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Effects of non-invasive brain stimulation for degenerative cerebellar ataxia: a protocol for a systematic review and meta-analysis

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ABSTRACT

Introduction To date, the medical and rehabilitation needs of people with degenerative cerebellar ataxia (DCA) are not fully met because no curative treatment has yet been established. Movement disorders such as cerebellar ataxia and balance and gait disturbance are common symptoms of DCA. Recently, non-invasive brain stimulation (NIBS) techniques, including repetitive transcranial magnetic stimulation and transcranial electrical stimulation, have been reported as possible intervention methods to improve cerebellar ataxia. However, evidence of the effects of NIBS on cerebellar ataxia, gait ability, and activity of daily living is insufficient. This study will aim to systematically evaluate the clinical effects of NIBS on patients with DCA.

Methods and analysis We will conduct a preregistered systematic review and meta-analysis based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement. We will include randomised controlled trials to assess the effects of NIBS on patients with DCA. The primary clinical outcome will be cerebellar ataxia, as measured by the Scale for Assessment and Rating of Ataxia and the International Cooperative Ataxia Rating Scale. The secondary outcomes will include gait speed, functional ambulatory capacity and functional independence measure, as well as any other reported outcomes that the reviewer considers important. The following databases will be searched: PubMed, Cochrane Central Register of Controlled Trials, CINAHL and PEDro. We will assess the strength of the evidence included in the studies and estimate the effects of NIBS.

Ethics and dissemination Because of the nature of systematic reviews, no ethical issues are anticipated. This systematic review will provide evidence on the effects of NIBS in patients with DCA. The findings of this review are expected to contribute to clinical decision-making towards selecting NIBS techniques for treatment and generating new clinical questions to be addressed.

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STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This systematic review and meta-analysis will address the effect of non-invasive brain stimulation (NIBS) on widely degenerative cerebellar ataxia (DCA).
⇒ The effect sizes of the repetitive transcranial magnetic stimulation and transcranial electrical stimulation on symptoms of cerebellar ataxia will be calculated and compared.
⇒ This study will provide the parameters of NIBS montages for DCA, based on a systematic review.
⇒ This systematic review may reveal a lack of solid and strong evidence, due to the heterogeneity of intervention parameters and diseases.

INTRODUCTION

Degenerative cerebellar ataxia (DCA)[1] is a group of inherited neurodegenerative disorders that are characterised by progressive cerebellar ataxia.[2] Representative diseases include autosomal dominant spinocerebellar ataxia (ADSCA),[3] spinocerebellar ataxia (SCA),[4–6] Friedreich's ataxia (FA),[7] multiple system atrophy with cerebellar ataxia (MSA-C),[8] sporadic adult-onset ataxia of unknown aetiology (SAOA)[9] and autosomal recessive spastic ataxia of Charlevoix-Saguenay (ARSACS).[10] The pathological hallmark of almost all types of DCA is the loss of neurons such as Purkinje cells in the cerebellum, which leads to its atrophy. In addition, degeneration of other neuronal populations in the cerebellum, brainstem and spinal cord contributes to the wide range of clinical manifestations of DCA. These diseases lack adequate treatment, and the associated movement disorders are progressive and have a significant impact on the patients' daily living activities and quality of life.[11] These diseases are rare, and while treatment methods are being developed, they remain insufficient to meet patients' medical needs.[12–14]

Some pharmacological and non-pharmacological treatments have been recommended in previous systematic research based on clinical studies.[15] One of the treatments for movement disorders

and disabilities is neurorehabilitation, including high-intensity physical and occupational therapy.[11] Some conventional interventions, such as weighted orthoses and balance training,[16] are applied by clinicians. Additionally, non-invasive brain stimulation (NIBS), such as repetitive transcranial magnetic stimulation (rTMS)[17–22] and transcranial electrical stimulation (tES),[23–29] is also used for neuromodulation.[30]

Single-pulse TMS can induce action potentials in the focal cortical site of the brain, resulting in temporal effects on motor and sensory function.[31] Moreover, rTMS can induce more long-term changes in neural activity and function than single-pulse stimulation.[32] rTMS has thus been studied as a potential treatment[33] for mental disorders,[34] cognitive dysfunction,[35] pain,[36] movement disorders after stroke,[37] symptoms of Parkinson's disease,[38] multiple sclerosis[39] and cerebellar ataxia.[19] These studies have indicated that rTMS can be performed to obtain long-term desirable effects on the symptoms of cerebellar and other neural diseases and in a safe manner in these patients.[32]

Recent systematic reviews and meta-analyses have investigated the effects of rTMS on cerebellar ataxia, including patients with DCA and patients who had a stroke.[40] One review[40] has reported that rTMS improves scores on the International Cooperative Ataxia Rating Scale (ICARS),[41] the Scale for the Assessment and Rating of Ataxia (SARA),[42] the Berg Balance Scale and in Timed Up and Go tests.[40] These findings indicate that rTMS has the potential to improve cerebellar ataxia, balance and gait dysfunction. However, the effect of rTMS may be affected by other conditions, including stroke and degenerative diseases. About 80% of cases with cerebellar ataxia after cerebellar stroke reach an independent level of activity of daily living within 3 months after onset.[43] DCA, on the other hand, causes a gradual loss of Purkinje cells in the cerebellar cortex and functional compensations in the deep cerebellar nuclei and cerebral cortex, gradually resulting in significant dynamic changes in the cerebrocerebellar system over time.[44] Because the pathophysiologies of stroke and DCA differ considerably, there may be too much heterogeneity to unify the effects of rTMS. In addition, the quality and heterogeneity of the studies should be considered. One systematic review on the effect of rTMS on DCA[19] included seven randomised controlled trials (RCTs), but a recent report[21] that aimed to improve cerebellar ataxia with a novel stimulus parameter of rTMS was not included. The reason this RCT was excluded is that the prior systematic review limited the disease to SCA, that is, it did not cover MSA-C, a neurodegenerative disease that presents with cerebellar ataxia. Therefore, we will estimate the effect of rTMS on cerebellar ataxia in DCA based on recent clinical studies.

Another important use of NIBS is tES for the treatment of DCA. This method,[45] which includes transcranial direct current stimulation (tDCS),[46] transcranial alternating current stimulation[47] and transcranial random noise stimulation,[48] applies a low-level electrical current to the scalp to modulate the activity of the underlying brain tissue. This technique involves placing one or more electrodes on the scalp and applying a weak direct/alternating/random noise current that flows between the electrodes. The mechanism of tDCS is thought to involve changes in the resting membrane potential of neurons in the brain.[45] A continuous weak electrical current can depolarise or hyperpolarise neurons, depending on the polarity and intensity of the current. However, despite many reports of its clinical efficacy, the underlying mechanism remains controversial.[8]

The tDCS is most often used in clinical trials for DCA treatment. Recently, two systematic reviews and meta-analyses reported the effects of tES on cerebellar ataxia.[28 49] These two reports have shown that tDCS dramatically improves symptoms of cerebellar ataxia, including upper/lower limb movement, balance of stance and gait function. The review included four RCTs[25–27 50] for DCA until 2019, while more recent RCTs[23 29 51] could not be included. Therefore, we will estimate the effects of tDCS on cerebellar ataxia through a systematic review and meta-analysis including the most recent studies.

The aforementioned previous systematic reviews and meta-analyses about tES and rTMS were appropriately conducted, but they considered each intervention independently. Furthermore, several important, more recent RCTs were published after analysis. In the current study, tES and rTMS are treated as a single NIBS approach same as previous systematic review and meta-analysis,[52] and their joint effect size will be assessed at the present time. This comprehensive analysis may contribute to estimate whether brain stimulation itself improves DCA symptoms. Moreover, we will create tES and rTMS subgroups and compare their effect sizes on the outcomes. In clinical practice, only one tES or rTMS technique can be employed at a time, and clinicians must have a rationale for choosing one technique over the other. Therefore, an indirect comparison of their effect sizes and new recommendations for their selection may be useful for patients with DCA and clinicians.

Regarding the safety and tolerability of rTMS[19] and tES[28] in patients with DCA, no severe harmful side effects and only minimal unfavourable events were recorded. In contrast, additional investigations are necessary to ascertain the most suitable NIBS parameters and evaluate their influence on the clinical outcomes of patients with DCA. More specifically, the polarity of tES, the frequency (high or low) of rTMS and the site of stimulation (cerebellum itself or other sites) are also important. The effects of these stimulus parameters on efficacy should also be examined in this systematic review and meta-analysis.

This study will aim to systematically review the available data on the use of NIBS, including rTMS or tES, as a therapeutic intervention for cerebellar ataxia in patients with DCA. This review will address the following research questions: (1) What is the impact of rTMS and tES on the degree of ataxia; (2) Which rTMS and tES stimulation parameters have been used in previous studies, and how

these have impacted the results; and (3) What must be evaluated in future research.

METHODS AND ANALYSIS

This systematic review will be conducted based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) statement (see online supplemental file 'PRISMA-P-checklist').[53] This protocol has been registered in the International Prospective Register of Systematic Reviews (PROSPERO) database.

Patient and public involvement

None.

Participants

We will include studies involving patients with DCA and exclude studies involving individuals with ataxia other than DCA. DCA encompasses a large number of diagnoses,[1] which typically are ADSCA,[3] SCA,[4–6] FA,[7] MSA-C,[8] SAOA[9] and ARSACS.[10] SCA is most typically of the SCA1, 2, 3, 6 and 31 subtypes, among others.[54] These diseases mainly arise with a later onset, being even rarer in patients less than 18 years old. Therefore, the age range covered in this systematic review is restricted to above 18 years old.[54] Pharmacological treatment and rehabilitation therapies are standard treatments[55] and are usually preferred over NIBS. Since most of the cases treated with NIBS also receive these two treatments concurrently, they will be included in both the intervention and comparator groups.

Interventions

NIBS, namely rTMS and tES, will be included as interventions for cerebellar ataxia. Transcranial alternating current stimulation, tDCS, and transcranial random noise electrical stimulation will be included as tES types.

Comparators

No intervention and active control interventions, such as sham stimulation or treatment, will be included as comparators. However, physical therapy, occupational therapy and pharmacotherapy will not be included solely as control treatments for NIBS. These therapies will be included in both the intervention and comparator groups.

Outcomes of interest

The primary clinical outcome will be cerebellar ataxia, as measured by SARA[42] and ICARS scores.[41] The use of these scales is recommended for assessment of cerebellar ataxia as a clinician-reported outcome measure.[56] The secondary outcomes will include gait speed, functional ambulatory capacity (FAC)[57] and functional independence measure (FIM),[58] as well as any other reported outcomes that the reviewer considers important. The weighted mean difference and the mean and SD will be used for continuous data. The standard mean difference will be used to summarise multiple measures of the same outcome items.

Study design

The inclusion criteria for the studies are single-blind or double-blind RCTs published in English with full-text availability. Only peer-reviewed articles will be included. The exclusion criteria are review articles, conference abstracts and letters to the editor.

Information sources and search strategy

The following databases will be searched: PubMed, Cochrane Central Register of Controlled Trials, CINAHL and PEDro. The searches will be restricted to English and human participants. Abstract and conference proceedings will not be included. The main search words are set to be the following: 'cerebellum', 'spinocerebellar degeneration', 'ataxia', 'transcranial magnetic stimulation', 'transcranial electrical stimulation' and 'clinical trial'. A draft of the search strategy for the above databases is provided in the supplementary file (online supplemental appendix 1). The review will encompass all eligible studies published from database inception until the present time.

Data extraction (selection and coding)

The search will be performed by one independent reviewer using the databases, and four other reviewers will confirm the initial list of papers. The search terms will consist of a combination of medical subject heading (MeSH) terms and free text search terms in the database, based on author consensus. Rayyan and EndNote V.20 will be used to manage the studies across databases.

For each study, a pair of two independent reviewers randomly assigned from a group of five reviewers (AM, HO, KB, YKo and YKi) will screen the study title and abstract for determining whether the study meets the inclusion criteria. Studies that cannot be judged only by the title and abstract will be evaluated by referring to the full text. During the initial evaluation, the identity of the other reviewer is blinded to the pair. If the decisions of the two reviewers are inconsistent, a third reviewer will participate in the discussion and make the final decision. At this stage, the pair is informed about the identity of the reviewer assessing the applicable study.

Data extraction will be performed by two independent reviewers to obtain precise information on the study design and methodology, participant demographics and baseline characteristics, sample size and effect measurements. Discrepancies will be resolved by the participation of a third reviewer in the discussion. We will contact study authors for any missing data, if needed. If the authors do not respond to our request or refuse to provide data, we will analyse only the available data. Data extraction will be performed using Microsoft Excel spreadsheets.

Risk of bias in individual studies

The risk of bias will be assessed using the Cochrane risk of bias tool (RoB 2.0). Two of the five independent reviewers will critically evaluate the included studies. The

evaluation items include the following: (1) bias arising from the randomisation process; (2) bias due to deviation from the intended intervention; (3) bias due to missing outcome data; (4) bias in the measurement of outcomes; (5) bias in the selection of reported results. For each item, we will evaluate each study as having a low, uncertain or high risk of bias. Any discrepancies will be discussed and resolved by a third reviewer, if necessary.

Data synthesis

If more than two randomised (or quasi-randomised) controlled trials report the same outcome, such as SARA and ICARS scores, FAC gait speed or FIM, a meta-analysis will be performed. RevMan V.5.4 software will be used for the meta-analysis and to calculate the weighted mean difference, and the mean and SD will be used for continuous data. The standard mean difference will be used to summarise multiple measures of the same outcome items. Random effect models will be used to obtain pooled estimates, and the results will be described using forest plots. The I^2 test will be used to evaluate heterogeneity; if the I^2 value exceeds 50%, heterogeneity will be judged to be high, and a subgroup analysis will be performed. A summary table of the published results will be prepared. If a quantitative synthesis is not appropriate, we will provide a summary table about NIBS montage, stimulation parameters, patient diagnosis, effect size of the intervention on outcomes and main findings in individual studies.

Analysis of subgroups or subsets

First, to examine the effects of NIBS, one meta-analysis will be conducted without separating tES and rTMS. Next, a subgroup analysis will be performed based on the type of intervention such as polarity of tES, frequency and location of rTMS. Furthermore, a subgroup analysis will be performed based on participant characteristics, such as sex and diagnosis (such as DCA or multiple system atrophy), and use of control (no intervention or active control) if there was more than one arm in each trial. Z-tests will be used to elucidate the differences in NIBS (tES and rTMS).[38]

Assessment of strength of evidence

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework will be employed to assess the overall quality of evidence across all outcomes. This will involve evaluating the individual risk of bias, meta-bias, precision, consistency, directedness and magnitude of effect. These indicators are used to determine the level of certainty associated with the estimated effect, which is classified as 'very low', 'low', 'high' or 'very high'.

ETHICS AND DISSEMINATION

There will be no requirement for ethical approval because this systematic review will not include original data from human beings. The results will be disseminated through peer-reviewed publication.

DISCUSSION

The present review will aim to summarise the available evidence on the effects of rTMS and tES in the treatment of DCA. The review will encompass all eligible studies published from inception until the present time and will assess the quality of the studies and analyse outcome data. One strength of this study is the expansion of the target population to patients with DCA, as in the past the study population was limited to patients with SCA and MSA. Another strength is the calculation and comparison of the effect sizes of tES and rTMS in the same systematic review and meta-analysis study, as they have been difficult to compare in the past. Furthermore, with the publication of several new RCTs since the latest systematic review, a better estimation of the effect size of NIBS is expected. The findings generated by this systematic review and meta-analysis may contribute to the clinical decision-making regarding the use of NIBS and the choice of NIBS technique for treating an individual patient with DCA.

There are potential concerns in the interpretation of the results in the current systematic review and meta-analysis. One concern is that stimulation methods for tES and rTMS have evolved over time. For example, attention should be paid to probing placement and stimulation duration in electrical stimulation, and coil geometry and pulse intervals in magnetic stimulation. It is important to note that these technological developments may lead to differences in the size of NIBS effects on the outcomes. We plan to report a detailed summary of the intervention methods for each study and discuss their impact on outcomes. Furthermore, we should note that the effects of rTMS and tES may differ due to differences in the areas that can be stimulated. Moreover, the price of the equipment and the cost of the application of rTMS and tES may differ. Additionally, while patients can receive tES at home, this is more difficult with rTMS treatment. Therefore, recommendations should consider the effectiveness as well as the accessibility of the devices. Moreover, the anticipated limitations to the study include the scarcity of high-quality trials and an insufficient homogeneity of data to allow quantitative analysis. We should also pay attention to the heterogeneity and diverse baseline severity of the included diseases. These concerns may have to be addressed in future clinical studies, and a future research agenda will be proposed accordingly.

The treatment of DCA aims to reduce symptoms associated with ataxia, including gait disturbance. The use of NIBS for treating these symptoms is still in the research stage and has not yet been implemented in clinical practice. To establish optimal clinical practices, evidence regarding stimulation parameters is critical. These parameters include not only the stimulation site of the brain but also factors such as polarity and intensity in tES, as well as frequency in rTMS. Taken together, we believe

that the results of our systematic review and meta-analysis study will provide valuable insights that will help patients with DCA and healthcare professionals make decisions regarding the selection of NIBS as a treatment approach. If our systematic review and meta-analysis do not provide sufficient insights regarding clinical use, we will propose specific clinical questions regarding research on the impact of these parameters on treatment outcomes.

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Contributors AM, HO, KB, YKo and YKi conceptualised the study. AM and HO designed the protocol. AM and HO defined the search items, data extraction process and statistical analysis. AM drafted the initial manuscript. All authors have appraised the whole methodology, and revised and approved the final manuscript.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

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