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Non-invasive brain stimulation techniques for chronic pain in adults

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Protocol information

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What's new

Date / Event	Description

History

Date / Event	Description

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. They include repetitive transcranial magnetic stimulation (rTMS), transcranial direct current stimulation (tDCS) and cranial electrotherapy stimulation (CES).

rTMS involves stimulation of the cortex by a stimulating coil applied to the scalp. Electric currents are induced in the brain 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 cortical excitability both locally and in remote cortical and subcortical brain regions (Leo 2007). 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 (Leung 2009).

tDCS and 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 6 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 excitatory and inhibitory neural 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 processing painful stimuli.

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 (≤ 1Hz) results in lowered cortical excitability at the site of stimulation, whereas high frequency stimulation (≥ 5Hz) 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 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 cortical and subcortical 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,
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 robustly assess the existing literature 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 are:

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

Randomized controlled trials (RCTs) and quasi-randomised trials that utilise a sham control group will be included. Parallel and cross-over study designs will be included. Studies will be included regardless of language or blinding.

Types of participants

Studies including male or female adult participants over the age of 18 years with any chronic pain syndrome (within a duration of > 3 months) will be included. It is not anticipated that any studies are likely to exist in a younger population. Headache and migraine studies will not be included due to the episodic nature of these conditions.

Types of interventions

Studies investigating the therapeutic use of non-invasive form of brain stimulation (tDCS, rTMS or CES) will be included. Studies of electroconvulsive therapy (ECT) will not be included 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 will also not be included.

Types of outcome measures

Primary outcomes

The primary outcome measure will be 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 will be extracted where available include self-reported disability scale 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 will be 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 will include a combination of controlled vocabulary (MeSH) and free text terms. All database searches will be based on this strategy but will be appropriately revised to suit each database.

Electronic databases

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

- OVID MEDLINE (1966 to present)
- OVID EMBASE (1974 to present)
- SCOPUS (1960 to present)
- CENTRAL (all years)
- Cochrane pain, palliative and supportive care register (current issue)
- Psychinfo (all years)
- CINAHL (1982 to present)
- LILACS (1982 to present)

Searching other resources

Reference lists

Reference lists of all eligible trials, key textbooks and previous systematic reviews will be searched to identify additional relevant articles.

Unpublished data

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)) will be searched to identify research in progress and unpublished research.

Language

The search will attempt to identify all relevant studies irrespective of language. Non-English papers will be assessed and, if necessary, translated with the assistance of a native speaker.

A final list of included articles will be sent 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

Search results will be independently checked by two review authors (NOC & BW) and eligible studies will be included. Initially the titles and/or abstracts of identified studies will be read by two review authors (NOC & BW). If it is clear from the study title or abstract that the study is not relevant or does not meet the selection criteria it will be excluded. If unclear then the full paper will be assessed, as will all studies that appear to meet the selection criteria. Disagreement between review authors will be resolved through discussion between the two review authors. Where resolution is not achieved the paper(s) in question will be considered by a third review author (LDS).

Data extraction and management

Data will be extracted independently by two review authors (NOC/BW) using a standardised form. Discrepancies will be resolved by consensus. Where agreement cannot be reached a third review author (LDS) will consider the paper. The form is to include:

- 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

Risk of bias will be assessed 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). Studies will be given an overall rating of high, low or unclear risk of bias based on the Cochrane criteria.

The criteria assessed for parallel study designs (using yes/no/unclear judgements) will be: Adequate sequence generation? Adequate allocation concealment? Adequate blinding of assessors? Adequate blinding of participants? Incomplete outcome data adequately assessed? Free of suggestion of selective outcome reporting? Free of other bias?

The criteria assessed for cross-over study designs (using yes/no/unclear judgements) will be: Adequate sequence generation? Is the date clearly free from carry-over effects? Adequate blinding of assessors? Adequate blinding of participants? Free of the suggestion of selective outcome reporting? Free of other bias?

Risk of bias will be independently checked by two review authors (NOC & BW). Disagreement between review authors will be resolved through discussion between the two review authors. Where resolution is not achieved the paper(s) in question will be considered by a third review author (LDS).

Assessment of sham credibility

The type of sham used in studies of rTMS will be rated for credibility as optimal (the sham controls for the auditory and sensory characteristics of stimulation and is visually indistinguishable from real stimulation) and sub optimal (fails to account for either the auditory and sensory characteristics of stimulation or both, or is visually distinguishable from the active stimulation). A judgement of unclear will be made where studies do not adequately describe the sham condition. Rating of sham credibility will be performed by two independent review authors (NOC and BW). Disagreement between review authors will be resolved through consensus. Where resolution is not achieved the paper(s) in question will be considered by a third review author (LDS). Sensitivity analysis will investigate the influence of sham credibility on the primary outcome measure.

Measures of treatment effect

Standardised mean difference (SMD) difference will be used 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 the SMD will be back-transformed to a 0 to 100 mm VAS format on the basis of the mean standard deviation from trials using 0 to 100 mm VAS. The likely clinical importance of the pooled effect size will be considered using the criteria proposed in the IMMPACT consensus statement (Dworkin 2008). Specifically a decrease in pain of < 15% will be judged as no important change, ≥ 15% will be judged as a minimally important change, of ≥ 30% as a moderately important change and of ≥ 50% as substantially important change.

Unit of analysis issues

Cross-over trials will be entered into a meta-analysis where it is clear that the data is free of carry-over effects. Where appropriate the possible impact of cross-over versus parallel trial design on outcomes will be investigated through subgroup analysis.

Dealing with missing data

Where insufficient data is presented to enter a study into the meta-analysis, study authors will be contacted to request access to the missing data.

Data synthesis

Pooling of results will be performed where adequate data exist using RevMan. The meta-analysis will compare active stimulation with sham treatment. Separate meta-analyses will be considered for different forms of stimulation intervention (i.e. rTMS, tDCS and CES) where adequate data are identified 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. Short-term outcomes will be the primary outcomes of interest. For all analyses the outcome of the risk of bias assessments will be explicitly and clearly presented in the reporting. If the risk of bias varies across studies then studies at low risk of bias will be combined for the primary meta-analysis.

Where inadequate data are found to support statistical pooling, narrative synthesis of the evidence will be performed using the GRADE system (Guyatt 2008).

Subgroup analysis and investigation of heterogeneity

Heterogeneity and its impact will be assessed using the chi squared test and the I squared test. Where significant heterogeneity ($P < 0.1$) is present subgroup analysis will be explored. Proposed comparisons include site of stimulation, frequency of TMS stimulation (low ≤ 1Hz, High ≥ 5Hz), 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 will include pain due to identifiable pathology of the central nervous system (e.g. stroke, spinal cord injury), peripheral neuropathic pain will include injury to the nerve root or peripheral nerves, facial pain will include trigeminal neuralgia and other idiopathic chronic facial pains, non-neuropathic pain will include 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 are available, sensitivity analyses will be conducted on the following study factors: Risk of bias, sham credibility (for rTMS studies), cross-over versus parallel group designs.

Acknowledgements

The authors would like to thank James Langridge of the Brunel University Library for sharing his expertise in the use of electronic databases.

Contributions of authors

NOC: has conceived and designed the review protocol, will implement the search strategy, apply eligibility criteria, assess studies and extract and analyse data, lead the write up and updating of the review.

BM: has closely informed the protocol design, will apply eligibility criteria, assess studies, extract and analyse data and assist the write up and updating of the review.

LM: has provided statistical advice and support and will advise on the data analysis process. Has also contributed to the writing of the protocol.

LDS: has been involved in the conception and design of the review. Will act as a third review author for conflicts in applying eligibility criteria and assessing included studies.

SS: will overview the study, has informed design of the protocol and will inform implementation and reporting

of the review.

Declarations of interest

None known

Published notes

Additional tables

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Other published versions of this review

Figures

Sources of support

Internal sources

- No sources of support provided

External sources

- No sources of support provided

Feedback

Appendices

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

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

1. randomized 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