



Non-invasive brain stimulation techniques for chronic pain. A report of a Cochrane systematic review and meta-analysis

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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).

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

Design. A Cochrane systematic review with meta-analyses.

Methods. We employed a comprehensive search strat-

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Acknowledgements.—This review was undertaken with the Cochrane Pain, Palliative and Supportive Care Review Group (PaPas). The authors would like to thank James Langridge of the Brunel University library for sharing his expertise in the use of electronic databases, Arturo Lawson, Ana Bela Nascimento, Andrea Wand, Peter and Maria Heine and Dr Evgeny Makaroy for assistance with interpretation. We would like to extend particular thanks to Caroline Struthers at the Cochrane PaPas review group for her tireless assistance throughout the review and to the whole training team at the UK Cochrane Centre for their wisdom, expertise and guidance. We would also like to thank the following authors for generously providing additional data for this review upon request: Dr Nathalie André-Obadia, Dr Didier Bouhassira, Dr Ruth Defrin, Dr Bradford Fenton, Dr Felipe Fregni, Dr Linda Gabis/ Dr Ranann Raz, Dr Eman Khedr, Prof. Jean-Pascale Lefaucheur, Dr Francesco Mori, Dr Burkhard Pleger, Prof. Jens Rollnik and Dr Youichi Saitoh. We would like to thank Dr Felipe Fregni for his help with reviewing our search results.

This review is published as a Cochrane Review in the Cochrane Database of Systematic Reviews (O'Connell NE, Wand BM, Marston L, Spencer S, DeSouza LH. Non-invasive brain stimulation techniques for chronic pain. Cochrane Database of Systematic Reviews 2010, Issue 9. Art. No.: CD008208. DOI: 10.1002/14651858.CD008208.pub2).

Epub ahead of print on April 14, 2011.

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egy. Randomised and quasi-randomised studies of rTMS, CES or tDCS were included 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. Where possible we entered data into meta-analyses.

Results. We included 33 trials in the review (19 rTMS, eight CES and six tDCS). Only one study was judged as being at low risk of bias. Studies of rTMS 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. 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 pre-determined 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.

KEY WORDS: Chronic pain - Non-invasive brain stimulation - Meta-analysis..

Background

This paper is based on a Cochrane Review published in The Cochrane Library 2010, Issue 11 (see www.thecochranelibrary.com for information). Cochrane Reviews are regularly updated as new evidence emerges and in response to feedback, and The Cochrane Library should be consulted for the most recent version of the review.

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.¹ 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.² Chronic pain is a heterogeneous 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.³

Brain stimulation techniques have been used to address a variety of pathological pain conditions including fibromyalgia, chronic post-stroke pain and complex regional pain syndrome⁴⁻⁶ and clinical studies of both invasive and non-invasive techniques have produced preliminary data showing reductions

in pain.^{4, 5, 7} Various types of brain stimulation, both invasive and non-invasive are currently in clinical use for the treatment of chronic pain⁴. 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 by a stimulating coil applied to the scalp. Electric currents are induced in neural tissue directly using rapidly changing magnetic fields.⁵ 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.⁸ A recent meta-analysis suggested that rTMS may be more effective in the treatment of neuropathic pain conditions with a central compared to a peripheral nervous system origin.⁹

Transcranial direct current stimulation (tDCS) and cranial electrotherapy stimulation (CES) involve the safe and painless application of low intensity electrical current to the cerebral cortex of the brain.^{5, 6} 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.¹⁰ 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.^{11, 12} 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.¹³ The electrical current in CES is commonly pulsed and is applied via clip electrodes that are attached to the patient's earlobes. A Cochrane Review of non-invasive treatments for headaches¹⁴ identified limited evidence that CES is superior to placebo in reducing pain intensity after six to 10 weeks of treatment.

Brain stimulation techniques primarily seek to modulate activity in brain regions by directly altering the level of brain activity. The aim of brain stimulation in the management of pain is to reduce pain by altering activity in the areas of the brain that are involved in pain processing. Both tDCS and rTMS have been shown to modulate brain activity specific to the site of application and the stimulation parameters. As a general rule low-frequency rTMS (≤ 1 Hz) results in lowered cortical excitability at the site of stimulation, whereas high-frequency stimulation (≥ 5 Hz) results in

raised cortical excitability.^{10, 15} 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.¹⁶ It is suggested that the observed alterations in cortical excitability following rTMS and tDCS that last beyond the time of stimulation are the result of long-term synaptic changes.¹⁰ 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.⁶

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.¹⁷⁻¹⁹ 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.^{7, 9, 20.}

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

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.

We included studies which recruited male or female participants over the age of 18 years with any chronic pain syndrome (with a duration of > 3 months). 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 seizure²¹) 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.

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

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.

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.²² We adapted this filter to include the term “sham” in the title or abstract. The full search strategy and filter included a combination of controlled vocabulary (MeSH) and free-text terms and can be viewed in the full review.²³

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). We also 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.

Data collection and analysis

Selection of studies

Two reviewers independently checked search results and included eligible studies. Initially the titles and/or abstracts of identified studies were read by two review authors. 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 was resolved through

discussion between the two review authors. Where resolution was not achieved a third review author considered the paper in question.

Data extraction and management

Two review authors extracted data independently using a standardised form that was piloted by both authors on three randomised controlled trials of transcutaneous electrical nerve stimulation prior to the searches. Discrepancies were resolved by consensus.

Assessment of risk of bias in included studies

Two review authors independently 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 5.0.1.²² Disagreement was resolved through discussion between the two review authors. Where resolution was not achieved a third review author considered the paper in question.

The criteria assessed (using yes/no/unclear judgements) were: adequate sequence generation; adequate allocation concealment (for parallel studies); adequate blinding of assessors; adequate blinding of participants; adequate assessment of incomplete outcome data; whether free of suggestion of selective outcome reporting; whether data were clearly free from carry-over effects (for cross-over studies) and whether free of other bias.

Assessment of sham credibility

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.^{24, 25} 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

*et al.*²⁴ and Loo *et al.*²⁵ suggest that an ideal sham condition for rTMS should not stimulate the cortex; be the same as active stimulation in visual terms and in terms of its position on the scalp; and not differ from active stimulation in terms of the acoustic and afferent sensory sensations that it elicits.

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^{24, 25} 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 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. 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.²⁶ 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 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 pa-

tient 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 16.4.6.2.²²

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)²⁷ 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 Chi² test and the I² statistic. 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

Results of the search

PUBLISHED DATA

The search strategy identified 1148 citations, including 305 duplicates. Screening of the 843 unique citations by title and abstract identified 39 as potentially eligible for the review. Three studies were identified from hand-searching 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 identified 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.

EXCLUDED STUDIES

We excluded 11 studies after consideration of the full study report. Of these one was not a study of brain stimulation, two did not assess self-reported pain as an outcome, four were not restricted to participants with chronic pain, one study was unclear on the duration of participants' symptoms, two were single case studies, one study presented duplicate data from a study already accepted and one did not employ a sham control.

INCLUDED STUDIES

There follows an abridged description of the characteristics of the included studies. Full details of both included and excluded studies can be found in the full review report in the Cochrane library.²³ Of the 44 studies considered 33 met the eligibility criteria. All but one of the studies was written in English. Most studies were based in a laboratory or outpatient pain clinic setting. The included studies were published between 2000 and 2010. Nineteen studies investigated rTMS,²⁸⁻⁴⁶ eight studies investigated CES⁴⁷⁻⁵⁴ and six studies investigated tDCS.^{11, 12, 55-58} There was a mixture of parallel and cross-over study designs.

Sample sizes at the study outset were small, ranging from 4 to 75 participants. Studies included participants with a variety of chronic pain conditions including neuropathic pain of mixed origins (peripheral and centrally evoked), phantom limb pain, fibromyalgia, chronic pancreatitis pain, complex regional pain syndrome type I (CRPSI), osteoarthritis of the hip and knee, chronic back and neck pain, "neuromuscular" pain, chronic pelvic pain. The majority (13) of rTMS studies and 3 studies of tDCS specified chronic pain that was refractory to current medical management, varyingly described as intractable, resistant to medical intervention or drug management.

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. Five studies used measures of disability or pain interference and five studies collected measures of quality of life.

The parameters of stimulation varied across studies for all stimulation types. The majority of studies of rTMS and TDCS included stimulation applied to the motor cortex. CES studies either attached electrodes to the earlobes via clips, or applied electrodes to the mastoid processes and forehead. Full details regarding the parameters of stimulation for each included study can be found in the full review report in the Cochrane library.²³

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 specified that the coil was also elevated from the scalp and five studies specified that the coil was angled 45° away from the scalp of which two studies also simultaneously electrically stimulated the skin of the scalp in both the active and sham stimulation conditions in order to mask the sensations elicited by active rTMS and thus preserve participants’ blinding. 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. Six studies did not specify whether the sham coil controlled for the auditory characteristics of active stimulation.

Five studies of CES utilised inert sham units. 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 of CES utilised an “active placebo” treatment unit. This sham device was visually indistinguishable and delivered a current of much lower intensity (≤ 0.75 mA) than the active stimulator to evoke a similar sensation to ensure patient blinding. Similarly one study utilised a visually indistinguishable sham device that delivered brief pulses of current of <1 mA. The placebo conditions used in

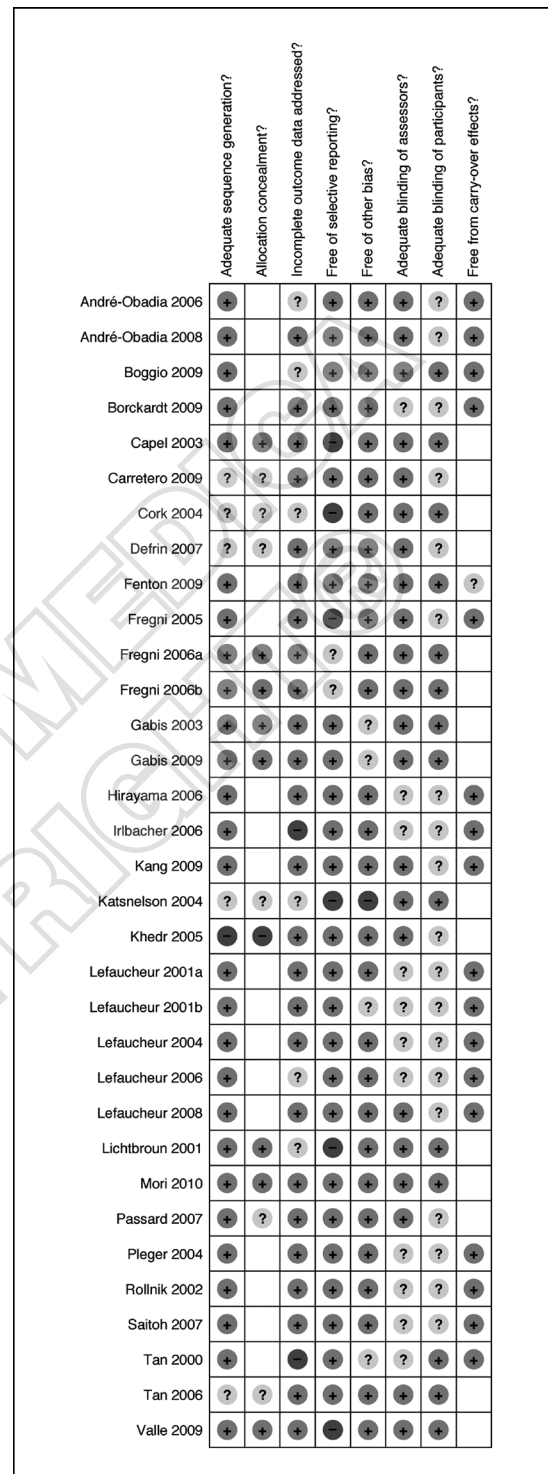


Figure 1.—Forest plot of comparison: 3 tDCS, outcome: 3.5 Pain short-term follow up, subgroup analysis: motor cortex studies only.

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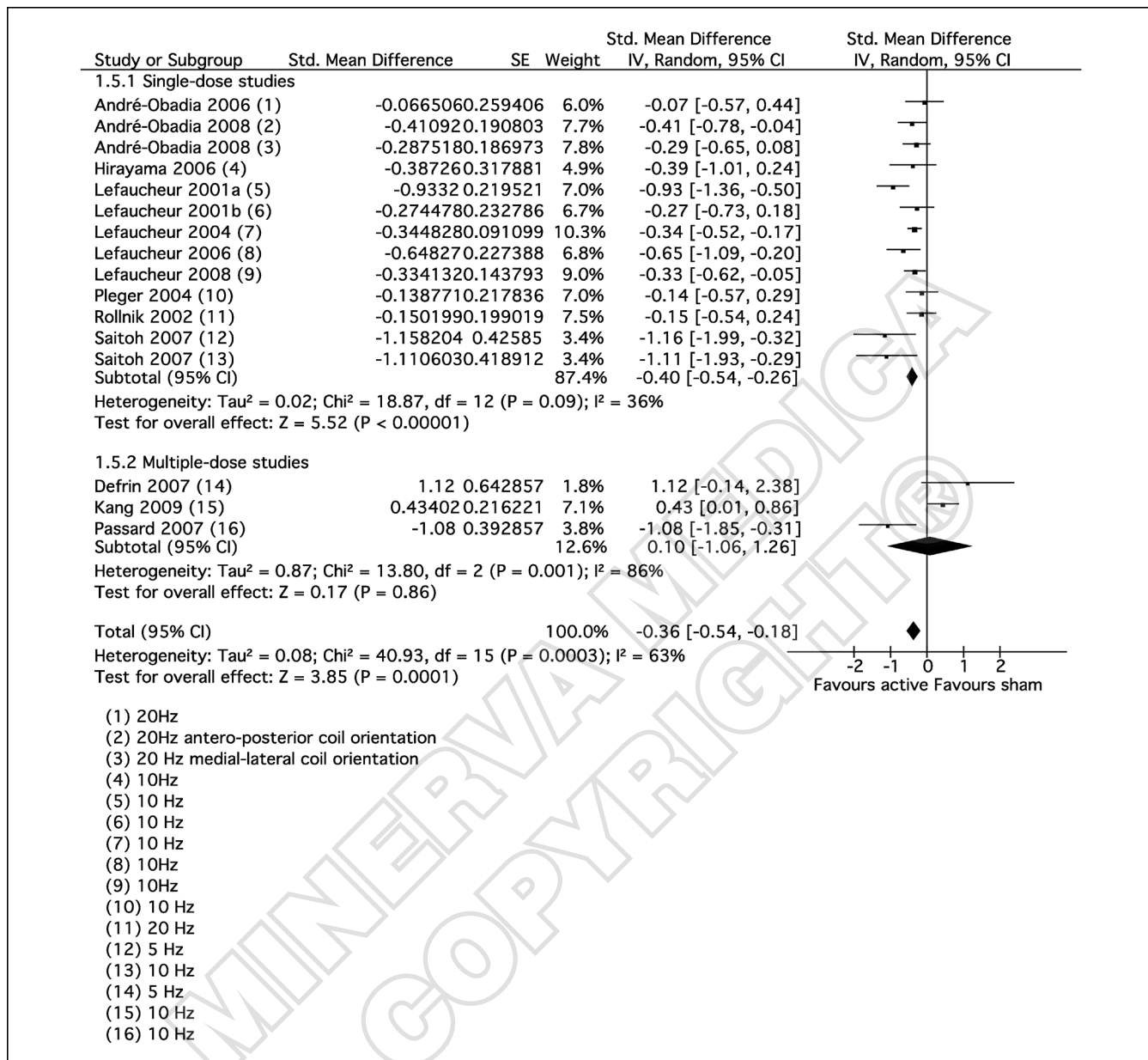


Figure 2.—Forest plot of comparison: rTMS, outcome: Pain at short-term follow up, subgroup analysis: motor cortex studies only (low-frequency studies excluded).

these three studies delivered current at much greater intensities than those used in the active stimulation conditions of the other CES studies.

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

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. Only one study was judged to be at low risk of bias across all criteria⁵⁷. 9 studies were judged to be at high risk of bias and were not entered into the meta-analysis. Full details of the risk of bias results can be found in the full review report in the Cochrane library²³.

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.^{28-32, 34, 36, 38-46} The correlation coefficient used to calculate the SE(SMD) for cross-over studies was imputed from data extracted from the study by André-Obadia *et al.*²⁹. 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.

Substantial heterogeneity ($I^2=71\%$) was observed and was investigated using pre-planned subgroup analyses. 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 2 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-analysis⁴⁰. 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 criterion. Sensitivity analysis removing these studies reduced heterogeneity to $I^2=0\%$ although only three studies 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 ($I^2=86\%$).

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 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 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 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

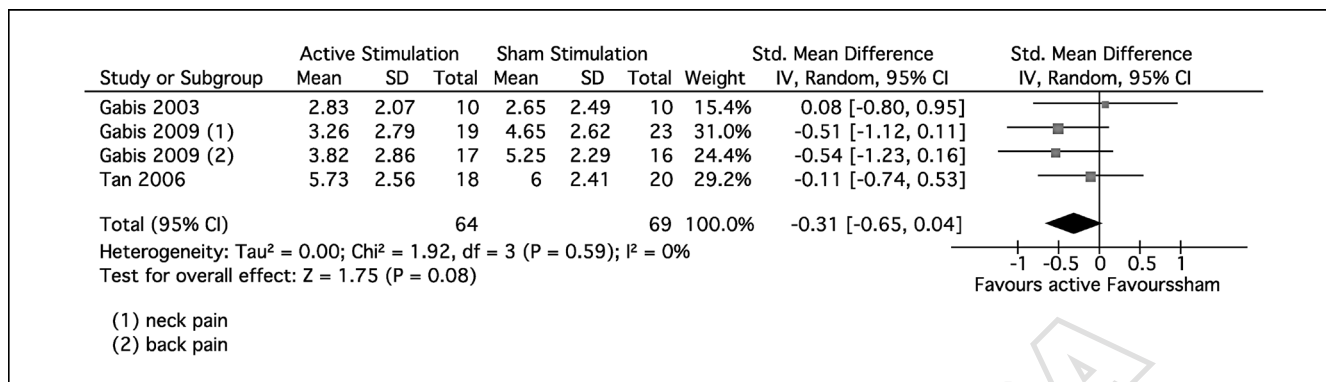


Figure 3.—Forest plot of comparison: CES, outcome: Pain at short-term follow up.

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 I²=59%, correlation decreased I²=5%).

To assess the impact of excluding the studies judged at high risk of bias, the analysis was performed with data from these studies included. While this produced a modest increase in the SMD it increased heterogeneity slightly. Inclusion of the Khe-dr *et al.* 2005 study to the multiple-dose studies of high-frequency motor cortex stimulation subgroup increased heterogeneity (I²=92%). Inclusion of the Irlbacher *et al.* 2006 study to the single-dose studies of high-frequency motor cortex stimulation subgroup also increased heterogeneity (I²=46%).

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

Five studies provided data on medium-term pain outcomes.^{31, 36-38, 43} Of these, one study was excluded as it was classified as having a high risk of bias³⁷. The analysis included 42 participants. Overall heterogeneity was high (I²=75%). We performed sensitivity analysis to assess the impact of excluding the study with a high risk of bias.³⁷ Including this study did not reduce heterogeneity (I²=81%). There was insufficient data from which to draw any firm conclusions and the existing data are conflicting.

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

Only two studies provided data for long-term pain relief.^{36, 43} The analysis included 37 participants. There was no heterogeneity (I²=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).

CES for short-term pain relief

Three studies^{49, 50, 54} 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^{47, 48, 51, 52} and two studies were classified as being at high risk of bias on criteria other than 'free of selective outcome reporting'.^{51, 53} See Figure 3 for the forest plot of this analysis.

Two studies included in the analysis^{49, 50} differ substantially the other⁵⁴ on the location of electrodes and the intensity of the current provided. Despite this there was no heterogeneity (I²=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).

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

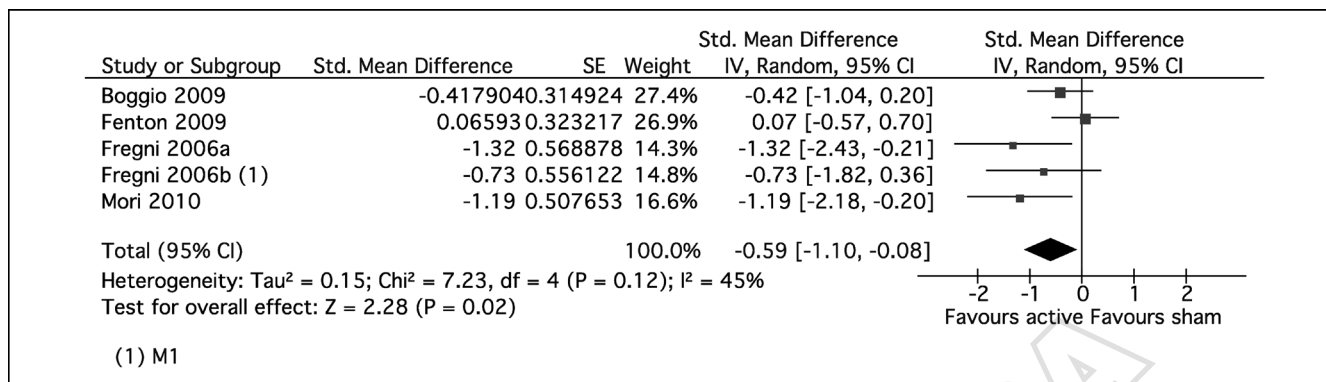


Figure 4.—Forest plot of comparison: tDCS, outcome: Pain at short-term follow up, subgroup analysis: motor cortex studies only.

tDCS for short-term pain relief

Adequate data were available from five studies for this analysis (n=83).^{11, 12, 55-57} The correlation coefficient used to calculate the SE(SMD) for cross-over studies was imputed from data extracted from the study by Boggio *et al.*⁵⁵. One study compared two distinct active stimulation conditions to one sham condition.¹¹ Combining the treatment conditions was considered inappropriate as each study 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 did not demonstrate a significant effect of active stimulation (P=0.37) but heterogeneity was substantial (I²=71%). Subgroup analysis restricted to comparisons of active motor cortex stimulation (Figure 4) (excluding one group from ¹¹) reduced heterogeneity to a level of non-statistical significance (I²=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.

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 (I²=51%).

Adverse events

Thirteen studies did not report any information regarding adverse events. Of the rTMS studies that reported adverse events eight studies reported none. One study 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. One study 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) and tinnitus (two participants in the sham group) and dizziness (one participant in the sham group). A different study reported that one participant experienced headache but it is unclear in the report whether this was following active or sham stimulation.

Only two studies of CES reported the incidence of adverse events^{47,49}. In these studies no adverse events were reported.

All studies of tDCS reported the incidence of adverse events. Of these two studies reported none. One study reported that one participant experienced headache with active stimulation. One study 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. One study 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. One study reported "minor and uncommon" side effects such as skin redness and tingling which were equally distributed between active and sham stimulation. Four studies monitored for possible effects on cognitive function using the Mini Mental State Examination questionnaire and three of these also used a battery of cognitive tests variously including the digit-span memory test and the Stroop word-colour test and simple reaction time tasks. 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.

Small study effects/publication bias

Small study effects were investigated using Egger's test for each meta-analysis. The results were not suggestive of a significant influence of small study effects.

Discussion

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 conflict-

ing 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

Adverse effects reporting is inconsistent. 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 study³³ 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 result of 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 studies⁵¹ 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 tDCS⁵⁸ 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%.⁵⁹ 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 audito-

ry 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 studies⁴⁹⁻⁵¹ 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.⁵⁷ However, the one study⁵⁸ 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 participants⁶⁰ 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 scalp sensations. The discussion of one study report⁵⁷ alludes to 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 protocol⁶¹ 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 studies³² 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.⁵⁶ 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 used⁴⁰ 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 this study 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 2007⁴ following a review of the existing literature. Using a narrative synthesis of the evidence they similarly concluded that there was moderate evidence (two randomised controlled trials) that high-frequency rTMS (≥ 5 Hz) of the motor cortex induces significant pain relief in central post-stroke pain and several other neuropathic conditions but that the effect is modest and short-lived. They did not recommend its use as a sole clinical treatment but suggest that it might be considered in the treatment of short-lasting pain.

A recent review⁹ 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 *et al.*³⁷). 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^{32, 36} failed to demonstrate superiority of active over sham stimulation.

All but one of the included studies in the review by Leung *et al.*⁹ 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 *et al.*³⁷ that was excluded from the current analysis. This review preceded the studies by Defrin *et al.*³² and Kang *et al.*³⁶ which 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 Fregni²⁰ 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 *et al.*³⁷ (excluded from this review due to high risk of bias) and Canavero *et al.*⁶² (excluded 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.^{28, 32, 36, 41-43, 46} Neither the review of Leung *et al.*⁹ or Lima and Fregni²⁰ 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 and Smith¹³ 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.

Conclusions

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.

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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