

BMJ Open Does non-invasive brain stimulation modify hand dexterity? Protocol for a systematic review and meta-analysis

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ABSTRACT

Introduction Dexterity is described as coordinated hand and finger movement for precision tasks. It is essential for day-to-day activities like computer use, writing or buttoning a shirt. Integrity of brain motor networks is crucial to properly execute these fine hand tasks. When these networks are damaged, interventions to enhance recovery are frequently accompanied by unwanted side effects or limited in their effect. Non-invasive brain stimulation (NIBS) are postulated to target affected motor areas and improve hand motor function with few side effects. However, the results across studies vary, and the current literature does not allow us to draw clear conclusions on the use of NIBS to promote hand function recovery. Therefore, we developed a protocol for a systematic review and meta-analysis on the effects of different NIBS technologies on dexterity in diverse populations. This study will potentially help future evidence-based research and guidelines that use these NIBS technologies for recovering hand dexterity.

Methods and analysis This protocol will compare the effects of active versus sham NIBS on precise hand activity. Records will be obtained by searching relevant databases. Included articles will be randomised clinical trials in adults, testing the therapeutic effects of NIBS on continuous dexterity data. Records will be studied for risk of bias. Narrative and quantitative synthesis will be done.

Ethics and dissemination No private health information is included; the study is not interventional. Ethical approval is not required. The results will be reported in a peer-review journal.

Registration details PROSPERO International prospective register of systematic reviews registration number: CRD42016043809.

INTRODUCTION

The hand's somatotopy is extensively represented in the human motor cortex.^{1,2} Phylogenetically, this relates to the development of corticomotoneuronal cells that specialise in creating patterns of muscle activity that synergises into highly skilled movements.³ This organised hand-and-finger movement to use objects during a specific task is known as dexterity.⁴ Evolutionary, dexterity played a pivotal role in human survival and

Strengths and limitations of this study

- This is a novel systematic review and meta-analysis focusing specifically on dexterity.
- We use continuous data not dependent on the evaluator or participant.
- This work will potentially help future evidence-based research and guidelines to refine non-invasive brain stimulation.

is fundamental to actives of daily living, and hence quality of life.^{5,6}

This precision motor movement relies on integration of information from the cerebral cortex, the spinal cord, several neuromusculoskeletal systems and the external world to coordinate finger force control, finger independence, timing and sequence performance.⁷ During these tasks, multivoxel pattern decoding shows bilateral primary motor cortex activation (M1), which was responsible for muscle recruitment timing and hand movement coordination.^{8,9} This is related to motor cortex connectivity through the corpus callosum, to motor regions of the cerebellum and white matter integrity.^{10–15} Adequate motor output translates into successfully executed tasks, like picking up objects, turning over cards, manipulating cutlery, writing, using computer–hand interfaces like smartphones, playing an instrument and performing many other similarly precise skills.¹⁶

These motor tasks are negatively impacted when motor output networks are affected, as seen in stroke or Parkinson's disease.^{17,18} Therapeutic interventions that restore these damaged motor networks can be vital to restore fine motor movement after injury occurs. Pharmaceutical approaches often lead to adverse effects such as dyskinesias in Parkinson's disease. Moreover, even after intensive rehabilitation programmes, only about 5%–20% of patients with stroke fully

recover their motor function.^{19–21} Non-invasive brain stimulation (NIBS) techniques, like transcranial direct current stimulation (tDCS) and repetitive transcranial magnetic stimulation (rTMS), are proposed adjuvant or stand-alone interventions to target these affected areas and improve fine motor function.^{22–23} Briefly, these NIBS interventions are shown to influence the nervous system's excitability and modulate long-term plasticity, which may be beneficial to the brain's recovery of functions after injury.^{24–27}

Fine hand motor ability is not studied as much in previous reviews of NIBS. Specifically, one narrative review focuses on rTMS in affected hand recovery poststroke; however, it does not consider the implications of varying International Classification of Functioning, Disability and Health (ICF) domains, data types and rater dependent outcomes, and its interpretability is limited without quantitative synthesis.^{28–31} The overarching conclusion was supportive of rTMS for paretic hand recovery, though with limited data to support its regular use, and a pressing need to study individualised patient parameters.²⁸ One meta-analysis had positive and significant results when specifically studying the effects of rTMS on finger coordination and hand function after stroke.³² However, while various meta-analysis, and another systematic review, studied upper-limb movement after NIBS in distinct populations, they did not focus on precise hand function, pooled upper-limb outcomes with hand outcomes and presented mixed results.^{33–38}

Motivated by this gap in the evidence for NIBS in dexterity, we will do a systematic review and meta-analysis of the literature on these brain stimulation technologies using outcomes that focus exactly on manual dexterity. These outcomes will be continuous and not dependent on the participant's or rater's observation (ie, they will be measured in seconds, or number of blocks/pegs placed, and not by an individual's interpretation). They will be comprised of multiple domains as defined by the ICF, providing an appreciation of function rather than only condition or disease.^{29–31} By focusing on the ICF model, we will be able to study dexterity across a larger sample of studies, NIBS techniques and conditions in order to provide a better understanding of brain stimulation efficacy on hand function in various populations.

METHODS

General statement

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P).^{39–40}

Search strategy and eligibility criteria

Using the strategy in [table 1](#) we will obtain records from PubMed, EMBASE, Web of Science, SciELO and OpenGrey. Eligible records will be focused on adult humans, enrolled in randomised clinical trials with primary or secondary outcomes for continuous manual dexterity data (box and block test, nine-hole peg test, Purdue pegboard

test, Jebsen Taylor and functional dexterity test) in which sole or combined NIBS intervention (tDCS/TMS, transcranial alternative current stimulation, transcranial pulsed stimulation and transcranial random noise stimulation) trials are being studied therapeutically. Records will be excluded if they do not match the inclusion criteria and have at least one of the following characteristics: (1) non-randomised clinical trials; (2) observational studies; (3) case series/reports; (4) non-blinded studies (eg, open-label); (5) studies that do not have results for at least one of the continuous manual dexterity instruments being extracted (box and block test, nine-hole peg test, Purdue pegboard test, Jebsen Taylor and functional dexterity test); (6) studies that do not use at least one of the previously brain stimulation interventions therapeutically; and (7) studies not published in English/Spanish/French.

Screening and selection of records

Two independent researchers will screen the records from the publication's title and abstract. A Cochrane recommended web and mobile application, Rayyan, will be used to ensure that the screening process is blinded between the two independent researchers.⁴¹ A third researcher will resolve disagreements among screened records. Three independent researchers will assess the records' eligibility, which will be cross-validated within the group. This will be documented on a modified spreadsheet by The University of Texas Health Center at Houston for studying eligibility.⁴² After which the references of included records will be reviewed, screened and undergo the same inclusion/exclusion process. The results of the search strategy, screening and eligibility will be summarised into a PRISMA Flow Diagram.⁴⁰

Assessment of risk of bias in included studies

Risk of bias will be assessed using the Cochrane Collaboration tool for assessing the risk of bias (table 8.4a of the Cochrane Collaboration Handbook for Systematic Reviews of Interventions).⁴³ The following elements will be reviewed and recorded: (1) random sequence generation; (2) allocation concealment; (3) blinding of participants and personnel; (4) blinding of outcome assessment; (5) incomplete outcome data; and (6) selective reporting. For each record, each item will be judged as low, unclear or high risk as set out in by Green and Higgins.⁴³ Three independent researchers will perform the risk of bias review, with cross-validation within the group. We will use custom checklists generated in Microsoft Office Excel 2007 (V.12.0) to capture data. These data will be incorporated into tables, figures, graphs and descriptive narrative, which will guide evaluation of the records' internal validity.

Data extraction

Data will be extracted into a custom spreadsheet that will incorporate at the following: (1) bibliographic details of primary paper (author, title of study, year and journal); (2) demographics (number of participants, age and gender); (3) clinical information (eg, diagnosis and

Table 1 Search engine and query

Search engine	Search query	Date of search
PubMed	((‘manual’[All Fields] AND dexterity[All Fields]) OR (motor[All Fields] AND ‘movement’[All Fields]) OR (‘hand’[All Fields] AND dexterity[All Fields] OR (motor[All Fields] AND skills[All Fields]))OR ((box[All Fields] AND block[All Fields] AND ‘test’[All Fields]) OR (nine-hole[All Fields] AND peg[All Fields] AND ‘test’[All Fields]) OR (purdue[All Fields] AND pegboard[All Fields] AND ‘test’[All Fields]) OR (functional[All Fields] AND dexterity[All Fields] AND ‘test’[All Fields]) OR (Jebsen[All Fields] AND (‘test’[All Fields])) AND ((‘transcranial direct current stimulation’[MeSH Terms] OR (‘transcranial’[All Fields] AND ‘direct’[All Fields] AND ‘current’[All Fields] AND ‘stimulation’[All Fields]) OR (‘transcranial direct current stimulation’[All Fields] OR ‘tdcs’[All Fields]) OR (TMS[All Fields] OR ‘transcranial’[All Fields] AND ‘magnetic’[All Fields] AND ‘stimulation’) OR (‘transcranial’[All Fields] AND ‘pulsed’[All Fields] AND ‘current’[All Fields] AND ‘stimulation’ OR tPCS [All Fields]) OR (‘transcranial’[All Fields] AND ‘alternating’[All Fields] AND ‘current’[All Fields] AND ‘stimulation’ OR tACS) OR (‘random’ [All Fields] AND ‘noise’) OR Transcranial[All Fields] OR NIBS[All Fields] OR (Non[All Fields] AND invasive[All Fields] AND (‘brain’[All Fields] AND ‘stimulation’[All Fields]) OR ‘brain stimulation’[All Fields])) AND (‘randomized controlled trial’[pt] OR ‘controlled clinical trial’[pt] OR randomized[tiab] OR placebo[tiab] OR randomly[tiab] OR trial[tiab] OR groups[tiab]) AND ‘humans’[MeSH Terms]	1-Aug-16
Embase	(box AND block AND test) OR (nine AND hole AND peg AND test) OR (purdue AND pegboard AND test) OR (functional AND dexterity AND test) OR (Jebsen) AND (test) AND (transcranial AND direct AND current AND stimulation OR tdcs OR tms OR tpcs OR tacs OR (transcranial AND magnetic AND stimulation) OR (transcranial AND pulsed AND stimulation) OR (transcranial AND alternating AND current AND stimulation) OR (random AND noise) OR (transcranial AND magnetic AND stimulation) OR nibs OR (non AND invasive AND brain AND stimulation) OR (brain AND stimulation)) AND (‘randomized controlled trial’/exp OR ‘controlled clinical trial’/exp OR randomized:ab,ti OR placebo:ab,ti OR randomly:ab,ti OR trial:ab,ti OR groups:ab,ti)	1-Aug-16
Web of Science	(manual dexterity or motor movement or motor skills) AND TOPIC: (box block test OR nine hole peg test OR functional pegboard test OR purdue pegboard test OR functional dexterity test OR Jebsen Test) AND TOPIC: (transcranial direct current stimulation OR tdcs OR transcranial magnetic stimulation OR tms OR NIBS or non invasive brain stimulation OR brain stimulation OR tpcs OR tacs OR transcranial pulsed current stimulation OR transcranial alternating current stimulation OR random noise)	1-Aug-16
ScieLo*	(manual dexterity) OR (motor movement) AND (box block test) OR (nine hole peg test) OR (purdue pegboard test) OR (functional dexterity test) OR (Jebsen test) AND (transcranial direct current stimulation) OR (tdcs) OR (transcranial magnetic stimulation) OR (tms) OR (non invasive brain stimulation) OR (NIBS) OR (brain stimulation) OR (tpcs) OR (tacs) OR (transcranial pulsed current stimulation) OR (transcranial alternating current stimulation) OR (random noise) AND (human) AND (Randomized clinical trial) OR (rct)	1-Aug-16

The PubMed and Embase search queries include the ‘Highly Sensitive Search Strategy’ designed by the Cochrane Collaboration, which yield a sensitivity of 98% and precision of 13% for randomised clinical trials.^{43 53} The search strategy for ScieLo was also modified to Spanish accordingly.

diagnostic criteria, medications, therapy, adverse events, comorbidities, inclusion and exclusion criteria for individual studies, type of lesion and extension and time since onset in stroke); (4) trial characteristics (trial design, duration, number of follow-ups, groups and limitations reported by authors); (5) parameters of NIBS will be noted (eg, montage, site of stimulation, current intensity, electrode size, current density, duration of stimulation, polarity, number of pulses, trains, sessions, frequency of pulse, duration of pulse, number of pulses per train, number of trains, number of pulses per session, total number of pulses delivered and %RMT); (6) the primary and secondary outcomes measures; (7) the results of the continuous manual dexterity activity outcomes (box and block test, nine-hole peg test, Purdue pegboard test, Jebsen Taylor hand function test and functional dexterity test); and (8) funding source and conflict of interest.

These data will be organised into tables, figures, graphs and descriptive narrative. All spreadsheets in this review will be piloted in a sample of two records prior to use.

Data synthesis

We anticipate the confines of this approach will parallel former systematic reviews and meta-analysis on upper-limb function; for example, there will be heterogeneous study design, pathophysiological variability like different brain architecture between chronic and acute conditions, parameters for stimulation will vary, alternate trial designs will be present and even outcomes will be recorded through different instruments.^{28 32–38 44–48} For this reason, a random effects assumption will be assumed for measuring the pooled data. That is, we expect the true effect to differ from study to study. In regards to the outcome, even though the selected outcomes objectively

measure improvement in manual dexterity on a continuous scale, we expect the scale will differ from study to study, and it will not be meaningful to combine raw means.⁴⁹ Therefore, we will divide the mean difference of each study by the study's SD to create a comparable index. Prescores and post scores will be used and also compared against real versus sham conditions.

Using Stata V.13 ME (⁵⁰ *Stata Statistical Software: Release 13*), we will combine the records' effect size and present this information graphically via a forest plot, with the estimated effect size, 95% CI and 0.15642d p value.⁵⁰ Heterogeneity will be assessed by means of Q-statistics and I². Metabias will be evaluated with Begg's funnel plots. Sensitivity analysis based on pathology, NIBS technique and risk of bias will be done.

Dealing with missing data

When data are unclear or missing, we will attempt to contact authors for data. However, when not successful, we will use available data from record where possible.

Summary of findings table

We will organise a summary of findings table based on chapter 11 of the Cochrane Handbook for Systematic Reviews of Interventions.⁴³ The main dexterity outcomes studied will be pooled and also looked at individually. The body of evidence will be reviewed with the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system.⁵¹

ETHICS AND DISSEMINATION

No private health information will be included, and the study is not interventional. Therefore, ethical approval is not required. The results will be reported in an international peer-reviewed journal. Furthermore, we will attempt to publish the findings in an open-label peer-reviewed journal.

PROTOCOL AMENDMENTS

Protocol deviations will be noted and explained in the final published product. Also, amendments will be noted in the corresponding PROSPERO registry.⁵²

Correction notice This paper has been amended since it was published Online First. Owing to a scripting error, some of the publisher names in the references were replaced with 'BMJ Publishing Group'. This only affected the full text version, not the PDF. We have since corrected these errors and the correct publishers have been inserted into the references.

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Competing interests The authors state that they have no significant competing financial, professional or personal interests that might have influenced the performance or presentation of the work described in this manuscript.

Patient consent Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement We plan on making data used for analysis openly available after publication. We will attempt to publish data in open access journals and eventually data repositories.

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