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

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TABLE OF CONTENTS

[Intervention Review]

Non-invasive brain stimulation techniques for chronic pain

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ABSTRACT

Background

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) and transcranial direct current stimulation (tDCS).

Objectives

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

Search methods

We searched CENTRAL, MEDLINE, EMBASE, CINAHL, PsycINFO, LILACS, the Cochrane PaPaS Group Trials Register and clinical trials registers.

Selection criteria

Randomised and quasi-randomised studies of rTMS, CES or tDCS 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.

Main results

We included 33 trials in the review (involving 937 people)(19 rTMS, eight CES and six tDCS). Only one study was judged as being at low risk of bias.

Studies of rTMS (involving 368 participants) demonstrated significant heterogeneity. Pre-specified subgroup analyses suggest that low-frequency stimulation is ineffective. A short-term effect on pain of active high-frequency stimulation of the motor cortex in single-dose studies was suggested (standardised mean difference (SMD) -0.40, 95% confidence interval (CI) -0.26 to -0.54, P < 0.00001). This

equates to a 15% (95% CI 10% to 20%) reduction in pain which does not clearly exceed the pre-established criteria for a minimally clinically important difference (> 15%).

For CES (four studies, 133 participants) no statistically significant difference was found between active stimulation and sham. Analysis of tDCS studies (five studies, 83 people) demonstrated significant heterogeneity and did not find a significant difference between active and sham stimulation. Pre-specified subgroup analysis of tDCS applied to the motor cortex suggested superiority of active stimulation over sham (SMD -0.59, 95% CI -1.10 to -0.08).

Non-invasive brain stimulation appears to be associated with minor and transient side effects.

Authors' conclusions

Single doses of high-frequency rTMS of the motor cortex may have small short-term effects on chronic pain. The effects do not clearly exceed the predetermined threshold of minimal clinical significance. Low-frequency rTMS is not effective in the treatment of chronic pain. There is insufficient evidence from which to draw firm conclusions regarding the efficacy of CES or tDCS. The available evidence suggests that tDCS applied to the motor cortex may have short-term effects on chronic pain and that CES may be ineffective. There is a need for further, rigorously designed studies of all types of stimulation.

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. There are three 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 and transcranial direct current stimulation (tDCS), 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 included 33 studies, 19 of rTMS, eight of CES and six of tDCS. Only one study was judged as having a low risk of bias. Analysis suggests that low-frequency rTMS is 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. There is limited and conflicting evidence from studies involving multiple doses of rTMS. Most studies of rTMS are small and there is substantial variation between studies in terms of the treatment methods used.

There was insufficient evidence from which to draw strong conclusions regarding CES or tDCS but the available evidence does not suggest that CES is an effective treatment. There is limited evidence that tDCS to the motor cortex may have short-term effects on chronic pain but it is not possible to estimate the size of this effect accurately.

The reporting of side effects varied across the studies. Of the studies that clearly reported side effects only short-lived and minor side effects such as headache, nausea and skin irritation were reported.

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

BACKGROUND

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 tissue injury such as arthritis, peripheral nerve injury, 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 $\leq$ 2 mA) electrical current to the cerebral cortex of the brain (Fregni 2007; Gilula 2007). 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 patients earlobes. A Cochrane Review of non-invasive treatments for headaches (Bronfort 2004) identified limited evidence that CES is superior to placebo in reducing pain intensity after six to 10 weeks of treatment.

How the intervention might work

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

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

Devices have been developed that 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.

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 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 or blinding.

Types of participants

We included studies including male or female participants over the age of 18 years with any chronic pain syndrome (with a duration of > 3 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 or CES). 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.

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 were extracted when available include 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, the subject search was run with the Cochrane Highly Sensitive Search Strategy (CHSSS) 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 2008). The authors have slightly adapted this filter to include the term "sham" in the title or abstract. The search strategy and filter proposed for MEDLINE is presented in Appendix 1 and included a combination of controlled vocabulary (MeSH) and free-text terms. All database searches were based on this strategy but were appropriately revised to suit each database.

Electronic databases

To identify studies for inclusion in this review we searched the following electronic databases to identify published articles:

- the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2009, issue 4);
- the Cochrane Pain, Palliative and Supportive Care Group Trials Register (current issue);
- OVID MEDLINE (1950 to November Week 3 2009);
- OVID EMBASE ((1980 to Week 47 2009);
- PsycINFO (1806 to November Week 4 2009);
- CINAHL (1982 to 11 January 2010); and
- LILACS (1982 to 15 December 2009).

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 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 search results and included eligible studies. Initially the titles and/or abstracts of identified studies were read by two review authors (NOC & BW). Where it was clear from the study title or abstract that the study was not relevant or did not meet the selection criteria it was excluded. If it was unclear then we assessed the full paper, as well as all studies that appeared to meet the selection criteria. 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.

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. Discrepancies were resolved 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-term, intermediate and long-term follow up.
- Adverse effects.

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 2008).

The criteria assessed for parallel study designs (using yes/no/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 yes/no/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.

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 the paper(s) in question were considered by a third review author (LDS).

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. Two independent review authors (NOC and BW) performed rating of sham credibility. Disagreement between review authors was resolved through consensus. Where resolution was not achieved the paper(s) in question were considered by a third review author (LDS). Where sham credibility was assessed as unclear or sub-optimal we made a judgement of 'unclear' for the criteria '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 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 the data were free of carry-over effects. We entered cross-over trials into a meta-analysis where it was clear that the data were free of carry-over effects. We combined the results of cross-over studies with parallel studies by imputing the post-treatment between-condition correlation coefficient from an included study that presented individual patient data and using this to calculate the standard error of the standardised mean difference (SE(SMD)). This data was entered into the meta-analysis using the generic inverse-variance method as suggested in the *Cochrane Handbook for Systematic Reviews of Interventions,* section 16.4.6.2 (Higgins 2008).

Dealing with missing data

Where insufficient data were presented in the study report to enter a study into the meta-analysis, we contacted 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 5.0.23) (RevMan 2008) using a random effects model. We considered separate meta-analyses for different forms of stimulation intervention (i.e. rTMS, tDCS and CES) 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, 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.

Subgroup analysis and investigation of heterogeneity

We assessed heterogeneity using the Chi^2 test to investigate it's 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 ≤ 1 Hz, high ≥ 5 Hz), multiple versus single-dose studies, 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, 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; Characteristics of studies awaiting classification.

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

Results of the search

Published data

The search strategy identified 1148 citations, including 305 duplicates. See Appendix 3 for full details of the search results. 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. Three more papers were identified by the review authors that were not picked up from the search strategy. These were also deemed 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. The kappa level of agreement between authors for eligibility from full-text screening was 0.87.

Unpublished data

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. The level of agreement between review authors for eligibility from the trial register records, calculated using the kappa statistic was 0.89. The contact author for each of these studies was contacted 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.

Included studies

Country of origin and language of publication

Of the 44 studies considered 33 met the eligibility criteria (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). All but one of the studies (Irlbacher 2006, written in German) was 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

Nineteen studies investigated rTMS (André-Obadia 2006; André-Obadia 2008; Borckardt 2009; Carretero 2009; Defrin 2007; Fregni 2005; Hirayama 2006; Irlbacher 2006; Kang 2009; Khedr 2005; Lefaucheur 2001a; Lefaucheur 2001b; Lefaucheur 2004; Lefaucheur 2006; Lefaucheur 2008; Passard 2007; Pleger 2004; Rollnik 2002; Saitoh 2007). Eight studies investigated CES (Capel 2003; Cork 2004; Gabis 2003; Gabis 2009; Katsnelson 2004; Lichtbroun 2001; Tan 2000; Tan 2006) and six studies investigated tDCS (Boggio 2009; Fenton 2009; Fregni 2006a; Fregni 2006b; Mori 2010; Valle 2009).

Study designs

There was a mixture of parallel and cross-over study designs. For rTMS there were four parallel studies (Carretero 2009; Defrin 2007; Khedr 2005; Passard 2007) and 15 cross-over studies (André-Obadia 2006; André-Obadia 2008; Borckardt 2009; Fregni 2005; Hirayama 2006; Irlbacher 2006; Kang 2009; Lefaucheur 2001a; Lefaucheur 2001b; Lefaucheur 2004; Lefaucheur 2006; Lefaucheur 2008; Pleger 2004; Rollnik 2002; Saitoh 2007). For CES there were five parallel studies (Gabis 2003; Gabis 2009; Katsnelson 2004; Lichtbroun 2001; Tan 2006) and three cross-over studies (Capel 2003; Cork 2004; Tan 2000) of which two were considered 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 four parallel studies (Fregni 2006a; Fregni 2006b; Mori 2010; Valle 2009) and two cross-over studies (Boggio 2009; Fenton 2009).

Study participants

The included studies were published between 2000 and 2010. In rTMS studies sample sizes at the study outset ranged from four to 60 participants with a total of 422 participants randomised. Of these studies nine had 20 or more participants (André-Obadia 2008; Carretero 2009; Hirayama 2006; Irlbacher 2006; Khedr 2005; Lefaucheur 2004; Lefaucheur 2006; Lefaucheur 2008; Passard 2007). In CES studies sample size ranged from 20 to 75 with a total of 391 randomised participants and in tDCS studies sample size ranged from seven to 32 participants with a total of 83 randomised participants. Only one study of tDCS had over 20 participants (Fregni 2006b).

Studies included a variety of chronic pain conditions. Eight rTMS studies included participants with neuropathic pain of mixed origin; of these five included a mix of central, peripheral and facial neuropathic pain patients (André-Obadia 2006; André-Obadia 2008; Hirayama 2006; Lefaucheur 2004; Lefaucheur 2008), two included a mix of central and peripheral neuropathic pain patients (Lefaucheur 2006; Saitoh 2007) of which one study (Saitoh 2007) included a patient with phantom limb pain. 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 four studies included non-neuropathic chronic pain including fibromyalgia (Carretero 2009; Passard 2007), chronic pancreatitis pain (Fregni 2005) and complex regional pain syndrome type I (CRPSI) (Pleger 2004). 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 (13) of rTMS studies specified chronic pain that was refractory to current medical management (André-Obadia 2006; André-Obadia 2008, Defrin 2007, Hirayama 2006; Kang 2009; Khedr 2005; Lefaucheur 2001a; Lefaucheur 2001b; Lefaucheur 2004; Lefaucheur 2006; Lefaucheur 2008; Rollnik 2002; Saitoh 2007). This inclusion criteria was varyingly described as intractable, resistant to medical intervention or drug management.

Of studies of CES, one study included participants with pain related to osteoarthritis of the hip and knee (Katsnelson 2004), 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. Two studies included participants with fibromyalgia (Cork 2004; Lichtbroun 2001) and two studies included participants with chronic pain following spinal cord injury (Capel 2003; Tan 2006), although it is unclear from these study reports whether the pain was classified as neuropathic or non-neuropathic. 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 detail was not reported on.

Of 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), one included participants with central neuropathic pain following spinal cord injury (Fregni 2006a) and two studies included non neuropathic pain, specifically chronic pelvic pain (Fenton 2009) and fibromyalgia (Fregni 2006b). Three studies of tDCS specified recruiting participants with pain that was refractory to medical management (Boggio 2009; Fenton 2009; Fregni 2006a).

Most studies included both male and female participants except the studies of Fenton 2009 (chronic pelvic pain) and Fregni 2006b (fibromyalgia). 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. Twelve studies reported collecting outcome data for medium-term (≥ 1 to 6 weeks post-treatment) (André-Obadia 2008; Borckardt 2009; Carretero 2009; Defrin 2007; Fenton 2009; Fregni 2006a; Fregni 2006b; Gabis 2009; Kang 2009; Khedr 2005; Lefaucheur 2001a; Mori 2010; Passard 2007; Valle 2009). Of these data could be extracted from four study reports (Carretero 2009; Gabis 2009; Kang 2009) and the authors of three studies provided the data upon request (Khedr 2005; Mori 2010; Passard 2007). Four studies reported collecting outcome data for long-term (> 6 weeks) follow up (Gabis 2009; Kang 2009; Passard 2007; Valle 2009). Of these data could be extracted from Gabis 2009 and Kang 2009 and the authors of Passard 2007 provided the data upon request.

Secondary outcomes

Only secondary outcomes that distinctly measured self-reported disability or quality of life were considered for extraction and included in the Characteristics of included studies table. Five studies used measures of disability or pain interference (Cork 2004; Kang 2009; Passard 2007; Tan 2000; Tan 2006) and five studies collected measures of quality of life (Fregni 2006b; Lichtbroun 2001; Mori 2010; Passard 2007; Valle 2009).

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) (André-Obadia 2006; André-Obadia 2008; Defrin 2007; Hirayama 2006; Irlbacher 2006; Kang 2009; Khedr 2005; Lefaucheur 2001a; Lefaucheur 2001b; Lefaucheur 2004; Lefaucheur 2006; Lefaucheur 2008; Passard 2007; Pleger 2004; Rollnik 2002; Saitoh 2007). Of these one study specified stimulation of the right hemisphere (Kang 2009), two studies specified stimulation over the midline (Defrin 2007; Pleger 2004) and the remainder stimulated over the contralateral cortex to the side of dominant pain. One

of these studies (Hirayama 2006) also investigated stimulation of the supplementary motor area (SMA), pre-motor area (PMA) and primary somatosensory cortex (S1). Two studies stimulated the pre-frontal cortex (PFC) with one study stimulating the left PFC (Borckardt 2009) and one study the right dorsolateral PFC (DLPFC) (Carretero 2009). One study investigated stimulation of the left and right secondary somatosensory cortex as separate treatment conditions (Fregni 2005).

Stimulation parameters

Frequency

Eight studies investigated low-frequency (< 5 Hz) rTMS (André-Obadia 2006; Carretero 2009; Fregni 2005; Irlbacher 2006; Lefaucheur 2001b; Lefaucheur 2006; Lefaucheur 2008; Saitoh 2007). 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. Eighteen studies investigated high-frequency ($\geq$ 5 Hz) rTMS (André-Obadia 2006; André-Obadia 2008; Borckardt 2009; Defrin 2007; Fregni 2005; Hirayama 2006; Irlbacher 2006; Kang 2009; Khedr 2005; Lefaucheur 2001a; Lefaucheur 2001b; Lefaucheur 2004; Lefaucheur 2006; Lefaucheur 2008; Passard 2007; Pleger 2004; Rollnik 2002; Saitoh 2007). Of these three studies used 5 Hz stimulation (Defrin 2007; Hirayama 2006; Irlbacher 2006), 10 studies used 10 Hz stimulation (Borckardt 2009; Kang 2009; Lefaucheur 2001a; Lefaucheur 2001b; Lefaucheur 2004; Lefaucheur 2006; Lefaucheur 2008; Passard 2007; Pleger 2004; Saitoh 2007) and four studies used 20 Hz stimulation (André-Obadia 2006; André-Obadia 2008; Fregni 2005; Khedr 2005; Rollnik 2002).

Other parameters

Wide variation was observed 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 25000 pulses. Six studies specified a posteroanterior orientation of the stimulating coil (André-Obadia 2006; Lefaucheur 2001b; Lefaucheur 2004; Lefaucheur 2006; Lefaucheur 2008; Passard 2007) one study specified a coil orientation 45º posterolateral to the midline (Kang 2009), one study compared a posteroanterior coil orientation with a medial-lateral coil orientation (André-Obadia 2008) 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. One study did not report this information (Fregni 2005).

Type of sham

rTMS studies employed a variety of sham controls. In nine studies the stimulating coil was angled away from the scalp to prevent significant cortical stimulation. Of these four studies (André-Obadia 2006; André-Obadia 2008; Kang 2009; Khedr 2005) specified that the coil was also elevated from the scalp and five studies specified that the coil was angled 45º away from the scalp Carretero 2009; Hirayama 2006; Pleger 2004; Rollnik 2002; Saitoh 2007) of which two studies (Hirayama 2006; Saitoh 2007) also simultaneously electrical 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. The remaining 10 studies utilised sham coils. Of these four studies specified that the sham coil made similar or identical sounds to those elicited during active stimulation (Borckardt 2009; Defrin 2007; Irlbacher 2006; Passard 2007). 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).

Adverse event reporting

Thirteen studies did not report any information regarding adverse events (Borckardt 2009; Cork 2004; Defrin 2007; Gabis 2009; Kang 2009; Katsnelson 2004; Khedr 2005; Lefaucheur 2006; Lefaucheur 2008; Lichtbroun 2001; Pleger 2004; Tan 2000; Tan 2006).

Studies of CES

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

Stimulation device, parameters and electrode location

Four 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; Tan 2000; Tan 2006) 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 (Katsnelson 2004) used the "Nexalin" device (Kalaco Scientific Inc, Scottsdale, AZ, USA). With this device current is applied to a forehead electrode and returned via electrodes placed behind the patient's ears. These three studies utilised significant 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. Capel 2003 delivered treatments twice daily for four days. Cork 2004 delivered treatment once daily for a three-week period. Gabis 2003 and Gabis 2009 delivered treatment once daily for eight days, Katsnelson 2004 for five days, Lichtbroun 2001 for 30 days and Tan 2006 for 21 days. Tan 2000 delivered 12 treatments although the frequency of these is unclear from the study report.

Type of sham

Five studies utilised inert sham units (Capel 2003; Cork 2004; Lichtbroun 2001; Tan 2000; Tan 2006). 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 (Gabis 2003; Gabis 2009) utilised an "active placebo" treatment unit. 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). Six studies stimulated the motor cortex (Boggio 2009;Fenton 2009; Fregni 2006a; Fregni 2006b; Mori 2010; Valle 2009). Of these four stimulated the cortex contralateral to the side of worst pain (Boggio 2009; Fregni 2006a; Fregni 2006b; Mori 2010) of which two studies stimulated the opposite hemisphere to the dominant hand where pain did not have a unilateral dominance (Fregni 2006a; Fregni 2006b). One study stimulated the left hemisphere for all conditions (Valle 2009). One study of chronic pelvic pain stimulated the opposite hemisphere to the dominant hand in all subjects (Fenton 2009). One study specifically investigated the use of tDCS in conjunction with transcutaneous electrical nerve stimulation (TENS) therapy (Boggio 2009). Data comparing active tDCS and sham TENS with sham tDCS and sham TENS were extracted for the purposes of this review.
Three studies (Fregni 2006a; Fregni 2006b; Mori 2010) delivered a current intensity of 2 mA for 20 minutes once a day for five days. One study (Fenton 2009) applied a current intensity of 1 mA once a day for two days and one study (Boggio 2009) applied one treatment per stimulation condition at an intensity of 2 mA for 30 minutes.
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. 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).

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. The (kappa statistic) level of agreement between the two review authors across all risk of bias criteria was 0.73.

Sequence generation

For the criteria 'adequate sequence generation' cross-over trials were awarded a judgement of 'Yes' where the study report mentioned that the order of treatment conditions was randomised. Since this criteria has a greater potential to introduce bias in parallel designs a judgement of 'Yes' was only awarded where the method of randomisation was specified and adequate.
All cross-over trials were judged as having a low risk of bias for this criteria. Of the parallel trials five trials were judged as having an unclear risk of bias (Carretero 2009; Cork 2004; Defrin 2007; Katsnelson 2004; Tan 2006) as they did not specify the method of randomisation used. One study was judged as having a high risk of bias for this criteria (Khedr 2005) as the report suggests that patients were allocated depending on the day of the week on which they were recruited, which was not judged as being genuinely random.

Allocation concealment

The criteria 'Adequate concealment of allocation' was only considered for studies with parallel designs. Six studies did not report concealment of allocation and were judged as 'Unclear' (Carretero 2009; Cork 2004; Defrin 2007; Katsnelson 2004; Passard 2007; Tan 2006) and one study (Khedr 2005) was judged as having a high risk of bias for this criteria since the method of randomisation employed would not have supported concealment of allocation.

Blinding

Blinding of assessors

Eleven studies did not specify whether they blinded outcome assessors (Borckardt 2009; Hirayama 2006; Irlbacher 2006; Lefaucheur 2001a; Lefaucheur 2001b; Lefaucheur 2004; Lefaucheur 2006; Pleger 2004; Rollnik 2002; Saitoh 2007; Tan 2000). While 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 suggests that a lack of blinding of researchers engaged in the collection of outcomes might potentially introduce bias. As such, where blinding of assessors was not clearly stated a judgement of 'Unclear' was made for this criteria.

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) an assessment was made of sham credibility. Where sham coils were utilised they did not control for the sensory aspects of stimulation. 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 (Hirayama 2006; Saitoh 2007) simultaneously electrically stimulated the scalp during rTMS stimulation to mask the differences in sensation between conditions. However, by angulating the coil away from the scalp participants may have been able to visually distinguish between the conditions. All rTMS studies were assessed as having sub-optimal sham control conditions and were therefore assessed as having an 'Unclear' risk of bias.

All studies of tDCS and CES were assessed as having a low risk of bias for this criteria.

Incomplete outcome data

Seven studies were assessed as having an unclear risk of bias for this criteria (André-Obadia 2006; Boggio 2009; Cork 2004; Katsnelson 2004; Lefaucheur 2006; Lichtbroun 2001). 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 subjects (25% of the cohort) failed to complete the study. Four studies did not clearly report levels of drop-out (Cork 2004; Katsnelson 2004; Lefaucheur 2006; Lichtbroun 2001). Two studies were assessed as having a high risk of bias for this criteria (Irlbacher 2006; Tan 2000). In the study by Irlbacher 2006 only 13 of the initial 27 participants completed all of the treatment conditions. 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

Studies were assessed as having a high risk of bias for this criteria 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. Six studies (Capel 2003; Cork 2004; Fregni 2005; Katsnelson 2004; Lichtbroun 2001; Valle 2009) were assessed as having a high risk of bias for this criteria. Two studies were judged 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.The remaining studies were assessed as having a low risk of bias for this criteria.

Other potential sources of bias

Carry-over effects in cross-over trials

One study (Fenton 2009) was judged as unclear on this criteria as no pre-stimulation data were provided and no investigation of carry-over effects was discussed in the study report. In one cross-over study (Saitoh 2007) baseline differences between the sham and the 10 Hz stimulation condition were notable. A paired t-test did not show a significant difference ($P > 0.1$) and this study was judged as having a low risk of bias for carry-over effects.

Other sources of bias

One study of CES (Katsnelson 2004) did not clearly present relevant baseline group characteristics of the included participants and was judged as being at high risk of bias for this criteria. One study of CES (Tan 2000) also applied electrical stimulation to the painful body area as part of the treatment which may have affected the final outcomes. Two studies of CES (Gabis 2003; Gabis 2009) 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. 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. These three studies were judged as 'Unclear' on this criteria.

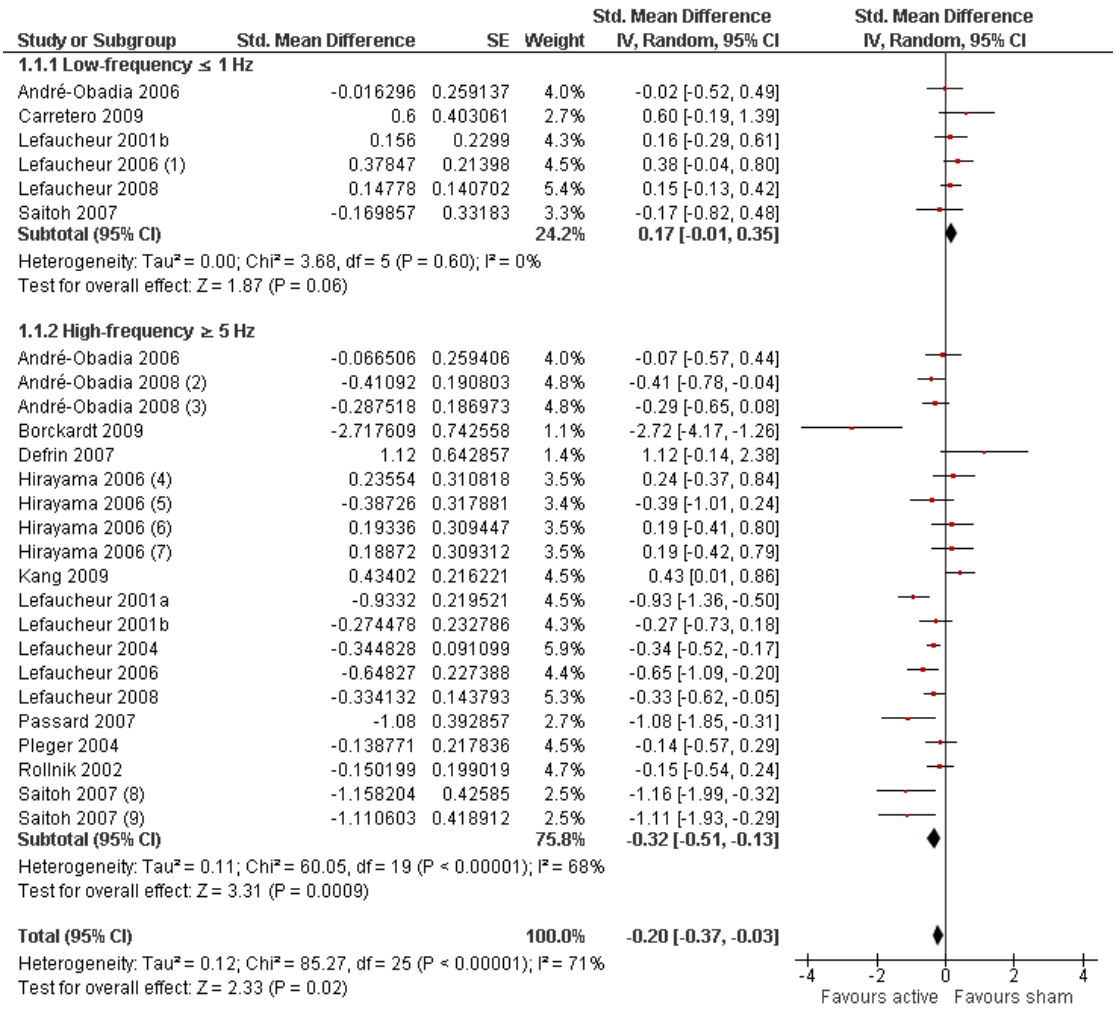
Effects of interventions

Primary outcome: pain

rTMS for short-term relief of chronic pain

The primary meta-analysis pooled data from all rTMS studies with low or unclear risk of bias where data were available (n = 368, after correction for multiple comparisons n = 267) including cross-over and parallel designs (André-Obadia 2006; André-Obadia 2008; Borckardt 2009; Carretero 2009; Defrin 2007; Hirayama 2006; Kang 2009; Lefaucheur 2001a; Lefaucheur 2001b; Lefaucheur 2004; Lefaucheur 2006; Lefaucheur 2008; Passard 2007; Pleger 2004; Pleger 2004; Rollnik 2002; Saitoh 2007). The studies by Khedr 2005, and Irlbacher 2006 were excluded as they were classified as having a high risk of bias on at least one criteria. The correlation coefficient used to calculate the SE(SMD) for cross-over studies was imputed from data extracted from André-Obadia 2008 (as outlined in Unit of analysis issues). The number of participants in each cross-over study was divided by the number of comparisons made by that study. For parallel studies the SEM was calculated from the 95% confidence intervals of the standardised mean difference (SMD) and both the SMD and the SEM were entered into the meta-analysis. This was then entered into the meta-analysis with the SMD using the generic inverse variance method. Figure 2 shows the forest plot for this analysis.

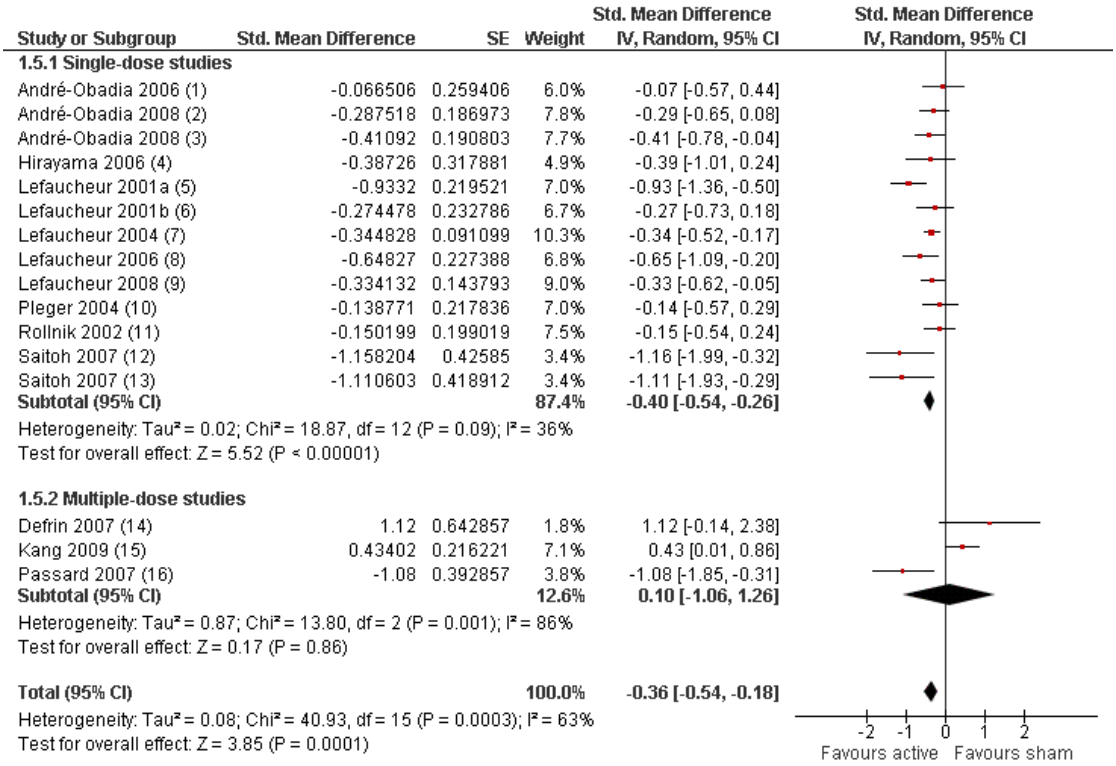
Figure 2. Forest plot of comparison: 1 rTMS, outcome: 1.1 Pain short-term follow up



(1) 1Hz
(2) antero-posterior coil orientation
(3) medial-lateral coil orientation
(4) S1
(5) M1
(6) PMA
(7) SMA
(8) 5Hz
(9) 10 Hz

Substantial heterogeneity (I^2 = 71%) was observed and was investigated using pre-planned subgroup analysis. Categorising studies by high (≥ 5 Hz) or low (< 5 Hz) frequency rTMS reduced heterogeneity in the low-frequency group (I^2 = 0%). In this group there was evidence of no effect of low-frequency rTMS for short-term relief of chronic pain. However, substantial heterogeneity was observed in the high-frequency group (I^2 = 68%). Separating studies that deliver a single treatment per condition with those that delivered multiple treatment sessions did not reduce heterogeneity substantially in multiple-dose studies (I^2 = 87%) or single-dose studies (I^2 = 61%). Restricting the analysis to single-dose studies of high-frequency stimulation of the motor cortex (corrected n = 184) reduced heterogeneity (I^2 = 36%). Figure 3 shows the forest plot for this subgroup analysis. In this group the pooled SMD was -0.40 (95% confidence interval (CI) -0.26 to -0.54), P < 0.00001. The SMD was back transformed to a mean difference using the pooled standard deviation from the largest trial in the analysis that carried the most weight in the meta-analysis (Lefaucheur 2004). This was then used to estimate the real percentage change on a 0 to 100 mm VAS of active stimulation compared with the sham condition in that study. This equated to a reduction of 9.3 mm (95% CI 6.2 mm to 12.5 mm), or a percentage change of 15% (95% CI 10% to 20%) of the control group outcome. This estimate just reaches the pre-established criteria for a minimally clinically important difference (> 15%) although the confidence intervals do not clearly fall above this threshold. Of the included studies in this subgroup eight did not clearly report blinding of assessors and were awarded a judgement of 'Unclear' risk of bias for this criteria (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 (André-Obadia 2006; André-Obadia 2008; Lefaucheur 2008) were preserved in the analysis. There remained a statistically significant difference between sham and active stimulation although the SMD reduced to -0.31 (95% CI -0.13 to -0.49). This equates to a pain reduction of 7 mm (95% CI 3 mm to 11 mm) on a 0 to 100 mm VAS pain scale or a percentage change of 12% (95% CI 9% to 18%) in comparison with sham stimulation. For multiple-dose studies of high-frequency motor cortex stimulation heterogeneity was high (I^2 = 86%).

Figure 3. Forest plot of comparison: 1 rTMS, outcome: 1.5 Pain short-term, subgroup analysis: motor cortex studies only (low-frequency studies excluded).



(1) 20Hz
(2) 20 Hz medial-lateral coil orientation
(3) 20Hz antero-posterior coil orientation
(4) 10Hz
(5) 10 Hz
(6) 10 Hz
(7) 10 Hz
(8) 10Hz
(9) 10Hz
(10) 10 Hz
(11) 20 Hz
(12) 5 Hz
(13) 10 Hz
(14) 5 Hz
(15) 10 Hz
(16) 10 Hz

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 (excluding Carretero 2009; Passard 2007; Pleger 2004; Rollnik 2002) there was little impact on heterogeneity (I^2 = 71%). 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 -0.45, 95% CI -0.60 to -0.29) or heterogeneity (I^2 = 37%). However, when the same process was applied to multiple-dose studies of high-frequency motor cortex stimulation (excluding data from Passard 2007) heterogeneity was reduced to a negligible level (I^2 = 2%) and the results suggest a significant benefit of sham over active therapy (SMD 0.5, 95% CI 0.09 to 0.93, P = 0.02).

Sensitivity analysis

To assess whether the imputation of standard errors for cross-over studies was robust the analysis was repeated with the correlation coefficient reduced to 0.65 and increased to 0.85. This had no marked effect on the overall analysis. The same process was applied to the subgroup analysis of single-dose studies of high-frequency motor cortex stimulation. This had a negligible impact on the effect size or the statistical significance of this subgroup but a large impact on heterogeneity (increased correlation coefficient I^2 = 59%, correlation decreased I^2 = 5%).

To assess the impact of excluding the studies of Irlbacher 2006 and Khedr 2005, the analysis was performed with data from these studies included. While this produced a modest increase in the SMD it increased heterogeneity from 71% to 73%. Inclusion of the Khedr 2005 study to the multiple-dose studies of high-frequency motor cortex stimulation subgroup increased heterogeneity (I^2 = 92%). Inclusion of the Irlbacher 2006 study to the single-dose studies of high-frequency motor cortex stimulation subgroup also increased heterogeneity (I^2 = 46%).

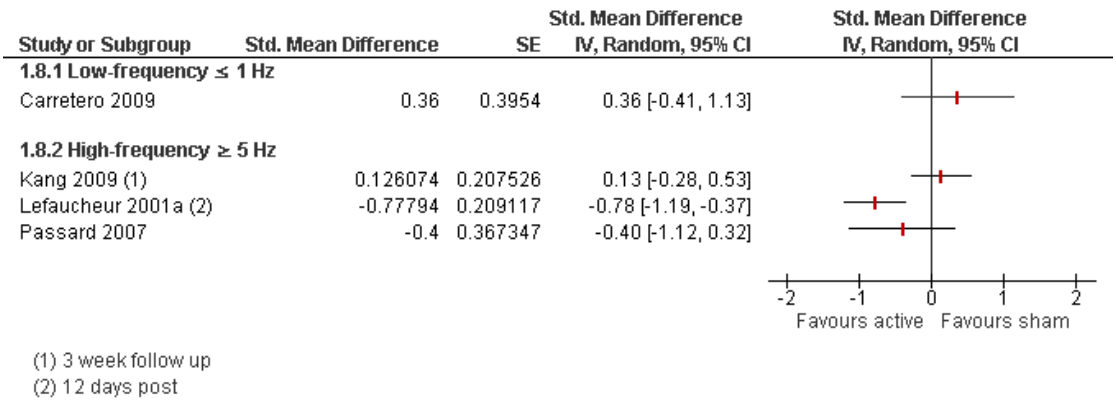
Small study effects/publication bias

Small study effects were investigated using Egger's test. The results are not suggestive of a significant influence of small study effects (P = 0.570).

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

Three studies provided data on medium-term pain outcomes (Carretero 2009; Lefaucheur 2001a; Kang 2009; Khedr 2005; Passard 2007). Of these the study by Khedr 2005 was excluded as it was classified as having a high risk of bias (see Figure 4). The analysis included 42 participants. Overall heterogeneity was high (I^2 = 75%). We performed sensitivity analysis to assess the impact of excluding the study by Khedr 2005. Including this study did not reduce heterogeneity (I^2 = 81%). There was insufficient data from which to draw any firm conclusions and the existing data are conflicting.

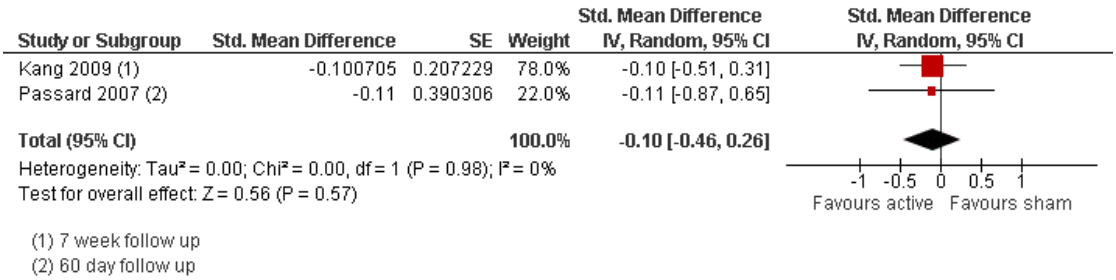
Figure 4. Forest plot of comparison: 1 rTMS, outcome: 1.6 Pain: medium-term follow up.



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

Only two studies provided data for long-term pain relief (Kang 2009; Passard 2007) (see Figure 5). The analysis included 37 participants. There was no heterogeneity (I^2 = 0%). There was insufficient evidence from which to draw firm conclusions for this comparison but the available data are not suggestive of a long-term effect of rTMS on chronic pain (P = 0.57).

Figure 5. Forest plot of comparison: 1 rTMS, outcome: 1.7 Pain: long-term follow up.



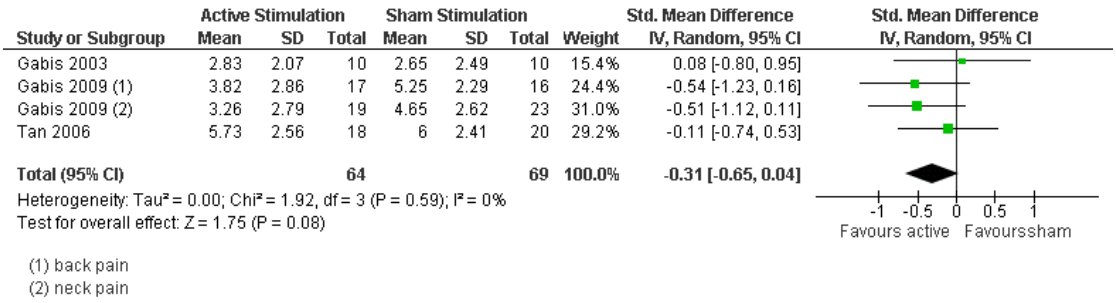
Adverse events

Of the rTMS studies that reported adverse events eight studies reported none (André-Obadia 2006; André-Obadia 2008; Fregni 2005; Hirayama 2006; Lefaucheur 2001a; Lefaucheur 2001b; Lefaucheur 2004; 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.

CES for short-term pain relief

Three studies (Gabis 2003; Gabis 2009; Tan 2006) provided data for this analysis. 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) and two studies were classified as being at high risk of bias on criteria other than 'free of selective outcome reporting' (Katsnelson 2004; Tan 2000). See Figure 6 for the forest plot of this analysis. The studies by Gabis 2003 and Gabis 2009 differ substantially to that of Tan 2006 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 (P = 0.08).

Figure 6. Forest plot of comparison: 2 CES, outcome: 2.1 Pain: short-term follow up.



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

Adverse events

Only two studies of CES reported the incidence of adverse events (Capel 2003; Gabis 2003). In these studies no adverse events were reported.

tDCS for short-term pain relief

Adequate data were available from five studies (Boggio 2009; Fenton 2009; Fregni 2006a; Fregni 2006b; Mori 2010) for this analysis (n = 83). The correlation coefficient used to calculate the SE(SMD) for cross-over studies was imputed from data extracted from Boggio 2009. One study (Fregni 2006b) compared two distinct active stimulation conditions to one sham condition. Combining the treatment conditions was considered inappropriate as each involved stimulation of different locations and combination would hinder subgroup analysis. Instead both comparisons were included separately with the number of participants in the sham control group divided by the number of comparisons (corrected n = 73). The overall meta-analysis (Figure 7) did not demonstrate a significant effect of active stimulation (P = 0.37) but heterogeneity was substantial (I^2 = 71%). Subgroup analysis restricted to comparisons of active motor cortex stimulation (Figure 8) (excluding one group from Fregni 2006b) reduced heterogeneity to a level of non-statistical significance (I^2 = 45%) and suggests superiority of active over sham stimulation (SMD -0.59, 95% CI -1.10 to -0.08, P = 0.02). Given the wide confidence interval it was considered inappropriate to back transform the SMD to a VAS as the resulting estimate would be difficult to interpret.

Figure 7. Forest plot of comparison: 3 tDCS, outcome: 3.2 Pain short-term follow up.

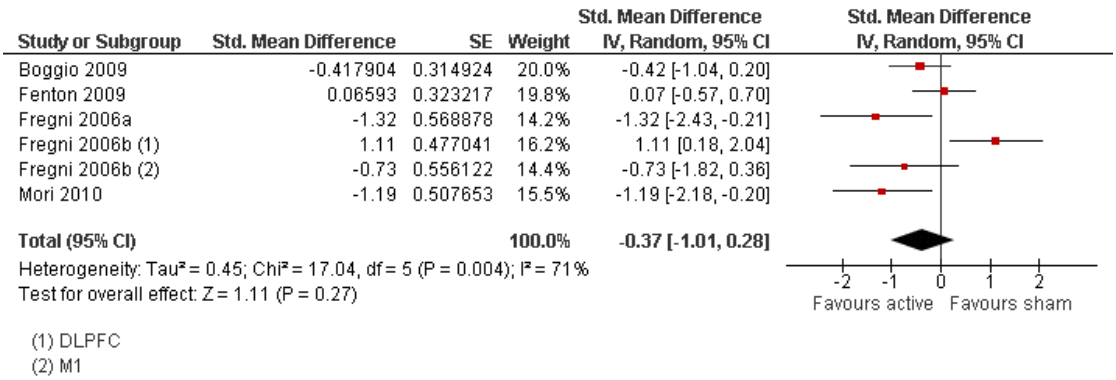
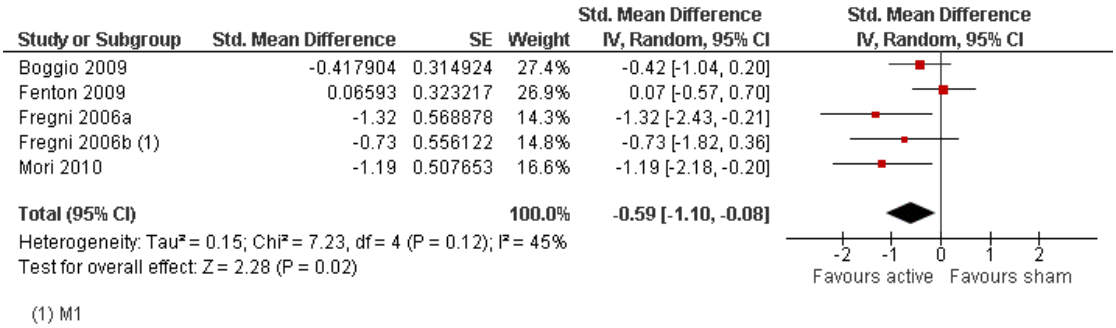


Figure 8. Forest plot of comparison: 3 tDCS, outcome: 3.5 Pain short-term follow up, subgroup analysis: motor cortex studies only.



Sensitivity analysis

To assess whether the imputation of standard errors for cross-over studies was robust the analysis was repeated with the imputed correlation coefficient reduced and increased by a value of 0.1. This had little impact on the overall meta-analysis but when the correlation was increased in the subgroup analysis of motor cortex studies the level of heterogeneity reached statistical significance (I^2 = 51%).

Small study effects/publication bias

Small study effects were investigated using Egger's test. The results are not suggestive of a significant influence of small study effects for the overall analysis (P = 0.528) or for the motor cortex subgroup analysis (P = 0.075).

Adverse events

All studies of tDCS reported the incidence of adverse events. Of these two studies reported none (Fregni 2006a; Mori 2010). 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. Valle 2009 reported "minor and uncommon" side effects such as skin redness and tingling which where equally distributed between active and sham stimulation. 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.

Secondary outcomes: disability and quality of life

There were insufficient data from which to draw reliable conclusions for any secondary outcome measure for any stimulation type.

DISCUSSION

Summary of main results

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 beneficial short-term effect of single-dose high-frequency rTMS applied to the motor cortex. This effect is small and does not conclusively exceed the threshold of minimal clinical significance. The limited 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. There is insufficient and conflicting evidence at medium-term follow-up points to allow firm conclusions to be drawn and at long-

term follow-up points there is limited evidence suggesting no benefit of active stimulation over sham.

Cranial electrotherapy stimulation (CES) for chronic pain

There is insufficient evidence from which to draw firm conclusions regarding the efficacy of CES. However, the evidence from trials where it is possible to extract data is not suggestive of a significant beneficial effect. 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

There is insufficient evidence from which to draw firm conclusions regarding the efficacy of tDCS. The existing evidence demonstrates substantial heterogeneity. Subgroup analysis suggests superiority of active over sham stimulation of the motor cortex for short-term pain relief but the confidence intervals are too wide for the purposes of estimating the effect size.

Adverse effects

Across all stimulation modalities there is no evidence of serious or lasting adverse effects of non-invasive brain stimulation. rTMS, 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.

Secondary outcome measures

There were insufficient data from which to draw any reliable conclusions regarding the effect of any stimulation type on disability or quality of life.

Overall completeness and applicability of evidence

The evidence for rTMS in this review is relatively complete. We were unable to extract data from one study (Fregni 2005) but this included five subjects and so we consider it unlikely that this would have affected the results of the analysis significantly. We are aware of no missing data that might have affected the subgroup analysis of high-frequency motor cortex stimulation.

We were unable to extract data from four out of seven studies of CES and these data were not available upon request. This may have impacted upon the results of our meta-analysis although one of those studies (Katsnelson 2004) would have been excluded from the meta-analysis as it was judged as being at a risk of bias on criteria other than selective outcome reporting.

We were unable to extract data from one study of tDCS (Valle 2009) and these data were not available upon request. These data would have significantly contributed to the power of the meta-analysis by the introduction of a further 41 participants. Therefore our meta-analyses of tDCS and CES should be considered an incomplete summary of the evidence.

Quality of the evidence

No study of rTMS could be judged as having a low risk of bias across all criteria. 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 that did not report assessor blinding reduced both heterogeneity and the pooled effect size. A recent meta-epidemiological study has provided empirical evidence that incomplete blinding in controlled trials that measure subjective outcomes may exaggerate the observed effect size by 25% (Wood 2008). It is therefore reasonable to expect that incomplete blinding may have exaggerated the effect size seen in the current analysis of rTMS. 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 the included studies were unable to control conclusively for these factors. Additionally there are insufficient data relating to stimulation of cortical regions other than the motor cortex from which to draw reliable comparisons. The effect size for the high-frequency studies of motor cortex rTMS approaches our predetermined threshold for clinical significance but the lower 95% confidence intervals do not meet this threshold. This estimate is based solely on single-dose studies and the evidence for multiple-dose studies is currently both limited and conflicting.

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 (Gabis 2003; Gabis 2009; Katsnelson 2004) utilised an "active placebo" control in which stimulating current was delivered but at much lower intensities. 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 does not suggest such a trend and statistical heterogeneity between studies entered into the analysis was low.

One study of tDCS was judged as having a low risk of bias on all criteria (Mori 2010). However, the one study (Valle 2009) that we could not enter into the meta-analysis would have been judged at low risk of bias had this data been available. There is evidence that the sham control used in tDCS does achieve effective blinding of participants (Gandiga 2006) and studies were judged as being at low risk of bias if they reported formally blinding the participants. However, while this form of blinding is validated for stimulation intensities of 1 mA all of the studies identified in this review used stimulation intensities of 2 mA which may be more likely to elicit sensation. One study report (Mori 2010) alludes in the discussion to experiencing difficulties with blinding at 2 mA. This suggests a possible source of bias within the existing evidence base in favour of active stimulation but we are unaware of any systematic evaluation of the integrity of tDCS sham controls at this stimulation intensity.

All of the 33 studies may be considered to be small in terms of sample size. Given the trend seen in tDCS studies of the motor cortex towards a beneficial effect on short-term pain outcomes it is possible that the existing analysis lacks adequate power and that further large studies may demonstrate therapeutic benefit.

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, subgroup investigation significantly reduced this heterogeneity. While the subgroup analyses used in this review were prespecified in the review protocol they should be considered as observational rather than randomised data and thus the evidence from them is less robust.

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 be as accurate a reflection of their efficacy across all chronic pain conditions.

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

The analysis of tDCS for short-term pain included a combination of studies that delivered a varied number of treatments but there were insufficient data to support a subgroup analysis specific to this variable. This analysis is also affected by one study that does not demonstrate a trend toward superiority of active over sham stimulation (Fenton 2009). This study delivered fewer treatment sessions compared with some others in the analysis. Additionally the authors of this study concluded in favour of active stimulation by comparing the average pain outcome over a one-week period, whereas in the current analysis post-stimulation data from the day of the final treatment session was used. However, this study fulfils the criteria for inclusion into the analysis and post-hoc sensitivity analysis excluding this study was considered inappropriate.

The method used to back transform the pooled SMD to a visual analogue scale and subsequent calculation of the effect as a percentage improvement does rest upon the assumption that the standard deviation and the pain levels in the study used (Lefaucheur 2004) are representative of the wider body of evidence. The study was chosen as it was the largest study and contributed the most weight to the analysis. Review of both the standard deviation and the control group pain scores in Lefaucheur 2004 suggests that they fall around the middle of distributed values. However, the results of this back transformation should be considered an estimate.

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 ($\geq$ 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 suggest that it might be considered in the treatment of short-lasting pain.

A recent review (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 neuro-anatomical 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 (Defrin 2007; Kang 2009) failed to demonstrate superiority of active over sham stimulation.

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 results of the subgroup analysis of multiple-dose studies of high-frequency motor cortex rTMS in neuropathic pain do not suggest a benefit of active stimulation over sham.

Lima and Fregni (Lima 2008) undertook a systematic review and meta-analysis of motor cortex stimulation for chronic pain. 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% 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 or 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.

Kirsch 2000 reviewed studies of CES in the management of chronic pain and concluded in favour of the use of CES. 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.

AUTHORS' CONCLUSIONS

Implications for practice

There is evidence that low-frequency rTMS is not clinically effective in 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 although the limited evidence from multiple-dose studies of high-frequency rTMS to the motor cortex is conflicting. As such it is not currently clear whether rTMS represents a useful clinical tool and more evidence is needed. There is insufficient evidence from which to draw firm conclusions regarding the efficacy of tDCS or CES for the treatment of chronic pain.

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. Studies should endeavour to report primary outcomes clearly in a format that facilitates data extraction so that an inclusive meta-analysis might be possible, particularly in studies of CES and tDCS. All studies of non-invasive brain stimulation techniques should measure, record and clearly report adverse events to both active and sham stimulation. Further studies of tDCS should give consideration to the integrity of participant blinding, particularly when utilising stimulation intensities that exceed 1 mA.

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. All 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. The current results suggest that any future trial of rTMS in chronic pain should utilise high-frequency stimulation parameters. The influence of other stimulation parameters on efficacy is currently unclear. The results suggest that the motor cortex is the most promising site for stimulation, however this may be a function of the small number of studies that stimulated other cortical regions. There is a particular need for more multiple-dose studies of rTMS that measure both short and long-term clinical

outcomes to determine whether the effect seen in this review can be considered clinically useful.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[author-defined order]*

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 mins, 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	Adverse events: none Data requested from authors and received

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	Comment: method of randomisation not specified but less likely to introduce bias in a cross-over design Quote: "Three different sessions of stimulation were administered in random order to each patient."
Incomplete outcome data addressed? 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

André-Obadia 2006 (*Continued*)

Free of selective reporting?	Low risk	Pain outcomes reported for all participants. Change from baseline figures given, point measures requested from study authors and received
Free of 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

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

André-Obadia 2008 (*Continued*)

	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 When taken: daily for 2 weeks post stimulation.	
Notes	Adverse events: none Data requested from authors	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Low risk	Quote: "the order of sessions was randomised (by computerized random-number generation)"
Incomplete outcome data addressed? 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
Free of selective reporting?	Low risk	Comment: medial-lateral coil orientation condition data not presented but provided by authors on request
Free of other bias?	Low risk	Comment: no significant other bias detected
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

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	Adverse events: 1 headache reported during active stimulation

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	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 addressed? 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
Free of selective reporting?	Low risk	Comment: primary outcome data presented clearly and in full
Free of other bias?	Low risk	Comment: no significant other bias detected
Adequate blinding of assessors?	Low risk	Quote: "All evaluations were carried out by a blinded rater"

Boggio 2009 (*Continued*)

Adequate blinding of participants?	Low risk	Comment: there is evidence in supporting type of sham control as credible
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)."

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**

Borckardt 2009 (*Continued*)

Adequate sequence generation?	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 addressed? All outcomes	Low risk	Comment: no drop-out
Free of selective reporting?	Low risk	Comment: all results reported clearly and in full
Free of other bias?	Low risk	Comment: no significant other bias detected
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

Capel 2003

Methods	Partial cross-over randomised controlled trial. NB: Only first phase results will be considered therefore the trial will be 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

Capel 2003 (*Continued*)

	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 mins Stimulation location: ear clip electrodes Number of treatments: x 2 daily for 4 days Control type: sham CES unit indistinguishable from active unit
Outcomes	Primary: 0 to 10 VAS "level of pain", anchors not specified When taken: daily during the treatment period Secondary: none
Notes	Adverse events: none

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	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?	Low risk	Comment: this is achieved through the method of randomisation
Incomplete outcome data addressed? 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."

Capel 2003 (*Continued*)

Free of selective reporting?	High risk	Comment: pain score values are not provided for any time point
Free of 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."
Adequate blinding of participants?	Low risk	Quote: "neither the administrators nor the recipients of the treatment could distinguish between the devices."

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	Adverse events Active group: neck pain/headache 6/14 participants, worsening depression 1/14 participants Sham group: 2/12 neck pain/headache, 4/12 nausea/tiredness

Risk of bias

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

Carretero 2009 (*Continued*)

Adequate sequence generation?	Unclear risk	Comment: method of randomisation not specified
Allocation concealment?	Unclear risk	Comment: allocation concealment not specified
Incomplete outcome data addressed? All outcomes	Low risk	Comment: only one participant in each group did not complete the study. Unlikely to have strongly influenced the findings
Free of selective reporting?	Low risk	Comment: outcomes presented clearly and in full
Free of 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 45° away from scalp. Does not control for sensory characteristics of active stimulation and is visually distinguishable

Cork 2004

Methods	Cross-over randomised controlled trial (to be considered as parallel - first treatment phase only)
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 mins 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

Cork 2004 (*Continued*)

Notes	Adverse events: not reported	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	Comment: method of randomisation not specified
Allocation concealment?	Unclear risk	Comment: allocation concealment not specified
Incomplete outcome data addressed? All outcomes	Unclear risk	Comment: drop-out rate not reported
Free of selective reporting?	High risk	Comment: pain score numerical values are not provided clearly with measures of variance for any time point
Free of 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."

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
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 make 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**
Adequate sequence generation?	Unclear risk	Comment: method of randomisation not specified Quote: "Patients were randomised into 2 groups that received either real or sham rTMS"
Allocation concealment?	Unclear risk	Comment: allocation concealment not specified
Incomplete outcome data addressed? All outcomes	Low risk	Comment: only one participant withdrew for "logistic reasons". Unlikely to have strongly influenced the findings
Free of selective reporting?	Low risk	Comment: while group means/SD are not presented in the study report, the study authors have provided the requested data
Free of other bias?	Low risk	Comment: no significant other bias detected
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 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, is likely to have elicited muscle twitches in peripheral muscles

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	Adverse events: Active group: 3 headache, 2 neck ache, 1 scalp pain, 5 scalp burning sensation Sham group: 1 headache, 0 neck ache, 0 scalp pain, 0 scalp burning sensation

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Low risk	Comment: method of randomisation not specified but less critical in cross-over design
Incomplete outcome data addressed? All outcomes	Low risk	Comment: no drop-out reported
Free of selective reporting?	Low risk	Comment: variance measures not presented for group means post-stimulation but data provided by author on request
Free of 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."

Fenton 2009 (*Continued*)

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

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
Notes	Adverse events: none

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Low risk	Quote: "The order of stimulation was randomised and counterbalanced across patients using a Latin square design."
Incomplete outcome data addressed? All outcomes	Low risk	Comment: no drop-out reported

Fregni 2005 (*Continued*)

Free of selective reporting?	High risk	Comment: pain score numerical values are not provided clearly with measures of variance for any time point for the sham condition
Free of 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."

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 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 10cm, anchors "no pain" to "worst pain possible" When taken: before and after each stimulation and at 16-day follow up Secondary: none	
Notes	Adverse events: none	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**

Fregni 2006a (*Continued*)

Adequate sequence generation?	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?	Low risk	Comment: the use of a pre-generated randomisation list should ensure this
Incomplete outcome data addressed? 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."
Free of selective reporting?	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
Free of other bias?	Low risk	Comment: no significant other bias detected
Adequate blinding of assessors?	Low risk	Quote: "All evaluations were performed by a blinded rater"
Adequate blinding of participants?	Low risk	Quote: "3-week double-blinded treatment"

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

Fregni 2006b (*Continued*)

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	Adverse events: Condition 1 (DLPFC): sleepiness (1/11 participants), headache (1/11) Condition 2 (motor cortex): sleepiness (3/11), headache (3/11) Sham group: sleepiness (1/10), headache (2/10)

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	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?	Low risk	Comment: the use of a pre-generated randomisation list should have adequately ensured this
Incomplete outcome data addressed? 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."
Free of selective reporting?	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 one follow-up point but not for other follow-up points

Fregni 2006b (*Continued*)

Free of other bias?	Low risk	Comment: no significant other bias detected
Adequate blinding of assessors?	Low risk	Quote: "All of the assessments were conducted by raters who were blinded to the treatment arm."
Adequate blinding of participants?	Low risk	Quote: "a period of double-blinded treatment, during which patients received daily treatment"

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 $\leq$ 4 mA; waveform shape biphasic asymmetric; duration 30 mins Stimulation location: 3 electrodes, one attached to either mastoid process and one 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 $\leq$ 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	Adverse events: mild skin redness under electrodes in some patients. 5% experienced mild short duration headaches or dizziness during or up to 10 mins following treatment

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Low risk	Quote: "The paramedic administered treatments based on a computer-elicited randomisation list."

Gabis 2003 (*Continued*)

Allocation concealment?	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 addressed? All outcomes	Low risk	Comment: all participants completed the study
Free of selective reporting?	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
Free of 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"

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
Interventions	Stimulation type: CES Stimulation parameters: frequency 77 Hz; pulse width 3.3 msec; intensity $\leq$ 4 mA; waveform shape biphasic asymmetric; duration 30 mins Stimulation location: 3 electrodes, one attached to either mastoid process and one to the

Gabis 2009 (*Continued*)

	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**
Adequate sequence generation?	Low risk	Quote: "The paramedic administered treatments based on a computer-elicited randomisation list"
Allocation concealment?	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 addressed? All outcomes	Low risk	Comment: no drop-out is indicated comparing the results with the number enrolled
Free of selective reporting?	Low risk	Comment: results for primary outcomes are reported clearly and in full
Free of 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"

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	Adverse events: none

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	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 addressed? All outcomes	Low risk	Quote: "All 20 patients underwent all planned sessions of navigation- guided rTMS"
Free of selective reporting?	Low risk	Comment: pain score numerical values are not provided clearly with measures of variance for any time point but data provided upon request
Free of other bias?	Low risk	Comment: no significant other bias detected

Hirayama 2006 (*Continued*)

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

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 SD14.8, 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

Irlbacher 2006 (*Continued*)

Notes	Adverse events: one participant reported increased pain following 5 Hz active stimulation

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	Comment: method of randomisation not specified but less critical in cross-over design
Incomplete outcome data addressed? 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
Free of selective reporting?	Low risk	Comment: primary outcome data presented clearly and in full
Free of 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	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"

Kang 2009

Methods	Cross-over randomised controlled trial
Participants	Country of study: S 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
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**
Adequate sequence generation?	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 addressed? All outcomes	Low risk	Comment: no participants withdrew after receiving the first treatment condition
Free of selective reporting?	Low risk	Comment: results for primary outcomes are reported clearly and in full
Free of 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

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 mins Stimulation location: appears to be one electrode attached to either mastoid process and one 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**
Adequate sequence generation?	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?	Unclear risk	Comment: not specified
Incomplete outcome data addressed? All outcomes	Unclear risk	Comment: drop-out level not specified
Free of selective reporting?	High risk	Comment: it is unclear in the report which time points are reported for primary outcomes
Free of 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."

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**
Adequate sequence generation?	High risk	Quote: "Patients were randomly assigned to one of the two groups, depending on the day of the week on which they were recruited" Comment: not truly random
Allocation concealment?	High risk	Comment: the method of sequence generation makes concealment of allocation unlikely

Khedr 2005 (*Continued*)

Incomplete outcome data addressed? All outcomes	Low risk	Comment: no drop-out is apparent from the presented data
Free of selective reporting?	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
Free of 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

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 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	Adverse events: none
Risk of bias	

Lefaucheur 2001a (*Continued*)

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	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 addressed? All outcomes	Low risk	Comment: no drop-out is apparent from the presented data
Free of selective reporting?	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
Free of 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 of an ideal sham
Free from carry-over effects?	Low risk	Comment: 3/52 wash-out period makes carry-over effects unlikely

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

Lefaucheur 2001b (*Continued*)

	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	Adverse events: none

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	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 addressed? All outcomes	Low risk	Comment: no drop-out is apparent from the presented data
Free of selective reporting?	Low risk	Comment: results for primary outcomes are reported clearly and in full
Free of 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 of 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

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

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	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 addressed? All outcomes	Low risk	Comment: no drop-out is apparent from the presented data
Free of selective reporting?	Low risk	Comment: results for primary outcomes are reported clearly and in full
Free of 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 electri-

		cal 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

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**
Adequate sequence generation?	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 de-

Lefaucheur 2006 (*Continued*)

		sign
Incomplete outcome data addressed? All outcomes	Unclear risk	Comment: level of drop-out not reported and unclear from the presented data
Free of selective reporting?	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
Free of other bias?	Low risk	Comment: no significant other bias detected
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 Lefaucheur 2004, which in that paper is stated as not meeting the criteria of 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"

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

Lefaucheur 2008 (*Continued*)

	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	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	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 addressed? All outcomes	Low risk	Comment: 2 participants dropped out but this is < 5% of the cohort. Unlikely to have strongly influenced the findings
Free of selective reporting?	Low risk	Comment: results for all outcomes are reported clearly and in full
Free of 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 of 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

Lichtbroun 2001

Methods	Parallel randomised controlled study
Participants	Country of study: USA Setting: outpatient fibromyalgia clinic Condition: fibromyalgia Prior management details: unclear n = 60 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 mins 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**
Adequate sequence generation?	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?	Low risk	Comment: probably given the quote above
Incomplete outcome data addressed? All outcomes	Unclear risk	Drop-out levels are not specified in the report. Intention-to-treat analysis not discussed in the report
Free of selective reporting?	High risk	Comment: pain score numerical values are not provided clearly with measures of variance for any time points in the study report
Free of 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"

Lichtbroun 2001 (*Continued*)

Adequate blinding of participants?	Low risk	Comment: see previous quote

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**
Adequate sequence generation?	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?	Low risk	Comment: likely given that the randomisation list was generated pre-study
Incomplete outcome data addressed? All outcomes	Low risk	Comment: no drop-out observed Quote: "none of the patients enrolled discontinued the study."
Free of selective reporting?	Low risk	Comment: between-group means are not presented clearly to allow meta-analysis but data provided on request

Free of other bias?	Low risk	Comment: no significant other bias detected
Adequate blinding of assessors?	Low risk	Quote: "Patients and assessing physician were blinded to group allocation while the treating physician, who had to set the tDCS or sham-stimulation protocol on the stimulator, was aware of the stimulation condition. To minimize communication between blinded and non-blinded participants, the treating physician was instructed not to talk to patients and the assessing physician about the study protocol"
Adequate blinding of participants?	Low risk	Comment: see quote above

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 secs; ITI 52 secs; 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	Adverse events: headaches 4 active, 5 sham, nausea 1 active, tinnitus 2 sham, dizziness 1 sham

Risk of bias

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

Passard 2007 (*Continued*)

Adequate sequence generation?	Low risk	Quote: "patients who met all inclusion criteria were randomly assigned, according to a computer-generated list, to two groups"
Allocation concealment?	Unclear risk	Comment: allocation concealment not specified
Incomplete outcome data addressed? 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"
Free of selective reporting?	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
Free of 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

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
Interventions	Stimulation type: rTMS Stimulation parameters: frequency 10 Hz; coil orientation unspecified; 110% RMT; no. of trains 10; duration of trains 1.2 secs; ITI 10 secs; 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 secs, 15, 45 and 90 mins 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**
Adequate sequence generation?	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 addressed? All outcomes	Low risk	Comment: no drop-out is apparent from the presented data
Free of selective reporting?	Low risk	Comment: while sham group results not presented in the study report, the study authors have provided the requested data
Free of 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)."

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	Adverse events: headaches - 1 participant (unclear whether during active or sham stimulation)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	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 addressed? All outcomes	Low risk	Comment: only one participant withdrew due to "headaches". Unlikely to have strongly influenced the findings
Free of selective reporting?	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
Free of other bias?	Low risk	Comment: no significant other bias detected

Rollnik 2002 (*Continued*)

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)

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	Adverse events: none	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	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 addressed? All outcomes	Low risk	Quote: "All 13 patients participated in all planned sessions of navigation-guided rTMS" Comment: no drop-out observed
Free of selective reporting?	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
Free of 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

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**
Adequate sequence generation?	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 addressed? 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
Free of selective reporting?	Low risk	Comment: primary outcome data presented clearly
Free of 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

Tan 2000 (*Continued*)

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"

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

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	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?	Unclear risk	Comment: allocation concealment not specified

Tan 2006 (*Continued*)

Incomplete outcome data addressed? All outcomes	Low risk	Comment: only 2 (5%) patients withdrew from the study. Unlikely to have strongly influenced the findings
Free of selective reporting?	Low risk	Comment: primary outcomes presented clearly and in full
Free of 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

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	Adverse events: Quote: "minor and uncommon - such as skin redness and tingling - and distributed equally across groups of stimulation"
Risk of bias	

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	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?	Low risk	Comment: the use of a pre-generated randomisation list should have adequately ensured this
Incomplete outcome data addressed? All outcomes	Low risk	Comment: no drop-out occurred
Free of selective reporting?	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
Free of other bias?	Low risk	Comment: no significant other bias detected
Adequate blinding of assessors?	Low risk	Quote: "Subjects remained blinded to treatment group throughout the study"
Adequate blinding of participants?	Low risk	Quote: "blinded raters carried out all assessments"

CES: cranial electrotherapy stimulation
CNP: central neuropathic pain
BPI: brief pain inventory
F: female
ITI: inter-train interval
L: left
M: male
MCS: motor cortex stimulation (MCS)
NRS: numerical rating scale
PLP: phantom limb pain
R: right
RMT: resting motor threshold
rTMS: repetitive transcranial magnetic stimulation
SCI: spinal cord injury
SD: standard deviation
tDCS: transcranial direct current 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
Evtiukhin 1998	A study of postoperative pain. No sham control employed
Frentzel 1989	Not a study of brain stimulation
Johnson 2006	Self-reported pain is not measured
Katz 1991	Study not confined to chronic pain
Longobardi 1989	Not clearly studying chronic pain
Pujol 1998	Subjects are a mixture of acute and chronic pain patients
Roizenblatt 2007	Duplicated data from Fregni 2006a study
Silva 2007	A single case report
Zaghi 2009	A single case report with no sham control utilised

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

Shklar 1997

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

Vatashsky 1997

Methods	Unable to retrieve study report
Participants	-
Interventions	-

Vatashsky 1997 (*Continued*)

Outcomes	-
Notes	-

DATA AND ANALYSES

Comparison 1. rTMS

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pain short-term follow up	16		Std. Mean Difference (Random, 95% CI)	-0.20 [-0.37, -0.03]
1.1 Low-frequency ≤ 1 Hz	6		Std. Mean Difference (Random, 95% CI)	0.17 [-0.01, 0.35]
1.2 High-frequency ≥ 5 Hz	15		Std. Mean Difference (Random, 95% CI)	-0.32 [-0.51, -0.13]
2 Sensitivity analysis - imputed correlation coefficient increased	17		Std. Mean Difference (Random, 95% CI)	-0.21 [-0.38, -0.05]
2.1 Low-frequency ≤ 1 Hz	6		Std. Mean Difference (Random, 95% CI)	0.16 [0.02, 0.30]
2.2 High-frequency ≥ 5 Hz	16		Std. Mean Difference (Random, 95% CI)	-0.33 [-0.52, -0.15]
3 Sensitivity analysis - imputed correlation coefficient decreased	16		Std. Mean Difference (Random, 95% CI)	-0.19 [-0.37, -0.01]
3.1 Low-frequency ≤ 1 Hz	6		Std. Mean Difference (Random, 95% CI)	0.18 [-0.03, 0.38]
3.2 High-frequency ≥ 5 Hz	15		Std. Mean Difference (Random, 95% CI)	-0.31 [-0.51, -0.11]
4 Pain short-term follow up, subgroup analysis: multiple-dose vs single-dose studies	17		Std. Mean Difference (Random, 95% CI)	-0.20 [-0.37, -0.03]
4.1 Single-dose studies	12		Std. Mean Difference (Random, 95% CI)	-0.22 [-0.37, -0.06]
4.2 Multiple-dose studies	5		Std. Mean Difference (Random, 95% CI)	-0.24 [-1.25, 0.76]
5 Pain short-term follow up, subgroup analysis: motor cortex studies only, low frequency studies excluded	14		Std. Mean Difference (Random, 95% CI)	-0.36 [-0.54, -0.18]
5.1 Single-dose studies	11		Std. Mean Difference (Random, 95% CI)	-0.40 [-0.54, -0.26]
5.2 Multiple-dose studies	3		Std. Mean Difference (Random, 95% CI)	0.10 [-1.06, 1.26]
6 Sensitivity analysis - imputed correlation increased. Pain short-term follow up, subgroup analysis: motor cortex studies only, low frequency studies excluded	14		Std. Mean Difference (Random, 95% CI)	-0.37 [-0.55, -0.19]
6.1 Single-dose studies	11		Std. Mean Difference (Random, 95% CI)	-0.42 [-0.57, -0.28]
6.2 Multiple-dose studies	3		Std. Mean Difference (Random, 95% CI)	0.10 [-1.04, 1.24]
7 Sensitivity analysis - imputed correlation decreased. Pain short-term follow up, subgroup analysis: motor cortex studies only, low frequency studies excluded	14		Std. Mean Difference (Random, 95% CI)	-0.35 [-0.55, -0.16]
7.1 Single-dose studies	11		Std. Mean Difference (Random, 95% CI)	-0.39 [-0.52, -0.25]
7.2 Multiple-dose studies	3		Std. Mean Difference (Random, 95% CI)	0.10 [-1.08, 1.29]
8 Pain medium-term follow up	4		Std. Mean Difference (Random, 95% CI)	Totals not selected
8.1 Low-frequency ≤ 1 Hz	1		Std. Mean Difference (Random, 95% CI)	0.0 [0.0, 0.0]
8.2 High-frequency ≥ 5 Hz	3		Std. Mean Difference (Random, 95% CI)	0.0 [0.0, 0.0]

9 Pain long-term follow up	2	Std. Mean Difference (Random, 95% CI)	-0.10 [-0.46, 0.26]
10 Disability/pain interference short term follow up	2	Std. Mean Difference (Random, 95% CI)	Totals not selected
11 Disability/pain interference medium term follow up	2	Std. Mean Difference (Random, 95% CI)	Totals not selected
12 Disability/pain interference long-term follow up	2	Std. Mean Difference (Random, 95% CI)	Totals not selected
13 Quality of life short-term follow up	1	Std. Mean Difference (Random, 95% CI)	Totals not selected
14 Quality of life medium-term follow up	1	Std. Mean Difference (Random, 95% CI)	Totals not selected
15 Quality of life long-term follow up	1	Std. Mean Difference (Random, 95% CI)	Totals not selected

Comparison 2. CES

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pain short-term follow up	3	133	Std. Mean Difference (IV, Random, 95% CI)	-0.31 [-0.65, 0.04]

Comparison 3. tDCS

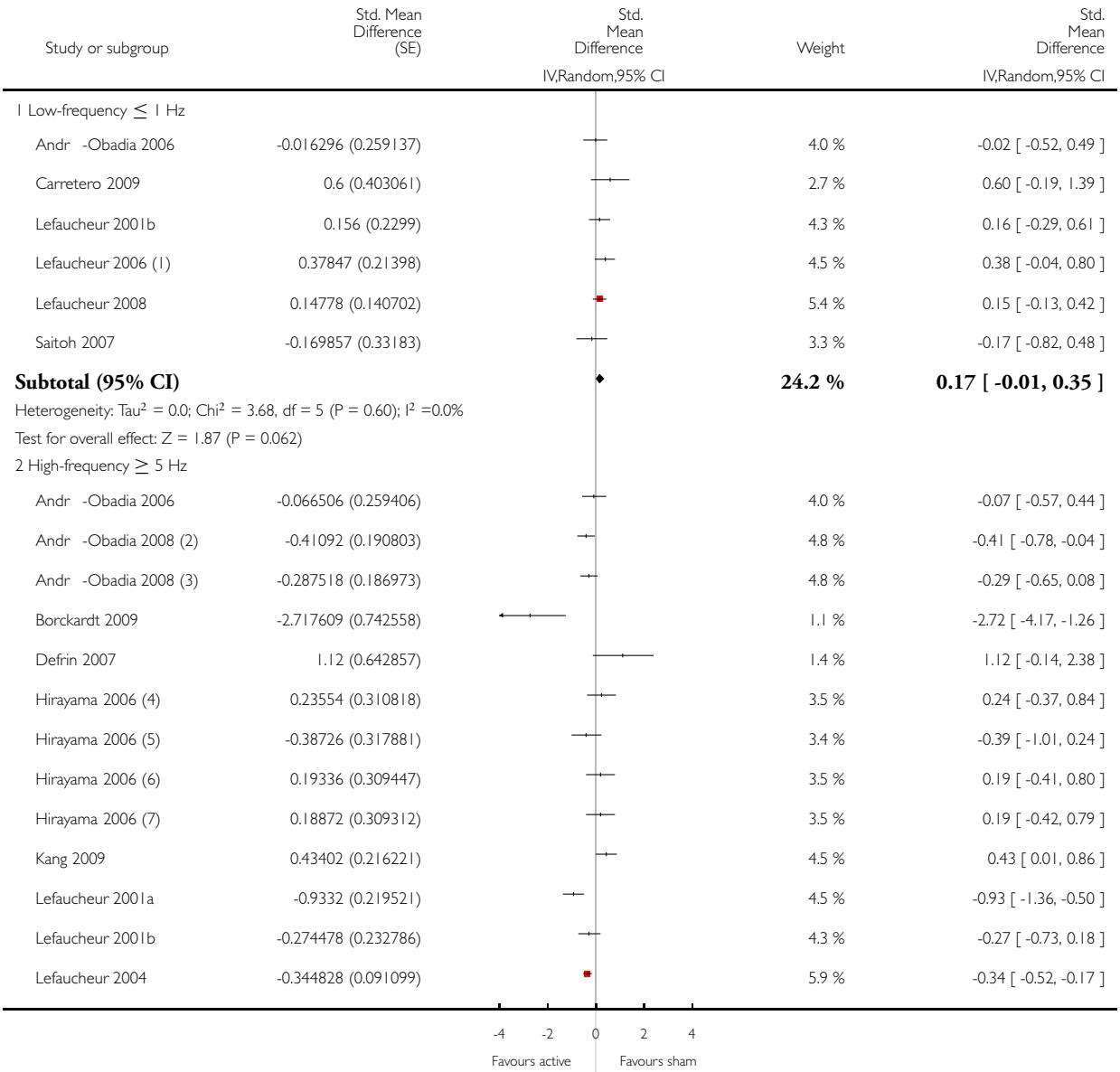
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pain post single treatment	5		Std. Mean Difference (Random, 95% CI)	Totals not selected
2 Pain short-term follow up	5		Std. Mean Difference (Random, 95% CI)	-0.37 [-1.01, 0.28]
3 Pain short-term sensitivity analysis: correlation increased	5		Std. Mean Difference (Random, 95% CI)	-0.36 [-0.97, 0.26]
4 Pain short-term sensitivity analysis: correlation decreased	5		Std. Mean Difference (Random, 95% CI)	-0.37 [-1.05, 0.30]
5 Pain short-term follow up, subgroup analysis: motor cortex studies only	5		Std. Mean Difference (Random, 95% CI)	-0.59 [-1.10, -0.08]
6 Pain short-term follow up, motor cortex subgroup, sensitivity analysis: correlation increased	5		Std. Mean Difference (Random, 95% CI)	-0.57 [-1.07, -0.07]
7 Pain short-term follow up, motor cortex subgroup, sensitivity analysis: correlation decreased	5		Std. Mean Difference (Random, 95% CI)	-0.61 [-1.12, -0.10]
8 Pain medium-term follow up	2		Std. Mean Difference (Random, 95% CI)	Totals not selected
9 Quality of life short-term follow up	1		Std. Mean Difference (IV, Random, 95% CI)	Totals not selected
10 Quality of life medium-term follow up	1		Std. Mean Difference (IV, Random, 95% CI)	Totals not selected

Analysis 1.1. Comparison 1 rTMS, Outcome 1 Pain short-term follow up.

Review: Non-invasive brain stimulation techniques for chronic pain

Comparison: 1 rTMS

Outcome: 1 Pain short-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 2006	-0.64827 (0.227388)		4.4 %	-0.65 [-1.09, -0.20]
Lefaucheur 2008	-0.334132 (0.143793)		5.3 %	-0.33 [-0.62, -0.05]
Passard 2007	-1.08 (0.392857)		2.7 %	-1.08 [-1.85, -0.31]
Pleger 2004	-0.138771 (0.217836)		4.5 %	-0.14 [-0.57, 0.29]
Rollnik 2002	-0.150199 (0.199019)		4.7 %	-0.15 [-0.54, 0.24]
Saitoh 2007 (8)	-1.158204 (0.42585)		2.5 %	-1.16 [-1.99, -0.32]
Saitoh 2007 (9)	-1.110603 (0.418912)		2.5 %	-1.11 [-1.93, -0.29]
Subtotal (95% CI)			**75.8 %**	**-0.32 [-0.51, -0.13]**
Heterogeneity: Tau^2 = 0.11; Chi^2 = 60.05, df = 19 (P<0.00001); I^2 =68%				
Test for overall effect: Z = 3.31 (P = 0.00094)				
Total (95% CI)			**100.0 %**	**-0.20 [-0.37, -0.03]**
Heterogeneity: Tau^2 = 0.12; Chi^2 = 85.27, df = 25 (P<0.00001); I^2 =71%				
Test for overall effect: Z = 2.33 (P = 0.020)				

(1) 1Hz

(2) antero-posterior coil orientation

(3) medial-lateral coil orientation

(4) S1

(5) M1

(6) PMA

(7) SMA

(8) 5Hz

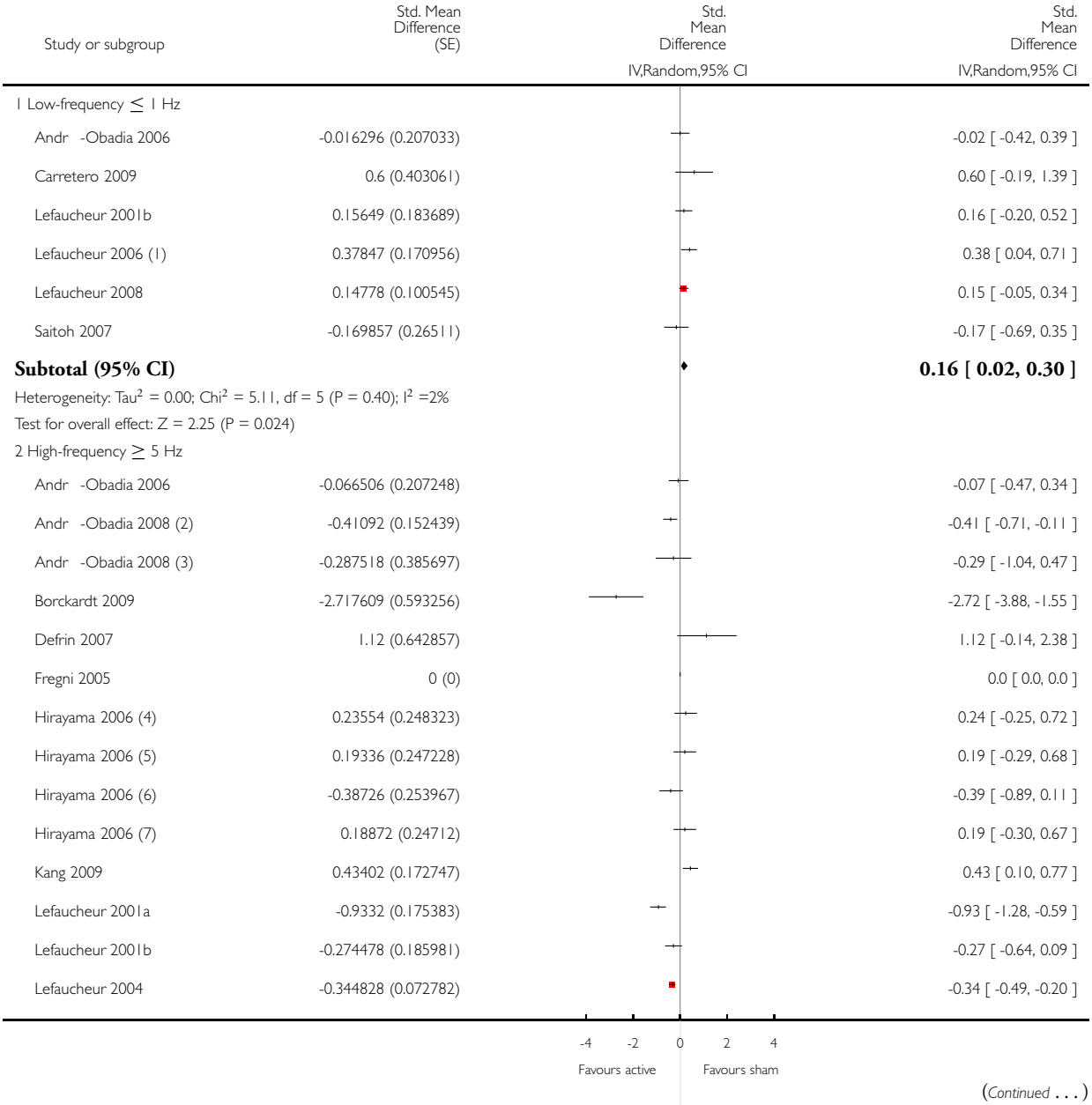
(9) 10 Hz

Analysis 1.2. Comparison 1 rTMS, Outcome 2 Sensitivity analysis - imputed correlation coefficient increased.

Review: Non-invasive brain stimulation techniques for chronic pain

Comparison: 1 rTMS

Outcome: 2 Sensitivity analysis - imputed correlation coefficient increased



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Study or subgroup	Std. Mean Difference (SE)	Std. Mean Difference IV,Random,95% CI	Std. Mean Difference IV,Random,95% CI
Lefaucheur 2006	-0.64827 (0.181669)		-0.65 [-1.00, -0.29]
Lefaucheur 2008	-0.334132 (0.102753)		-0.33 [-0.54, -0.13]
Passard 2007	-1.08 (0.392857)		-1.08 [-1.85, -0.31]
Pleger 2004	-0.138771 (0.174037)		-0.14 [-0.48, 0.20]
Rollnik 2002	-0.150199 (0.159003)		-0.15 [-0.46, 0.16]
Saitoh 2007 (8)	-1.110603 (0.334683)		-1.11 [-1.77, -0.45]
Saitoh 2007 (9)	-1.158204 (0.340227)		-1.16 [-1.83, -0.49]
Subtotal (95% CI)			**-0.33 [-0.52, -0.15]**
Heterogeneity: Tau^2 = 0.12; Chi^2 = 89.10, df = 19 (P<0.00001); I^2 =79%			
Test for overall effect: Z = 3.48 (P = 0.00051)			
Total (95% CI)			**-0.21 [-0.38, -0.05]**
Heterogeneity: Tau^2 = 0.13; Chi^2 = 128.56, df = 25 (P<0.00001); I^2 =81%			
Test for overall effect: Z = 2.50 (P = 0.013)			

(1) 1Hz

(2) antero-posterior coil orientation

(3) medial-lateral coil orientation

(4) S1

(5) PMA

(6) M1

(7) SMA

(8) 5Hz

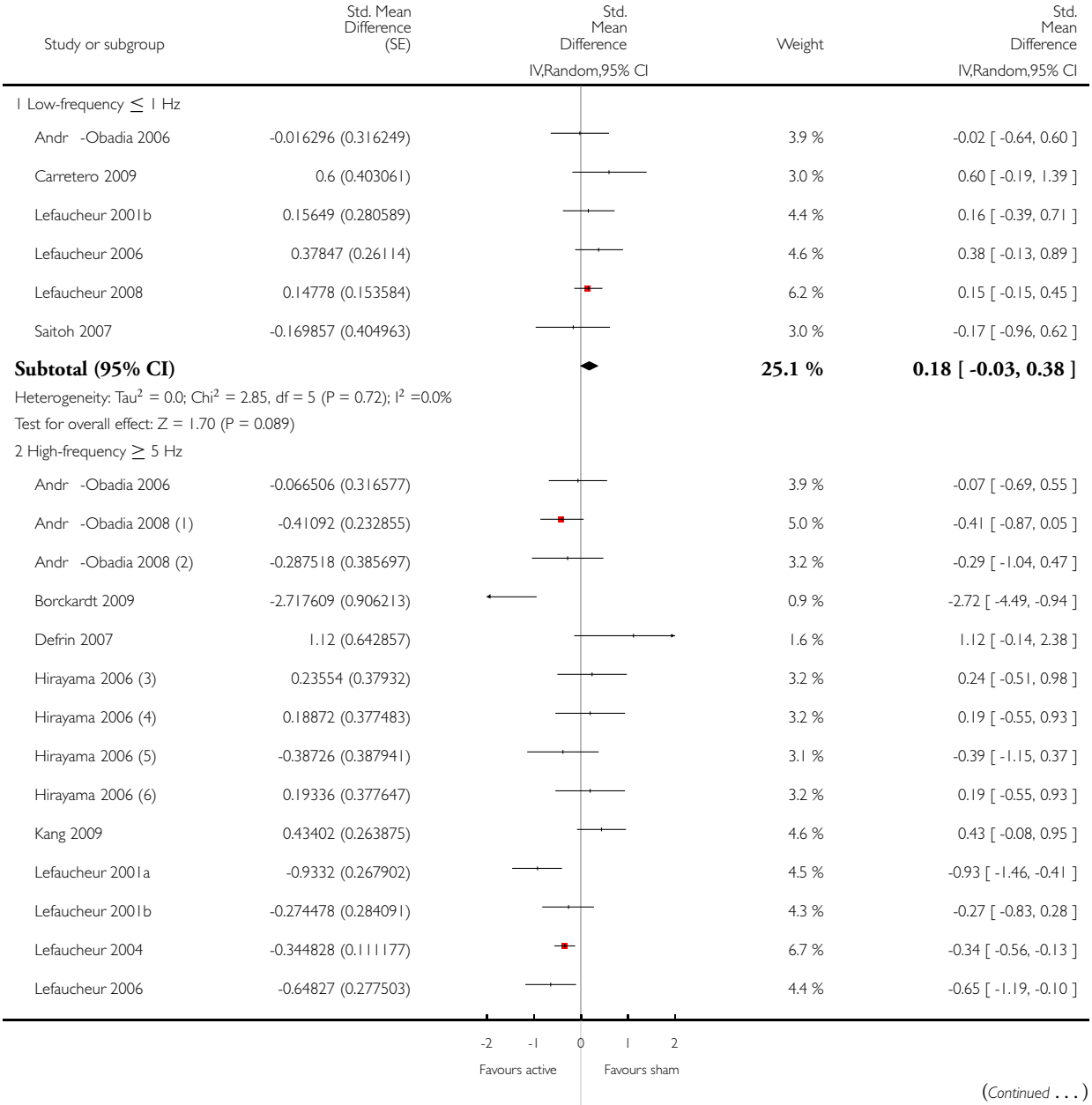
(9) 10 Hz

Analysis 1.3. Comparison 1 rTMS, Outcome 3 Sensitivity analysis - imputed correlation coefficient decreased.

Review: Non-invasive brain stimulation techniques for chronic pain

Comparison: 1 rTMS

Outcome: 3 Sensitivity analysis - imputed correlation coefficient decreased



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Study or subgroup	Std. Mean Difference (SE)	Std. Mean Difference IV,Random,95% CI	Weight	Std. Mean Difference IV,Random,95% CI
Lefaucheur 2008	-0.334132 (0.156958)		6.1 %	-0.33 [-0.64, -0.03]
Passard 2007	-1.08 (0.392857)		3.1 %	-1.08 [-1.85, -0.31]
Pleger 2004	-0.138771 (0.265846)		4.5 %	-0.14 [-0.66, 0.38]
Rollnik 2002	-0.150199 (0.242881)		4.9 %	-0.15 [-0.63, 0.33]
Saitoh 2007 (7)	-1.158204 (0.519705)		2.2 %	-1.16 [-2.18, -0.14]
Saitoh 2007 (8)	-1.110603 (0.511237)		2.2 %	-1.11 [-2.11, -0.11]
Subtotal (95% CI)			**74.9 %**	**-0.31 [-0.51, -0.11]**
Heterogeneity: Tau² = 0.10; Chi² = 43.21, df = 19 (P = 0.001); I² =56%				
Test for overall effect: Z = 3.08 (P = 0.0021)				
Total (95% CI)			**100.0 %**	**-0.19 [-0.37, -0.01]**
Heterogeneity: Tau² = 0.11; Chi² = 62.64, df = 25 (P = 0.00004); I² =60%				
Test for overall effect: Z = 2.08 (P = 0.038)				

(1) antero-posterior coil orientation

(2) medial-lateral coil orientatioin

(3) S1

(4) SMA

(5) M1

(6) PMA

(7) 5Hz

(8) 10 Hz

Analysis 1.4. Comparison 1 rTMS, Outcome 4 Pain short-term follow up, subgroup analysis: multiple-dose vs single-dose studies.

Review: Non-invasive brain stimulation techniques for chronic pain

Comparison: 1 rTMS

Outcome: 4 Pain short-term follow up, subgroup analysis: multiple-dose vs single-dose studies

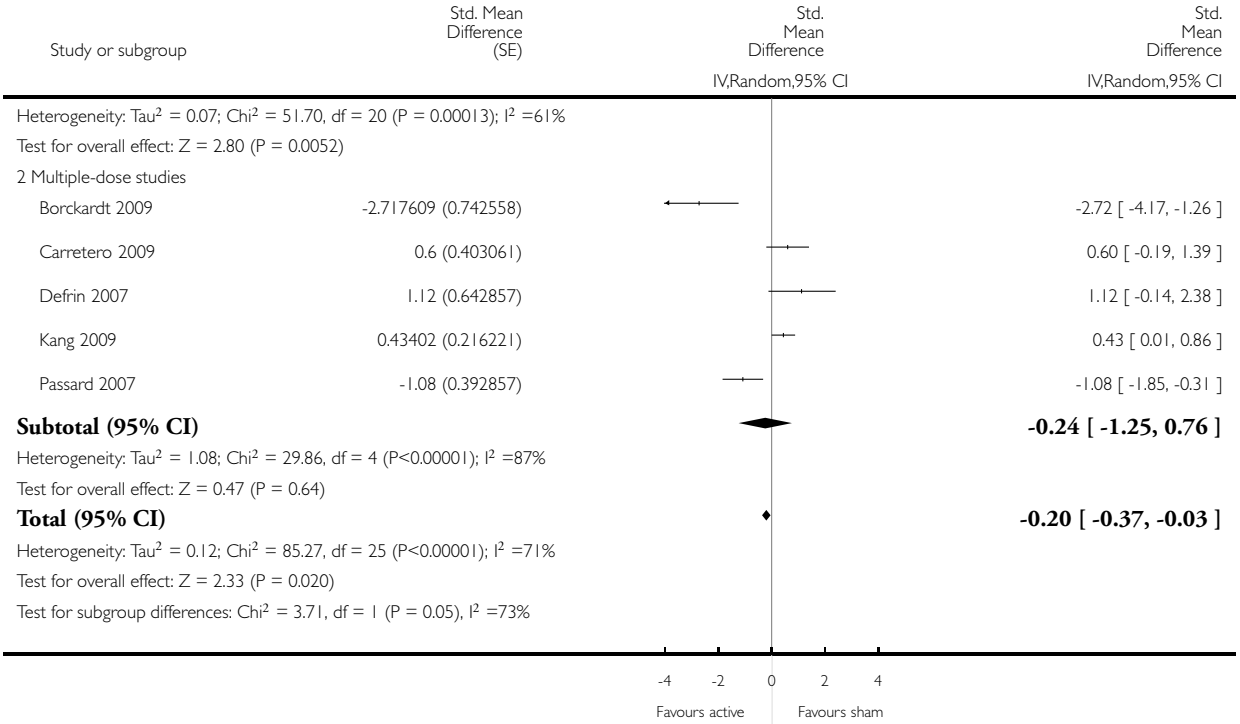
Study or subgroup	Std. Mean Difference (SE)	Std. Mean Difference IV,Random,95% CI	Std. Mean Difference IV,Random,95% CI
1 Single-dose studies			
Andr -Obadia 2006 (1)	-0.016296 (0.259137)		-0.02 [-0.52, 0.49]
Andr -Obadia 2006 (2)	-0.066506 (0.259406)		-0.07 [-0.57, 0.44]
Andr -Obadia 2008 (3)	-0.41092 (0.190803)		-0.41 [-0.78, -0.04]
Andr -Obadia 2008 (4)	-0.287518 (0.186973)		-0.29 [-0.65, 0.08]
Fregni 2005	0 (0)		0.0 [0.0, 0.0]
Hirayama 2006 (5)	-0.38726 (0.317881)		-0.39 [-1.01, 0.24]
Hirayama 2006 (6)	0.18872 (0.309312)		0.19 [-0.42, 0.79]
Hirayama 2006 (7)	0.23554 (0.310818)		0.24 [-0.37, 0.84]
Hirayama 2006 (8)	0.19336 (0.309447)		0.19 [-0.41, 0.80]
Lefaucheur 2001a	-0.9332 (0.219521)		-0.93 [-1.36, -0.50]
Lefaucheur 2001b (9)	0.156 (0.2299)		0.16 [-0.29, 0.61]
Lefaucheur 2001b (10)	-0.274478 (0.232786)		-0.27 [-0.73, 0.18]
Lefaucheur 2004	-0.344828 (0.091099)		-0.34 [-0.52, -0.17]
Lefaucheur 2006 (11)	-0.64827 (0.227388)		-0.65 [-1.09, -0.20]
Lefaucheur 2006 (12)	0.37847 (0.21398)		0.38 [-0.04, 0.80]
Lefaucheur 2008 (13)	0.14778 (0.140702)		0.15 [-0.13, 0.42]
Lefaucheur 2008 (14)	-0.334132 (0.143793)		-0.33 [-0.62, -0.05]
Pleger 2004	-0.138771 (0.217836)		-0.14 [-0.57, 0.29]
Rollnik 2002	-0.150199 (0.199019)		-0.15 [-0.54, 0.24]
Saitoh 2007 (15)	-0.169857 (0.33183)		-0.17 [-0.82, 0.48]
Saitoh 2007 (16)	-1.158204 (0.42585)		-1.16 [-1.99, -0.32]
Saitoh 2007 (17)	-1.110603 (0.418912)		-1.11 [-1.93, -0.29]
Subtotal (95% CI)			**-0.22 [-0.37, -0.06]**

-4 -2 0 2 4

Favours active Favours sham

(*Continued . . .*)

(. . . *Continued*)



(1) 1Hz

(2) 20Hz

(3) 20Hz antero-posterior coil orientation

(4) 20 Hz medial-lateral coil orientation

(5) M1

(6) SMA

(7) S1

(8) PMA

(9) 0.5 Hz

(10) 10Hz

(11) 10Hz

(12) 1Hz

(13) 1Hz

(14) 10 Hz

(15) 1Hz

(16) 5Hz

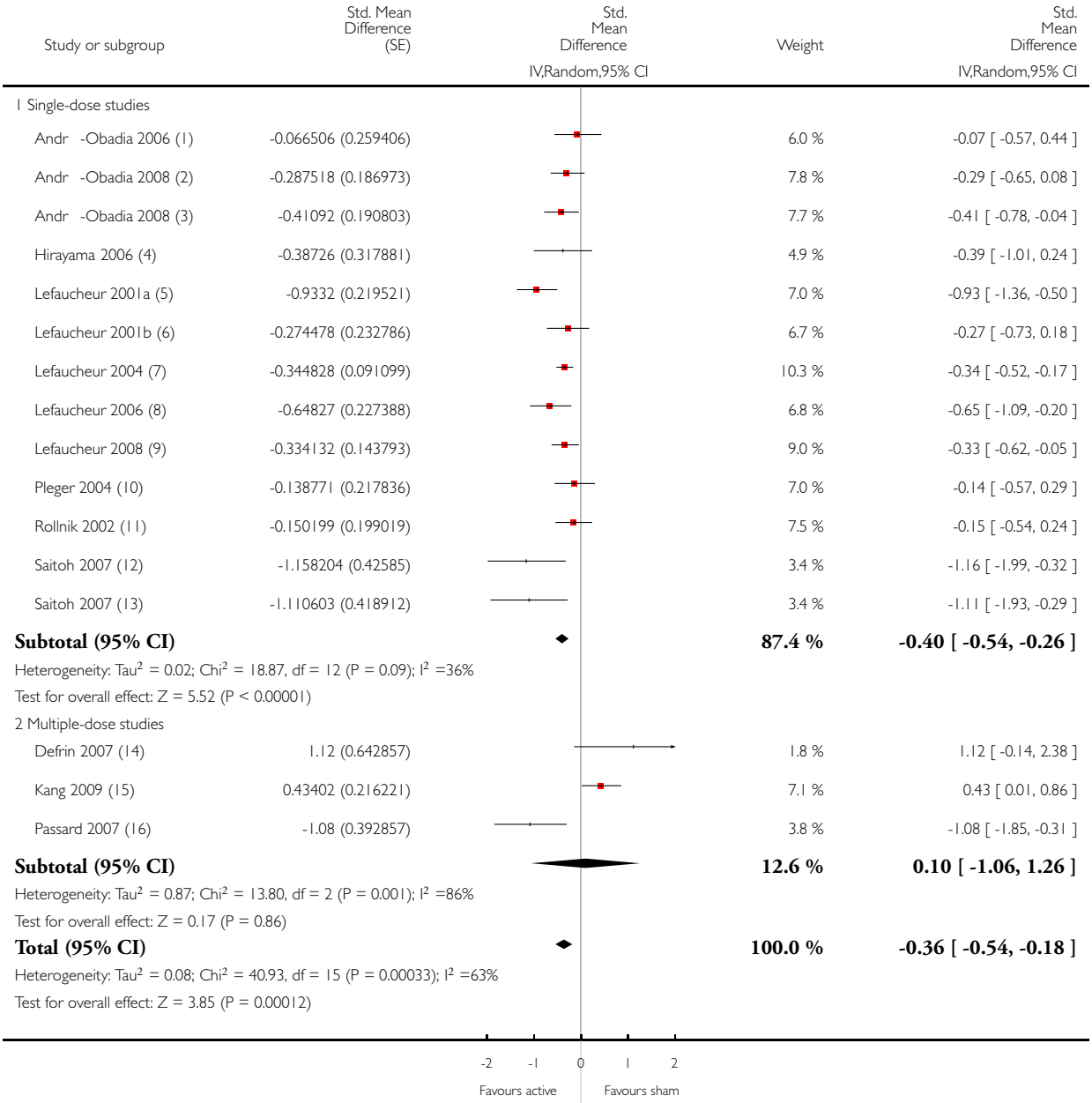
(17) 10Hz

Analysis 1.5. Comparison 1 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 rTMS

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



(1) 20Hz

(2) 20 Hz medial-lateral coil orientation

(3) 20Hz antero-posterior coil orientation

(4) 10Hz

(5) 10 Hz

(6) 10 Hz

(7) 10 Hz

(8) 10Hz

(9) 10Hz

(10) 10 Hz

(11) 20 Hz

(12) 5 Hz

(13) 10 Hz

(14) 5 Hz

(15) 10 Hz

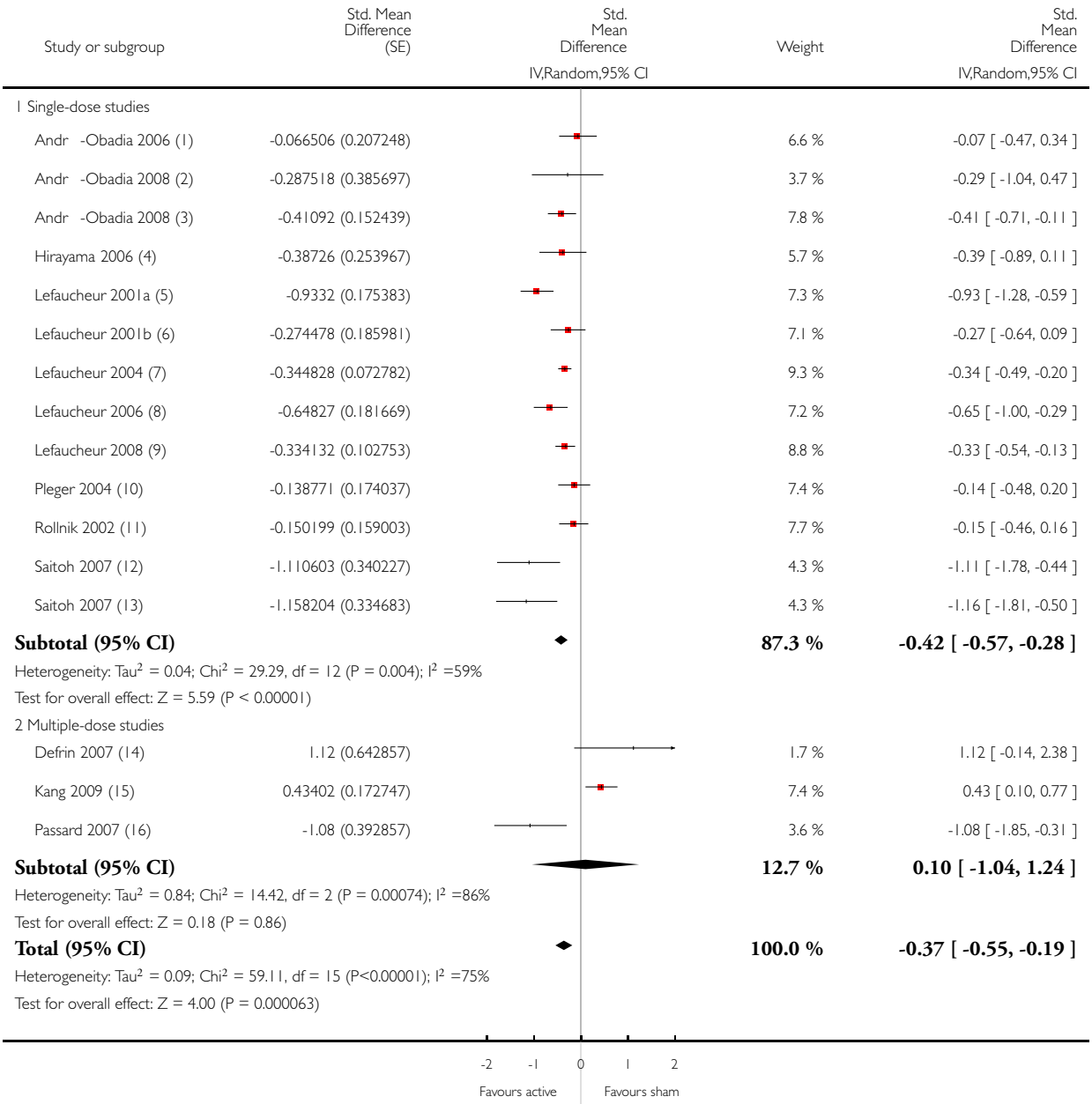
(16) 10 Hz

Analysis 1.6. Comparison 1 rTMS, Outcome 6 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 rTMS

Outcome: 6 Sensitivity analysis - imputed correlation increased. Pain short-term follow up, subgroup analysis: motor cortex studies only, low frequency studies excluded



(1) 20Hz

(2) 20 Hz medial-lateral coil orientation

(3) 20Hz antero-posterior coil orientation

(4) 10Hz

(5) 10 Hz

(6) 10 Hz

(7) 10 Hz

(8) 10Hz

(9) 10Hz

(10) 10 Hz

(11) 20 Hz

(12) 10 Hz

(13) 5 Hz

(14) 5 Hz

(15) 10 Hz

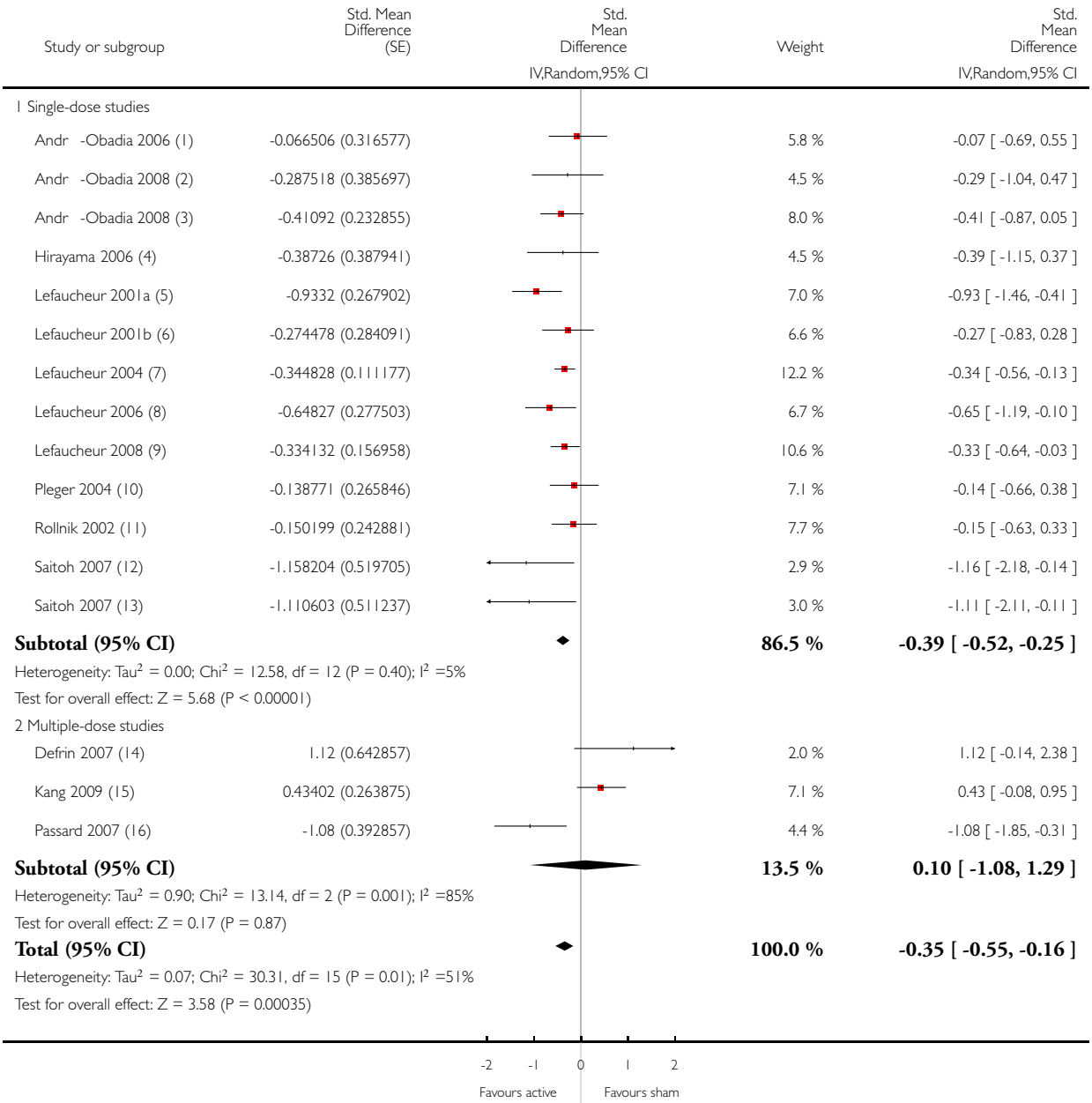
(16) 10 Hz

Analysis 1.7. Comparison 1 rTMS, Outcome 7 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 rTMS

Outcome: 7 Sensitivity analysis - imputed correlation decreased. Pain short-term follow up, subgroup analysis: motor cortex studies only, low frequency studies excluded



(1) 20Hz

(2) 20 Hz medial-lateral coil orientation

(3) 20Hz antero-posterior coil orientation

(4) 10Hz

(5) 10 Hz

(6) 10 Hz

(7) 10 Hz

(8) 10Hz

(9) 10Hz

(10) 10 Hz

(11) 20 Hz

(12) 5 Hz

(13) 10 Hz

(14) 5 Hz

(15) 10 Hz

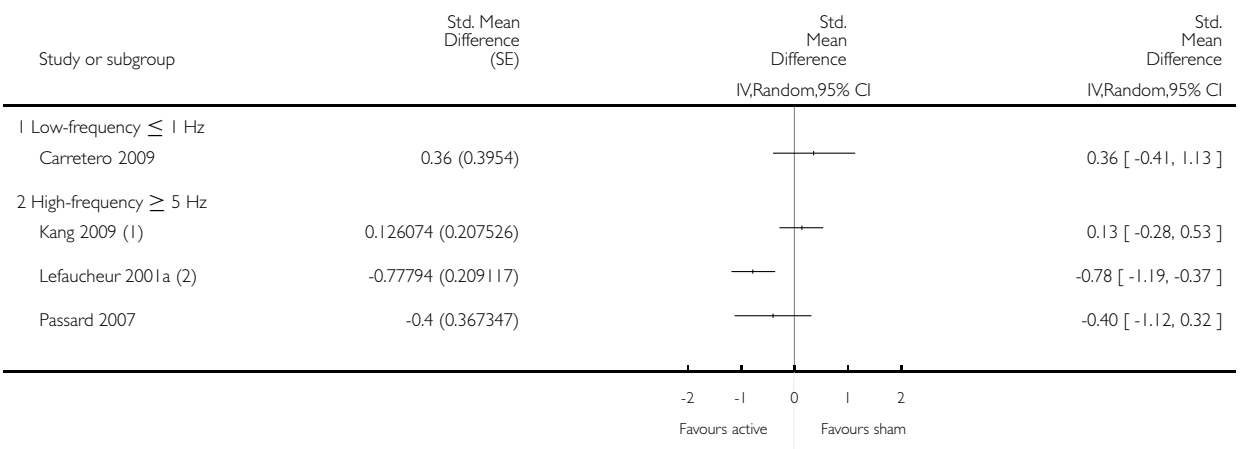
(16) 10 Hz

Analysis 1.8. Comparison 1 rTMS, Outcome 8 Pain medium-term follow up.

Review: Non-invasive brain stimulation techniques for chronic pain

Comparison: 1 rTMS

Outcome: 8 Pain medium-term follow up



(1) 3 week follow up

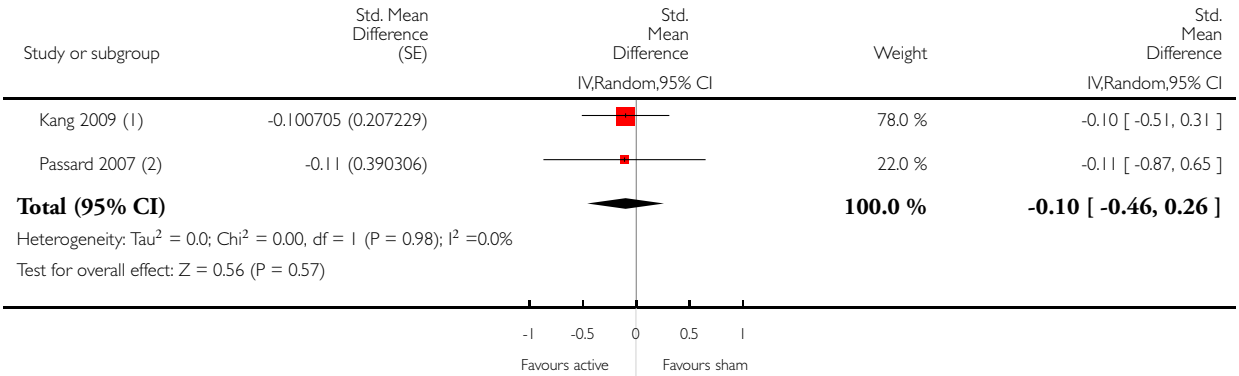
(2) 12 days post

Analysis 1.9. Comparison 1 rTMS, Outcome 9 Pain long-term follow up.

Review: Non-invasive brain stimulation techniques for chronic pain

Comparison: 1 rTMS

Outcome: 9 Pain long-term follow up



(1) 7 week follow up

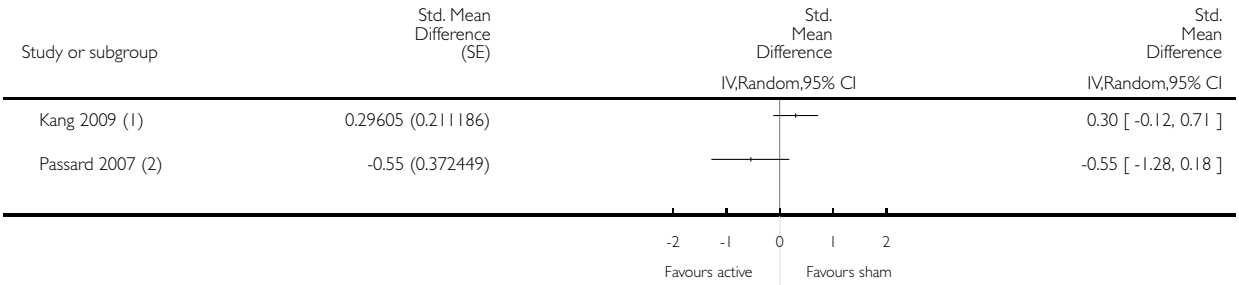
(2) 60 day follow up

Analysis 1.10. Comparison 1 rTMS, Outcome 10 Disability/pain interference short term follow up.

Review: Non-invasive brain stimulation techniques for chronic pain

Comparison: 1 rTMS

Outcome: 10 Disability/pain interference short term follow up



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

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

Analysis 1.11. Comparison 1 rTMS, Outcome 11 Disability/pain interference medium term follow up.

Review: Non-invasive brain stimulation techniques for chronic pain

Comparison: 1 rTMS

Outcome: 11 Disability/pain interference medium term follow up

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

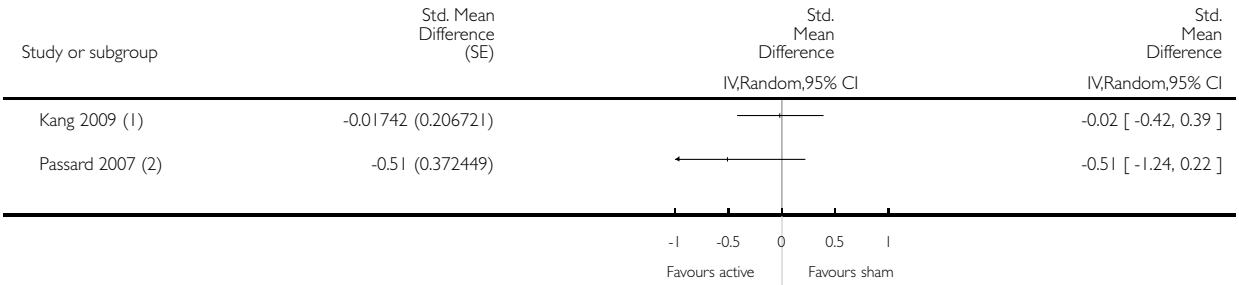
(2) BPI general activity subscale. 16 days post stim period

Analysis 1.12. Comparison 1 rTMS, Outcome 12 Disability/pain interference long-term follow up.

Review: Non-invasive brain stimulation techniques for chronic pain

Comparison: 1 rTMS

Outcome: 12 Disability/pain interference long-term follow up



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

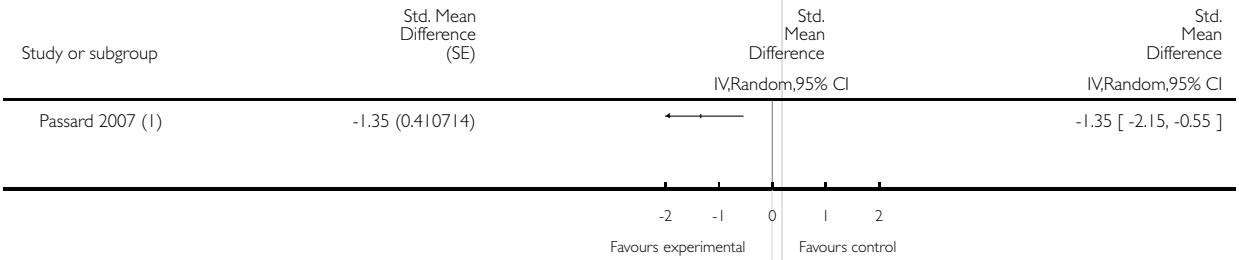
(2) BPI general activity subscale. 46 days post stim period

Analysis 1.13. Comparison 1 rTMS, Outcome 13 Quality of life short-term follow up.

Review: Non-invasive brain stimulation techniques for chronic pain

Comparison: 1 rTMS

Outcome: 13 Quality of life short-term follow up



(1) 1 day post stimulation period. Fibromyalgia impact questionnaire (total score)

Analysis 1.14. Comparison 1 rTMS, Outcome 14 Quality of life medium-term follow up.

Review: Non-invasive brain stimulation techniques for chronic pain

Comparison: 1 rTMS

Outcome: 14 Quality of life medium-term follow up

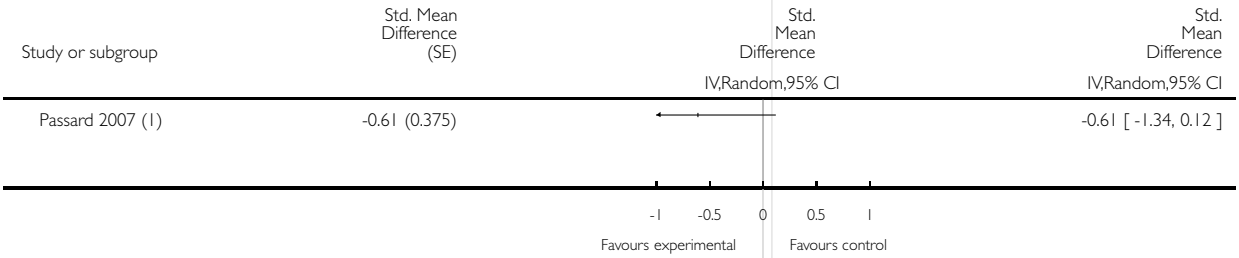
(1) 16 days post stimulation. Fibromyalgia impact questionnaire (total score)

Analysis 1.15. Comparison 1 rTMS, Outcome 15 Quality of life long-term follow up.

Review: Non-invasive brain stimulation techniques for chronic pain

Comparison: 1 rTMS

Outcome: 15 Quality of life long-term follow up



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

Analysis 2.1. Comparison 2 CES, Outcome 1 Pain short-term follow up.

Review: Non-invasive brain stimulation techniques for chronic pain

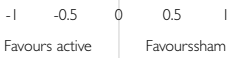
Comparison: 2 CES

Outcome: 1 Pain 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
Gabis 2003	10	2.83 (2.07)	10	2.65 (2.49)		15.4 %	0.08 [-0.80, 0.95]
Gabis 2009 (1)	17	3.82 (2.86)	16	5.25 (2.29)		24.4 %	-0.54 [-1.23, 0.16]
Gabis 2009 (2)	19	3.26 (2.79)	23	4.65 (2.62)		31.0 %	-0.51 [-1.12, 0.11]
Tan 2006	18	5.73 (2.56)	20	6 (2.41)		29.2 %	-0.11 [-0.74, 0.53]
Total (95% CI)	**64**		**69**			**100.0 %**	**-0.31 [-0.65, 0.04]**

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 1.92$, df = 3 (P = 0.59); $I^2 = 0.0\%$

Test for overall effect: Z = 1.75 (P = 0.080)



(1) back pain

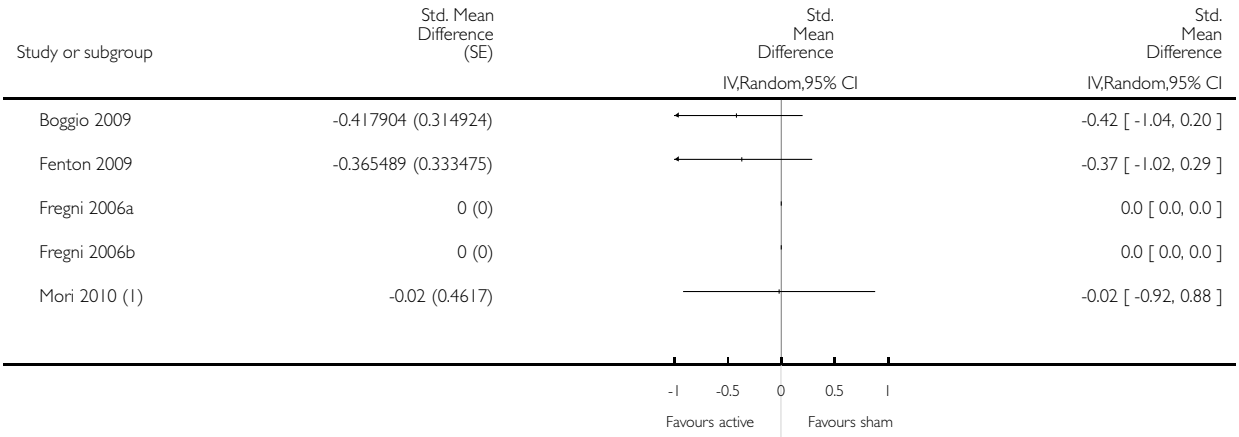
(2) neck pain

Analysis 3.1. Comparison 3 tDCS, Outcome 1 Pain post single treatment.

Review: Non-invasive brain stimulation techniques for chronic pain

Comparison: 3 tDCS

Outcome: 1 Pain post single treatment



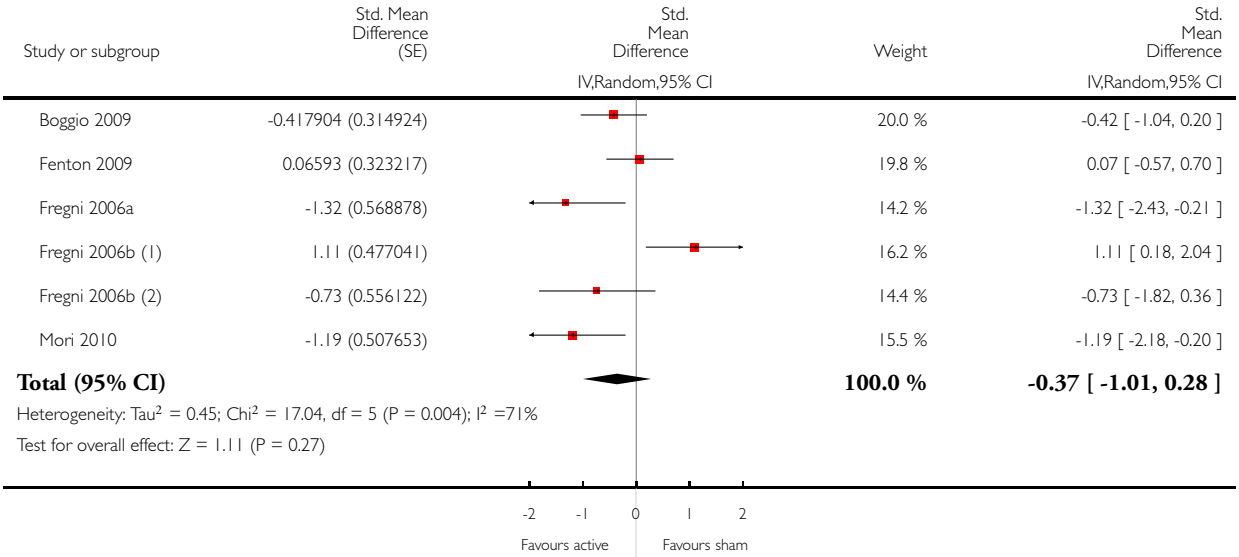
(1) post stim treatment 1

Analysis 3.2. Comparison 3 tDCS, Outcome 2 Pain short-term follow up.

Review: Non-invasive brain stimulation techniques for chronic pain

Comparison: 3 tDCS

Outcome: 2 Pain short-term follow up



(1) DLPFC

(2) M1

Analysis 3.3. Comparison 3 tDCS, Outcome 3 Pain short-term sensitivity analysis: correlation increased.

Review: Non-invasive brain stimulation techniques for chronic pain

Comparison: 3 tDCS

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

Study or subgroup	Std. Mean Difference (SE)	Std. Mean Difference IV,Random,95% CI	Weight	Std. Mean Difference IV,Random,95% CI
Boggio 2009	-0.417904 (0.268318)		20.9 %	-0.42 [-0.94, 0.11]
Fenton 2009	0.06593 (0.275383)		20.8 %	0.07 [-0.47, 0.61]
Fregni 2006a	-1.32 (0.568878)		13.6 %	-1.32 [-2.43, -0.21]
Fregni 2006b (1)	1.11 (0.477041)		15.7 %	1.11 [0.18, 2.04]
Fregni 2006b (2)	-0.73 (0.556122)		13.9 %	-0.73 [-1.82, 0.36]
Mori 2010	-1.19 (0.507653)		15.0 %	-1.19 [-2.18, -0.20]
Total (95% CI)			**100.0 %**	**-0.36 [-0.97, 0.26]**

Heterogeneity: $Tau^2 = 0.40$; $Chi^2 = 17.54$, df = 5 (P = 0.004); $I^2 = 71\%$

Test for overall effect: Z = 1.15 (P = 0.25)

Test for subgroup differences: Not applicable

(1) DLPFC

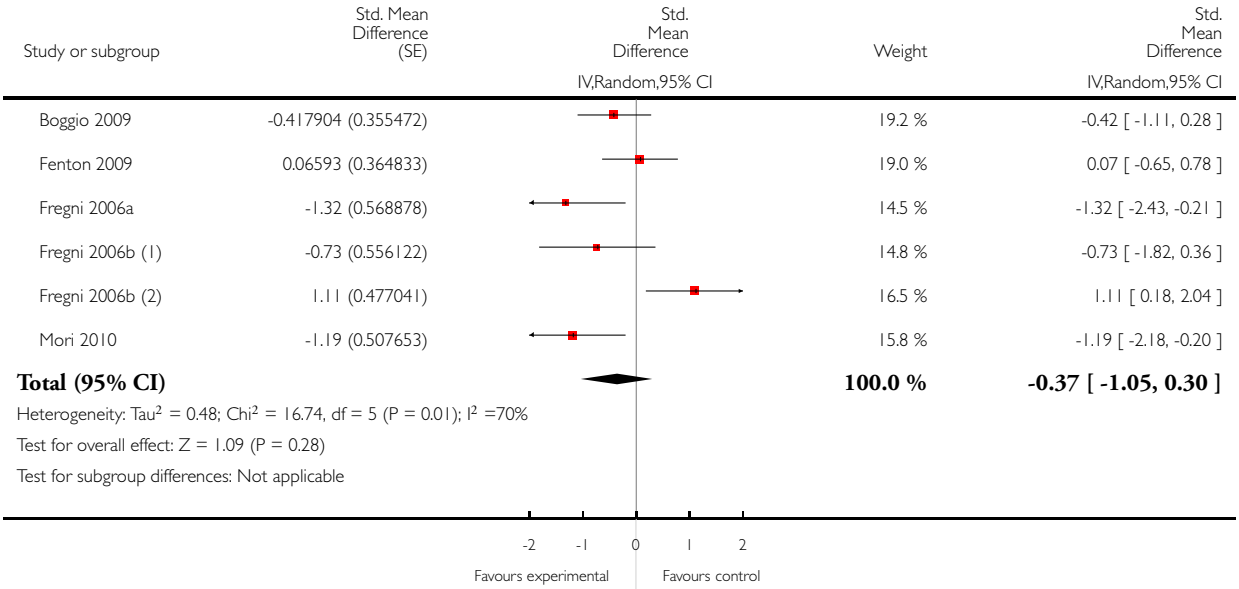
(2) M1

Analysis 3.4. Comparison 3 tDCS, Outcome 4 Pain short-term sensitivity analysis: correlation decreased.

Review: Non-invasive brain stimulation techniques for chronic pain

Comparison: 3 tDCS

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



(1) M1

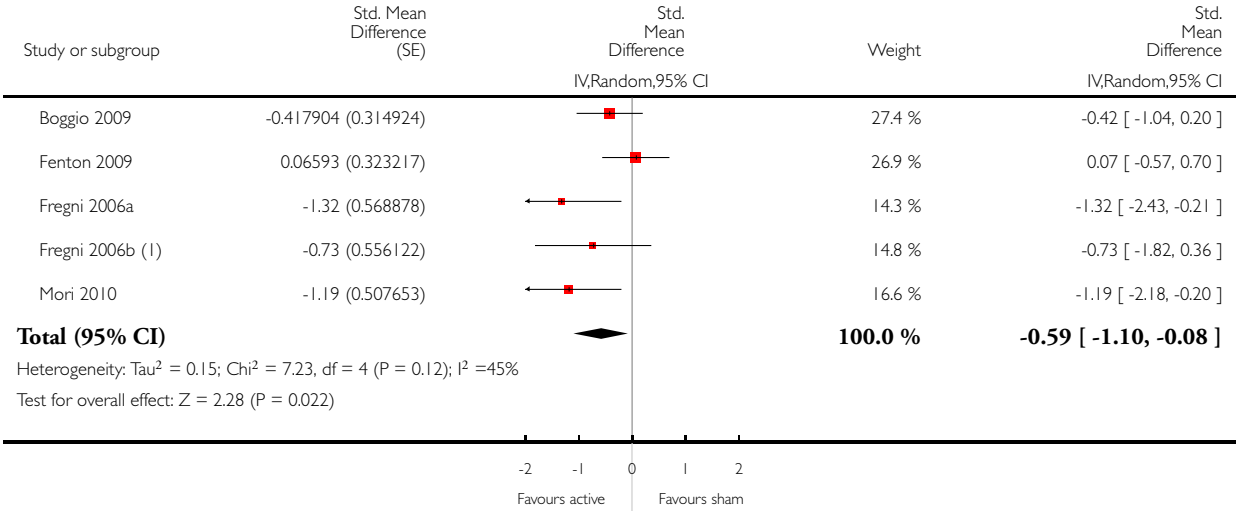
(2) DLPFC

Analysis 3.5. Comparison 3 tDCS, Outcome 5 Pain short-term follow up, subgroup analysis: motor cortex studies only.

Review: Non-invasive brain stimulation techniques for chronic pain

Comparison: 3 tDCS

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



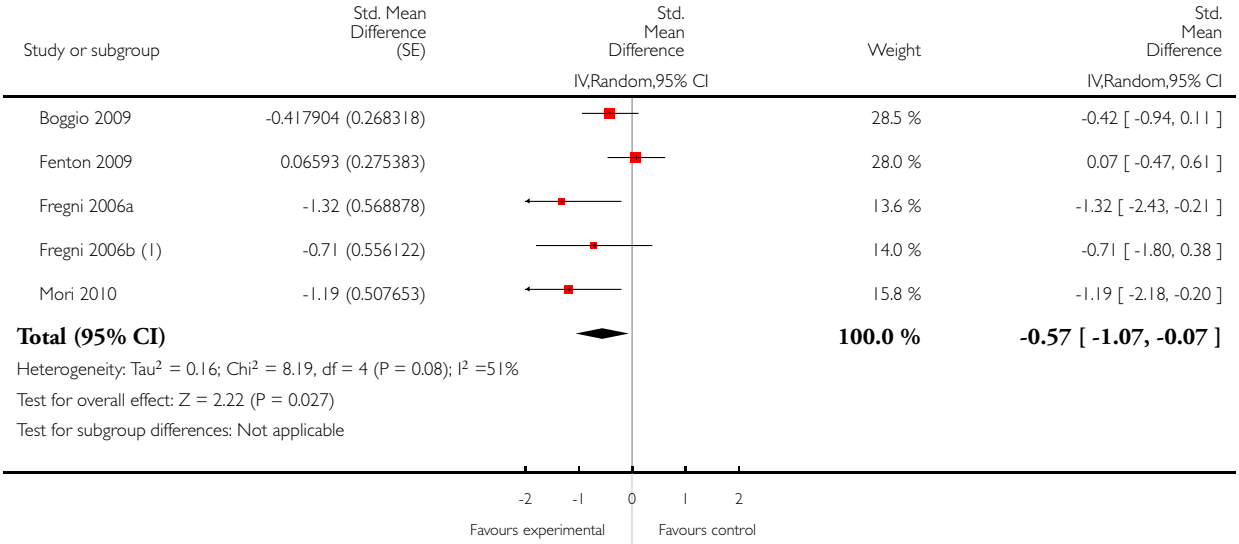
(1) M1

Analysis 3.6. Comparison 3 tDCS, Outcome 6 Pain short-term follow up, motor cortex subgroup, sensitivity analysis: correlation increased.

Review: Non-invasive brain stimulation techniques for chronic pain

Comparison: 3 tDCS

Outcome: 6 Pain short-term follow up, motor cortex subgroup, sensitivity analysis: correlation increased



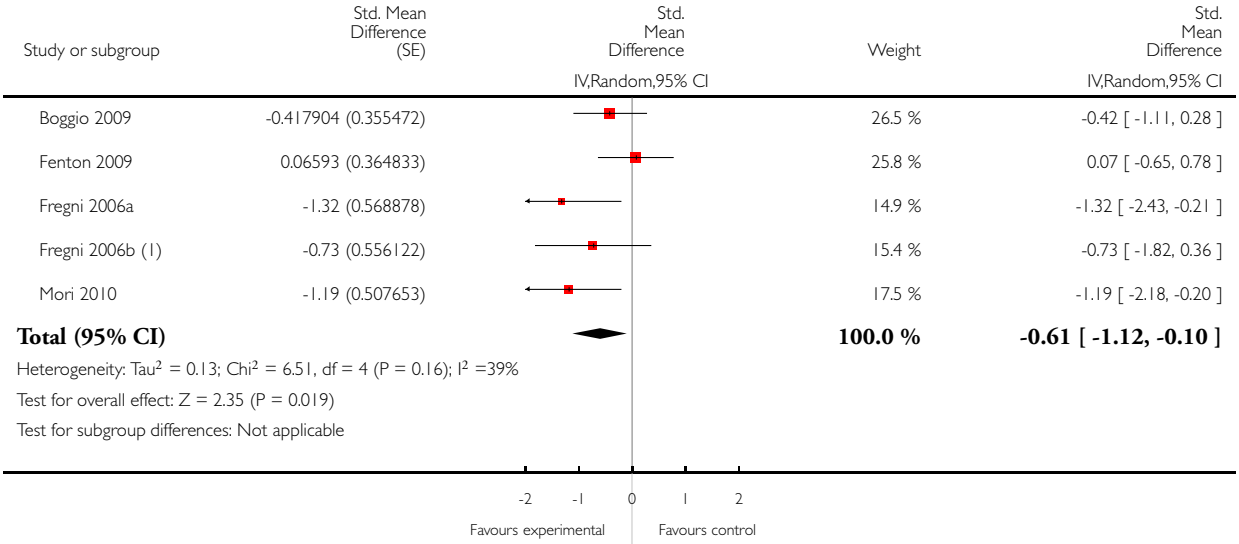
(1) MI

Analysis 3.7. Comparison 3 tDCS, Outcome 7 Pain short-term follow up, motor cortex subgroup, sensitivity analysis: correlation decreased.

Review: Non-invasive brain stimulation techniques for chronic pain

Comparison: 3 tDCS

Outcome: 7 Pain short-term follow up, motor cortex subgroup, sensitivity analysis: correlation decreased



(1) MI

Analysis 3.8. Comparison 3 tDCS, Outcome 8 Pain medium-term follow up.

Review: Non-invasive brain stimulation techniques for chronic pain

Comparison: 3 tDCS

Outcome: 8 Pain medium-term follow up

Study or subgroup	Std. Mean Difference (SE)	Std. Mean Difference IV,Random,95% CI	Std. Mean Difference IV,Random,95% CI
Fenton 2009 (1)	0.23766 (0.327394)		0.24 [-0.40, 0.88]
Mori 2010 (2)	-0.96 (0.492347)		-0.96 [-1.92, 0.00]

(1) 10-14 days post stimulation.

(2) 3/52 post stimulation period.

Analysis 3.9. Comparison 3 tDCS, Outcome 9 Quality of life short-term follow up.

Review: Non-invasive brain stimulation techniques for chronic pain

Comparison: 3 tDCS

Outcome: 9 Quality of life short-term follow up

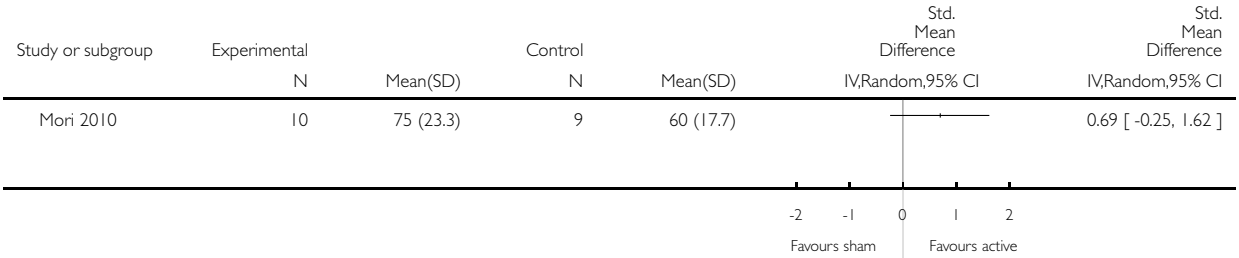
Study or subgroup	Experimental N	Mean(SD)	Control N	Mean(SD)	Std. Mean Difference IV,Random,95% CI	Std. Mean Difference IV,Random,95% CI
Mori 2010	10	74.1 (19.5)	9	51.9 (15.2)		1.20 [0.21, 2.20]

Analysis 3.10. Comparison 3 tDCS, Outcome 10 Quality of life medium-term follow up.

Review: Non-invasive brain stimulation techniques for chronic pain

Comparison: 3 tDCS

Outcome: 10 Quality of life medium-term follow up



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	Treatment sessions per group
André-Obadia 2006	M1 contralateral to painful side	Posteroanterior	20, 1	90	20 Hz: 20 1Hz: 1	20 Hz: 4 sec 1Hz: 26 mins	20 Hz: 84	1600	1
André-Obadia 2008	M1 contralateral to painful side	Posteroanterior Medial-lateral	20	90	20	4 sec	84	1600	1
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
Hirayama 2006	M1, S1, PMA, SMA	Not specified	5	90	10	10 sec	50	500	1
Irlbacher 2006	M1 contralateral to painful side	Not specified	5, 1	95	Not specified	Not specified	Not specified	500	1
Kang 2009	Right M1	45º 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
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 mins	10 Hz: 55	10 Hz: 1000 0.5 Hz: 600	1
Lefaucheur 2004	M1 contralateral to painful side	Posteroanterior	10	80	20	5 sec	55	1000	1
Lefaucheur 2006	M1 contralateral to painful side	Posteroanterior	10 , 1	90	10 Hz: 20 1 Hz: 1	10 Hz: 6 sec 1 Hz: 20 mins	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 mins	10Hz: 54	10Hz: 1200 1Hz: 1200	1
Passard 2007	M1 contralateral to painful side	Posteroanterior	10	80	25	8 sec	52	2000	10, x 1 daily (working days)

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

Pleger 2004	M1 hand area	Not specified	10	110	10	1.2 sec	10	120	1
Rollnik 2002	M1 midline	Not specified	20	80	20	2 sec	Not specified	800	1
Saitoh 2007	M1 over motor representation of painful area	Not specified	10, 5 , 1	90	10 Hz; 5 5 Hz: 10 1 Hz: 1	10 Hz: 10 sec 5 Hz: 10 sec 1 Hz: 500 sec	10 Hz: 50 5 Hz: 50	500	1

M1 = primary motor cortex, DLPFC = dorsolateral prefrontal cortex, PFC = prefrontal cortex,S1 = primary somatosensory cortex, SII = secondary somatosensory cortex, PMA = pre-motor area, SMA = supplementary motor area.

Table 2. CES studies - characteristics of stimulation

Study	Electrode placement	Frequency (Hz)	Pulse width (msec)	Waveform shape	Intensity	Duration (mins)	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
Tan 2000	Ear clip electrodes	0.5	Not specified	Not specified	10 to 600 μA		12 (timing not specified)

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

Tan 2006	Ear clip electrodes	Not specified	Not specified	Not specified	100 to 500 μA	60	x 1 daily for 21 days

Table 3. tDCS studies - characteristics of stimulation

Study	Location of stimulation	Electrode pad size	Intensity (mA)	Anodal or cathodal?	Stimulus duration (mins)	Treatment sessions per group
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 & DLPFC contralateral to painful side or dominant hand	35 cm^2	2 mA	Anodal	20	5, x 1 daily
Mori 2010	M1 contralateral to painful side	35 cm^2	2 mA	Anodal	20	5, x 1 daily
Valle 2009	M1 & DLPFC contralateral to painful side or dominant hand	35 cm^2	2 mA	Anodal	20	5, x 1 daily

M1 = primary motor cortex, DLPFC = dorsolateral prefrontal cortex

APPENDICES

Appendix 1. MEDLINE search strategy (via Ovid)

1. exp Pain/
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.
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.
4. 1 or 3 or 2
5. exp Electric Stimulation Therapy/
6. ((brain* or cortex or cortical or transcranial* or cranial or magneti* or direct current or DC or electric*) adj4 stimulat*).ab,ti.
7. ((crani* or brain*) adj4 (electrostim* or electro-stim* or electrotherap* or electro-therap*)).ab,ti.
8. ((non-invasive or non*invasive) adj4 stimulat*).ab,ti.
9. (theta burst stimulat* or iTBS or cTBS).ab,ti.
10. (transcranial magnetic stimulation or rTMS or transcranial direct current stimulation or tDCS or cranial electrostimulation or cranial electrotherapy).ab,ti.
11. (electrosleep or electronarco*).ab,ti.
12. 8 or 6 or 11 or 7 or 10 or 9 or 5
13. 4 and 12

Cochrane highly sensitive search strategy

Adapted Cochrane Highly Sensitive Search Strategy for MEDLINE (Higgins 2008) designed to identify RCTs and other trials which may be suitable for inclusion in the review:

1. randomised controlled trial.pt.
2. controlled clinical trial.pt.
3. randomized.ab.
4. (placebo or sham).ab,ti.
5. drug therapy.fs.
6. randomly.ab.
7. trial.ab.
8. groups.ab.
9. or/1-8
10. exp animals/ not humans.sh.
11. 9 not 10

Appendix 2. Full list of searches and results

1. PaPaS 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

<November 25, 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 to 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 3. Summary table of search results

	Version	Date of Search	Records retrieved	RCT/CCT filter applied	Records retrieved	Duplicates	Unique records
1. PaPaS register	July 09	17/11/09	177	no	177	2	175
2. CENTRAL, *The Cochrane Library*	Issue 4 2009	30/11/09	106	CENTRAL	98	30	68
3a. Ovid MEDLINE	1950 to November Week 3	30/11/09	1069	Adapted CHSSS	219	96	123
3b. Ovid MEDLINE In-Process & Other Non-Indexed Citations	25 November	30/11/09	39	no	39	6	33
4. EMBASE (Ovid)	1980 to 2009 Week 47	30/11/09	1331	yes	234	89	145
5. PsycINFO (Ovid)	1806 to November Week 4 2009	30/11/09	277	yes	64	45	19
6. CINAHL	1981 to present	11/01/10	836	yes	226	37	189
7. SCOPUS	Not searched						
8. LILACS		15/12/09		yes	68	0	68

(*Continued*)

REVIEWS and TAs							
9. COCHRANE REVIEWS (CDSR)	Issue 4 2009	30/11/09	106		3		3
10. DARE	Issue 4 2009	30/11/09	106		3		3
11. Tech assessments	Issue 4 2009	30/11/09	106		2		2
12. Articles identified by authors post search (not from search process)					3		3
13. Additional articles identified from searching the reference lists (original papers and reviews)			15				15
TOTALS				Not including extras	1133	305	843

Appendix 4. Trials register search results

Database	Date of search	Search strategy	No. hits	Agreed potential studies
National Research Register (NRR) Archive (NIHR)	23/10/09	(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 com-	366	**2**

(*Continued*)

		plex 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 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*) IN "TITLE" Field		
Clinicaltrials.gov	23/10/09 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	62	

(*Continued*)

		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		
Clinicaltrials.gov	23/10/09 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 central OR post*stroke OR complex OR regional OR spinal cord OR sciatica OR back-ache OR back*ache OR lumbago **INTERVENTION:** transcranial magnetic stimulation OR rTMS OR transcranial direct current stimulation OR tDCS OR cranial electrostimulation OR cranial electrotherapy OR electrosleep OR electronarco* **OUTCOME:** pain	8 (all also picked up in search 1)	
Clinicaltrials.gov	23/10/09 Search 3	**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:** 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		
Clinicaltrials.gov	23/10/09 Search 4	**Field - Interventional studies** **CONDITION:** fibromyalg* OR trigem* neuralg* OR herp* neuralg* OR diabet* neuropath* OR reflex dystroph* OR sudeck* atroph* OR causalg* OR whip-lash OR whip*lash or polymyalg* OR failed back surg* OR failed back syndrome **INTERVENTION:** transcranial magnetic stimulation OR rTMS OR transcranial direct current stimulation OR tDCS OR cranial electrostimulation OR cranial electrotherapy OR electrosleep OR electronarco* **OUTCOME:** pain	0	
		TOTAL UNIQUE RESULTS FOR CLINICAL TRIALS.GOV	**62**	7

(*Continued*)

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 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*)	77	**0**
Current Controlled Trials	23/10/09 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	0	

(*Continued*)

		electronarco*)		
Current Controlled Trials	23/10/09 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	23/10/09 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 electro-therap* OR non-invasive OR non*invasive OR theta burst stimulat* OR iTBS)	4	
Current Controlled Trials	23/10/09 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	23/10/09 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 electrostimula-	0	

(*Continued*)

		tion OR cranial electrotherapy OR electrosleep OR electronarco*)		
Current Controlled Trials	23/10/09 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	03/11/09 Search 7	(back-ache OR back*ache OR lumbago OR fibromyalg* OR trigem* neuralg* OR herp* neuralg* OR diabet* neuropath* OR reflex dystroph*) AND (crani* OR electrostim* OR electrotherap* OR electro-therap*)	36	
Current Controlled Trials	23/10/09 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*	52	

(*Continued*)

		OR direct current OR DC)		
Current Controlled Trials	03/11/09 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	03/11/09 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	
Current Controlled Trials	03/11/09 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	03/11/09 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	03/11/09 Search 14	(central OR post*stroke OR complex OR regional OR spinal cord OR sciatica) AND (electrotherap* OR electrotherap* OR non-inva-	199	

(*Continued*)

		sive OR non*invasive OR theta burst stimulat*)		
Current Controlled Trials	03/11/09 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	03/11/09 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	
Current Controlled Trials	03/11/09 Search 17	(temp?romandib joint) AND (iTBS OR cTBS OR transcranial magnetic stimulation OR rTMS)	0	
Current Controlled Trials	03/11/09 Search 18	(temp?romandib joint) AND (non-invasive OR non*invasive OR theta burst stimulat*)	0	
Current Controlled Trials	03/11/09 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	

(*Continued*)

Current Controlled Trials	03/11/09 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	03/11/09 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	
Current Controlled Trials	03/11/09 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	19/11/09 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	19/11/09 Search 24	(temp*romandibular joint) AND (electro-therap* OR non-invasive OR non*invasive	1	

(*Continued*)

		OR theta burst stimulat* OR iTBS OR Ctbs OR transcranial magnetic stimulation)		
Current Controlled Trials	19/11/09 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**
		DUPLICATES BETWEEN DATABASES		7
		FINAL TOTAL FROM TRIALS REGISTERS SEARCHES		**16**

WHAT'S NEW

Last assessed as up-to-date: 22 April 2010.

Date	Event	Description
11 May 2011	Amended	Contact details updated.

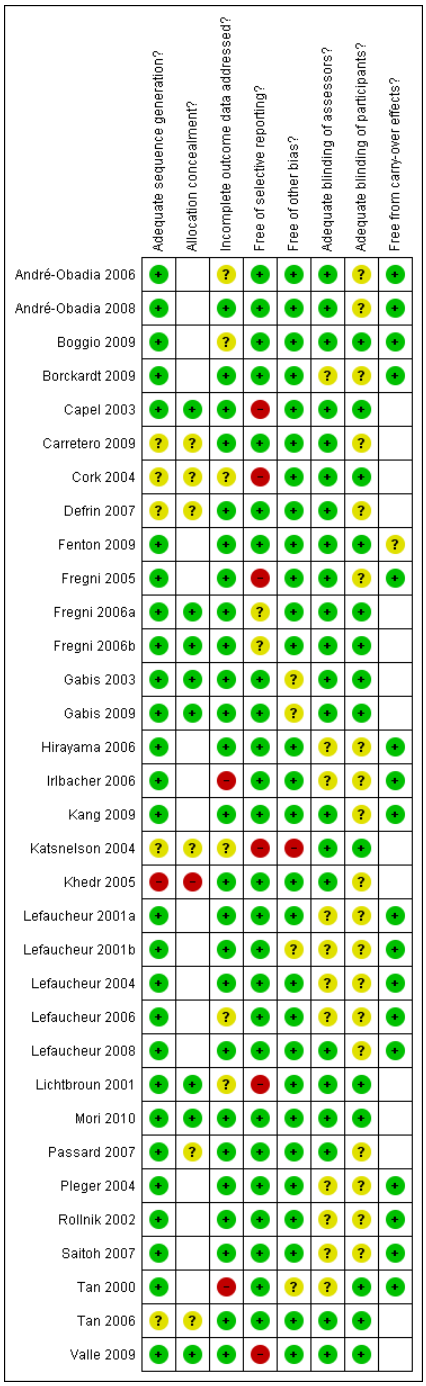
HISTORY

Protocol first published: Issue 1, 2010

Review first published: Issue 9, 2010

Date	Event	Description
13 September 2010	Amended	The risk of bias tables have been amended so that the criteria "allocation concealment" is not assessed for studies with cross-over designs and the criteria "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 lead 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 parallel and cross-over studies were meta-analysed 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. It was decided to pool data from studies with a low or unclear risk of bias as it was 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 have not used the GRADE approach (Guyatt 2008) to synthesising the evidence as we felt that individual discussion of the available data would be more informative.

We did not use overall risk of bias in sensitivity analyses as we found that it lacked sensitivity. Instead we considered individual criteria on 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.

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