Non-invasive Brain Stimulation for Autism Spectrum Disorder: A Systematic Review and Network Meta-Analysis Postprint

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Abstract

Background Previous studies have demonstrated inconsistent efficacy of non-invasive brain stimulation (NIBS) in improving autism spectrum disorder (ASD), with a paucity of comparative efficacy analyses among different NIBS modalities.

Objective To systematically evaluate the rehabilitative efficacy of NIBS for ASD and compare the differential efficacy between two distinct NIBS modalities.

Methods Randomized controlled trials investigating NIBS for ASD improvement were retrieved from domestic and international databases, with search periods extending from database inception to December 2021. Following risk-of-bias assessment of included studies, statistical analyses were conducted using RevMan 5.3 and R 4.0.2 software.

Results Twenty-two studies comprising 661 patients were ultimately included. Meta-analysis revealed that NIBS significantly reduced Autism Behavior Checklist (ABC) scores (MD=-8.80, 95%CI -10.98~-6.62, P<0.05), Childhood Autism Rating Scale (CARS) scores (MD=-2.93, 95%CI -3.63~-2.24, P<0.05), Autism Treatment Evaluation Checklist (ATEC) scores (MD=-9.13, 95%CI -12.79~-5.47, P<0.05), Self-Rating Anxiety Scale (SAS) scores (MD=-7.20, 95%CI -10.55~-3.85, P<0.05), Self-Rating Depression Scale (SDS) scores (MD=-8.89, 95%CI -13.21~-4.57, P<0.05), and mismatch negativity latency (MD=-5.97, 95%CI -9.42~-2.53, P<0.05), while increasing Developmental Quotient (DQ) scores (MD=5.22, 95%CI 3.41~7.04, P<0.05) and mismatch negativity amplitude (MD=1.54, 95%CI 0.57~2.51, P<0.05). Network meta-analysis indicated that the optimal probability ranking for the effects of two different NIBS modalities on ABC scores in ASD patients was: transcranial direct current stimulation (tDCS) (P=0.93) > repetitive transcranial magnetic stimulation (rTMS) (P=0.06).

Conclusion Current evidence suggests that NIBS can improve ASD to a certain extent, with tDCS demonstrating superiority over rTMS.

Full Text

Effect of Non-invasive Brain Stimulation for Autism Spectrum Disorder: A Systematic Review and Network Meta-analysis

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Abstract

Background Previous studies have shown inconsistent effects of non-invasive brain stimulation (NIBS) for autism spectrum disorder (ASD), and there is a lack of comparison between different NIBS modalities. **Objective** To systematically evaluate the rehabilitative efficacy of NIBS for ASD and compare the therapeutic effects of two different NIBS approaches. **Methods** Randomized controlled trials (RCTs) investigating NIBS for ASD were searched in domestic and international databases from inception to December 2021. After assessing the risk of bias in the included studies, statistical analysis was performed using RevMan 5.3 and R 4.0.2 software. **Results** Twenty-two studies involving 661 patients were ultimately included. Meta-analysis showed that NIBS could reduce Autism Behavior Checklist (ABC) scores (MD=-8.80, 95%CI -10.98~-6.62, P<0.05), Childhood Autism Rating Scale (CARS) scores (MD=-2.93, 95%CI -3.63~-2.24, P<0.05), Autism Treatment Evaluation Checklist (ATEC) scores (MD=-9.13, 95%CI -12.79~-5.47, P<0.05), Self-Rating Anxiety Scale (SAS) scores (MD=-7.20, 95%CI -10.55~-3.85, P<0.05), Self-Rating Depression Scale (SDS) scores (MD=-8.89, 95%CI -13.21~-4.57, P<0.05), and mismatch negativity latency (MD=-5.97, 95%CI -9.42~-2.53, P<0.05), while increasing Developmental Quotient (DQ) scores (MD=5.22, 95%CI 3.41~7.04, P<0.05) and mismatch negativity amplitude (MD=1.54, 95%CI 0.57~2.51, P<0.05). Network meta-analysis indicated that the optimal probability ranking for the effects of two different NIBS modalities on ABC scores was: transcranial direct current stimulation (tDCS) (P=0.93) > repetitive transcranial magnetic stimulation

(rTMS) (P=0.06). **Conclusion** Current evidence suggests that NIBS can improve ASD to some extent, with tDCS being superior to rTMS.

Keywords: non-invasive brain stimulation; autism spectrum disorder; systematic review; network meta-analysis

Introduction

The Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-V) defines autism spectrum disorder (ASD) as persistent deficits in social communication and social interaction across contexts, accompanied by restricted, repetitive patterns of behavior, interests, or activities, classifying it as a neurodevelopmental disorder [1,2]. The prevalence of ASD has reportedly increased steadily in recent years [3], with the Centers for Disease Control and Prevention reporting a rate of 1/44 among children aged 0-8 years in 2021 [4], and approximately 1.5% in developed countries [5], imposing substantial burdens on individuals, families, and society. Current treatments for ASD primarily include antipsychotic medications, antidepressants, stimulants, and behavioral therapy [6]; however, patient recovery varies considerably, and effects remain limited.

Non-invasive brain stimulation (NIBS) modulates cortical excitability primarily through electric or magnetic fields, offering advantages such as non-invasiveness, ease of operation, and minimal side effects [7], making it highly promising for clinical applications. Repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS) represent the two most commonly used NIBS methods [8]. These modalities differ in their mechanisms [9]. rTMS delivers multiple pulses at a fixed frequency, using magnetic fields acting on the cerebral cortex to generate induced currents that alter action potentials in cortical neurons, thereby influencing cerebral metabolism and neural activity [10]. Frequency selection enables excitatory or inhibitory effects: high frequencies enhance cortical excitability and facilitate local neural activity, while low frequencies reduce cortical excitability and suppress local neural function [11]. In contrast, tDCS is a physical stimulation technique that uses continuous low-intensity direct current to stimulate the cerebral cortex, modulating transmembrane potentials of neural cells to induce depolarization or hyperpolarization, consequently altering neural plasticity and cortical excitability [12]. Different electrode placements achieve excitatory or inhibitory effects: anodal placement on the affected side causes depolarization of the resting membrane potential, increasing neuronal excitability at the stimulation site, whereas cathodal stimulation induces hyperpolarization of neuronal membrane potentials, reducing cortical excitability [13].

Previous studies have demonstrated that NIBS can improve ASD compared with control groups [14], yet other research shows no significant therapeutic effects after NIBS intervention [15]. Although existing studies have explored the

rehabilitative efficacy of NIBS for ASD, most are two-arm studies comparing NIBS with sham stimulation, with few comparative studies between different NIBS modalities, resulting in a lack of efficacy comparisons. This absence of evidence-based data makes clinical decision-making difficult for rehabilitation practitioners selecting among NIBS options. Therefore, this study employs evidence-based methodology to systematically evaluate the rehabilitative efficacy of NIBS for ASD and compare therapeutic differences between different NIBS approaches, providing a theoretical basis for NIBS application in ASD rehabilitation.

This study has been registered with the PROSPERO International Prospective Register of Systematic Reviews (No. CRD42021283409).

Methods

1.1 Search Strategy We systematically searched PubMed, Embase, Cochrane Library, Scopus, Web of Science, CNKI, Wanfang, VIP, and Chinese Biomedical Literature Database for all RCTs investigating NIBS for ASD, supplemented by reviewing relevant reviews and their reference lists. Each database was searched using a combination of Medical Subject Headings (MeSH) and free-text terms from inception to December 2021.

Using PubMed as an example, the specific search strategy was: #1 "autism spectrum disorder" [MeSH] OR autism spectrum disorders OR autism OR autistic disorder OR autistic spectrum disorder OR autistic spectrum disorders OR disorder, autistic spectrum; #2 "transcranial magnetic stimulation" [Mesh] OR repetitive transcranial magnetic stimulation OR repetitive transcranial magnetic OR transcranial direct current OR noninvasive brain stimulation OR noninvasive brain stimulation OR transcranial electrical stimulation OR rTMS OR tDCS OR TMS OR NIBS; #3 "randomized controlled trial" [MeSH] OR random OR random allocation OR RCT OR RCTs; #4 #1 AND #2 AND #3.

1.2 Inclusion and Exclusion Criteria **Inclusion criteria:** Study type: RCTs investigating NIBS for ASD, limited to Chinese and English literature; Participants: patients with a clear diagnosis of ASD meeting DSM-V diagnostic criteria [2,16]; Interventions: NIBS (including tDCS and rTMS); Outcome measures: Primary outcomes included Autism Behavior Checklist (ABC), Childhood Autism Rating Scale (CARS), and Autism Treatment Evaluation Checklist (ATEC); secondary outcomes included Developmental Quotient (DQ), Self-Rating Anxiety Scale (SAS), Self-Rating Depression Scale (SDS), and mismatch negativity (MMN) latency and amplitude.

Exclusion criteria: Non-randomized controlled trials such as pre-post self-control studies, cohort studies, case-control studies, and cross-sectional studies; Studies without comparable baselines or baseline reporting; Studies with inadequate design or inappropriate statistical methods; Studies with incomplete data where original data or full text could not be obtained after contacting

authors; Non-Chinese or non-English literature; Studies without relevant outcome measures; Studies with unclear diagnostic criteria, intervention duration, or protocols; Duplicate publications; Conference abstracts, animal experiments, trial protocols, expert experience summaries, case reports, meta-analyses, and review articles.

1.3 Literature Screening and Data Extraction Two researchers independently screened literature and extracted data, with cross-checking. Disagreements were resolved through discussion with a third reviewer. Extracted data included first author, publication year, patient age, sample size, intervention duration, intervention protocol, outcome measures, adverse effects, follow-up data, and quality assessment information.

1.4 Risk of Bias Assessment Two researchers assessed the risk of bias in included studies using the Cochrane Handbook for Systematic Reviews of Interventions (version 5.1.0), covering six domains: selection bias (random sequence generation and allocation concealment); performance bias (blinding of participants and personnel); detection bias (blinding of outcome assessment); attrition bias (incomplete outcome data); reporting bias (selective reporting); and other biases. Each domain was rated as "low risk," "high risk," or "unclear" [17].

1.5 Statistical Analysis **Traditional Meta-analysis** was conducted using RevMan 5.3 software: Heterogeneity testing: A fixed-effects model was used if P$ 0.1andI^{\{2\}\$\$\ 50}\{2\}\$>50\%$, indicating significant heterogeneity. When substantial heterogeneity existed, subgroup analysis and sensitivity analysis were performed to explore sources. Effect size calculation: All outcomes were continuous variables, using weighted mean difference (MD) as the effect measure with 95% confidence intervals (CI), with α=0.05 as the significance level [18].

Network Meta-analysis was performed using R software to plot network relationship diagrams comparing the efficacy of two different NIBS modalities. A consistency model based on Markov chain Monte Carlo simulation was used for network meta-analysis and optimal probability ranking to compare therapeutic differences. Initial values were set at 0.5, step size at 10, and iterations at 50,000, with the first 20,000 used as burn-in to eliminate initial value effects and the remaining 30,000 for sampling. Convergence was assessed using the Bandwidth value, with values closer to 0 indicating better convergence and more reliable consistency model results [19].

Results

2.1 Literature Search Results and Basic Characteristics The database search yielded 534 records, with 273 remaining after duplicate removal using EndNote X9. After screening, 22 studies [15,20-40] were ultimately included, comprising 4 English [15,20-22] and 18 Chinese articles [23-40]. The literature

screening process is shown in [Figure 1: see original paper], and basic characteristics of included studies are presented in .

2.2 Quality Assessment and Risk of Bias All 22 included studies [15,20-40] mentioned randomization, but 4 [25,28,31-32] did not specify the randomization method. Four studies [15,20-22] blinded researchers or participants, and 8 [15,20-22,26-27,30,33] blinded outcome assessors. The risk of bias assessment is shown in [Figure 2: see original paper].

2.3 Meta-Analysis Results ABC Score: Seventeen RCTs [15,23-30,33-40] reported ABC scores, with 553 patients in experimental groups and 539 in control groups. Meta-analysis showed that both rTMS and tDCS groups had lower ABC scores than controls (MD=-8.28, 95%CI -10.46~-6.09, P<0.05) and (MD=-15.98, 95%CI -27.52~-4.43, P<0.05), respectively. The pooled effect indicated that NIBS groups had lower ABC scores than control groups (MD=-8.80, 95%CI -10.98~-6.62, P<0.05). See [Figure 3: see original paper].

CARS Score: Thirteen RCTs [15,20,25-26,30-33,35-36,38-40] reported CARS scores, with 385 patients in experimental groups and 373 in control groups. Meta-analysis showed that rTMS groups had lower CARS scores than controls (MD=-3.24, 95%CI -3.81~-2.67, P<0.05), while tDCS groups showed no statistically significant difference (MD=-1.17, 95%CI -4.20~1.87, P>0.05), though most effect estimates favored the tDCS group. The pooled effect showed that NIBS groups had lower CARS scores than control groups (MD=-2.93, 95%CI -3.63~-2.24, P<0.05). See [Figure 4: see original paper].

ATEC Score: Three RCTs [20-22] reported ATEC scores, with 62 patients in experimental groups and 61 in control groups. Meta-analysis showed that NIBS groups had lower ATEC scores than control groups (MD=-9.13, 95%CI -12.79~-5.47, P<0.05). See [Figure 5: see original paper].

DQ Score: Five RCTs [25-26,29,32,35] reported DQ scores, with 167 patients in experimental groups and 166 in control groups. Meta-analysis showed that NIBS groups had higher DQ scores than control groups (MD=5.22, 95%CI 3.41~7.04, P<0.05). See [Figure 6: see original paper].

SAS Score: Two RCTs [39-40] reported SAS scores, with 89 patients in each group. Meta-analysis showed that NIBS groups had lower SAS scores than control groups (MD=-7.20, 95%CI -10.55~-3.85, P<0.05). See [Figure 7: see original paper].

SDS Score: Two RCTs [39-40] reported SDS scores, with 89 patients in each group. Meta-analysis showed that NIBS groups had lower SDS scores than control groups (MD=-8.89, 95%CI -13.21~-4.57, P<0.05). See [Figure 8: see original paper].

MMN Latency: Two RCTs [23-24] reported MMN latency, with 34 patients in experimental groups and 30 in control groups. Meta-analysis showed that

NIBS groups had shorter MMN latency than control groups (MD=-5.97, 95%CI -9.42~-2.53, P<0.05). See [Figure 9: see original paper].

MMN Amplitude: Two RCTs [23-24] reported MMN amplitude, with 34 patients in experimental groups and 30 in control groups. Meta-analysis showed that NIBS groups had higher MMN amplitude than control groups (MD=1.54, 95%CI 0.57~2.51, P<0.05). See [Figure 10: see original paper].

2.4 Network Meta-Analysis **2.4.1 Evidence Network** Using ABC score as the outcome, 16 of the 22 included RCTs [25-40] used rTMS interventions, while 4 [15,20,23-24] used tDCS. The network relationship for comparing different NIBS modalities is shown in [Figure 11: see original paper], where connecting lines between nodes represent direct comparisons from RCTs, and line thickness indicates the number of RCTs.

2.4.2 Consistency Testing No closed loops were formed among interventions, so consistency testing was not required.

2.4.3 Convergence Diagnosis Convergence diagnosis for included studies is shown in [Figure 12: see original paper]. The Bandwidth value was close to 0, indicating good convergence.

2.4.4 Probability Ranking The optimal probability ranking from network meta-analysis is shown in [Figure 13: see original paper]. For ABC scores (a reverse-scored measure), higher Rank N values indicate better probability ranking. The optimal probability ranking for two different NIBS modalities on ABC scores was: tDCS (P=0.93) > rTMS (P=0.06).

2.5 Adverse Effects No adverse effects were reported in the included studies.

2.6 Publication Bias Funnel plots for the primary outcome (ABC score) are shown in [Figure 14: see original paper]. The funnel plot showed no obvious asymmetry, though publication bias cannot be completely ruled out.

Discussion

As an emerging neuromodulation technology, NIBS has been reviewed for its clinical application value in improving ASD [41]. This study objectively evaluated the rehabilitative efficacy of NIBS for ASD from an evidence-based medicine perspective and compared therapeutic differences between two NIBS modalities.

Research indicates that patients with pervasive developmental disorders such as ASD often exhibit impaired executive function [42], which encompasses a range of mental processes involving planning, working memory, attention, problem-solving, verbal reasoning, and mental flexibility, and is highly correlated with activation of the dorsolateral prefrontal cortex (DLPFC) [43]. A meta-analysis also demonstrated that ASD is closely associated with structural and functional

alterations in the DLPFC [44]. The stimulation sites in included studies primarily targeted the DLPFC, which exerts top-down modulatory control over task-relevant information processing and plays a crucial role in cognitive control [45]. Enticott et al. showed that rTMS intervention over bilateral DLPFC could reduce social-related impairments and social anxiety. Furthermore, DLPFC represents the highest cortical region involved in motor planning, organization, and regulation/inhibition, with extensive connections to other regions including the orbitofrontal cortex, thalamus, and parts of the basal ganglia (particularly the dorsal caudate nucleus) [43]. These functional connections link DLPFC to behavioral abnormalities such as restricted and repetitive behaviors, hypersensitivity (over-responsiveness), and hyporesponsiveness to various stimuli [15]. Therefore, DLPFC is considered a primary target for ASD treatment. Studies by Li and Ren et al. [25,29,31,35] stimulated Broca' s area, and after rTMS intervention, patients showed significant improvements in language, motor function, and social interaction, consistent with our findings.

The severity of restricted and repetitive behaviors in ASD patients is often closely related to anxiety and depression severity [46,47]. This study showed that anxiety and depression symptoms were alleviated after rTMS intervention, consistent with Avirame et al. [48]. However, only two studies reported SAS and SDS scores, representing a limited evidence base requiring further research. Additionally, this study could not determine the causal relationship between anxiety/depression symptom reduction and improvement in ASD core symptoms, which may represent a future research direction. Current evidence suggests that MMN latency reflects the functional status of auditory sensory pathways, while amplitude is closely related to cortical state [49]. This study demonstrated that rTMS intervention effectively shortened MMN latency and increased MMN amplitude. Sun et al. [24] showed that changes in MMN latency were linearly correlated with ABC scale improvements and could reflect behavioral capacity in ASD patients to some extent, potentially serving as an objective quantitative assessment tool in the future.

Network meta-analysis results indicated that for improving ASD, tDCS is superior to rTMS. Both techniques can produce similar effects on ASD by altering cortical excitability, but through different mechanisms. tDCS induces weak sustained currents causing hyperpolarization or depolarization in stimulated regions, while rTMS induces synaptic efficacy changes through long-term potentiation and depression mechanisms, generating near-threshold intensity pulses [50]. This suggests that tDCS may produce longer-lasting cortical modulation and induce broader, more durable therapeutic effects compared with rTMS. Reportedly, rTMS carries a risk of inducing seizures [51], whereas tDCS adverse effects are mostly transient dizziness and headache [52]. Bai and Yuan [53] suggested that tDCS has better safety and tolerability than rTMS, making it more suitable for young children.

Stimulation frequency, intensity, and treatment sessions are important factors affecting rTMS efficacy, while tDCS is similarly influenced by current intensity

and electrode size. In included studies, rTMS predominantly used 1-10 Hz at 90%-100% resting motor threshold, while tDCS primarily used 1-1.5 mA for 20 minutes. Current evidence remains inconsistent regarding optimal treatment parameters such as frequency, current intensity, stimulation site, and how to prolong therapeutic effects. This study could not determine the relationship between intervention duration/cumulative intervention time and ASD improvement. Future large-scale, multicenter trials are needed to comprehensively evaluate the role of NIBS in ASD clinical management, combined with functional magnetic resonance imaging and functional near-infrared spectroscopy to explore mechanisms of action.

This study has several potential limitations. Currently, few RCTs investigate NIBS for ASD, resulting in a small number of included studies. All included literature was published in Chinese or English, with limited grey literature, potentially introducing selection bias. Sample sizes were small in included studies, and some did not describe specific randomization methods, allocation concealment, or blinding. No included studies reported follow-up data, lacking observation of long-term NIBS effects on ASD. Patient baseline characteristics, intervention duration, and disease severity may all influence results.

In summary, current evidence indicates that NIBS can improve ASD to some extent, with tDCS being superior to rTMS. However, definitive conclusions require more high-quality RCTs with larger sample sizes, multicenter design, and double-blinding to explore NIBS efficacy and mechanisms in ASD. Additionally, NIBS showed no obvious adverse effects during ASD treatment, warranting clinical promotion and application.

Author Contributions: LI Lingling conceived and designed the study and drafted the manuscript; HUANG Hailiang supervised quality control and revision, taking overall responsibility for the manuscript; YU Ying and LIU Xinyue revised the manuscript; JIA Yuqi and LIU Zhiyao conducted literature screening and data extraction; SHI Xin and WANG Fangqi performed data analysis.

Conflict of Interest: The authors declare no conflicts of interest.

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Note: Figure translations are in progress. See original paper for figures.