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Transcranial direct current stimulation (tDCS) for improving fatigue, motor function, and pain in people with multiple sclerosis.
Cochrane Database of Systematic Reviews 2019, Issue 3. Art. No.: CD013296.
DOI: 10.1002/14651858.CD013296.

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[Intervention Protocol]

Transcranial direct current stimulation (tDCS) for improving fatigue, motor function, and pain in people with multiple sclerosis

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Editorial group: Cochrane Multiple Sclerosis and Rare Diseases of the CNS Group.
Publication status and date: New, published in Issue 3, 2019.

Citation: Sivaramakrishnan A, Hombali AS, Shankar R, Fregni F, Thibaut A. Transcranial direct current stimulation (tDCS) for improving fatigue, motor function, and pain in people with multiple sclerosis. *Cochrane Database of Systematic Reviews* 2019, Issue 3. Art. No.: CD013296. DOI: 10.1002/14651858.CD013296.

ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

To assess the effects of transcranial direct current stimulation (tDCS) on fatigue, motor function, and pain in people with MS.

BACKGROUND

Description of the condition

Multiple sclerosis (MS) is a chronic autoimmune, inflammatory, and neurodegenerative disease of the central nervous system (CNS) with global prevalence rates estimated at 2.3 million (Browne 2014; MSIF 2013). The prevalence of MS is known to follow a geographical gradient, with higher prevalence rates in areas that are farther from the equator such as North America and Europe (140 and 108 per 100,000 respectively) and lower prevalence rates in areas that are closer to the equator such as sub-Saharan Africa (2.1 per 100,000) (MSIF 2013). Multiple sclerosis is known to have a varied disease course, and traditional clinical models have categorised MS phenotypes as relapsing-remitting MS (RRMS), primary-progressive MS (PPMS), secondary-progressive MS (SPMS), and progressive-relapsing MS (PRMS). However, recent recommendations call for improved clinical and radiological descriptors to better characterise currently existing phenotypes (Lublin 2014). In addition, clinically isolated syndrome (CIS) has been proposed as a phenotype in the MS spectrum (Lublin 2014). Individuals with MS are known to present with a wide array of neurological symptoms that may occur in isolation as sudden attacks, or in combination, arising from different areas of the CNS (Milo 2014). Classical signs and symptoms include sensory loss, motor symptoms, such as muscle weakness and/or spasticity, autonomic symptoms such as bowel, bladder, and sexual dysfunction, and deficits in co-ordination and balance, vision, and cognition (Milo 2014). Fatigue is another frequently reported symptom that is known to affect approximately 50% to 80% of adults with MS

(Krupp 2010; Lerdal 2007). Fatigue is more frequently reported in people with PPMS and SPMS compared to RRMS (Leocani 2008; Patrick 2009). Although the pathophysiology of fatigue is not completely understood, experts believe that fatigue in MS may have a central origin, and studies have reported an impairment in the corticomotor drive to the descending motor system as a causative mechanism (Leocani 2008; Patrick 2009). Fatigue appears to be at its worst in the afternoon (Krupp 2010; Leocani 2008), and is known to increase in hot or humid environments (Bakshi 2003). Over the course of the disease, individuals with MS experience significant functional disability that can severely affect their quality of life and eventually increase caregiver burden (Lobentanz 2004). In particular, deficits in walking can be particularly frustrating for those with MS and their caregivers. Individuals with MS can have limitations in day-to-day mobility due to muscle weakness, spasticity, sensory loss, and problems with balance. In addition, cognitive deficits can worsen walking and increase risk of fall. Spasticity is highly prevalent in MS and can impede functional activities such as transfers and ambulation, thus increasing disability (Barnes 2003). Moreover, spasticity is correlated with pain, and therefore has an impact on patients' quality of life. Eventually, decrease in mobility can further increase the severity of MS-related symptoms (e.g. a decrease in activity and sustaining one position for a long time can increase fatigue and pain and cause other comorbidities such as respiratory- and urinary tract-related complications). In addition to functional dysfunction, individuals with MS may suffer from pain. Pain prevalence reports in MS are variable; a recent study reported that around 63% of adults with MS manifest with pain at some point during their disease (Foley 2013). Multiple sclerosis is characterised by different pain syndromes such as headache, neuropathic pain, Lhermitte's phenomenon, painful tonic spasms, musculoskeletal pain, trigeminal neuralgia, and others (Foley 2013; Truini 2013). Given that individuals with MS can present with various combinations of these symptoms, current research is seeking to explore the efficacy of different rehabilitation approaches.

Description of the intervention

Transcranial direct current stimulation (tDCS) is a non-invasive neuromodulatory tool that can potentially improve motor function in several neurological disorders such as stroke, spinal cord injury, Parkinson's disease, and others (Fregni 2005; Fregni 2006; Gandiga 2006; Hummel 2005). Low intensity direct currents are delivered through electrodes on the scalp that can modulate cortical excitability (Nitsche 2000) and produce behavioural changes to promote functional performance (Giordano 2017; Roche 2015). The dosage typically includes a current intensity of 1 to 2 mA delivered for 5 to 20 minutes with electrodes sizes ranging from 25 to 35 cm^2 (Nitsche 2008). Stimulation related after-effects are dependent on stimulation polarity and duration, current intensity, and electrode size. tDCS is a safe technique and usually elicits a mild itching sensation that fades after a few seconds of stimulation (Nitsche 2000). tDCS protocols can be controlled with a sham condition, also known as placebo tDCS. Sham stimulation includes the ramp up and ramp down of current (producing initial tingling sensations to mimic the active stimulation), but the current is delivered for a very short period of time (e.g. 30 seconds) .

How the intervention might work

Transcranial direct current stimulation can modulate corticomotor excitability by inducing bidirectional polarity specific effects. Anodal tDCS (where the anode (+) is placed over the target area) increases cortical excitability, and cathodal tDCS (cathode (-) placed over the target area) decreases cortical excitability (Nitsche 2000). tDCS modulates neuronal membrane potentials that affect neuronal excitability and the resulting effects can last longer than the stimulation period (Stagg 2011). Studies have also shown that tDCS-related after effects may depend on glutamatergic mechanisms resulting in possible induction of long-term potentiation (LTP)-like effects that can promote neuronal plasticity (Nitsche 2000; Nitsche 2001; Pelletier 2014). Several studies have investigated the effects of tDCS on the primary motor cortex of the hand muscle representations. More often, researchers use protocols incorporating anodal tDCS to enhance motor function. Anodal stimulation when combined with a motor or cognitive task can render the brain's circuits more responsive to the accompanying task, thus increasing the effectiveness of tDCS (Fregni 2005a; Reis 2009). Recent studies suggest that in individuals with MS, anodal tDCS over the motor cortex or prefrontal area may reduce pain and improve fatigue severity as compared with sham tDCS (Ayache 2016; Ayache 2017; Ferrucci 2014; Mori 2010). Although research in tDCS is gaining momentum, optimal dosage parameters for stimulation such as current intensity, duration, and electrode size have yet to be identified.

Why it is important to do this review

The higher rates of prevalence of fatigue, movement disability, and pain in MS warrant an evidence-based approach to develop appropriate treatment modalities for people with MS. All these symptoms significantly impact individuals' quality of life, and even though tDCS is being explored as an intervention (Ferrucci 2014; Mori 2010), issues such as interindividual variability warrant a need for adequate synthesis of information regarding its efficacy. Although some studies report that tDCS may be effective in MS, it is unclear which target area of the brain (motor cortex versus other areas) may be optimal sites for stimulation. Currently, no systematic review has evaluated the effectiveness of tDCS in MS. Factors such as cost-effectiveness, ease of application, and portability of tDCS devices increase its potential as a clinical adjunct to other therapies. It is therefore important to comprehensively

synthesise the current literature to establish the clinical utility of tDCS for improving fatigue, motor function, and pain in people with MS.

OBJECTIVES

To assess the effects of transcranial direct current stimulation (tDCS) on fatigue, motor function, and pain in people with MS.

METHODS

Criteria for considering studies for this review

Types of studies

We will include randomized controlled trials with cross-over and parallel-group designs. We will also include quasi-randomized trials.

Types of participants

We will include adults, males and females (18 years or older) with clinically definite MS according to the McDonald criteria and its revisions and all subgroups of MS such as relapsing-remitting, primary-progressive, progressive-relapsing, and secondary-progressive (Polman 2005; Polman 2011; Poser 1983; Thompson 2018). We will exclude individuals with other neurological and non-neurological comorbidities that may affect motor function, pain, and fatigue.

Types of interventions

We will include all trials that evaluate tDCS in people with MS, regardless of unilateral or bilateral stimulation, anodal or cathodal stimulation, dosage, intensity, duration, electrode size, or cortical targets for stimulation. We will include as control interventions sham treatment or no treatment or conventional treatment. Acceptable conventional treatments will include interventions such as rehabilitation or exercise therapy or other training (such as yoga, tai-chi, etc.) or other therapies to improve motor function, fatigue, or pain.

We will investigate the following comparisons.

- tDCS only compared with sham tDCS
- tDCS and conventional therapy (for improving motor function, pain, and fatigue) compared with sham tDCS and conventional therapy
- tDCS and conventional therapy compared with conventional therapy alone
- tDCS only compared with no treatment

Types of outcome measures

We will examine outcomes that are measured pre- and postintervention and at the end of follow-up (e.g. six months or one year or other follow-up periods).

Primary outcomes

Fatigue measured using:

- Fatigue Impact Scale (FIS) (Fisk 1994);
- Modified Fatigue Impact Scale (MFIS) (Fisk 1994);
- Fatigue Severity Scale (FSS) (Krupp 1989);
- Multidimensional Fatigue Inventory (MFI) (Smets 1995);
- visual analogue scale (VAS);
- Patient-Reported Outcomes Measurement Information System (PROMIS) (Cella 2010).

Motor function measured using:

- muscle strength (Medical Research Council Scale); (Compston 2010)
- grip strength (measured by a dynamometer);
- pinch force (measured by a dynamometer or similar device).

- Upper limb motor function measured using:
  - Action Research Arm Test (ARAT) (Lyle 1981);
  - Nine-Hole Peg Test (NHPT) (Mathiowetz 1985).
- Lower limb motor function and mobility measured using:
  - Functional Ambulation Categories (FAC) (Holden 1984);
  - Timed Up and Go test (TUG) (Podsiadlo 1991);
  - MS-Walking Scale 12 (Hobart 2003);
  - 6-minute walk test (6 MWT) (Enright 2003).

Pain measured using:

- VAS;
- numerical rating scales (NRS) (Farrar 2001);
- McGill Pain Questionnaire (MPQ) (Melzack 1975);
- Short Form McGill Questionnaire (SF-MPQ) (Melzack 1987);
- Brief Pain Inventory-short form (BPI-sf) (Mendoza 2006).

Spasticity measured using:

- Ashworth Scale (AS); (Pandyan 1999)
- Modified Ashworth Scale (MAS) (Bohannon 1987);
- Composite Spasticity Scale (CSS);
- Multiple Sclerosis Spasticity Scale (MSSS-88) (Hobart 2006).

Adverse events - We will monitor the incidence (i.e. number) of tDCS related adverse events (AEs) and serious adverse events (SAEs). If enough studies do not report the total number of AEs, SAEs, and person-years, we will use the number of participants with at least one AE or SAE as defined in the study.
Adverse events of tDCS will include minor symptoms such as transient itching, burning, tingling, headache, scalp discomfort, pain, nausea, contact dermatitis, skin redness, fatigue and other sensations. Serious adverse events will include seizures and psychotic symptoms such as mood changes, irritability and all other serious adverse events reported in the included studies.

Secondary outcomes

- Quality of life measured using such tools as the 36-Item Short Form Health Survey (SF-36) (Ware 1992), 12-Item Short Form Health Survey (SF-12), and Multiple Sclerosis Quality of Life-54 (MSQoL-54) (Vickrey 1995).
- Depression measured using such tools as Beck's Depression Inventory (BDI) and Hamilton Depression Rating Scale (HDRS) (Beck 1996; Williams 1988).
- MS progression measured with the Kurtzke Expanded Disability Status Scale (EDSS) (Kurtzke 1983).
- Tactile perception measured using such tools as grating orientation task (GOT) and VAS (Craig 1999).
- Cognition measured using such tools as Symbol Digit Modalities Test (SDMT) (Smith 1982), Wisconsin Card Sorting Test (WCST) (Heaton 1981), Paced Auditory Serial Addition Test (PASAT) (Gronwall 1977), and Attention Network Test (ANT) (Macleod 2010).

Search methods for identification of studies

Electronic searches

The Information Specialist will search the Cochrane Multiple Sclerosis and Rare Diseases of the Central Nervous System Group Trials Register, which contains trials from the following sources, among others.

- The Cochrane Central Register of Controlled Trials (CENTRAL) (latest issue).
- MEDLINE (PubMed) (1966 to date).
- Embase (1974 to date).
- CINAHL (EBSCO host) (Cumulative Index to Nursing and Allied Health Literature) (1981 to date).
- LILACS (BIREME) (Latin American and Caribbean Health Science Information database) (1982 to date).
- PEDro (Physiotherapy Evidence Database) (1990 to date).
- ClinicalTrials.gov (www.clinicaltrials.gov).
- World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (apps.who.int/trialsearch).

Information on the Group's Trials Register and details of search strategies used to identify trials can be found in the 'Specialised Register' section within the Cochrane Multiple Sclerosis and Rare Diseases of the Central Nervous System Group's module. The keywords used to search for trials for this review are listed in Appendix 1.

Searching other resources

In addition we will:

- screen the reference lists of review articles and primary trials on this topic;
- screen the following relevant conference proceedings: World Congress of NeuroRehabilitation, American Congress of Rehabilitation Medicine, American Society of NeuroRehabilitation and Brain Stimulation;
- contact experts in the field for additional data and to identify further published or unpublished trials;
- contact principal authors of abstracts or unpublished manuscripts for sharing of their unpublished data.

Data collection and analysis

Selection of studies

Three review authors (AS, AH, and AT) will independently screen and select trials based on the inclusion criteria of the review. We will screen the titles and abstracts for all the citations. Next, we will obtain the full text of the selected citations, and based on their eligibility, select articles for inclusion. Any disagreements regarding inclusion will be resolved by mutual discussion or by referral to a fourth review author (FF) when necessary.

Data extraction and management

For each included study, two review authors (AS, AH) will independently extract data from the selected trials using data extraction forms, and enter the data into Review Manager 5 (Review Manager 2014). We will extract data based on the following:

- study characteristics (study design, inclusion and exclusion criteria);
- characteristics of participants (number, age, gender, type of MS, time from symptom onset to diagnosis);
- type and length of experimental intervention (stimulation site, parameters and dosage);
- type and length of control intervention;
- methodological quality of studies;
- description of outcomes.

Assessment of risk of bias in included studies

We will assess risk of bias using the Cochrane 'Risk of bias' assessment tool as outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a). For parallel-group designs, we will assess the following 'Risk of bias' domains: sequence generation, allocation concealment; blinding of participants and personnel; blinding of assessors; incomplete outcome data; selective reporting; and whether free of other bias. For cross-over study designs, we will assess the aforementioned domains as well as whether the data are free from carry-over effects. We will judge each domain as at low, high, or unclear risk of bias (we will assess a domain as unclear when information is insufficient to make a judgement of 'low' or 'high' and study authors do not respond to our queries when contacted). We will provide a quote from the study and justification for the judgement for each domain in the 'Risk of bias' table. We will assess risk of bias for all outcomes within a study. Overall risk of bias for each study will be judged at 'low risk of bias' when all three domains (allocation concealment, blinding of outcome assessment and incomplete outcome assessment) are assessed at 'low risk of bias'; 'high risk of bias' when at least one domain is assessed at 'high risk of bias'; and 'unclear risk of bias' in the remaining cases.

Two review authors (AS and AH) will independently assess risk of bias for each study. Any disagreements between the authors on the methodological quality of the identified studies will be resolved by referral to a third reviewer (AT). We will contact the authors of the included studies for any additional information on the study methods.

GRADE assessment and 'Summary of findings' table

We will provide the main findings of the review in 'Summary of findings' tables using GRADEpro GDT software (GRADEpro GDT 2015). The tables will include a list of all primary outcomes (fatigue, motor function, pain, spasticity and adverse events), magnitude of effect of the intervention, number of participants, and overall certainly of evidence for each outcome. For each primary outcome, we will assess the certainty of the evidence using the GRADE approach (Balshem 2010), which is based on consideration of risk of bias, inconsistency, indirectness, imprecision, and publication bias. We will assess the certainty of the evidence for each outcome as high, moderate, low, or very low.

Measures of treatment effect

Continuous data

For all continuous outcomes, we will compute the mean difference (MD) with 95% CI as a measure of treatment effect if the outcomes are measured in the same way among trials. If some studies report endpoint data, and others report change from baseline data, we will combine these studies in a meta-analysis if the outcomes have been reported using the same scale. We will compute the standardised mean difference (SMD) with 95% CI to combine trials that measure the same outcome using different scales. For every study, we will compute MD or SMD and the corresponding 95% CI. If the studies do not report mean and standard deviation (in case the data is skewed), we will use the method as proposed by the author to calculate mean and variance from median, range, and sample size (Hozo 2005). If the range is not mentioned in the article, we will contact the authors for this information.

Ordinal data

We will use the methods described in the *Cochrane Handbook for Systematic Reviews of Interventions* to analyse ordinal and measurement scale outcomes. We will consider the ordinal outcome as continuous if it has many categories (preferably more than four), or we will compute the proportional odds ratio and pool the data using the generic inverse-variance method (Deeks 2011). We will compute the proportional odds ratio using Stata 13.1 (Stata 2013). We will use risk ratio (RR) and 95% CI for AEs and SAEs.

Unit of analysis issues

Studies with more than two treatment groups

If we identify studies with two or more intervention groups (multi-arm studies), we will combine all intervention arms into a single intervention group (e.g. intervention arms with multiple tDCS dosages will be combined), and we will combine all relevant control groups into a single control group (e.g. sham tDCS, no treatment and/or conventional treatments will be combined) (Higgins 2011b). We will follow the method suggested in Table 7.7.a in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011c). While performing subgroup analysis, if the interventions belong to a different subgroup, we will consider that as a separate study. Additionally, we will divide the control group (events and total population) with the number of relevant subgroups to avoid double-counting of participants.

Cross-over trials

We will consider data only from the first period of measurement in the meta-analysis, or if possible we will perform an appropriate paired analysis (Higgins 2011b). If the studies do not provide a within-participant correlation coefficient, we will impute the value for a correlation coefficient from another study in the meta-analysis as per the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011b). We will also conduct a sensitivity analysis for different values of within-participant correlation coefficient.

Dealing with missing data

We will contact the authors if outcome data are unclear or have not been completely reported. We will capture the missing information in the data extraction form and report it in the 'Risk of bias' tables. For all outcomes, we will perform an intention-to-treat analysis and attempt to include all participants randomised to each group.

Assessment of heterogeneity

We will use a random-effects model, regardless of the level of heterogeneity. We will use the I^2 statistic to assess heterogeneity, considering an I^2 greater than 50% as substantial heterogeneity.

Assessment of reporting biases

If we identify at least 10 trials reporting the same outcome of interest, we will assess publication bias using funnel plots. Otherwise, we will use Egger's test for assessing reporting bias (Sterne 2011).

Data synthesis

We will analyse the data using Review Manager 5 (Review Manager 2014). We will perform a meta-analysis to provide an overall estimate of the treatment effect when data from more than one study using the same comparison are available. We will adopt a random-effects model for meta-analysis in anticipation of natural heterogeneity between studies that may be due to different tDCS target areas, dosages, intensities, durations, types of stimulation, electrode sizes, length of interventions, and types of MS. For continuous variables, we will use the inverse-variance method. If we are unable to perform a meta-analysis due to substantial differences between studies, we will perform a narrative synthesis of the data. We will not combine results from randomised and quasi-randomised trials together in the meta-analysis.

Subgroup analysis and investigation of heterogeneity

If we identify three or more studies, we will undertake subgroup analyses to explore potential sources of heterogeneity based on the following.

- Type of MS: RRMS, PPMS, SPMS, and PRMS
- Type of stimulation: cathodal versus anodal stimulation
- Target area of stimulation: dorsolateral prefrontal cortex, motor cortex and other areas
- Dosage of stimulation: current intensity, electrode size and duration of stimulation
- Length of intervention: single session versus multiple sessions
- Electrode size

All subgroup analyses will be accompanied by appropriate tests for interaction, that is statistical tests for subgroup differences as described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), and implemented in Review Manager 5 (Review Manager 2014).

Sensitivity analysis

We will perform a sensitivity analysis to examine the robustness of the estimates by removing studies at high risk of bias from the meta-analysis. If we include cross-over trials in the review, we will perform a sensitivity analysis for different values of the within-participant correlation coefficient.

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* *Indicates the major publication for the study*

APPENDICES

Appendix 1. Keywords

1	Electric Stimulation Therapy/
2	Electric Stimulation/
3	Electrodes/
4	(transcranial adj5 direct current adj5 stimulation).tw.
5	(transcranial adj5 DC adj5 stimulation).tw.
6	(transcranial adj5 electric$ adj5 stimulation).tw.
7	(tDCS or A-tDCS or C-tDCS or S-tDCS or electrode$ or anode or anodes or anodal or cathode or cathodes or cathodal).tw
8	or/1-8

CONTRIBUTIONS OF AUTHORS

AS drafted the protocol. All authors participated in reviewing and editing the manuscript. All authors have read and approved the final manuscript.

DECLARATIONS OF INTEREST

Anjali Sivaramakrishnan: none known

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Ravi Shankar: none known

Felipe Fregni: none known

Aurore Thibaut: none known