



A network meta-analysis of non-invasive brain stimulation interventions for autism spectrum disorder: Evidence from randomized controlled trials

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Abbreviations: ABC, Autism Behavior Checklist; AQ, Autism Quotient; ASD, autism spectrum disorder; ATEC, Autism Treatment Evaluation Checklist; atDCS_F3 + ctDCS_E, anodal transcranial direct current stimulation over the left dorsolateral prefrontal cortex plus cathodal transcranial direct current stimulation over the extracephalic location; atDCS_F3 + ctDCS_E/L, anodal transcranial direct current stimulation over the left dorsolateral prefrontal cortex plus cathodal transcranial direct current stimulation over the extracephalic location with the low sessions number; atDCS_F3 + ctDCS_F4, anodal transcranial direct current stimulation over the left dorsolateral prefrontal cortex plus cathodal transcranial direct current stimulation over the right dorsolateral prefrontal cortex; atDCS_F3 + ctDCS_FP2, anodal transcranial direct current stimulation over the left dorsolateral prefrontal cortex plus cathodal transcranial direct current stimulation over the right supraorbital area; atDCS_FC1/FC2 + ctDCS_FP1/FP2, anodal transcranial direct current stimulation over the bilateral dorsolateral prefrontal cortex plus cathodal transcranial direct current stimulation over the bilateral supraorbital areas; atDCS_FP2 + ctDCS_F3, anodal transcranial direct current stimulation over the right supraorbital area plus cathodal transcranial direct current stimulation over the left dorsolateral prefrontal cortex; CARS, Childhood Autism Rating Scale; CI, confidence interval; cTBS_F3, continuous theta-burst stimulation over the left dorsolateral prefrontal cortex; dTMS, deep transcranial magnetic stimulation; dTMS_Fz, deep transcranial magnetic stimulation over the bilateral dorsomedial prefrontal cortex; dLPFC, dorsolateral prefrontal cortex; GARS-2, Gilliam Autism Rating Scale, Second Edition; HD-atDCS_Cz, High-definition anodal transcranial direct current stimulation over the vertex; HD-atDCS_F3, High-definition anodal transcranial direct current stimulation over the left dorsolateral prefrontal cortex; iTBS, intermittent theta-burst stimulation; iTBS_F3/F4/L, intermittent theta-burst stimulation over the bilateral dorsolateral prefrontal cortex with a low session number; iTBS_P5/P6/L, intermittent theta-burst stimulation over the bilateral posterior superior temporal sulci with a low session number; iTBS_P5/P6, intermittent theta-burst stimulation over the bilateral posterior superior temporal sulci; NIBS, non-invasive brain stimulation; NMA, network meta-analysis; OR, odds ratio; pSTS, posterior superior temporal sulcus; RAADS, Ritvo Autism Diagnostic Scale; RCT, randomized controlled trials; rTMS, repetitive transcranial magnetic stimulation; rTPJ, right temporoparietal junction; SMD, standardized mean differences; SRS, Social Responsiveness Scale; SRS-2, Social Responsiveness Scale, Second Edition; SUCRA, surface under the cumulative ranking curve; tACS, transcranial alternating current stimulation; tDCS, transcranial direct current stimulation; tES, transcranial electrical stimulation; TPS, transcranial pulse stimulation.

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ABSTRACT

The efficacy and acceptability of various non-invasive brain stimulation (NIBS) interventions for autism spectrum disorder remain unclear. We carried out a systematic review for randomized controlled trials (RCTs) regarding NIBS for reducing autistic symptoms (INPLASY202370003). Sixteen articles (N = 709) met the inclusion criteria for network meta-analysis. Effect sizes were reported as standardized mean differences (SMDs) or odds ratios with 95 % confidence intervals (CIs). Fourteen active NIBS interventions, including transcranial direct current stimulation (tDCS), repetitive transcranial magnetic stimulation, and transcranial pulse stimulation were analyzed. Only anodal tDCS over the left dorsolateral prefrontal cortex paired with cathodal tDCS over an extracephalic location (atDCS_F3 + ctDCS_E) significantly improved autistic symptoms compared to sham controls (SMD = -1.40, 95 %CIs = -2.67 to -0.14). None of the NIBS interventions markedly improved social-communication symptoms or restricted/repetitive behaviors in autistic participants. Moreover, no active NIBS interventions exhibited significant dropout rate differences compared to sham controls, and no serious adverse events were reported for any intervention.

1. Introduction

Autism Spectrum Disorder (ASD) is a neurodevelopmental disorder characterized by a heterogeneous set of symptoms, including early-onset social-communication deficits and restricted/repetitive behaviors (Lai et al., 2014; Lord et al., 2020). It has a worldwide prevalence of about 1 % and affects males more than females, leading to life-long psychosocial functional impairments in individuals with ASD (Lai et al., 2014; Lord et al., 2020). Medications are evidenced to treat the co-occurring mental health symptoms (e.g. irritability, anxiety, inattention/hyperactivity symptoms, etc.) but do not directly address core symptoms such as social communication or restricted/repetitive behaviors (Lord et al., 2020). However, addressing these core symptoms fundamentally benefits ASD. Therefore, it is crucial to explore more potential non-pharmacological interventions, such as non-invasive brain stimulation (NIBS) (Baribeau et al., 2022).

Recent advances and empirical achievements in NIBS interventions have expanded the therapeutic potential of repetitive transcranial magnetic stimulation (rTMS), including intermittent theta-burst stimulation (iTBS) and deep transcranial magnetic stimulation (dTMS), transcranial electrical stimulation (tES, including transcranial direct current stimulation, tDCS, and transcranial alternating current stimulation, tACS), and transcranial pulse stimulation (TPS) to several psychiatric disorders, including schizophrenia (Tseng et al., 2022), major depressive disorder (Brian Chen et al., 2023), Tourette syndrome (Hsu et al., 2018), and ASD (Garcia-Gonzalez et al., 2021; Smith et al., 2022). A recent meta-analysis on intellectually able autistic people suggests low-frequency rTMS over the dorsolateral prefrontal cortex (DLPFC) may improve restricted/repetitive behaviors, and iTBS treatment over the bilateral posterior superior temporal sulcus (pSTS) may improve social symptoms (Smith et al., 2022). In addition, another meta-analysis shows promising results of anodal tDCS stimulation over the left DLPFC in ASD (Garcia-Gonzalez et al., 2021). However, these meta-analyses also included open-label trials. Hence, we are uncertain whether the results still support the efficacy of NIBS in improving autistic symptoms within the framework of randomized controlled trials (RCTs). This caveat raises concerns about potential bias, such as the placebo effects in ASD clinical trials (Ni et al., 2023; Siafis et al., 2022). Furthermore, while the traditional meta-analysis methods provide encouraging evidence for each NIBS intervention respectively, we do not know which modality is better compared to one another. More importantly, due to the novelty of NIBS treatment for ASD, studies are still testing different protocols and treatment modalities. Therefore, a comprehensive comparison between the different NIBS modalities could provide insights to develop and select optimal treatment options.

To fill knowledge gaps, we used network meta-analysis (NMA) to comprehensively analyze the comparative efficacy and acceptability of multiple NIBS modalities, providing a broader interpretation of the

current evidence base (Higgins and Welton, 2015). In this study, we systematically reviewed RCTs of ASD and examined the efficacy of different NIBS modalities on overall core autistic symptoms, social-communication symptoms, and restricted/repetitive behaviors, respectively. We also assessed their acceptability in terms of dropout rates and incidence of adverse events.

2. Methods

2.1. General study guidelines

This NMA adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA, Appendix 1) guidelines (Page et al., 2021). The study protocol was registered in the International Platform of Registered Systematic Review and Meta-analysis Protocols (No: INPLASY202370003). The Institutional Review Board of the Chang Gung Memorial Hospital reviewed the study protocol and waived the need for ethical approval (no. 202200827B1).

2.2. Search strategy and eligibility criteria

Using the keywords (“autism” OR “asperger”) AND (“non-invasive brain stimulation” OR “transcranial magnetic stimulation” OR “transcranial direct current stimulation” OR “transcranial pulse stimulation”) AND (“randomized controlled trial”), two authors (YC Chen and CW Hsu) systematically searched multiple electronic databases, including PubMed, Embase, and Cochrane CENTRAL, from the inception of each database until December 1, 2023, without language restriction. We also searched gray literature databases, such as Clinicaltrials.gov, and examined the reference lists of relevant review articles and meta-analyses (Barahona-Correa et al., 2018; Khaleghi et al., 2020; Salehinejad et al., 2022). We screened all titles and abstracts, and potentially eligible articles were selected for full-text review. The details of the search strings used for each database are provided in eTable 1.

The search strategy adhered to the following PICOS criteria: (1) Patient: participants with a diagnosis of ASD; (2) Intervention: any NIBS; (3) Comparison: sham, active, or waitlist controls; (4) Outcome: changes in overall core autistic symptoms, social difficulties, and repetitive/restricted behaviors, and dropout rates and serious adverse events; and (5) Study design: randomized controlled trials (RCTs).

The criteria for inclusion were: (1) studies involving human participants of all ages; (2) participants diagnosed with ASD or pervasive developmental disorders based on a valid method (i.e. using the Diagnostic and Statistical Manual of Mental Disorders, International Classification of Diseases, or diagnosis by a certified specialist (Hadoush et al., 2020)) with possible other comorbid mental disorders (e.g. attention-deficit/hyperactivity disorder (Ni et al., 2022)); (3) participants receive NIBS treatment, including various rTMS, tES, TPS, vagus

nerve stimulation, magnetic field stimulation, etc. (no electroconvulsive therapy); (4) studies providing both pre- and post-intervention scores or score changes regarding overall core autistic symptoms using an ASD assessment scale such as the Social Responsiveness Scale (SRS) (Bruni, 2014); (5) RCTs that utilized either sham, active, or waitlist controls and employed either a crossover or parallel study design. Conversely, studies were excluded based on the following criteria: (1) not RCT; (2) case series or reports, conference papers, and non-peer-reviewed articles; (3) those not reporting the outcome of interest (overall core autistic symptom scores); (4) overlapping datasets with another larger study. Notably, several studies were presented using overlapping datasets. Consequentially, we selected the study with the largest sample size and the most informative data. In instances of disagreement regarding the inclusion of a specific study, a third investigator (HC Ni) was consulted.

2.3. Data extraction and outcomes

Two authors (YC Chen and CW Hsu) independently extracted the following data from the included studies: first author's name, publication year, age (mean), sex (female participant percentage), treatment arms, sample sizes, treatment duration, stimulation protocol, and study location. We contacted the corresponding author if any required data were not reported.

Two main outcomes were examined in this study, including efficacy and acceptability. Efficacy was expressed as a change (pre- and post-intervention data) in the assessment score of overall core autistic symptoms after NIBS intervention. We considered the first available scores after completing NIBS treatment as post-intervention data. We also accepted a wide range of validated rating scales for overall core symptoms (e.g. SRS (Bruni, 2014), Childhood Autism Rating Scale [CARS] (Schopler et al., 1980), Autistic Behavior Checklist [ABC] (Aman et al., 1985), Autism Treatment Evaluation Checklist [ATEC] (Rimland and Edelson, 1999), Ritvo Autism Asperger Diagnostic Scale [RAADS] (Ritvo et al., 2008), Gilliam Autism Rating Scale [GARS-2] (Gilliam, 2006), and Autism Spectrum Quotient [AQ] (Baron-Cohen et al., 2001)) since no outcome measure was used universally (McCracken et al., 2021). However, if a study used more than one scale to assess overall core symptoms, we preferred clinician-rating followed by parent/caregiver-rating and used self-rating only when the other two were unavailable. Furthermore, social-communication symptoms and restricted/repetitive behaviors related to subdomains of the overall autism symptom category were treated as secondary outcomes of efficacy because only some of the included studies reported these results. eTable 2 shows the subscale scores representing social-communication symptoms and restricted/repetitive behaviors. Moreover, acceptability was expressed as the dropout rate, defined as the percentage of participants who discontinued the study for any reason before study completion. Additionally, we evaluated the serious adverse events during the period of NIBS intervention as the secondary outcome of acceptability, which included complications such as seizures, suicidal ideation, and auditory injuries (Muszkat et al., 2016; Rossi et al., 2021).

The different nodes of this NMA were represented by different stimulation methods and different stimulation sites. Some studies assessed the efficacy between different numbers of stimulation sessions (e.g. 5 vs 20 sessions (Auvichayapat et al., 2023)), while other studies investigated the treatment effects after a small number of sessions (1–5 sessions) (Amatachaya et al., 2015; Ni et al., 2022). Therefore, this NMA defined the treatment group with 5 or fewer stimulation sessions as "low" sessions to allow for better comparison.

2.4. Risk of bias assessment

Two authors (YC Chen and CW Hsu) independently assessed the risk of bias in each included trial using the Cochrane risk of bias tool version 2, which consists of the 5 bias risk domains of the randomization process, deviation from intended intervention, missing outcome data,

measurement of the outcome, and selection of reported result. The two investigators sought consensus for disagreements and consulted a third investigator (PT Tseng) when needed.

2.5. Data synthesis and statistical analysis

We conducted NMA to assess the pre-post changes for overall, social, and behavior symptoms (continuous variables) and incidence rates for dropout and side effects (categorical variables). We estimated standardized mean differences (SMDs) with 95 % confidence intervals (95 % CIs) for continuous variables and odds ratios (OR) and 95 % CIs for categorical variables. Some studies may report zero events in either treatment arm, but in order to include as many relevant studies as possible in this NMA, we applied a 0.5 zero-cell correction (Friedrich et al., 2007). For OR, inclusion of such trials would result in only small changes, even if they constitute the vast majority of included trials (Friedrich et al., 2007). Consistent with previous research methods from our team, random-effects and frequentist models were used for pairwise meta-analyses and NMA (Hsu et al., 2024; Tseng et al., 2024). Heterogeneity among the included studies was evaluated using the tau value, the estimated standard deviation of the effects across the studies. We used STATA (version 17.0, mvmeta command; StataCorp, College Station, TX, USA) to conduct the NMA (White, 2015). A two-tailed test was used for all comparisons, and p -values < 0.05 were considered statistically significant.

In our NMA, we employed mixed comparisons with generalized linear mixed models to integrate both direct and indirect comparisons (Tu, 2014). Through transitivity, we executed indirect comparisons that allowed for the calculation of differences between treatments A and B, derived from their respective comparisons with treatment C. The hypothesis of transitivity was validated by assessing the efficacy of various sham interventions, which was achieved by computing the changes in core autistic symptoms in relation to sham interventions such as tDCS and rTMS, utilizing Comprehensive Meta-Analysis software (version 4; Biostat, Englewood, NJ, USA). A comparison of multiple treatment arms was realized by amalgamating the direct and indirect evidence from the included studies (Lu and Ades, 2004). The restricted maximum likelihood method was employed to assess inter-study variance (Kontopantelis et al., 2013). To provide a more comprehensible representation of clinical applications, we calculated the relative ranking probabilities of the effects of all treatments on the target outcomes. The surface under the cumulative ranking curve (SUCRA) indicated the percentage of the mean rank of each intervention, juxtaposed with an idealized hypothetical intervention (Salanti et al., 2011). We checked for potential small study effects and publication bias by conducting comparison-adjusted funnel plots and employing Egger's regression. Inconsistencies were evaluated through the design-by-treatment interaction model, the loop-specific approach, and the node-splitting model (Higgins et al., 2014).

We also conducted a network meta-regression analysis to explore potential moderators, including age, sex (proportion of females), and the total number of NIBS sessions, that may affect the relative efficacy on the core symptoms of autism. Furthermore, although there were no age limitations for this NMA, ASD is a neurodevelopmental disorder characterized by early-onset symptom presentation and diagnosis (Lai et al., 2014). Therefore, we conducted a sensitivity analysis for only pediatric participants (i.e., excluding studies that included participants > 18 years old).

3. Results

3.1. Literature search and study characteristics

The study selection process is shown in Fig. 1. After excluding duplicates and screening titles and abstracts, we retrieved 44 studies for full-text review, of which 28 were excluded for various reasons

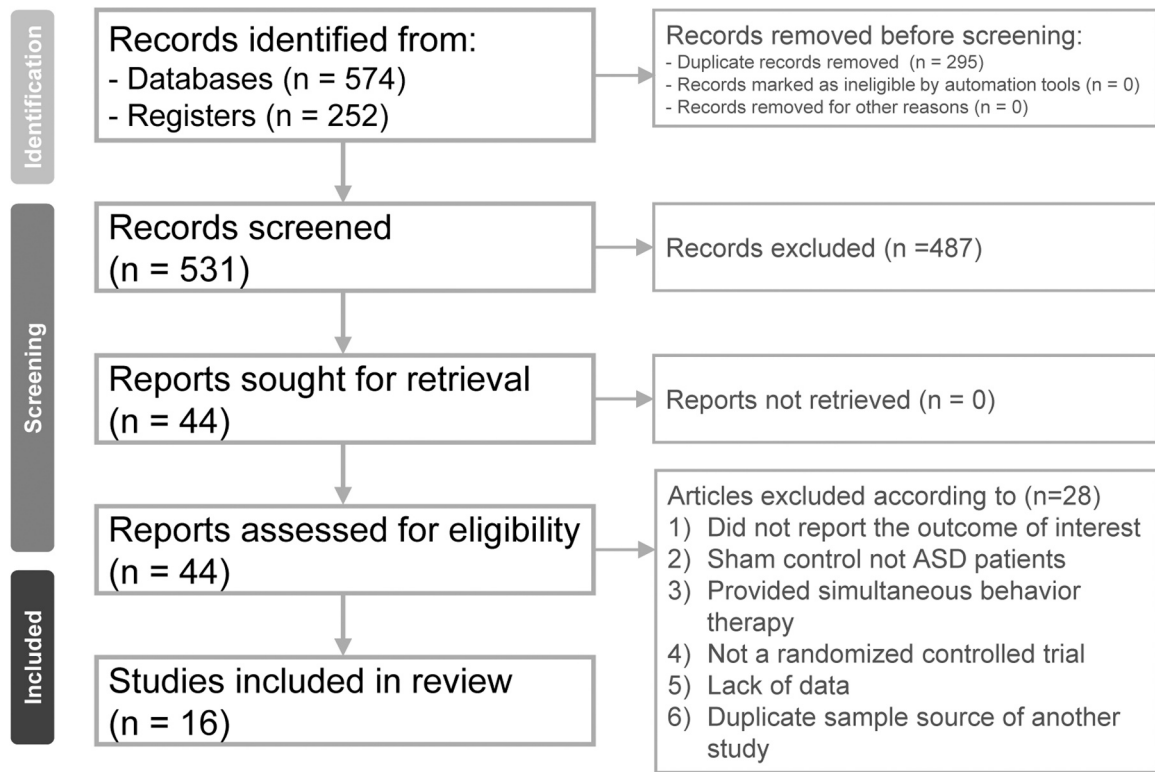


Fig. 1. Flowchart of study selection. Flowchart illustrating the procedure of the present network meta-analysis.

(eTable 3). In the end, we included 16 RCTs published between 2014–2023 and compared 14 different NIBS modalities in this NMA (Amatachaya et al., 2014, 2015; Auvichayapat et al., 2023; Cheung et al., 2023; Enticott et al., 2014; Hadoush et al., 2020; Han et al., 2023; Kaokhieo et al., 2023; Nazari et al., 2023; Ni et al., 2023, 2021, 2017, 2022; Qiu et al., 2021; Sun et al., 2022; Wang et al., 2023b; Zemestani et al., 2022). Demographic characteristics of participants from the

included studies are presented in eTable 4. In total, 709 participants diagnosed with ASD were included, and sample sizes of studies ranged from 21 to 97 participants. Participants' ages ranged from 2 to 59 years old, with a mean of 12.5, and female proportion ranged from 0 % to 29 %. The duration of treatment ranged from one day to eight weeks with 1–20 total sessions of NIBS.

Fig. 2 demonstrates the network structure of the treatment arms for

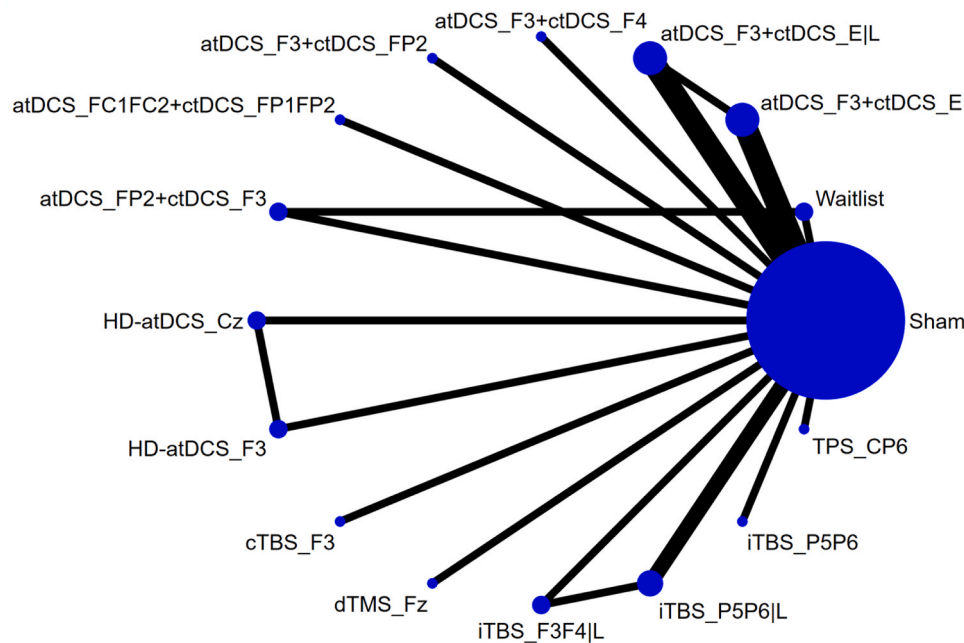


Fig. 2. Network structure of the primary outcomes. The overall network structure of the primary outcome. The lines connecting the nodes represent direct comparisons observed in different clinical trials. The size of each circle is proportionate to the number of participants who received a specific treatment. The thickness of the lines is proportional to the number of trials that are interconnected to the network.

the primary outcomes. Overall, 311 participants were randomly assigned to sham intervention, 30 to waitlist, and 368 to one of the following interventions: Eight tDCS protocols, including (1) anodal tDCS over the left DLPFC plus cathodal tDCS over the extracephalic location (atDCS_F3 + ctDCS_E, $k = 3$, $n = 42$) (Auvichayapat et al., 2023; Nazari et al., 2023; Qiu et al., 2021), (2) anodal tDCS over the left DLPFC plus cathodal tDCS over the extracephalic location with the low sessions number (atDCS_F3 + ctDCS_E|L, $k = 3$, $n = 52$) (Amatachaya et al., 2014, 2015; Auvichayapat et al., 2023), (3) anodal tDCS over the left DLPFC plus cathodal tDCS over the right DLPFC (atDCS_F3 + ctDCS_F4, $k = 1$, $n = 17$) (Zemestani et al., 2022), (4) anodal tDCS over the left DLPFC plus cathodal tDCS over the right supraorbital area (atDCS_F3 + ctDCS_FP2, $k = 1$, $n = 19$) (Sun et al., 2022), (5) anodal tDCS over the bilateral DLPFC plus cathodal tDCS over the bilateral supraorbital areas (atDCS_FC1/FC2 + ctDCS_FP1/FP2, $k = 1$, $n = 22$) (Hadoush et al., 2020), (6) anodal tDCS over the right supraorbital plus cathodal tDCS over the left DLPFC (atDCS_FP2 + ctDCS_F3, $k = 1$, $n = 34$) (Han et al., 2023), (7) High-definition anodal transcranial direct current stimulation over the vertex (HD-atDCS_Cz, $k = 1$, $n = 15$) (Wang et al., 2023b), and (8) High-definition anodal transcranial direct current stimulation over the left DLPFC (HD-atDCS_F3, $k = 1$, $n = 15$) (Wang et al., 2023b); five rTMS protocols, including (1) continuous theta-burst stimulation over the left DLPFC (ctBS_F3, $k = 1$, $n = 30$) (Ni et al., 2023), (2) deep rTMS over the bilateral dorsomedial prefrontal cortex (dTMS_Fz, $k = 1$, $n = 15$) (Enticott et al., 2014), (3) intermittent theta-burst stimulation over the bilateral DLPFC with the low sessions number (iTBS_F3/F4|L, $k = 1$, $n = 19$) (Ni et al., 2017), (4) intermittent theta-burst stimulation over the bilateral pSTS with the low sessions number (iTBS_P5/P6|L, $k = 2$, $n = 32$) (Ni et al., 2017, 2022), and (5) intermittent theta-burst stimulation over the bilateral pSTS (iTBS_P5/P6, $k = 1$, $n = 40$) (Ni et al., 2021); and one TPS protocol which is TPS over the right temporoparietal junction (TPS_CP6, $k = 1$, $n = 16$) (Cheung et al., 2023).

3.2. Efficacy

Core symptoms were measured mainly with the SRS/SRS-2 (5/16 studies, 47 % of participants (Han et al., 2023; Ni et al., 2023; Ni et al., 2021; Ni et al., 2017; Wang et al., 2023b)) and CARS (4/16 studies, 21 % of participants (Amatachaya et al., 2014; Auvichayapat et al., 2023; Cheung et al., 2023; Qiu et al., 2021)). Compared to the sham controls, only atDCS_F3 + ctDCS_E significantly improved core autistic symptoms ($SMD = -1.40$, 95 %CIs = -2.67 to -0.14 , Fig. 3A and eTable 5A). The effect sizes of the core autistic symptom reduction for the top four NIBS interventions were atDCS_F3 + ctDCS_E, HD-atDCS_Cz ($SMD = -1.24$, 95 %CIs = -3.45 – 0.97), HD-atDCS_F3 ($SMD = -1.21$, 95 %CIs = -3.42 to 1.00), and atDCS_F3 + ctDCS_E|L ($SMD = -1.12$, 95 %CIs = -2.36 to 0.12). According to SUCRA analysis, the top four interventions for reducing overall core symptoms were atDCS_F3 + ctDCS_E (77 %), followed by HD-atDCS_Cz (69 %), atDCS_F3 + ctDCS_E|L (68 %), and HD-atDCS_F3 (67 %) (eTable 6A).

We assessed the assumption of transitivity per the rationale in a previous NMA study (Tseng et al., 2022). No NIBS sham controls were significantly associated with improvements in overall core symptoms, such as tDCS ($SMD = -0.12$, 95 %CIs = -0.24 to 0.001), rTMS ($SMD = -0.15$, 95 %CIs = -0.43 to 0.12), or TPS ($SMD = -0.18$, 95 %CIs = -0.50 to 0.13). The sham control groups of these interventions showed no significant differences ($p = 0.922$; eFig. 1). Furthermore, in the network meta-regression analysis, variables including mean age ($p = 0.896$), sex ($p = 0.465$), and total number of NIBS sessions ($p = 0.889$) did not reach statistical significance as moderators affecting the overall core symptoms. Finally, the sensitivity analysis, which exclusively included studies on pediatric participants, yielded similar results, indicating that only atDCS_F3 + ctDCS_E significantly improved the overall core autistic symptoms ($SMD = -1.42$, 95 %CIs = -2.83 to -0.02 , eFig. 2A–B and eTable 7A–B) (Amatachaya et al., 2014, 2015; Auvichayapat et al., 2023; Cheung et al., 2023; Hadoush et al., 2020; Han et al., 2023; Nazari

et al., 2023; Ni et al., 2023, 2021; Qiu et al., 2021; Sun et al., 2022; Wang et al., 2023b; Zemestani et al., 2022).

Social-communication symptoms were measured mainly with the corresponding subscales of SRS/SRS-2 (5/12 studies, 56 % of participants (Han et al., 2023; Ni et al., 2023, 2021, 2017; Wang et al., 2023b)) and the corresponding subscales of ATEC (4/12 studies, 27 % of participants (Amatachaya et al., 2014, 2015; Auvichayapat et al., 2023; Hadoush et al., 2020)). Compared to the sham controls, none of the NIBS interventions significantly reduced social-communication symptoms (eFig. 3A–B and eTable 5B). In the SUCRA analysis, the top three interventions for reducing social-communication symptoms were HD-atDCS_Cz (86 %), followed by HD-atDCS_F3 (84 %), and atDCS_F3 + ctDCS_E|L (62 %) (eTable 6B). Restricted/repetitive behaviors were measured mainly with the corresponding subscales of SRS/SRS-2 (5/12 studies, 56 % of participants (Han et al., 2023; Ni et al., 2023, 2021, 2017; Wang et al., 2023b)) and the corresponding subscales of ATEC (4/12 studies, 27 % of participants (Amatachaya et al., 2014, 2015; Auvichayapat et al., 2023; Hadoush et al., 2020)). Compared to the sham controls, none of the NIBS significantly reduced restricted/repetitive behaviors (eFig. 4A–B and eTable 5C). According to the SUCRA values, the top three interventions for reducing restricted/repetitive behaviors were HD-atDCS_F3 (84 %), followed by HD-atDCS_Cz (78 %), and atDCS_F3 + ctDCS_E|L (73 %) (eTable 6C).

3.3. Acceptability

There was no significant difference between the dropout rates of any NIBS interventions compared to the sham controls (Fig. 3B, eTable 5D, and eTable 6D). Moreover, no serious adverse events were reported for any NIBS intervention groups or sham/waitlist control groups. Therefore, this NMA did not conduct further analysis on adverse event rates.

3.4. Risk of bias, publication bias, inconsistency, and heterogeneity

Results for risk of bias assessment are provided in eFig. 5 and eTable 8. Four studies had a low risk of bias (Cheung et al., 2023; Enticott et al., 2014; Ni et al., 2023; Zemestani et al., 2022), eleven studies had some risk of bias (Amatachaya et al., 2014, 2015; Auvichayapat et al., 2023; Hadoush et al., 2020; Han et al., 2023; Ni et al., 2021, 2017, 2022; Qiu et al., 2021; Sun et al., 2022; Wang et al., 2023b), and one study had a high risk of bias (Nazari et al., 2023). Based on the risk of bias items assessed, 84 % (67/80) showed a low risk of bias, 15 % (12/80) showed some risk of bias, and 1 % (1/80) showed a high risk of bias. Publication bias analysis using funnel plots and Egger's test indicated no significant publication bias (eFig. 6A–D). The NMA indicated significant global inconsistencies (design-by-treatment method) for outcomes related to overall core symptoms and restricted/repetitive behaviors; in contrast, outcomes concerning social-communication symptoms and dropout rates showed no significant inconsistencies. Moreover, no local inconsistencies (both loop-specific approach and node-splitting method) were detected for any of the outcomes (eTable 9–10). No significant heterogeneity was detected based on tau values (eTable 11). According to the GRADE assessment, the quality of evidence for overall core autistic symptoms predominantly fell within the low to very low range for most comparisons (eTable 12).

4. Discussion

This NMA provides comprehensive analyses of different NIBS modalities in reducing autistic symptoms. The results based on 16 RCTs using 14 NIBS modalities found that only atDCS_F3 + ctDCS_E improved overall core autism symptoms compared with sham controls. The results were consistent in a sensitivity analysis using studies that only included pediatric participants. No active NIBS interventions significantly improved subdomain symptoms of social-communication and restricted/repetitive behaviors compared to sham controls. Moreover,

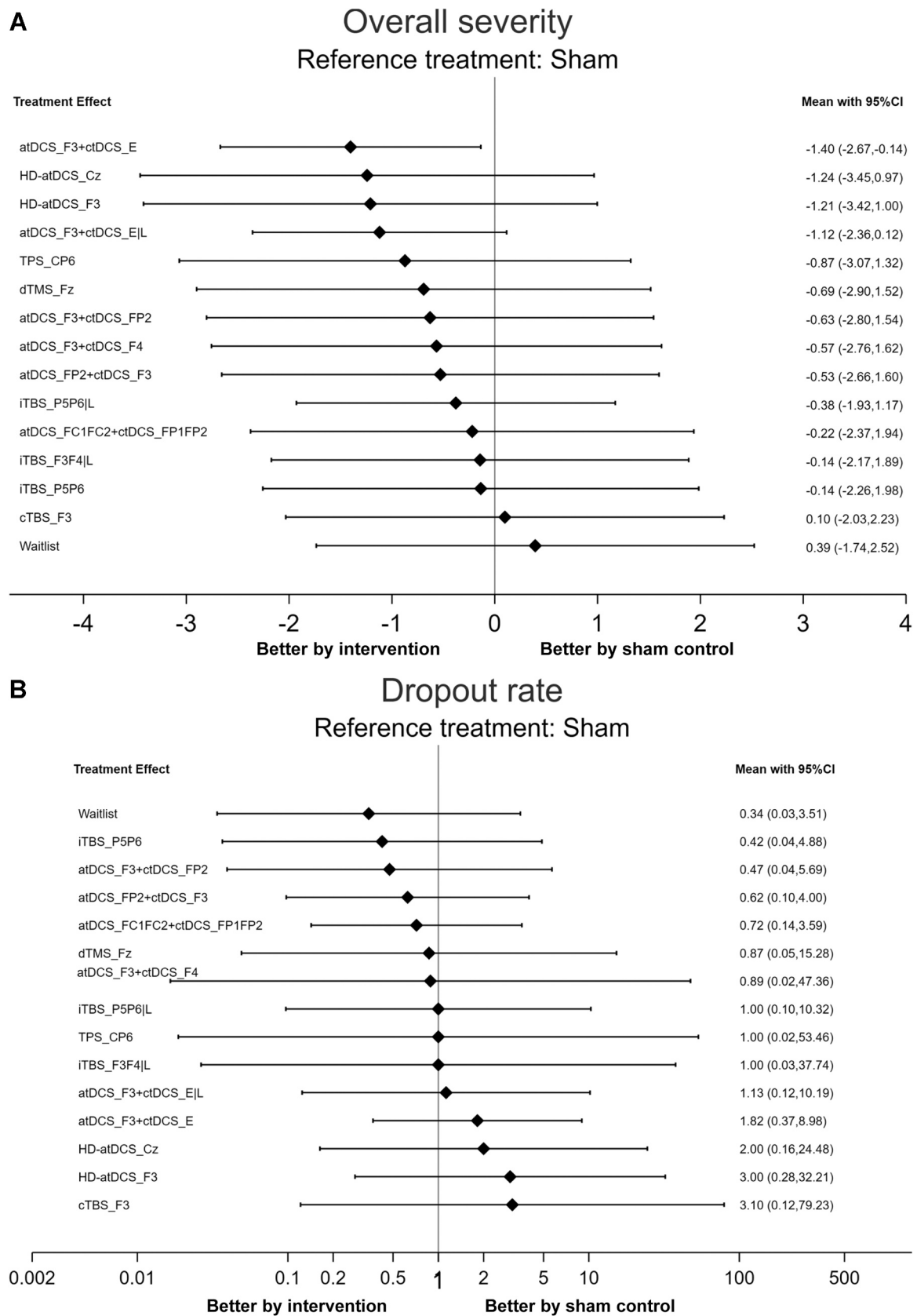


Fig. 3. Forest plot of the primary outcomes: (A) overall core symptoms and (B) dropout rates. When the effect size was less than zero, as presented by the standardized mean difference, the treatment under investigation resulted in a greater reduction in depression severity compared to the sham control. (B) When the effect size was less than one, as presented by the odds ratio, the treatment under investigation demonstrated lower dropout rate compared to the sham control.

the NMA also found no significant difference in the all-cause dropout rates between active NIBS interventions and sham controls. Finally, no serious adverse events were reported in the included studies.

Although previous meta-analyses showed the efficacies of individual NIBS methods for treating ASD (Barahona-Correa et al., 2018; Garcia-Gonzalez et al., 2021; Smith et al., 2022), this is the first NMA to comprehensively compare the efficacy of different NIBS modalities on overall core autism symptoms, social-communication symptoms, and restricted/repetitive behaviors. For overall core autism symptoms, this NMA found that only atDCS_F3 + ctDCS_E was significantly better than the sham control and ranked highest in the SUCRA analysis. This result is at odds with earlier meta-analyses on rTMS (Barahona-Correa et al., 2018; Smith et al., 2022), which suggested that rTMS could improve autistic symptoms. The plausible explanation for this inconsistency is that our study focused exclusively on RCTs, but previous meta-analyses included non-RCTs. For instance, certain open-label trials without a sham control group have shown that inhibitory rTMS on the left DLPFC in ASD has significant therapeutic effects (Baruth et al., 2010; Sokhadze et al., 2010, 2014, 2018), but this result was not reproduced in a more recent RCT using cTBS (Ni et al., 2023), which is considered an inhibitory protocol. Similarly, this phenomenon can be seen in other psychiatric disorders. For example, our previous meta-analysis on rTMS in Tourette syndrome showed significant improvements in tic symptoms when both RCTs and non-RCTs were considered. However, when only considering RCTs with a sham group, no significant differences between active and sham stimulation were found (Hsu et al., 2018). Another interesting finding from this NMA is that the DLPFC seems to be a potential stimulation target for improving autistic symptoms. Previous studies have identified structural alterations in the DLPFC in the individuals with ASD, including increased neuron numbers (Courchesne et al., 2011), hypoactivity (Carlisi et al., 2017), and enlarged brain volume (Carpner and Courchesne, 2005). These changes contribute to ASD-related impairments in emotional processing (Nejati et al., 2021), executive function (Friedman and Robbins, 2022), and language processing (Yeh et al., 2024). Moreover, excitatory-inhibitory imbalance from altered γ -Aminobutyric acid (GABA) and glutamate equilibrium over the DLPFC was found in autistic adults (Maier et al., 2022). An earlier study demonstrated tDCS over the left DLPFC could influence GABA levels (Bunai et al., 2021) which may modulate the cortico-striatal circuitry involved in the pathogenesis of ASD (Soghomonian, 2023). Altogether, our results further highlight the essential role of the DLPFC in ASD.

Further examining social-communication symptoms and restricted/repetitive behaviors, although none of the active NIBS treatments produced significant improvements over the sham control group, a trend from pooled effect sizes and SUCRA analysis suggests that tDCS may be more effective than rTMS in improving these subdomain symptoms. This discrepancy may partly arise from differences in neurophysiological and physical mechanisms between rTMS and tDCS. rTMS induces intracranial electrical currents and depolarizes neurons through modulating the magnetic field (Valero-Cabré et al., 2017). It may produce long-lasting changes through modulating synaptic plasticity, similar to long-term potentiation or long-term depression (Hoogendam et al., 2010; Huang et al., 2017), and altering neuronal excitability by changing the ionic balance around stimulated neurons (Chervyakov et al., 2015). In contrast, tDCS delivers a weak subthreshold current that modulates the resting membrane potential of neurons (Wang et al., 2023a). It can cause neuronal excitation (anodal tDCS) or inhibition (cathodal tDCS), achieving effects through alterations in neurotransmitter levels and release frequency (Yamada and Sumiyoshi, 2021). Another distinction is that, compared to the stimulation coil focus of rTMS (1.5–3 cm depth, approximately 25 mm² area), tDCS electrodes typically affect broader areas (distance between anode and cathode electrodes, approximately 2500 mm² area) (Priori et al., 2009; Wang et al., 2023a). Therefore, tDCS may bring about more diffuse effects than the focal change caused by rTMS. Future head-to-head translational studies and RCTs comparing

tDCS and rTMS are needed to replicate the current observation of this NMA and validate this neurophysiological speculation.

While the therapeutic NIBS has predominantly been utilized in neurotypical adults historically, recent evidence has also confirmed its applicability within pediatric populations (Zewdie et al., 2020). Our sensitivity analysis of this network meta-analysis, which only included studies on children and adolescents, echoed the primary analysis results across all efficacy outcomes. These findings reinforce the evidence supporting the applicability of the NIBS in patients with ASD of all ages. Furthermore, this evidence suggests that NIBS may induce cognitive-behavioral changes in children and adolescents and support the generation of neuroplasticity with potentially beneficial effects on many neurodevelopmental disorders (Bandeira et al., 2021). In this study, no serious adverse events were reported in any of the included studies, perhaps due to strict protocol restrictions advised by each country's food and drug administration (Ni et al., 2023) and the conservative approach regarding the acceptable stimulation intensity for the pediatric-predominant samples. Regarding acceptability, the NMA results showed no significant difference in all-cause dropout rates between any NIBS intervention group and sham control. The safety and tolerability of NIBS in children is of concern to the field, but pediatric-specific guidelines for the various NIBS treatments have not been established. Recent studies have shown that rTMS and tDCS pose minimal risk to school-aged children (Zewdie et al., 2020), and our NMA provides consistent evidence to endorse the acceptability of NIBS in neurodevelopmental populations.

This study has some limitations to be considered. First, owing to the ongoing development and exploration of treatment protocols for ASD in recent years, the number of studies included in this meta-analysis is nearly equivalent to the number of treatment arms (16 studies with 14 treatment arms). Consequently, many treatment arms in our study are represented solely by a single investigation. We, therefore, approach results from these individual studies with caution, given the possible masking of heterogeneity and incoherence. Additionally, we identified design-by-treatment inconsistencies with respect to outcomes related to overall core symptoms and restrictive/repetitive behaviors. This inconsistency might have arisen from one study with three treatment arms (sham, atDCS_F3 + ctDCS_E|L, and atDCS_F3 + ctDCS_E (Auvichayapat et al., 2023)) juxtaposed against other studies with two treatment arms (sham and atDCS_F3 + ctDCS_E|L (Amatachaya et al., 2014, 2015) or sham and atDCS_F3 + ctDCS_E (Qiu et al., 2021)) (eTable 12). Collectively, these factors ultimately led to the current evidence being rated as very low according to the GRADE framework. Nevertheless, many of the studies included in this NMA were published within the past 3 years, indicating that research on the relevant topics is still emerging and burgeoning. We may expect more data in the near future to provide more solid evidence. Second, this NMA used varied ASD assessment tools in different studies (eTable 2). This variation is in part due to the lack of a consensus on the outcome measures and the plethora of scales used to assess symptom severity. For example, despite our efforts to maintain consistency in the scales estimating overall core symptoms (CARS and SRS/SRS-2 used in 9/16 studies), 5 different scales (ATEC, AQ, RAADS, ABC, GARS-2) were used in the 7 remaining studies. Although we prioritized clinician-rating and used standard mean differences for evaluation, each scale may demonstrate different sensitivity to changes in symptoms or different susceptibility to placebo effects, which could have led to inconsistent results. Further research is warranted to investigate the applicability of different rating scales to measure treatment effects on the core autistic symptoms. Third, the age of the participants was not considered as an inclusion criterion during the systematic search since we were expecting a limited number of available studies. For this reason, we conducted a sensitivity analysis for pediatric participants. However, we did not perform the same sensitivity analysis for adult participants, as there were only four RCTs involving adults. Such a limited number of studies is not sufficiently powered to conduct a robust analysis. The disparity in the number of studies by age group

indicates that future studies are encouraged to explore the potential effects of age on NIBS efficacy for ASD. Lastly, we could not include executive function as an outcome in this NMA due to the diversity of the different executive function domains and the different methods used to assess them. However, impaired executive function plays an important role in contributing to associated symptoms and adaptive function in autistic people (Demetriou et al., 2018), warranting a separate meta-analysis dedicated to this essential topic.

5. Conclusion

This NMA presents a comprehensive analysis of all NIBS hitherto used to reduce autistic symptoms and assesses treatment efficacy and acceptability. Our results indicate that atDCS_F3 + ctDCS_E improves the overall core symptoms in autistic people, with similar efficacy in pediatric participants. NIBS is generally safe and well tolerated in autistic people across developmental stages. Furthermore, future studies may build on the preliminary findings from this NMA to improve current NIBS protocols and investigate novel NIBS modalities.

Ethics approval

The institutional review board of Chang Gung Memorial Hospital reviewed the study protocol and granted an exemption from the requirement for ethical approval (No.: 202200827B1).

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Conflict of interest statement

All authors declare no financial interests or potential conflicts of interest regarding the authorship and publication of this article.

Data availability

Data will be made available on request.

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Patient and public involvement

The current study did not directly involve individual participant, so we did not have the chance to approach or explore individual participant's information. Therefore, obtaining Consent to Participate or Consent to Publish in the current study is impossible.

Author's contributions

Yang-Chieh Brian Chen and Chih-Wei Hsu took full responsibility for the literature search, full-text screen, data extraction, and data analysis. Yang-Chieh Brian Chen drafted the manuscript. Hsiang-Yuan Lin, Liang-Jen Wang, Kuo-Chuan Hung, Andre R. Brunoni, Po-Han Chou, Ping-Tao

Tseng, Chih-Sung Liang, Yu-Kang Tu, Pao-Yen Lin, Andre F. Carvalho, Chih-Wei Hsu, Hsing-Chang Ni contributed in study design, concept formation, data interpretation, and manuscript revision. Chih-Wei Hsu and Hsing-Chang Ni took full responsibility for manuscript revision and summary of information from the other authors.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.neubiorev.2024.105807.

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