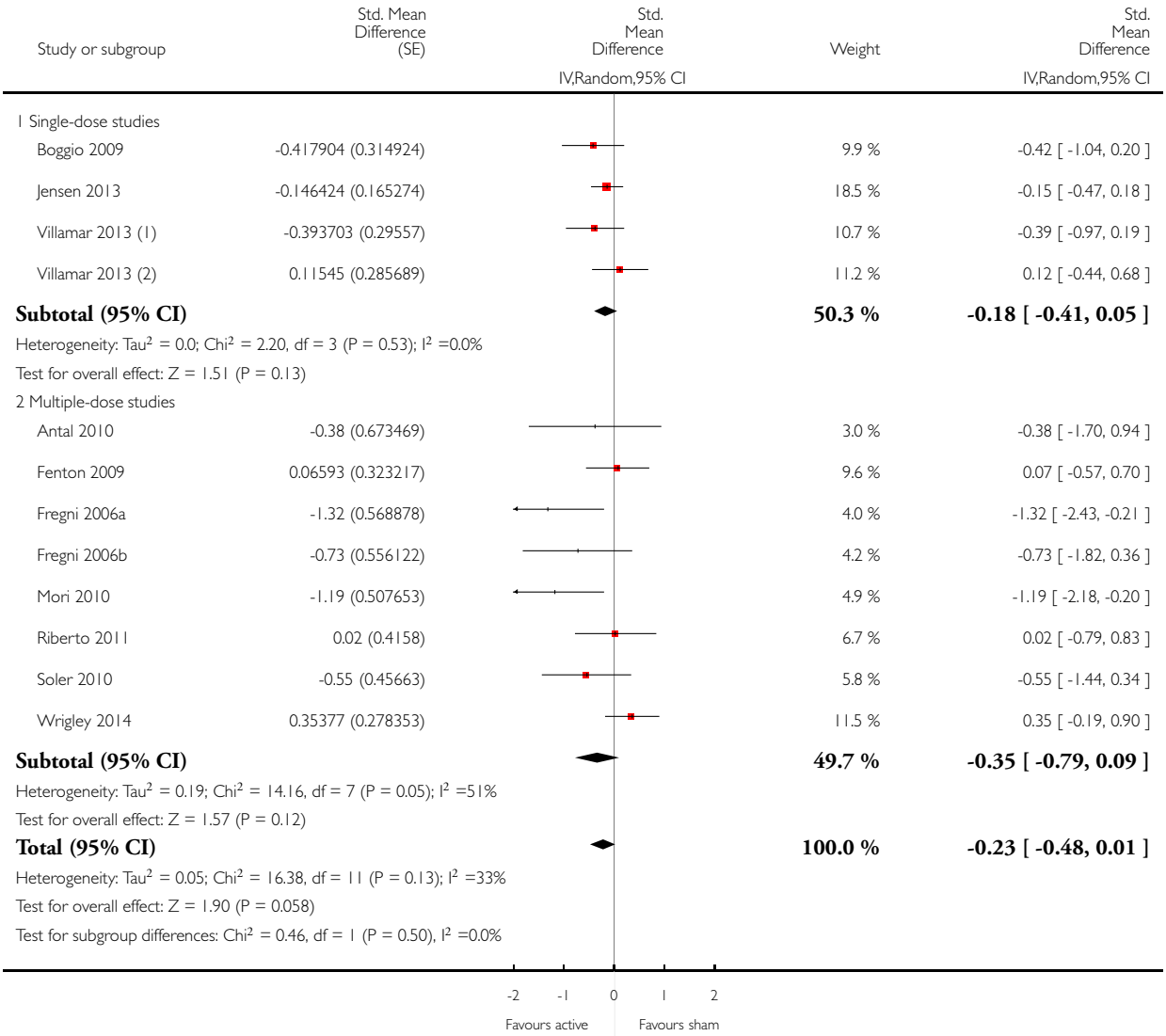
(5) tDCS+ sham illusion vs sham tDCS + sham illusion

Analysis 3.2. Comparison 3 Transcranial direct current stimulation (tDCS), Outcome 2 Pain: short-term 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: 2 Pain: short-term follow-up, subgroup analysis: motor cortex studies only



(1) cathodal

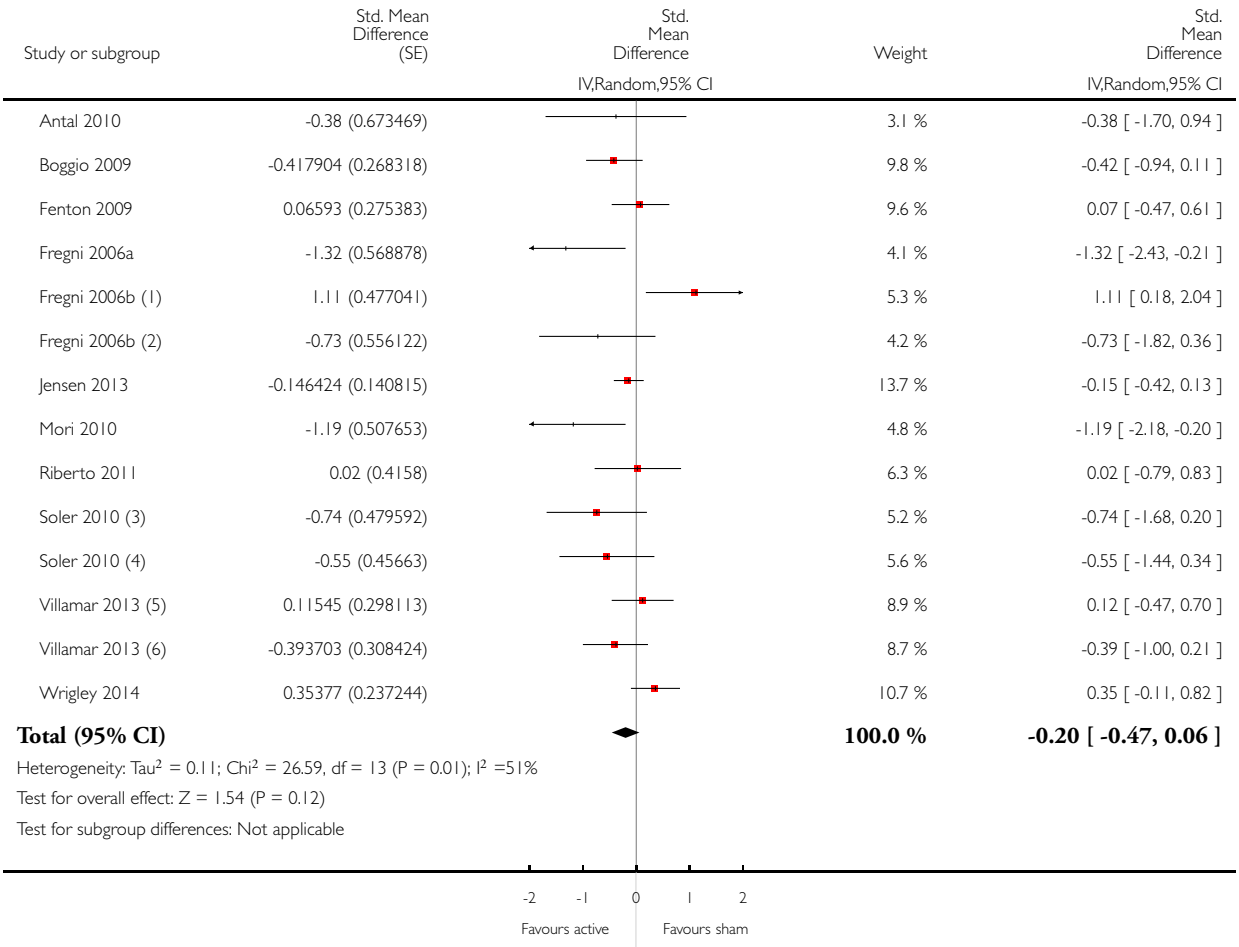
(2) anodal

Analysis 3.3. Comparison 3 Transcranial direct current stimulation (tDCS), Outcome 3 Pain: short-term sensitivity analysis: correlation increased.

Review: Non-invasive brain stimulation techniques for chronic pain

Comparison: 3 Transcranial direct current stimulation (tDCS)

Outcome: 3 Pain: short-term sensitivity analysis: correlation increased



(1) DLPFC

(2) M1

(3) tDCS+ illusion vs sham TDCS + illusion

(4) tDCS+ sham illusion vs sham TDCS + sham illusion

(5) anodal

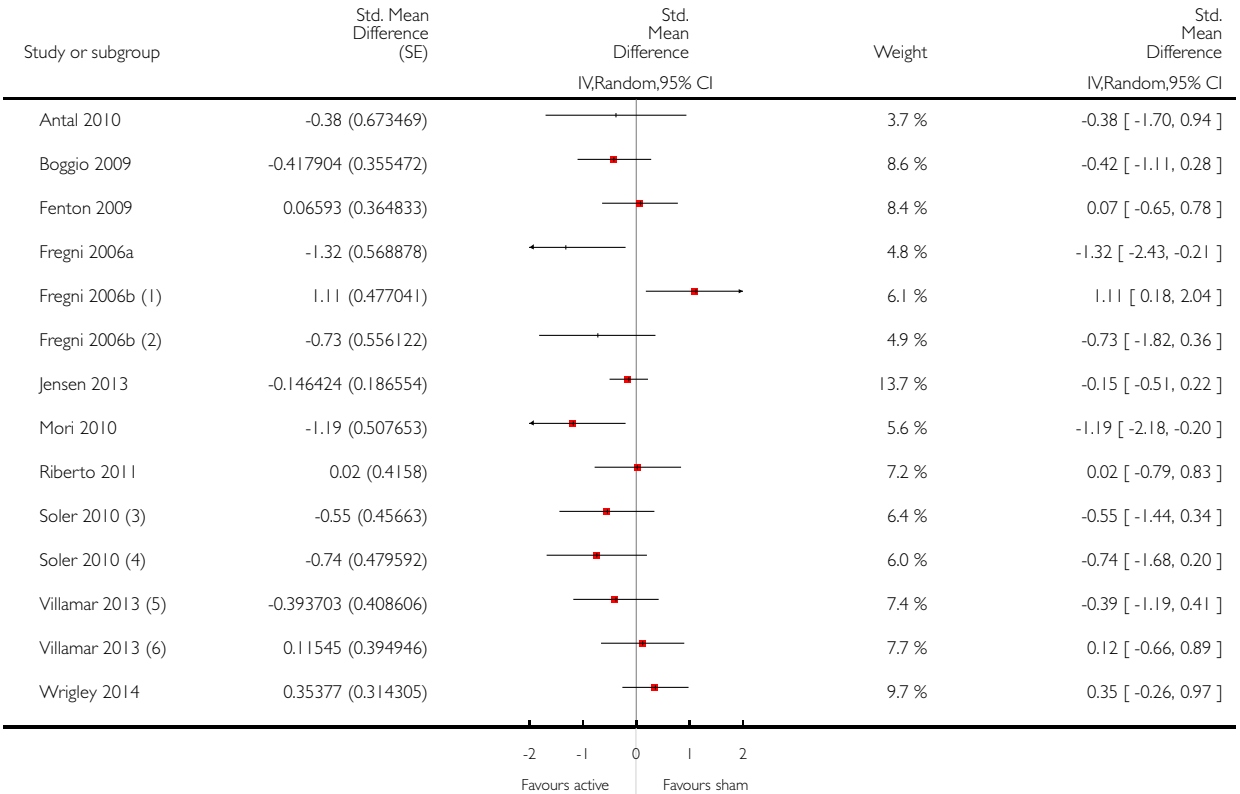
(6) cathodal

Analysis 3.4. Comparison 3 Transcranial direct current stimulation (tDCS), Outcome 4 Pain: short-term sensitivity analysis: correlation decreased.

Review: Non-invasive brain stimulation techniques for chronic pain

Comparison: 3 Transcranial direct current stimulation (tDCS)

Outcome: 4 Pain: short-term sensitivity analysis: correlation decreased



(*Continued* . . .)

(. . . *Continued*)

Study or subgroup	Std. Mean Difference (SE)	Std. Mean Difference IV,Random,95% CI	Weight	Std. Mean Difference IV,Random,95% CI
Total (95% CI)			**100.0 %**	**-0.23 [-0.51, 0.06]**

Heterogeneity: $Tau^2 = 0.12$; $Chi^2 = 23.26$, df = 13 (P = 0.04); $I^2 = 44\%$

Test for overall effect: Z = 1.56 (P = 0.12)

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) cathodal

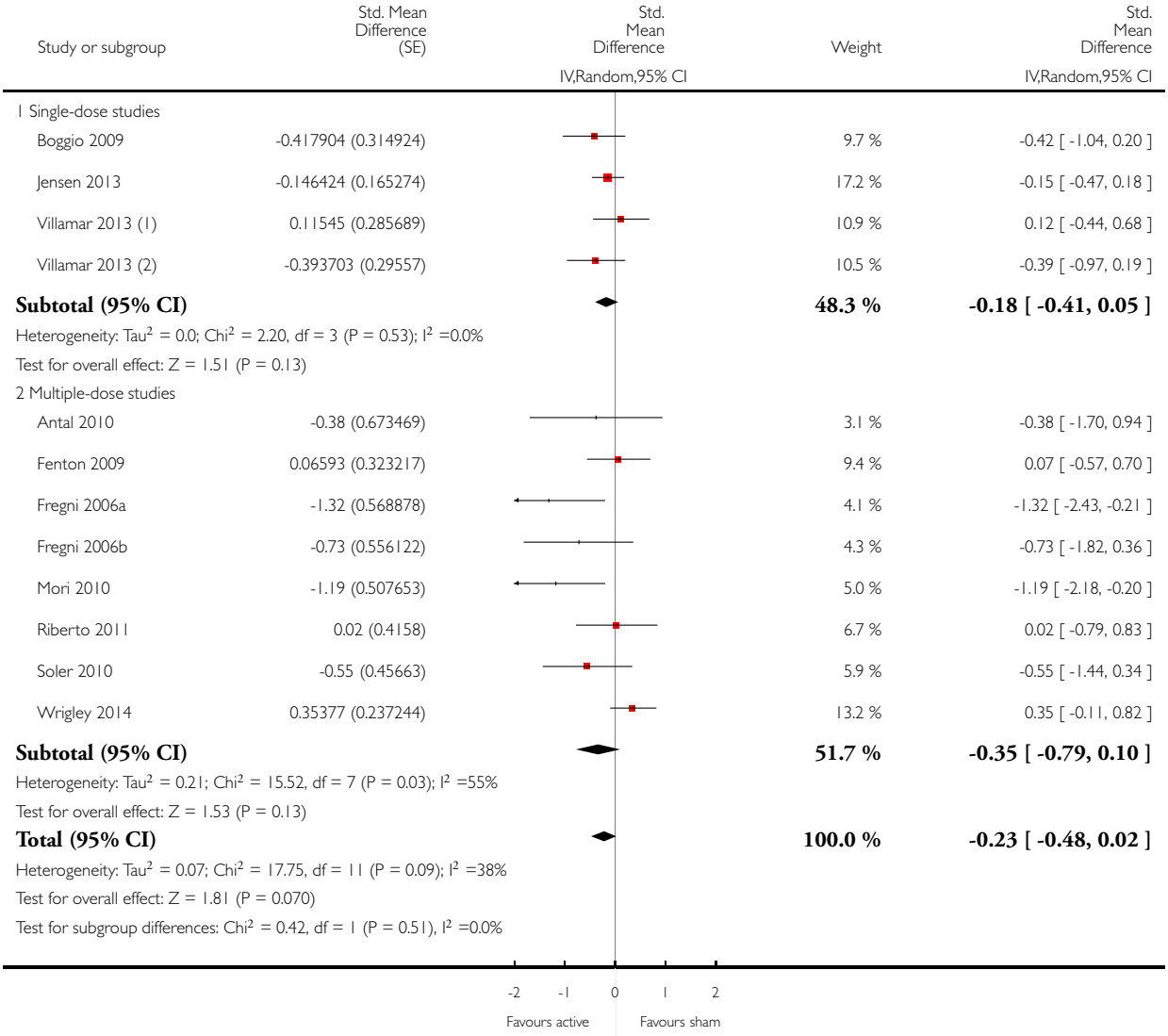
(6) anodal

Analysis 3.5. Comparison 3 Transcranial direct current stimulation (tDCS), Outcome 5 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: 5 Pain: short-term follow-up, subgroup analysis: motor cortex studies only, sensitivity analysis: correlation increased



(1) anodal

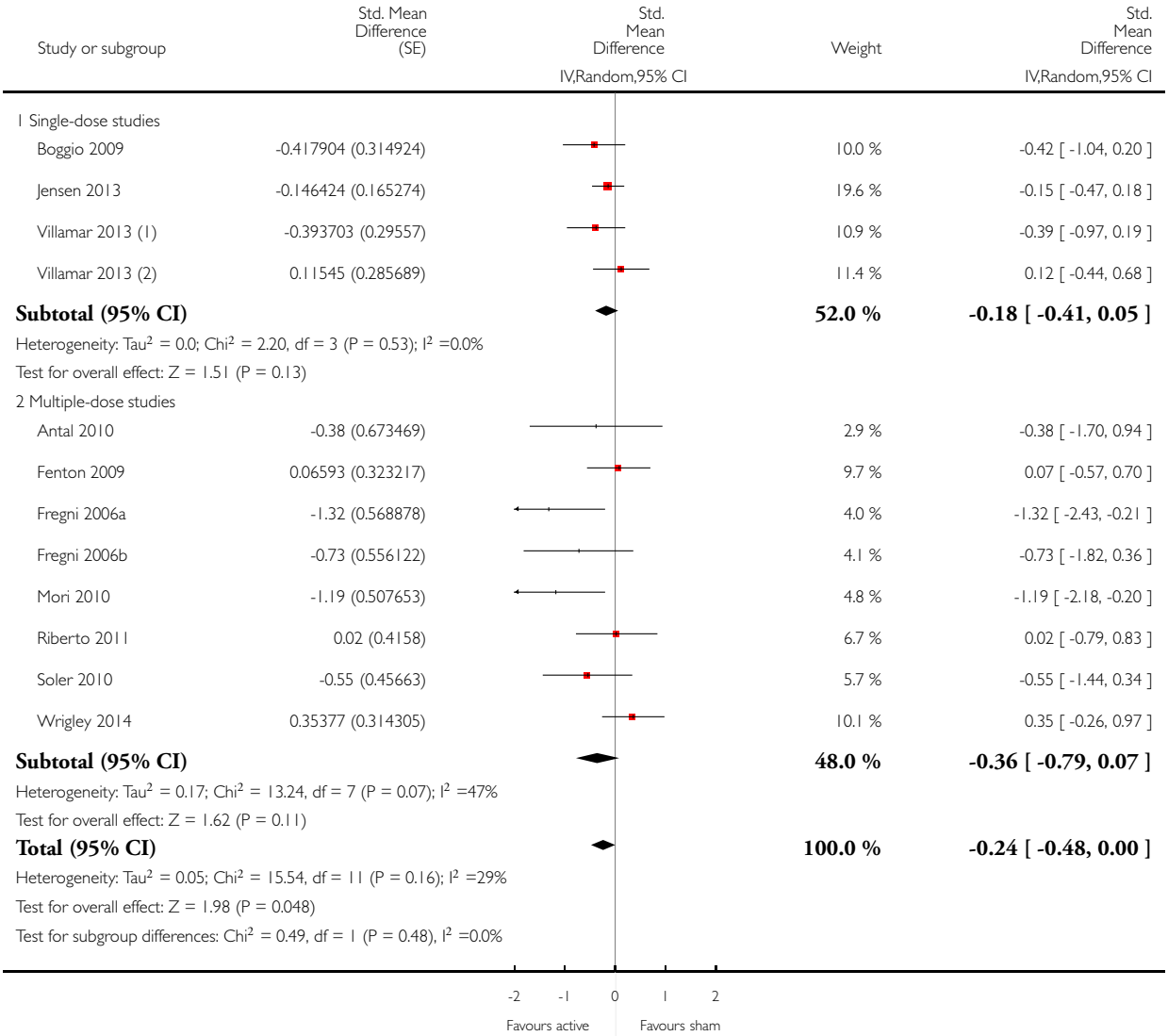
(2) cathodal

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 decreased.

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 decreased



(1) cathodal

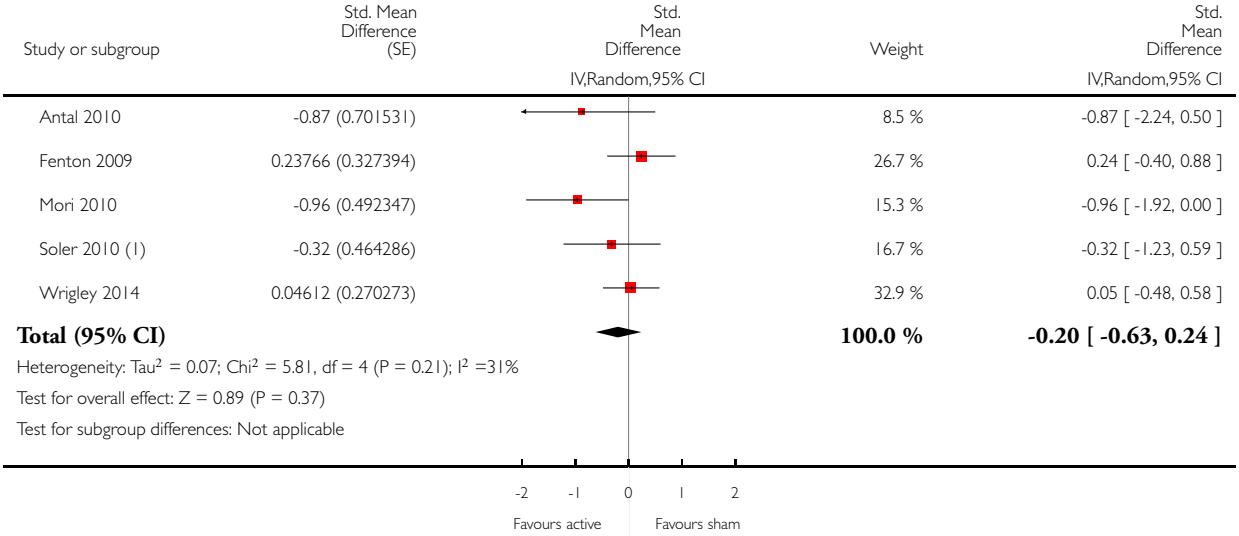
(2) anodal

Analysis 3.7. Comparison 3 Transcranial direct current stimulation (tDCS), Outcome 7 Pain: medium-term follow-up.

Review: Non-invasive brain stimulation techniques for chronic pain

Comparison: 3 Transcranial direct current stimulation (tDCS)

Outcome: 7 Pain: medium-term follow-up



(1) tDCS+sham illusion versus sham tDCS + sham illusion

Analysis 3.8. Comparison 3 Transcranial direct current stimulation (tDCS), Outcome 8 Disability (pain interference): short-term follow-up.

Review: Non-invasive brain stimulation techniques for chronic pain

Comparison: 3 Transcranial direct current stimulation (tDCS)

Outcome: 8 Disability (pain interference): short-term follow-up

Study or subgroup	Active N	Mean(SD)	Sham N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Soler 2010	10	4 (3.4)	10	4.9 (2.8)			-0.90 [-3.63, 1.83]
Subtotal (95% CI)	**0**		**0**				**0.0 [0.0, 0.0]**

Heterogeneity: not applicable

Test for overall effect: Z = 0.0 (P < 0.00001)

Test for subgroup differences: Not applicable

Analysis 3.9. Comparison 3 Transcranial direct current stimulation (tDCS), Outcome 9 Quality of life: short-term follow-up.

Review: Non-invasive brain stimulation techniques for chronic pain

Comparison: 3 Transcranial direct current stimulation (tDCS)

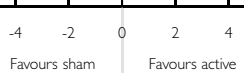
Outcome: 9 Quality of life: short-term follow-up

Study or subgroup	Active stimulation N	Mean(SD)	Sham stimulation N	Mean(SD)	Std. Mean Difference IV,Random,95% CI	Weight	Std. Mean Difference IV,Random,95% CI
Mori 2010 (1)	10	74.1 (19.5)	9	51.9 (15.2)		41.7 %	1.20 [0.21, 2.20]
Riberto 2011 (2)	11	49.8 (11.6)	12	37.9 (21.7)		58.3 %	0.65 [-0.19, 1.49]
Total (95% CI)	**21**		**21**			**100.0 %**	**0.88 [0.24, 1.53]**

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.69$, df = 1 (P = 0.41); $I^2 = 0.0\%$

Test for overall effect: Z = 2.68 (P = 0.0073)

Test for subgroup differences: Not applicable



(1) MS-QoL-54

(2) SF-36 total

Analysis 3.10. Comparison 3 Transcranial direct current stimulation (tDCS), Outcome 10 Quality of life: medium-term follow-up.

Review: Non-invasive brain stimulation techniques for chronic pain

Comparison: 3 Transcranial direct current stimulation (tDCS)

Outcome: 10 Quality of life: medium-term follow-up

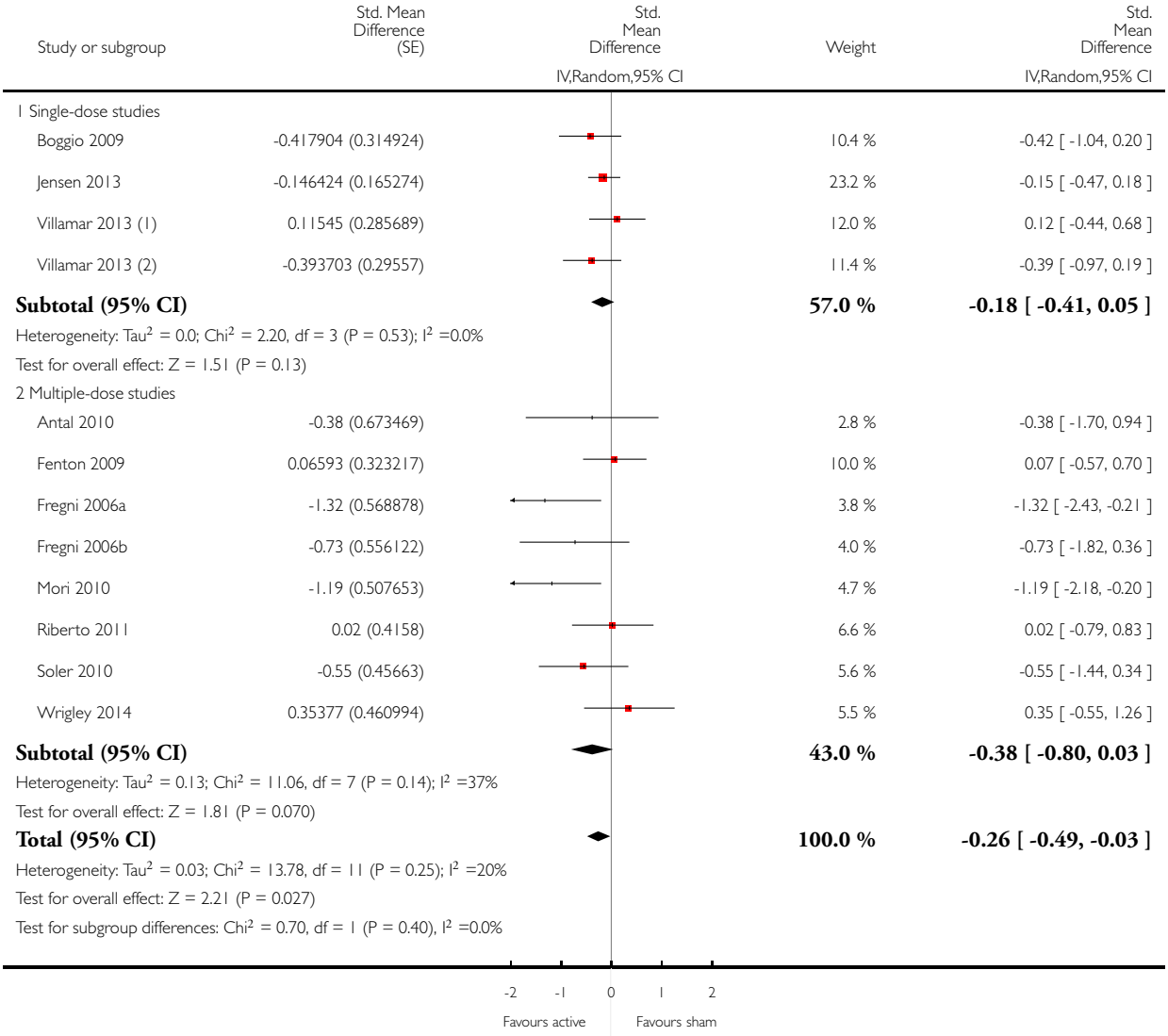
Study or subgroup	Active stimulation		Sham stimulation		Std. Mean Difference	Std. Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Random,95% CI	IV,Random,95% CI
Mori 2010	10	75 (23.3)	9	60 (17.7)		0.69 [-0.25, 1.62]

Analysis 3.11. Comparison 3 Transcranial direct current stimulation (tDCS), Outcome 11 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: 11 Pain: short-term follow-up, subgroup analysis: motor cortex studies only



(1) anodal

(2) cathodal

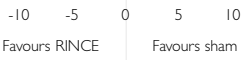
Analysis 4.1. Comparison 4 Reduced impedance non-invasive cortical electrostimulation (RINCE), Outcome 1 Pain: short-term follow-up.

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 N	Mean(SD)	Sham N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Hargrove 2012 (1)	39	4.6 (2.27)	38	6.01 (2.53)			-1.41 [-2.48, -0.34]
Subtotal (95% CI)	**0**		**0**				**0.0 [0.0, 0.0]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.0 (P < 0.00001)							
Test for subgroup differences: Not applicable							



(1) Per protocol analysis

Analysis 4.2. Comparison 4 Reduced impedance non-invasive cortical electrostimulation (RINCE), Outcome 2 Fibromyalgia Impact Questionnaire total score.

Review: Non-invasive brain stimulation techniques for chronic pain

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

Outcome: 2 Fibromyalgia Impact Questionnaire total score

Study or subgroup	Active N	Mean(SD)	Sham N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Hargrove 2012	39	45.96 (20.42)	38	52.46 (18.53)			-6.50 [-15.21, 2.21]
Subtotal (95% CI)	**0**		**0**				**0.0 [0.0, 0.0]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.0 (P < 0.00001)							
Test for subgroup differences: Not applicable							

ADDITIONAL TABLES

Table 1. 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
André-Obadia 2006	M1 contralateral to painful side	Posteroanterior	20, 1	90	20 Hz: 20 1Hz: 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
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
Short 2011	Left DLPFC	Para-sagittal	10	120	80	5 sec	10 sec	4000	10, x 1 daily (working days) for 2 weeks
Borckardt 2009	Left PFC	Not specified	10	100	40	10 sec	20	4000	3 over a 5-day period
Carretero 2009	Right DLPFC	Not specified	1	110	20	60 sec	45	1200	Up to 20 on consecutive working days
Defrin 2007	M1 midline	Not specified	5	115	500	10 sec	30	? 500*	10, x 1 daily

Table 1. rTMS studies - characteristics of stimulation (*Continued*)

Fregni 2005	Left and right SII	Not specified	1	90	Not specified	Not specified	Not specified	1600	1
Fregni 2011	Right SII	Not specified	1	70% maximum stimulator output intensity (not RMT)	1	Not specified	Not specified	1600	10, x 1 daily (week days 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 (week days only)
Irlbacher 2006	M1 contralateral to painful side	Not specified	5, 1	95	Not specified	Not specified	Not specified	500	1
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 (week days only)
Lefaucheur 2001a	M1 contralateral to painful side	Not specified	10	80	20	5 sec	55	1000	1
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

Table 1. rTMS studies - characteristics of stimulation (*Continued*)

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
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
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

Table 1. rTMS studies - characteristics of stimulation (*Continued*)

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
Tzabazis 2013	Targeted to ACC	4-coil configuration	1 Hz (10 Hz data excluded as not randomised)	110	Not reported	Not reported	Not reported	1800	20, x 1 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

Table 2. CES studies - characteristics of stimulation

Study	Electrode placement	Frequency (Hz)	Pulse width (msec)	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
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

Table 2. CES studies - characteristics of stimulation (*Continued*)

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. tDCS studies - characteristics of stimulation

Study	Location of stimulation	Electrode pad size	Intensity (mA)	Anodal or cathodal?	Stimulus duration (min)	Treatment sessions per group
Antal 2010	M1 left hand area	35 cm^2	1 mA	Anodal	20	5, x 1 daily
Boggio 2009	M1 contralateral to painful side	35 cm^2	2 mA	Anodal	30	1
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
Jensen 2013	M1 left	35cm^2	2 mA	Anodal	20	1
Mendonca 2011	Group 1: anodal left M1 Group 2: cathodal left M1 Group 3: anodal supraorbital Group 4: cathodal supraorbital Group 5: sham	35 cm^2	2 mA	Anodal or cathodal	20	1

Table 3. tDCS studies - characteristics of stimulation (*Continued*)

Mori 2010	M1 contralateral to painful side	35 cm^2	2 mA	Anodal	20	5, x 1 daily
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
Soler 2010	M1 contralateral to painful side or dominant hand	35 cm^2	2 mA	Anodal	20	10, x 1 daily (week days only)
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 cathodal	20	x 1 per condition
Wrigley 2014	M1 contralateral to painful side or dominant hand	35 cm^2	2 mA	Anodal	20	5, x 1 daily

DLPFC: dorsolateral prefrontal cortex; M1: primary motor cortex
HD-tDCS: High definition tDCS

Table 4. GRADE judgements for core comparisons

Comparison	Result	Limitations of studies	Inconsistency	Indirectness	Imprecision	Publication bias	GRADE judgement
rTMS							
Pain: short-term							
Low-frequency rTMS all	Ineffective SMD 0.15 (-0.01 to 0.31)	Down one < 75% at low risk of bias	None (I^2 = 0%, P = 0.78)	None	Down one, n = 81	No direct evidence	Low
High-frequency TMS all	Effective SMD -0.27 (-0.35 to -0.20)	Down one < 75% studies at low risk of bias	Down one (I^2 = 64%, P < 0.01)	None	None, n = 447	No direct evidence	Low

Table 4. GRADE judgements for core comparisons (*Continued*)

Single-dose, high-frequency rTMS applied to the motor cortex on chronic pain	Effective SMD -0.39 (-0.51 to -0.27)	Down one < 75% studies at low risk of bias	None (I^2 = 31%, P = 0.13)	None	Down one, n = 233	No direct evidence	Low
Multiple-dose, high-frequency rTMS applied to the motor cortex on chronic pain	Ineffective SMD -0.07 (-0.41 to 0.26)	Down one < 75% studies at low risk of bias	Down one (I^2 = 71%, P < 0.01)	None	Down one, n = 157	No direct evidence	Very low
rTMS prefrontal cortex	Ineffective SMD -0.47 (-1.48 to 0.54)	Down one < 75% studies at low risk of bias	Down one (I^2 = 82%, P < 0.01)	None	Down one, n = 68	No direct evidence	Very low
Pain: medium-term							
rTMS all	Ineffective SMD -0.15 (-0.41 to 0.11)	Down one < 75% studies at low risk of bias	Down one (I^2 = 60%, P = 0.01)	None	Down one, n = 184	No direct evidence	Very low
Pain: long-term							
rTMS all	Ineffective SMD -0.12, (-0.46 to 0.21)	Down one < 75% studies at low risk of bias	None (I^2 = 0%, P = 0.95)	None	Down one, n = 59	No direct evidence	Low
CES							
Pain: short-term							
CES all	Ineffective SMD -0.24 (-0.48 to 0.01)	Down one < 75% studies at low risk of bias	None (I^2 = 0%, P = 0.43)	None	Down one, n = 270	No direct evidence	Low
tDCS							
Pain: short-term							

Table 4. GRADE judgements for core comparisons (*Continued*)

tDCS all	Ineffective SMD -0.18 (-0.46 to 0.09)	Down one < 75% studies at low risk of bias	Down one (I^2 = 49%, P = 0.02)	None	Down one, n = 183	No direct evidence	Very low
tDCS motor cortex	Ineffective SMD -0.23 (-0.48 to 0.01)	Down one < 75% studies at low risk of bias	None (I^2 = 33%, P = 0.13)	None	Down one, n = 182	No direct evidence	Low
tDCS motor cortex multiple-dose studies	Ineffective SMD -0.35 (-0.79 to 0.09)	Down one < 75% studies at low risk of bias	Down one (I^2 = 51%, P = 0.05)	None	Down one, n = 129	No direct evidence	Very low
Pain: medium-term							
tDCS all	Ineffective SMD -0.32 (-0.76 to 0.11)	Down one < 75% studies at low risk of bias	None (I^2 = 40%, P = 0.14)	None	Down one n = 87	No direct evidence	Low
RINCE							
Pain: short-term	Effective SMD -1.41 (-2.48 to -0.34) P = 0.01	Down one - study at unclear risk of bias	n/a - single study only	None	Down two, as only a single study available	No direct evidence - only a single study	Very low

CES: cranial electrotherapy stimulation
RINCE: reduced impedance non-invasive cortical electrostimulation
rTMS: repetitive transcranial magnetic stimulation
SMD: standardised mean difference
tDCS: transcranial direct current stimulation
TMS: transcranial magnetic stimulation

APPENDICES

Appendix 1. Main database search strategies for current 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 2. Trials register search results for current 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 3. Search results summary table for current update: July 2013 search

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 4. 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 5. 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 electro-therap* 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**

Appendix 6. GRADE judgement summary table

Comparison	Result	Limitations of studies	Inconsistency	Indirectness	Imprecision	Publication bias	GRADE judgement
rTMS							
Pain: short-term							
Low-frequency rTMS all	Ineffective SMD 0.15 (-0.01 to 0.31)	Down one < 75% at low risk of bias	None (I^2 = 0%, P = 0.78)	None	Down one, n = 81	No direct evidence	Low
High-frequency TMS all	Effective SMD -0.27 (-0.35 to -0.20)	Down one < 75% studies at low risk of bias	Down one (I^2 = 64%, P < 0.01)	None	None, n = 447	No direct evidence	Low
Single-dose, high-frequency rTMS applied to the motor cortex on chronic pain	Effective SMD -0.39 (-0.27 to -0.51)	Down one < 75% studies at low risk of bias	None (I^2 = 31%, P = 0.13)	None	Down one, n = 233	No direct evidence	Low
Multiple-dose, high-frequency rTMS applied to the motor cortex on chronic pain	Ineffective SMD -0.07 (-0.41 to 0.26)	Down one < 75% studies at low risk of bias	Down one (I^2 = 71%, P < 0.01)	None	Down one, n = 157	No direct evidence	Very low
rTMS prefrontal cortex	Ineffective SMD -0.47 (-1.48 to 0.54)	Down one < 75% studies at low risk of bias	Down one (I^2 = 82%, P < 0.01)	None	Down one, n = 68	No direct evidence	Very low

(*Continued*)

Pain: medium-term							
rTMS all	Ineffective SMD -0.15 (-0.41 to 0.11)	Down one < 75% studies at low risk of bias	Down one (I^2 = 57%, P = 0.02)	None	Down one, N = 184	No direct evidence	Very low
Pain: long-term							
rTMS all	Ineffective SMD -0.12 (-0.46 to 0.21)	Down one < 75% studies at low risk of bias	None (I^2 = 0%, P = 0.95)	None	Down one, n = 59	No direct evidence	Low
CES							
Pain: short-term							
CES all	Ineffective SMD -0.24 (-0.48 to 0.01)	Down one < 75% studies at low risk of bias	None (I^2 = 0%, P = 0.43)	None	Down one, n = 270	No direct evidence	Low
tDCS							
Pain: short-term							
tDCS all	Ineffective SMD -0.18 (-0.46 to 0.09)	Down one < 75% studies at low risk of bias	Down one (I^2 = 45%, P = 0.05)	None	Down one, n = 183	No direct evidence	Very low
tDCS motor cortex	Ineffective SMD -0.23 (-0.48 to 0.01)	Down one < 75% studies at low risk of bias	None (I^2 = 33%, P = 0.13)	None	Down one, n = 172	No direct evidence	Low
tDCS motor cortex, multiple-dose studies	Ineffective SMD -0.35 (-0.79 to 0.09)	Down one < 75% studies at low risk of bias	Down one (I^2 = 51%, P = 0.05)	None	Down one, n = 119	No direct evidence	Very low
Pain: medium-term							
tDCS all	Ineffective SMD -0.42 (-0.63 to 0.24)	Down one < 75% studies at low risk of bias	None (I^2 = 31%, P = 0.21)	None	Down one, n = 77	No direct evidence	Low

WHAT'S NEW

Last assessed as up-to-date: 24 July 2013.

Date	Event	Description
25 July 2013	New citation required and conclusions have changed	We have performed a full update of the searches (January 2013) and a supplemental update of the main databases (July 2013). This involved the inclusion of 21 new trials with 747 participants. We have updated all analyses and made GRADE quality assessments for all core comparisons. The addition of these data has substantially altered our conclusions regarding transcranial direct current stimulation (tDCS), as our analysis no longer suggests that tDCS is effective compared with sham. While the broad conclusions for repetitive transcranial magnetic stimulation (rTMS) and cranial electrotherapy stimulation (CES) have not changed substantially, the addition of this new evidence and the application of the GRADE system has modified some of our interpretation. Previous readers should re-read this update
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 and Description of the intervention. We have also applied the GRADE approach to assessing the quality of evidence

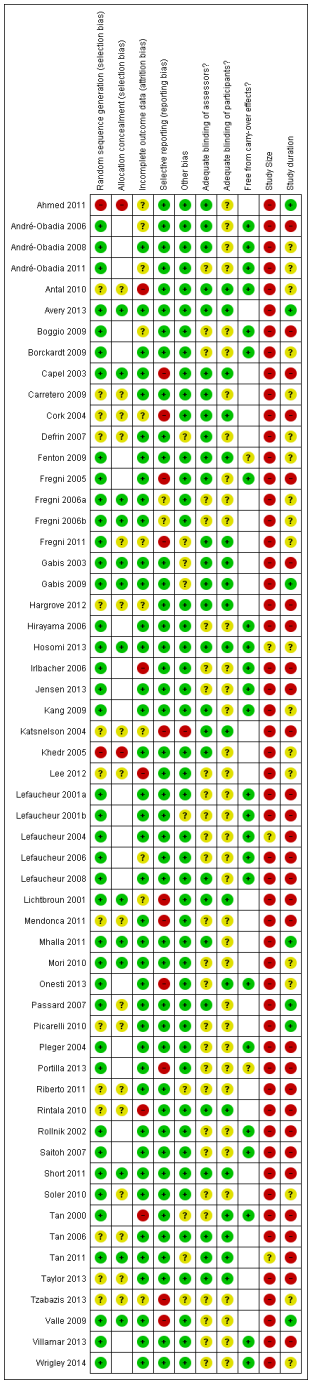
HISTORY

Protocol first published: Issue 1, 2010

Review first published: Issue 9, 2010

Date	Event	Description
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 1, 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.

Figure 1. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.



CONTRIBUTIONS OF AUTHORS

NOC: Conceived and designed the review protocol, co-implemented the search strategy alongside the Cochrane PaPaS Group Trials Search Co-ordinator, applied eligibility criteria, assessed studies, extracted and analysed data, and led the write-up of the review.

BM: 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 authors read and commented upon the systematic review and commented on and approved the final manuscript.

DECLARATIONS OF INTEREST

None known.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The database Scopus was not searched as the other searches had covered the full scope of this database.

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.

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.

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)

*Pain Management; Brain [*physiology]; Chronic Disease; Electric Stimulation Therapy [adverse effects; *methods]; Magnetic Field Therapy [adverse effects; *methods]; Randomized Controlled Trials as Topic

MeSH check words

Humans