Effects of Non-Invasive Neurostimulation on Autism Spectrum Disorder: A Protocol for a Systematic Review

Jiawei Zhang
Capital Medical University
Hao Zhang (crrczh2020@163.com)
China Architectural Culture Center https://orcid.org/0000-0001-8546-3757

Protocol

Keywords: Systematic review, meta-analysis, Noninvasive neurostimulation, autism spectrum disorder, Transcranial direct current stimulation, Transcranial magnetic stimulation.

Posted Date: December 20th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-1103851/v1

Abstract

Background

Autism Spectrum Disorder (ASD) is a neurodevelopmental disorder marked by characteristic impairments in social communication and interaction, as well as restricted and repetitive behavior. There is a continued need for exploring effective interventions and evaluating treatment options for ASD. Transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS) are non-invasive neurostimulation techniques which have shown clinical benefits in adult psychiatric conditions. While in ASD patients, no guideline has so-far recommended on the application of NIBS due to a lack of high-quality synthetic evidence. Therefore, objective of this study will be to systematically evaluate the evidence on clinical effects of non-invasive neurostimulation in patients with ASD.

Methods

We designed and registered a study protocol for a systematic review. A comprehensive search from database inception onwards will be conducted in PubMed, EMBASE and Cochrane library. Randomized and non-randomized sham-controlled studies assessing the effects of noninvasive neurostimulation in patients with ASD will be identified. Eligibility of citations retrieved will be independently screened by two reviewers. The risk of bias and quality of included studies will be appraised using appropriate tools. A narrative synthesis around the features of the evidences will provided. There may be a chance for meta-analysis to pool the estimates of studies included if three studies or more meet the requirements for meta-analysis. If so, a random-effects model maybe applied. And we will evaluate heterogeneity between studies using the I^2 statistic.

Discussion

This systematic review will provide a broad and comprehensive evaluation of the evidence on clinical effects of TMS and tDCS in patients with ASD. Our findings will be reported according to the PRISMA guidelines and may add more confidence when healthcare professionals are making informed decisions about the choice of this therapy. Results will be published in a peer-reviewed journal.

Systematic review registration:

Submitted to PROSPERO, 20/11/2021

Background

Autism Spectrum Disorder (ASD) is a neurodevelopmental disorder marked by characteristic impairments in social communication and interaction, as well as restricted and repetitive behavior. The overall

prevalence of ASD in Europe, Asia, and the United States has grown dramatically and was estimated to range from 2 to 25 per 1000 (1). Regarding the economic burden of this condition, it requires as high as $2.4 million in the United States and £1.5 million in the United Kingdom to support an individual with an ASD and intellectual disability during his or her lifespan. While for an individual with an ASD without intellectual disability, the cost of was still high, estimated to be $1.4 million in the United States and £0.92 million (US $1.4 million) in the United Kingdom (2). To date psychotherapy is the treatment of choice while only small to medium effects of improvement has been achieved. Therefore, there is a continued need for exploring effective interventions and evaluating treatment options for ASD.

In the past decade, noninvasive neurostimulation methods, including transcranial direct current stimulation (tDCS) and transcranial magnetic stimulation (TMS), have been proposed as potential therapeutic options for modification of the pathological neuroplasticity (or even plasticity induction) involved in neuropsychiatric disorders including ASD (3, 4). Application of noninvasive neurostimulation on child and adult populations has proved to be well tolerated and shows a favorable therapeutic profile. Thus, recommendations of this approach in dealing with neuropsychiatric disorders such as unipolar major depression was provided by several clinical guidelines, corresponding to a Level A of evidence (5). While in ASD patients, no guideline has so-far recommended on the application of NIBS due to a lack of high-quality synthetic evidence.

A systemic review by Ali Khaleghi et al has narratively synthesized published articles before April 2018 (6). It demonstrated that NIBS methods could be helpful for treating some dimensions of ASD such as repetitive behavior, sociability or some aspects of executive and cognitive functions. However, a majority of studies included showed a moderate to low quality and bias could easily be identified. Therefore, conclusion has been drawn to emphasize on further review and analysis on randomized, sham-controlled trials. Recently, trials investigating the effectiveness of NIBS on ASD patients are continuously rising. Christina Luckhardt et al. systematically searched for randomized, sham-controlled clinical trials of tDCS before may 2020 in individuals with ASD (7). Six eligible studies were identified and results indicated initial support for improved cognitive and social communication skills in ASD following tDCS stimulation. Nonetheless, the effects of TMS were not evaluated in their review. Therefore, a comprehensive review and evaluation of the up-to-date high-quality evidence in exploring effectiveness of NIBS including both tDCS and TMS in managing ASD patients, is till warranted.

Objectives

This study will systematically review available data on past, ongoing and upcoming studies using TMS or tDCS as a therapeutic intervention in patients with ASD diagnosed by a solid method. This review will cover the following aspects:

1. Evaluating the effects of TMS and tDCS on core symptoms in patients with ASD.
2. Evaluating the effects of TMS and tDCS on neurocognition or psychiatric comorbidities other than core deficits.

3. Summarizing stimulation parameters that have been used in current TMS and tDCS administration and explaining how have these parameters affected results?
4. Assessing the risk of bias and quality of the current evidence regarding this issue.

Methods

The present protocol is being reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) statement (8). This protocol has been submitted within the International Prospective Register of Systematic Reviews (PROSPERO) database (date: 20/11/2021). Any amendments made to this protocol when conducting the study will be outlined in PROSPERO and reported in the final manuscript. When this systematic review and meta-analysis being completed, it will be reported in accordance with the reporting guidance provided in the PRISMA statement (9). Since there is no human or animal experiment, the study will not require an ethical approval.

Eligibility criteria

Studies will be included according to the following criteria: participants, interventions and comparators, outcome(s) of interest and study design.

Participants

Patients diagnosed with autism spectrum disorder based on a valid method will be included. The Diagnostic and Statistical Manual of Mental Disorders (DSM) is used predominantly in the United States (US) and has been updated to the fifth version (DSM-5) (10). The World Health Organization International Classification of Diseases, 10th revision (ICD-10) is used in other countries other than the US (11). Other diagnostic tools include the Autism Diagnostic Interview-Revised (ADI-R) (12), the Autism Diagnostic Observation Schedule (ADOS) (13), etc.

Interventions

Noninvasive neurostimulations including both transcranial direct current stimulation and transcranial magnetic stimulation will be included. Variation of tDCS like transcranial alternating current stimulation (tACS) will also be included. As for TMS studies, we will include low-frequency rTMS (LF-rTMS), high-frequency rTMS (HF-rTMS), intermittent theta burst stimulation (iTBS), continuous theta burst stimulation (cTBS), paired associative stimulation (PAS), as well.

Comparators

Sham stimulation. For tDCS, to make sure the participant was blinded to the procedure, the power indicator which was visible to the participants was lit up for both active and sham stimulation. However, in the sham stimulation condition, the current was discontinued normally after 30 seconds (14). For TMS, the sham stimulation was delivered with the coil tilted one-wing 90° off the head, which is a valid sham condition commonly used in double- or single-blind, sham-controlled trials (15).

Outcomes of interest

Based on our preliminary searches, a variety of effect measurements have been used to evaluate the outcomes of noninvasive neurostimulation. These outcomes will be measured pre-and post-intervention. We will categorize these measurements into two major kinds, as test/scale/tasks and objective outcome measurements.

1. Test/scale/tasks includes but not limits to the Wisconsin Card Sorting Test (WCST), the Autism Spectrum Quotient (AQ), the Probabilistic Reversal Learning Task (PRLT), the Behaviour Rating Inventory of Executive Functioning (BRIEF; shift subscale), the Repetitive Behaviour Questionnaire 2A (RBQ-2A; total score), the Wechsler Memory Scale, 3rd Edition (WMS-III), the Brief Test of Attention (BTA), the Boston Naming Test (BNT), the Raven's Progressive Matrices (Raven, 2000), the the Movement Assessment Battery for Children-2 (MABC-2), the theory of mind test (TOMT), the featuring self-report clinical scales with good psychometric properties (RAADS), the Interpersonal Reactivity Index (IRI), the Childhood Autism Rating Scale (CARS), the Autism Treatment Evaluation Checklist (ATEC), the Clinical Global Impression-Improvement (CGI-I), the Aberrant Behavior Checklist (ABC), the Social Responsiveness Scale (SRS), the Repetitive Behavior Scale—Revised (RBS), the Eye-tracking apparatus, the Conner's Continuous Performance Test (CCPT), the Yale-Brown Obsessive Compulsive Scale (Y-BOCS), the Frith–Happe animations task, the Reading the Mind in the Eyes test (RMET), the Global Clinical Impression Scale (GCIS), the Autism Diagnostic Interview, Revisited Edition (ADI-R), the 3-back task, Empathy Quotient (EQ), the facial emotion recognition and processing (FERP) test, the verbal fluency (VF) test, the Test of Adolescent Social Skills-Modified (TASSK-M), Children's Sleep Habits Questionnaire (CSHQ), the Cambridge Neuropsychological Test Automated Battery (CANTAB), the Mini International Neuropsychiatric Interview (MINI), etc.
2. Objective outcome measurements includes the metabolites levels, the functional magnetic resonance imaging (fMRI), and Electroencephalogram (EEG).

Study design

We will consider randomized controlled trials, nonrandomized control trials, open-label trials, crossover trials. Cohort, case-control, case series, and case reports will also be searched for but not be included in the final paper. Only studies published in English will be included. No limitations will be imposed on publication status (unpublished studies will be eligible for inclusion) or study conduct period.

Information sources and search strategy

PubMed, Embase (1996 to 2021 Week 43), and Cochrane library databases will be retrieved according to the search strategy. No limitations regarding the study design, publication time, and age or sex of participants will be set when searching for the records. A draft search strategy is present in supplementary table 1.

Study selection

Studies will be selected based on the following *inclusion criteria*: (1) Sham-controlled designed studies comparing the effects of any noninvasive neurostimulations with that of a sham stimulation group; (2) Studies enrolling patients with solid diagnosis of autism spectrum disorder; (3) Studies providing outcomes measuring the therapeutic or side effects. *Exclusion criteria* will be: (1) Studies reported in language other than English; (2) Studies published in the form of editorial, comments, or conference abstract, which details of PICOS were not reported; (3) Studies comparing the responses of patients with ASD to noninvasive neurostimulations with that of other human subjects.

Records from database searches will be exported into EndNote and duplicates removed. Two reviewers will independently screen titles and abstracts for potentially eligible studies. The reviewers will then independently screen the full text of potentially eligible studies. Reasons for exclusions will be reported. At each stage of the review process, disagreements will be resolved by discussion or, if not achieve consensus, consulting a third review author acted as an arbitrator. The reviewers were not blinded to names of authors, institutions, outcomes, or journals.

Data extraction

Two authors will extract data independently from the included articles, using a pre-developed form adapted from the Cochrane data collection form for intervention reviews and extracted data form published by Ulrike Schmidt et al. (16, 17):

General information

First author of study, published date, published journal, DOI, author's contact information (if available).

Study details

Study design; country; setting; sample size; inclusion and exclusion criteria; comparability of groups; study period; stratification; stopping rules; funding source; conflict of interest.

'Risk of bias' assessment and justification for this judgement: sequence generation; allocation concealment; blinding (participants, personnel, outcome assessors); incomplete outcome data; selective outcome reporting; and other bias (recall bias). Characteristics of participants: age; gender; ethnicity; the number randomized, analyzed and lost to follow-up; and dropouts in each arm (with reasons).

Interventions: experimental and control interventions; details of noninvasive stimulation procedures (for current stimulation: anode site, cathode site, Current, Electrode size; for magnetic stimulation: coil placement, frequency, motor threshold, pulses); timing of intervention; uptake of intervention (acceptance of stimulation), whether studies assessed adherence (compliance) with interventions.

Outcomes measured

Tests, scales, tasks, EEG, metabolites measurement.

Risk of bias in individual studies

We will use the revised Cochrane risk-of-bias 2 (RoB-2) tool to assess the quality of each trial (18). Two reviewers will independently score each trial, each quality item will be graded as low risk, high risk, or unclear risk. We will resolve any discrepancies by consulting a third review author. We will assess the risk of bias for the 7 domains: randomization sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective reporting, and other bias. The included trials will be graded as low quality, moderate quality or, high quality based on the evaluation. To evaluate the possibility of publication bias, we will use funnel plots for analyses that contained more than 10 studies.

Data synthesis

We will perform a narrative synthesis around the features of existing evidences investigating the effects of noninvasive neurostimulation on ASD patients. All eligible trials will be summarized in narrative form. Tables will be constructed based on the information extracted (Table 1). These tables will include key study characteristics such as study design, population, diagnosis tool, randomization methods, intervention parameters, sham stimulation methods, outcomes, etc.

Table 1 Data extraction form

General
Paper title
Date form completed
Reference citation
Publication type
Reviewer signature
Notes
Study details
Aims
Study dates
Study design (randomized, non-randomized, crossover)
Blinding (Single, double, triple)
Allocation concealment
Comparison (Sham control, waiting list)
Primary outcome measures
Secondary outcome measure
Assessment time point
Missing data
Limitations
Participants
Number started
Number completed
A priori power calculation
Age (Mean, SD) and range
Gender
Ethnicity
Inclusion Criteria
Exclusion Criteria
ASD diagnosis tools

Treatment setting
Severity of illness
Group sub-division
Intervention – general
Was neurostimulation given as an add-on treatment? Details of basic treatment
Was neurostimulation coupled with cognitive or other tasks?
Intervention – TMS
Type of TMS used (high-frequency, low-frequency, deep TMS, cTBS, iTBS)
Number and frequency of sessions
Site of stimulation
TMS frequency (Hz)
Coil type
% of resting motor threshold
Number of trains
Train duration
Inter-train interval
Neuro-navigation use? Yes/No
Compliance with TMS regimen (number of sessions missed for exclusion)
Intervention – tDCS
tDCS machine used
Number and frequency of sessions
Site of stimulation
Current
Duration of current
Compliance with rTMS regimen (number of sessions missed for exclusion)
Outcomes
Main clinical outcomes
Secondary outcomes
Adverse outcomes

Main conclusion
Outcome measurement tools

There may be a chance for meta-analysis to pool the estimates of studies included if three studies or more meet the requirements for meta-analysis. If so, a random-effects model maybe applied. And we will evaluate heterogeneity between studies using the I^2 statistic. We planned not to pool data where there was considerable heterogeneity ($I^2 \geq 75\%$) that could not be explained by the diversity of methodological or clinical features among studies.

Subgroup analyses

If there are sufficient data provided by the qualified studies, we will do meta-analyses stratified by: age; sex; stimulation site, randomization procedures, stimulation intensity, montage, duration, number of stimulation session. We will use the test for subgroup differences available in RevMan 5 to determine whether there was evidence for a difference in treatment effect between subgroups.

Sensitivity analyses

Potential reasons for heterogeneity will be explored in sensitivity analyses; the pre-specified subgroup analyses, if feasible, will be examined to determine potential reasons for any observed statistical heterogeneity.

Strength of evidence

The overall quality of evidence for all outcomes will be evaluated using the Grading, Recommendations, Assessment, Development and Evaluation (GRADE) framework, estimating individual risk of bias, meta-bias, precision, consistency, directedness and the magnitude of effect (19). These indicators will determine the certainty of the estimated effect, which will be rated as either very low, low, high or very high.

Discussion

In this review, we aim to synthesize the current evidence addressing the effects of noninvasive neurostimulation on patients with ASD. To minimize bias, our review will only include eligible studies with sham-controlled design. In addition, the quality of the included studies will also be assessed based on their randomization sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias. After these pre-defined procedures, data extracted from all the included studies will then be synthesized. Therefore, it will provide information about what the effects of NIBS on core symptoms, neurocognition, and psychiatric comorbidities in patients with ASD. In addition, stimulation parameters that have been used in current TMS and tDCS administration and how have these parameters affected results will also be summarized. The findings may have valuable implications for multiple stakeholders including

patients, health care professionals, health system decision-makers and researchers working in noninvasive neurostimulation. There is a dilemma that researchers have found noninvasive neurostimulation as a promising approach for ASD while no guideline has so-far recommended on the application of noninvasive neurostimulation due to a lack of high-quality synthetic evidence. The use of our expected findings may add more confidence when healthcare professionals are making informed decisions about the choice of this therapy. Questions may also be raised in our review for a further investigation in related to using NIBS in patients with ASD. At last, anticipated limitations include the paucity of high-quality trials and high heterogeneity of data hampering quantitative analyses.

Declarations

Ethical approval and consent to participate: There is no human or animal experiment, thus the study will not require an ethical approval or a consent to participate.

Consent for publication: This manuscript does not contain any individual person dataand all authors agree on the publication of the manuscript.

Availability of supporting data: Not applicable.

Competing interests' statement: The authors declare no competing interests.

Funding: Not applicable.

Authors' contributions: All authors listed meet the authorship criteria according to the latest guidelines of the International Committee of Medical Journal Editors. ZH and ZJ both designed and completed the study. ZJ drafted the manuscript and ZH revised it.

Acknowledgements: None.

Authors' information: [1] School of Rehabilitation, Capital Medical University, Beijing Bo'ai Hospital, China Rehabilitation Research Center, Beijing, China.

[2] Department of Neurorehabilitation, Beijing Bo'ai Hospital, China Rehabilitation Research Center, School of Rehabilitation, Capital Medical University, Beijing, China Cheeloo College of Medicine, Shandong University, Jinan, Shandong, China University of Health and Rehabilitation Sciences, Qingdao, Shandong, China.

References

1. Kogan MD, Vladutiu CJ, Schieve LA, Ghandour RM, Blumberg SJ, Zablotsky B, et al. The Prevalence of Parent-Reported Autism Spectrum Disorder Among US Children. Pediatrics. 2018,142(6).
2. Buescher AV, Cidav Z, Knapp M, Mandell DS. Costs of autism spectrum disorders in the United Kingdom and the United States. JAMA Pediatr. 2014,168(8):721-8.

3. Demirtas-Tatlidede A, Vahabzadeh-Hagh AM, Pascual-Leone A. Can noninvasive brain stimulation enhance cognition in neuropsychiatric disorders? Neuropharmacology. 2013,64:566-78.
4. Lefaucheur JP, Aleman A, Baeken C, Benninger DH, Brunelin J, Di Lazzaro V, et al. Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS): An update (2014-2018). Clinical Neurophysiology. 2020,131(2):474-528.
5. Bauer M, Severus E, Köhler S, Whybrow PC, Angst J, Möller HJ. World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for biological treatment of unipolar depressive disorders. part 2: maintenance treatment of major depressive disorder-update 2015. World J Biol Psychiatry. 2015,16(2):76-95.
6. Khaleghi A, Zarafshan H, Vand SR, Mohammadi MR. Effects of Non-invasive Neurostimulation on Autism Spectrum Disorder: A Systematic Review. Clinical Psychopharmacology and Neuroscience. 2020,18(4):527-52.
7. Luckhardt C, Boxhoorn S, Schutz M, Fann N, Freitag CM. Brain stimulation by tDCS as treatment option in Autism Spectrum Disorder-A systematic literature review. Progress in Brain Research. 2021,264:233-57.
8. Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Syst Rev. 2015,4(1):1.
9. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. J Clin Epidemiol. 2009,62(10):1006-12.
10. Sharma N, Mishra R, Mishra D. The fifth edition of Diagnostic and Statistical Manual of Mental Disorders (DSM-5): what is new for the pediatrician? Indian pediatrics. 2015,52(2):141-3.
11. Organization WH. The ICD-10 classification of mental and behavioural disorders: clinical descriptions and diagnostic guidelines: World Health Organization, 1992.
12. Rutter M, Le Couteur A, Lord C. Autism diagnostic interview-revised. Los Angeles, CA: Western Psychological Services. 2003,29(2003):30.
13. Pruette JR. Autism diagnostic observation schedule-2 (ADOS-2). Google Scholar. 2013.
14. Qiu J, Kong X, Li J, Yang J, Huang Y, Huang M, et al. Transcranial Direct Current Stimulation (tDCS) over the Left Dorsal Lateral Prefrontal Cortex in Children with Autism Spectrum Disorder (ASD). Neural Plasticity. 2021,2021 (no pagination).
15. Enticott PG, Fitzgibbon BM, Kennedy HA, Arnold SL, Elliot D, Peachey A, et al. A double-blind, randomized trial of deep Repetitive Transcranial Magnetic Stimulation (rTMS) for autism spectrum disorder. Brain Stimulation. 2014,7(2):206-11.
16. Lewis YD, Gallop L, Campbell IC, Schmidt U. Effects of non-invasive brain stimulation in children and young people with psychiatric disorders: a protocol for a systematic review. Syst Rev. 2021,10(1):76.
17. Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al. Cochrane handbook for systematic reviews of interventions: John Wiley & Sons, 2019.

18. Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. Bmj. 2019,366:l4898.
19. Guyatt G, Oxman AD, Akl EA, Kunz R, Vist G, Brozek J, et al. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. J Clin Epidemiol. 2011,64(4):383-94.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- PRISMAPchecklist.doc
- SupplementaryTable1.docx