BMJ Open

Effects of non-invasive brain stimulation (NIBS) for executive function on subjects with ADHD: a protocol for a systematic review and meta-analysis

Lihong Peng ,[1] Liyan Tian,[1] Tiantian Wang,[2] Qiu Wang,[1] Na Li,[1] Hui Zhou[1]

To cite: Peng L, Tian L, Wang T, *et al*. Effects of non-invasive brain stimulation (NIBS) for executive function on subjects with ADHD: a protocol for a systematic review and meta-analysis. *BMJ Open* 2023;**13**:e069004. doi:10.1136/bmjopen-2022-069004

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2022-069004).

Received 10 October 2022
Accepted 20 February 2023

[1]Department of Rehabilitation Medicine, West China Second University Hospital, Sichuan University, Chengdu, Sichuan, China
[2]Rehabilitation Medical Center, West China Hospital, Sichuan University, Chengdu, Sichuan, China

Correspondence to
Dr Hui Zhou; 1103570489@qq.com and Dr Na Li; 36231411@qq.com

ABSTRACT

Introduction Attention-deficit/hyperactivity disorder (ADHD) is a prevalent neurodevelopmental disorder with a high risk of multiple mental health and social difficulties. Executive function domains are associated with distinct ADHD symptom burdens. Non-invasive brain stimulation (NIBS) mainly includes repetitive transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS), which is a promising technique, but its impact on the executive function of ADHD is uncertain. Therefore, the aim of this systematic review and meta-analysis is to derive solid and updated estimates on the effect of NIBS on executive function in children/adults with ADHD.

Methods and analysis A systematic search will be performed through EMBASE, MEDLINE, PsycINFO and Web of Science databases from inception until 22 August 2022. Handsearching of grey literature and the reference lists of selected articles will also be conducted. Empirical studies assessing the effect of NIBS (TMS or tDCS) on executive function in children or adults with ADHD will be included. Two investigators will independently perform literature identification, data extraction and risk of bias assessment. Relevant data will be pooled by a fixed-effects or random-effects model according to I^2 statistic. Sensitivity analysis will be performed to test the robustness of the pooled estimates. Subgroup analyses will be conducted to investigate the potential heterogeneity. This protocol will generate a systematic review and meta-analysis that comprehensively synthesises the evidence on the NIBS treatment of executive function deficit of ADHD.
Ethics approval is not required as this is a protocol for a systematic review of published literature. The results will be submitted to a peer-reviewed journal or a conference.
PROSPERO registration number CRD42022356476.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This is a protocol for defining a novel systematic review and meta-analysis, which will critically appraise the impact of non-invasive brain stimulation (NIBS) on the executive function of attention-deficit/hyperactivity disorder (ADHD).
⇒ The study deriving from this protocol will not only update the previous meta-analysis of attention and inhibitory control, but also include the analysis of working memory and cognitive flexibility for the first time.
⇒ The study deriving from this protocol will provide reference values for NIBS parameter selection in future evidence-based research, and may suggest which type of ADHD that NIBS should be applied to.
⇒ The lack of a unified executive function evaluation instrument may reduce the comparability between eligible studies, leading to heterogeneity.

INTRODUCTION

Attention-deficit/hyperactivity disorder (ADHD) is a prevalent, highly heritable and impairing condition. ADHD affects many functional areas of personal health, including physical health, academic, social and vocational functions.[1] Medication-based treatment strategies are recommended and widely used. Psychostimulants are the first-line medication for the treatment of ADHD symptoms, which have been confirmed in many clinical trials to reduce the symptoms of ADHD in a short period of time.[1] However, due to the accumulation of medication tolerance, stigma and adverse medication reactions related to ADHD, low adherence is a problem.[1] Moreover, the long-term effect of medication on educational, vocational and social outcomes remains uncertain. The limitations of medication treatment for ADHD highlight the importance of finding new management methods.

Executive function (EF) is an umbrella term for a set of advanced cognitive control functions that enables individuals to achieve goal-oriented outcomes.[2 3] The EF defect may be why adolescents with ADHD often encounter social problems. Tseng and Gau reported youth with ADHD with social problems

performed worse in several tasks of EF compared with youth with ADHD without social problems.[4] The study by Tseng and Gau demonstrated that EF mediated the effect of ADHD on social problems, independent of age, gender, IQ, the severity of ADHD symptoms and comorbid conditions.[4]

In recent decades, transcranial non-invasive brain stimulation (NIBS) has been widely used in basic research and clinical intervention. The most commonly used NIBS techniques are repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS). NIBS alters the cortical excitability and the metabolic activity of neurons in the stimulated area in a way that does not require surgical intervention. Evidence from physiology, pharmacology and behaviour suggests that the regulatory effect of NIBS may be produced through the plasticity mechanism.[5] rTMS and tDCS have been shown to induce long-term potentiation or long-term depression in stimulated brain regions.[6 7]

It was reported that EF depends on the connection between prefrontal cortex (PFC), basal ganglia and thalamus, which means that NIBS on PFC can alter EF.[6 8] tDCS provides low-strength direct current through electrodes connected to the scalp. The most common tDCS dose is 1–2 mA for 20–40 min.[5] It is generally believed that anode stimulation enhances cortical excitability; on the contrary, cathode stimulation inhibits cortical excitability. rTMS uses a short, strong current pulse to transmit to the coil, generating an electric field in the brain through electromagnetic induction. High-frequency rTMS (≥5 Hz) increased cortical excitability, while low-frequency rTMS (≤1 Hz) decreased it.[5]

A meta-analysis by Salehinejad *et al* summarised the effects of tDCS on inhibitory control and working memory in individuals with ADHD.[9] The results showed that the dorsolateral PFC (dlPFC) anode tDCS significantly improved inhibitory control, while tDCS had no significant effect on the accuracy of working memory tasks.[9] Brauer *et al* summarised the effect of tDCS in ADHD on attention, inhibition, working memory and interference control in a meta-analysis, and none of these indicators has a significant effect.[10] A meta-analysis published by Westwood *et al* in 2021 summarised the effects of NIBS on attention, inhibition and processing speed of individuals with ADHD, but they did not analyse working memory and cognitive flexibility.[11] The results showed that anode tDCS on left or bilateral dlPFC improved the inhibition and processing speed, but did not cause changes in attention.[11] According to the most common theoretical model of EF (the unity and diversity model), the three most common subcomponents of EF are inhibitory control, working memory and shifting (or cognitive flexibility).[2 3] Therefore, the above review included only some of the common subcomponents of EF. As the scope of EFs can be further expanded, and new trials have emerged in recent years, we considered it necessary to update the meta-analysis. The purpose of this study was to analyse the effects of NIBS on working memory, attention, inhibitory control and cognitive flexibility of subjects with ADHD. If there are enough trials, we will further analyse the impact of different ADHD subtypes, stimulation sites and stimulation parameters on the results.

METHODS

Patient and public involvement

No patient involved.

Design and registration

This protocol has been registered in PROSPERO (International Prospective Register of Systematic Reviews, registration no. CRD42022356476). This protocol followed the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols[12] and the Cochrane Handbook for Systematic Reviews of Interventions. The studies to be included in the systematic review will be evaluated according to the criteria established in this protocol.

Criteria for including studies in this review

Types of studies

Empirical papers containing statistical analysis of any type of design published until 22 August 2022 will be accepted, including cross-sectional, cohort, case–control studies, self-controlled before-and-after studies and clinical controlled trials.

Types of participants

Children or adults clinically diagnosed as ADHD (meeting the Diagnostic and Statistical Manual of Mental Disorders (DSM)/the International Statistical Classification of Diseases and Related Health Problems (ICD) diagnostic criteria or meeting the cut-off criteria of the validated ADHD rating scale or research diagnostic questionnaire).

Types of interventions

Subjects received TMS or tDCS intervention in cerebral cortex.

Types of control group

No NIBS or sham stimulation.

Types of outcome measures

Neuropsychological performance measures of EF (working memory, attention, inhibitory control and cognitive flexibility). Examples of possible working memory tests that will be analysed are digit span task, N-back task, Mindstreams Memory task and Corsi block-tapping test.[13] Examples of possible attention and inhibitory control tests that will be analysed are continuous performance test (CPT), go/no-go task, stop-signal task, Stroop task and flanker task.[14 15] For cognitive flexibility, the Wisconsin Card Sorting Test (WCST) or other relevant tests can be included.[16]

Language

The search will be restricted to only studies published in English.

Exclusion criteria

1. Reviews, monographs, letters, guidelines, surveys, comments, editorials, case reports and conference papers.
2. Animal studies or in vitro studies.

Data sources and search strategy

A systematic and comprehensive search will be performed through the EMBASE, MEDLINE, PsycINFO and Web of Science databases from inception until 22 August 2022. The search strategy for EMBASE (via OVID) is presented in online supplemental appendix 1. Open grey website (http://www.opengrey.eu/) will also be searched for grey literature. In addition to electronic search, we will manually search the reference lists of all selected articles to identify potential supplemental data.

Data collection and analysis

Study selection

We will apply EndNote V.X9 software to management literature. According to whether the title and abstract meet the inclusion criteria, two reviewers will independently conduct preliminary screening on relevant studies. The remaining articles will be evaluated by full-text reading to further exclude articles that do not meet the criteria. In case of substantial disagreement between the two reviewers, it will be resolved by discussion and solicited for arbitration by a third reviewer.

The study selection process follows the Preferred Reporting Items for Systematic reviews and Meta-Analysis guidance. Figure 1 shows the study flow chart from systematic search to selection process.

Data extraction

For working memory measures, we will extract backward order or forward order span in memory span task, accuracy in N-back task or scores in some other memory tasks. For attention measures, we will extract percentage (or number) of omission errors in CPT or visual attention test, percentage of omission go (or accuracy go) in go/no-go task, percentage of omission (or accuracy) of congruent trials in flanker or Stroop task, or some similar conversion scores. For inhibitory control, we will extract percentage (or number) of commission errors in CPT or visual attention test, percentage of commission no-go (or accuracy no-go) in go/no-go task, percentage of commission (or accuracy) of incongruent trials in flanker, Stroop or Simon task, stop-signal reaction time in stop-signal task or some similar conversion scores. For cognitive flexibility, percentage (or number) of perseverative errors in WCST will be extracted.

Data will be extracted by two reviewers independently. A data form will be used to extract the following data: general article information (first author, year of publication), study design, demographics, stimulation details including stimulation type, area, locating method, frequency, intensity, duration, sessions, and timing (online or offline) and outcome measures. If the relevant

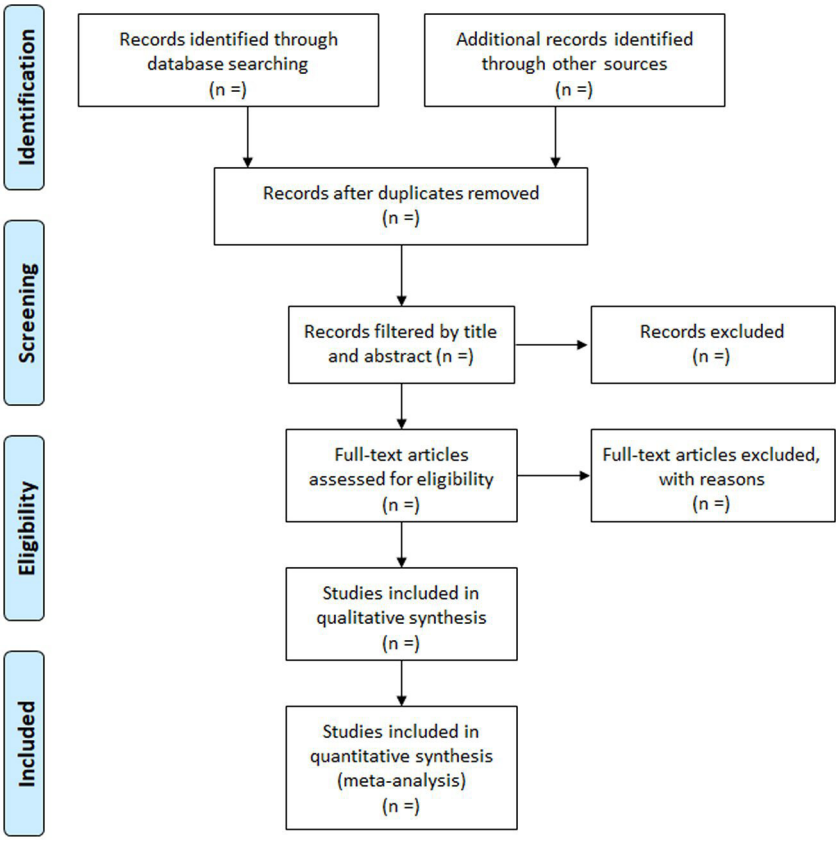

Figure 1 Flow chart of identification, screening, eligibility and inclusion of studies.

data are missing, the study authors will be contacted to obtain the missing data. If the data are not provided in the text but the information is displayed in the figure, the WebPlotDigitizer software[17] will be applied to calculate the data. Extracted data will be entered into a table and checked by another investigator.

Assessment of risk of bias

We will use the Cochrane Collaboration's risk of bias tool[18] to assess risk of bias, which rates risk of bias in five areas: selection bias, performance bias, detection bias, attrition bias and other biases. Two investigators will independently assess risk of bias and resolve any disagreements by a consensus.

If there are more than 10 eligible studies, the publication bias analysis will be conducted by funnel plot and Egger's test.

Data synthesis and statistical analysis

Comparison of dichotomous data between two groups will be expressed as risk ratio, and continuous outcomes will be expressed as standardised mean difference with 95% CIs. If some scales increase with disease severity while others decrease, then a series of studies need to be multiplied by −1 (or the mean can be subtracted from the maximum possible value of the scales) to ensure that all the scale points are in the same direction.[19] Heterogeneity among studies will be assessed with Cochrane's Q-statistic and I^2 statistic. After excluding apparent clinical heterogeneity, we will conduct meta-analyses by RevMan V.5.3 software using random-effects model if I^2 was above 50% or using fixed-effects model if I^2 was below 50%. If quantitative synthesis is not appropriate, we will conduct a descriptive analysis and report the characteristics of included studies.

Sensitivity analysis and subgroup analysis

Sensitivity analysis will be used to test the robustness of the pooled estimates by removing one trial at a time.

If the data are sufficient and available, subgroup analyses will be conducted based on stimulation type (tDCS or TMS), stimulation area, stimulation timing and subtypes of ADHD.

Grading of Recommendations, Assessment, Development and Evaluation profile evidence

The Grading of Recommendations, Assessment, Development and Evaluation approach will be used to assess the overall quality of the evidence for the outcomes. Five domains will be considered for downgrading the quality of evidence: risk of bias, inconsistency, indirectness, imprecision and publication bias.

DISCUSSION

There is still controversy about the effectiveness of NIBS on several components of executive function in individuals with ADHD. The intended review will provide an up-to-date summary of the effect of NIBS on individuals with ADHD. We will conduct a comprehensive literature search of eligible studies and use robust meta-analysis tools to estimate the role of NIBS reliably. If the data are sufficient and the intervention is effective, we will explore the most effective stimulation parameters to guide the clinical application of NIBS in individuals with ADHD. It was reported that after eliminating the influence of stimulus parameters, there is still large intersubject variability in the effect of NIBS.[20–22] One possible explanation is that it is challenging to target stimuli appropriately and reliably, and many studies have not yet applied modern MRI-guided neuronavigation systems to ensure accurate localisation.[23] The second possible explanation is that an individual's unique neurophysiology and anatomy (skull thickness, subcutaneous fat levels, cerebrospinal fluid density and cortical surface topography) may affect their reaction to NIBS.[23] Therefore, in this systematic review, we will also focus on whether the included research applies the neuronavigation system. At the same time, we also hope to have enough sample size to reduce the impact of individual differences on the results. Moreover, this systematic review and meta-analysis will provide evidence to trigger future research protocols.

Contributors HZ and NL originally conceived the study. LT, TW and QW conducted a preliminary search to formulate retrieval strategies. LP, NL and HZ designed the protocol. LP wrote the first draft of the protocol, which was reviewed and edited by NL and HZ. The final protocol has been approved by all authors.

Funding This work was supported by the National Natural Science Foundation (grant number 82102656).

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

ORCID iD

Lihong Peng http://orcid.org/0000-0002-3905-7085

REFERENCES

1 Posner J, Polanczyk GV, Sonuga-Barke E. Attention-deficit hyperactivity disorder. *Lancet* 2020;395:450–62.
2 Miyake A, Friedman NP, Emerson MJ, *et al*. The unity and diversity of executive functions and their contributions to complex " frontal lobe " tasks: a latent variable analysis. *Cogn Psychol* 2000;41:49–100.
3 Miyake A, Friedman NP. The nature and organization of individual differences in executive functions: four general conclusions. *Curr Dir Psychol Sci* 2012;21:8–14.

4 Tseng W-L, Gau SS-F. Executive function as a mediator in the link between attention-deficit/hyperactivity disorder and social problems. *J Child Psychol Psychiatry* 2013;54:996–1004.
5 He W, Fong P-Y, Leung TWH, *et al*. Protocols of non-invasive brain stimulation for neuroplasticity induction. *Neurosci Lett* 2020;719:S0304-3940(18)30127-7.
6 de Boer NS, Schluter RS, Daams JG, *et al*. The effect of non-invasive brain stimulation on executive functioning in healthy controls: a systematic review and meta-analysis. *Neurosci Biobehav Rev* 2021;125:122–47.
7 Huang Y-Z, Lu M-K, Antal A, *et al*. Plasticity induced by non-invasive transcranial brain stimulation: a position paper. *Clin Neurophysiol* 2017;128:2318–29.
8 Wei W, Wang XJ. Inhibitory control in the cortico-basal ganglia-thalamocortical loop: complex regulation and interplay with memory and decision processes. *Neuron* 2016;92:1093–105.
9 Salehinejad MA, Wischnewski M, Nejati V, *et al*. Transcranial direct current stimulation in attention-deficit hyperactivity disorder: a meta-analysis of neuropsychological deficits. *PLoS One* 2019;14:e0215095.
10 Brauer H, Breitling-Ziegler C, Moliadze V, *et al*. Transcranial direct current stimulation in attention-deficit/hyperactivity disorder: a meta-analysis of clinical efficacy outcomes. *Prog Brain Res* 2021;264:91–116.
11 Westwood SJ, Radua J, Rubia K. Noninvasive brain stimulation in children and adults with attention-deficit/hyperactivity disorder: a systematic review and meta-analysis. *J Psychiatry Neurosci* 2021;46:E14–33.
12 Shamseer L, Moher D, Clarke M, *et al*. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. *BMJ* 2015;350:g7647.
13 Gillett R. Assessment of working memory performance in self-ordered selection tests. *Cortex* 2007;43:1047–56.
14 Fuermaier ABM, Fricke JA, de Vries SM, *et al*. Neuropsychological assessment of adults with ADHD: a Delphi consensus study. *Appl Neuropsychol Adult* 2019;26:340–54.
15 Epstein JN, Johnson DE, Varia IM, *et al*. Neuropsychological assessment of response inhibition in adults with ADHD. *J Clin Exp Neuropsychol* 2001;23:362–71.
16 Miles S, Howlett CA, Berryman C, *et al*. Considerations for using the Wisconsin card sorting test to assess cognitive flexibility. *Behav Res Methods* 2021;53:2083–91.
17 Rohatgi A. WebPlotDigitizer user manual version 3.9. 2015.
18 Higgins JPT, Altman DG, Gøtzsche PC, *et al*. The Cochrane collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011;343:d5928.
19 Higgins J, Thomas J, eds. *Cochrane handbook for systematic reviews of interventions version 6.3*. 2022.
20 Fricke K, Seeber AA, Thirugnanasambandam N, *et al*. Time course of the induction of homeostatic plasticity generated by repeated transcranial direct current stimulation of the human motor cortex. *J Neurophysiol* 2011;105:1141–9.
21 Nitsche MA, Grundey J, Liebetanz D, *et al*. Catecholaminergic consolidation of motor cortical neuroplasticity in humans. *Cereb Cortex* 2004;14:1240–5.
22 Nitsche MA, Liebetanz D, Schlitterlau A, *et al*. Gabaergic modulation of DC stimulation-induced motor cortex excitability shifts in humans. *Eur J Neurosci* 2004;19:2720–6.
23 Horvath JC, Carter O, Forte JD. Transcranial direct current stimulation: five important issues we aren't discussing (but probably should be). *Front Syst Neurosci* 2014;8:2.