Non-invasive brain stimulation techniques for chronic pain. An updated Cochrane systematic review and meta-analysis.

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Introduction

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

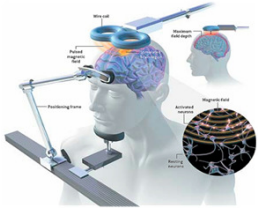
Purpose

To evaluate the efficacy of non-invasive brain stimulation techniques in chronic pain. This is an update of the original Cochrane review published in 2010.

Methods

We systematically searched CENTRAL, MEDLINE, EMBASE, CINAHL, PsycINFO, LILACS, the Cochrane PaPaS Group Trials Register and trials registers for randomised and quasi-randomised studies of rTMS, CES or tDCS that employed a sham stimulation control, recruited patients aged ≥18 with pain of ≥ three months duration and measured pain as a primary outcome. Two authors independently extracted data and assessed all studies for risk of bias using the Cochrane Risk of Bias Tool. Where possible we entered data into meta-analyses. We excluded studies judged as being at high risk of bias from the analysis. We used the GRADE system to summarise the quality of evidence for core comparisons

rTMS



CES

tDCS

Results

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

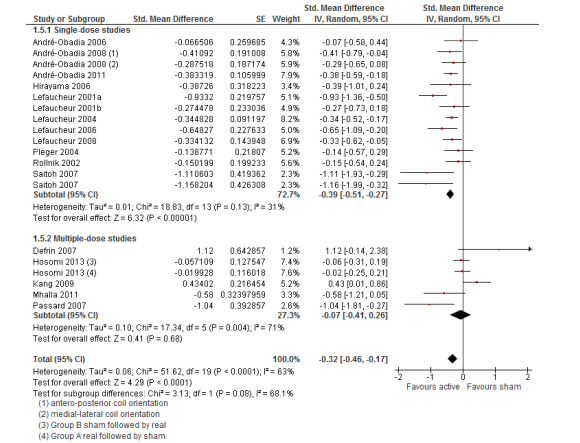
Meta-analysis of studies of rTMS (involving 528 participants) demonstrated significant heterogeneity. Pre-specified subgroup analyses suggest that low-frequency stimulation is ineffective (low quality evidence) and that rTMS applied to the dorsolateral prefrontal cortex is ineffective (very low quality evidence). A short-term effect on pain of active high-frequency stimulation of the motor cortex in single-dose studies was found (low quality evidence, standardised mean difference (SMD) 0.39 (95% confidence interval (CI) -0.27 to -0.51 p= < 0.00001)). This equates to a 12% (95%CI 8 to 15) reduction in pain which does not exceed the pre-established criteria for a minimally clinically important difference. Evidence for multiple dose studies was heterogeneous but did not demonstrate a significant effect (very low quality evidence)

For CES (six studies, 270 participants) no statistically significant difference was found between active stimulation and sham (low quality evidence). Analysis of tDCS studies (11 studies, 193 people) demonstrated significant heterogeneity and did not find a significant difference between active and sham stimulation (very low quality evidence). Pre-specified subgroup analysis of tDCS applied to the motor cortex (n=183) did not demonstrate a statistically significant effect and this lack of effect was consistent for subgroups of single or multiple dose studies.

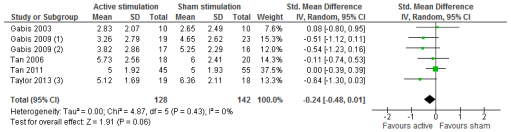
One small study (n=91) at unclear risk of bias suggested a positive effect of RINCE over sham stimulation on pain (very low quality evidence).

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

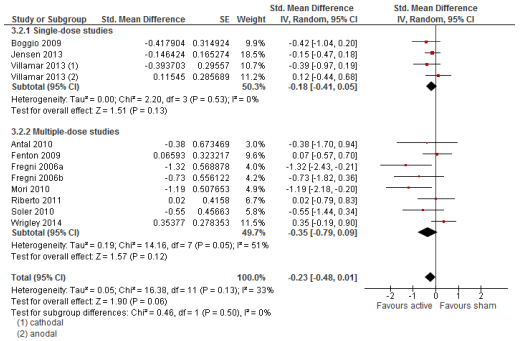
rTMS for pain short-term, subgroup analysis: motor cortex studies only (low-frequency studies excluded).



CES for pain: short-term follow up



tDCS for pain short-term follow up, subgroup analysis: motor cortex studies only



Discussion & Conclusions

Conclusions: Single doses of high-frequency rTMS of the motor cortex may have small short-term effects on chronic pain. The effects do not meet the predetermined threshold of minimal clinical significance and multiple dose studies do not consistently demonstrate effectiveness. It is likely that multiple sources of bias may exaggerate this observed effect.

The available evidence suggests that low-frequency rTMS, rTMS applied to the pre-frontal cortex, CES and tDCS may not be effective in the treatment of chronic pain.

There is a need for larger, rigorously designed studies, particularly of longer courses of stimulation. It is likely that future evidence may substantially impact upon the presented results.

Due to this uncertainty, any clinical application of non-invasive brain stimulation techniques would be most appropriate within a clinical research setting rather than in routine clinical care.

Acknowledgements

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