Research Square

Preprints are preliminary reports that have not undergone peer review.
They should not be considered conclusive, used to inform clinical practice,
or referenced by the media as validated information.

Multimodal rTMS-tDCS for Attention-Deficit/Hyperactivity Disorder in Children: A Randomized, Sham-Controlled Trial on Safety, Efficacy, and Prefrontal Hemodynamics via fNIRS

Zhuoru Zhou
West China Second University Hospital of Sichuan University
Xinping Du
The Affiliated Hospital of Southwest Medical University
Xiaoqin Hu
West China Second University Hospital of Sichuan University
Min Li
West China Second University Hospital of Sichuan University
Dewei Zheng
West China Second University Hospital of Sichuan University
Zhengyu Hu
Traditional Chinese medicine rehabilitation department, Zhejiang University School of Medicine
Qiu Wang
West China Second University Hospital of Sichuan University
Yurong Wen
YRWen611@163.com

West China Second University Hospital of Sichuan University

Study protocol

Keywords: attention deficit hyperactivity disorder, repetitive transcranial magnetic stimulation, transcranial direct current stimulation, functional near-infrared spectroscopy, randomized controlled trial

Posted Date: November 23rd, 2026

DOI: https://doi.org/10.21203/rs.3.rs-9532971/v1

License: This work is licensed under a Creative Commons Attribution 4.0 International License.
Read Full License

Additional Declarations: No competing interests reported.

Multimodal rTMS-tDCS for Attention-Deficit/Hyperactivity Disorder in Children: A Randomized, Sham-Controlled Trial on Safety, Efficacy, and Prefrontal Hemodynamics via fNIRS

Zhuoru Zhou[1,2], Xinping Du[3], Xiaoqin Hu[1,2], Min Li[1,2], Dewei Zheng[1,2], Zhengyu Hu[4], Qiu Wang[1,2], Yurong Wen[1,2]

1. Department of Rehabilitation, West China Second University Hospital, Sichuan University, Chengdu, China

2. Key Laboratory of Birth Defects and Related Diseases of Women and Children (Sichuan University), Ministry of Education, Chengdu, China

3. Department of Rehabilitation, The Affiliated Hospital of Southwest Medical University, Luzhou, China

4. Traditional Chinese medicine rehabilitation department, The Second Affiliated Hospital Zhejiang University School of Medicine, Hangzhou, China

Abstract

Background

Attention-deficit/hyperactivity disorder (ADHD) is a prevalent neurodevelopmental condition with limited treatment options for medication-resistant cases. While non-invasive brain stimulation (NIBS) techniques like repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS) show promise in modulating prefrontal dysfunction—a core pathology

in ADHD—their synergistic effects and neurophysiological mechanisms remain underexplored in pediatric populations. This trial addresses this gap by investigating the safety, clinical efficacy, and prefrontal hemodynamic changes induced by combined rTMS-tDCS in children with ADHD.

Methods

This single-center, randomized, double-blind, sham-controlled trial enrolled 88 children aged 6 – 12 years with DSM-5-diagnosed ADHD. Participants were allocated to four parallel arms: active rTMS + active tDCS, active rTMS + sham tDCS, sham rTMS + active tDCS, and sham rTMS + sham tDCS. Over 4 weeks, all groups received 20 sessions (5 sessions/week) targeting the right dorsolateral prefrontal cortex (r-DLPFC). The primary outcome measured oxygenated hemoglobin (HbO2) changes via functional near-infrared spectroscopy (fNIRS) during an N-back task. Secondary outcomes included executive function (BRIEF-2), attention (IVA-CPT), and behavioral scores (Conners, CBCL). Safety profiles were monitored through weekly adverse event reporting.

Discussion

Combining rTMS with tDCS may offer a novel approach for treating ADHD. Anodal tDCS can lower neuronal activation thresholds, thereby increasing cortical excitability. Subsequent application of rTMS may more effectively induce synaptic plasticity, such as long-term potentiation (LTP), which could enhance cognitive functions related to ADHD. Specifically, targeting these techniques at relevant brain regions may enhance neural activity, positively impacting the core pathophysiological mechanisms of ADHD. However, current research on this combined intervention is limited, necessitating further studies to validate its safety and efficacy.

Trial registration

Chinese Clinical Trial Registry ChiCTR2500096754. Registered on February 6, 2025. https://www.chictr.org.cn/bin/project/edit?pid=255392.

Keywords: attention deficit hyperactivity disorder, repetitive transcranial magnetic stimulation, transcranial direct current stimulation, functional near-infrared spectroscopy, randomized controlled trial.

Administrative information

Note: the numbers in curly brackets in this protocol refer to SPIRIT checklist item numbers. The order of the items has been modified to group similar items (see http://www.equator-network.org/reporting-guidelines/spirit-2013-statement-defining-standard-protocol-items-for-clinical-trials/).

Title {1}	Multimodal rTMS-tDCS for Attention-Deficit/Hyperactivity Disorder in Children: A Randomized, Sham-Controlled Trial on Safety, Efficacy, and Prefrontal Hemodynamics via fNIRS
Trial registration {2a and 2b}.	Chinese Clinical Trial Registry: ChiCTR2500096754. February 6, 2025.

Protocol version {3}	Version 1.0, 6 September 2024
Funding (1)	This work was supported by the Sichuan Provincial Health Commission Scientific Research Project (Grant No. 24CXTD17), titled "Multimodal Data Modeling and Evaluation of Developmental Dyscalculia and Development of the 'Nine-Grid Mathematics' Intelligent Training System", and the Key Research and Development Program of the Science and Technology Department of the Tibet Autonomous Region (Grant No. XZ202501ZY0116), titled "Chronobiological Study of Lung Development Adaptation in a Plateau Infant Cohort."
Author details {5a}	1. Zhuoru Zhou, Xiaoqin Hu, Min Li, Dewei Zheng, Qiu Wang, Yurong Wen, Department of Rehabilitation, West China Second University Hospital, Sichuan University, Chengdu, China; Key Laboratory of Birth Defects and Related Diseases of Women and Children (Sichuan University), Ministry of Education, Chengdu, China. 2. Xinping Du, Department of Rehabilitation, The Affiliated Hospital of Southwest Medical University, Luzhou, China.

	3. Zhengyu Hu, Traditional Chinese medicine rehabilitation department, The Second Affiliated Hospital Zhejiang University School of Medicine, Hangzhou, China.
Name and contact information for the trial sponsor {5b}	West China Second University Hospital, Sichuan University; No. 20, Section 3, Renmin South Road, Chengdu, Sichuan 610041, P.R. China.
Role of sponsor {5c}	The sponsor provided access to institutional research facilities and equipment, but had no involvement in: study execution, analysis, interpretation of the data, or decision to submit results.

Introduction

Background and rationale {6a}

Attention Deficit Hyperactivity Disorder (ADHD) is a common neurodevelopmental disorder characterized primarily by persistent patterns of inattention, hyperactivity, and impulsive behavior. It typically manifests in childhood, between the ages of 6 and 12, with a prevalence rate of 6.5%(2-4). Approximately 70-80% of individuals with ADHD have comorbid psychiatric disorders(5, 6). The core symptoms may persist into adulthood, necessitating long-term management and treatment. Although pharmacological treatment combined with behavioral education remains the mainstream approach, approximately 30% of ADHD patients do not benefit from conventional treatments. Some patients also experience medication resistance, with side effects such as insomnia, reduced appetite,

weight loss, tension, and low mood. Long-term medication use can also affect the growth rate of height and weight in children(7, 8), and may increase the risk of cardiovascular events(9).

There is a high demand for biomarkers in ADHD, as they could help eliminate the subjective nature of interview-based diagnoses and potentially enable earlier diagnosis and personalized medicine. functional near-infrared spectroscopy (fNIRS) can continuously and dynamically monitor the concentration of oxygenated hemoglobin in ADHD children during task performance(10), providing a quantitative image of brain function that reflects the activation of the cerebral cortex. It could serve as an important objective biomarker. Studies have found that children with ADHD experience functional impairments in the prefrontal cortex, particularly with lower concentrations of oxygenated hemoglobin in the right prefrontal cortex(11, 12). The abnormal brain activity patterns observed in brain regions such as the prefrontal cortex, which are associated with cognitive control, emotional processing, and interference response, are central to the pathological mechanisms of ADHD. Interventions targeting these abnormal patterns can significantly improve clinical symptoms.

Non-invasive brain stimulation (NIBS), as a treatment method that directly targets brain function, can significantly address the challenges in ADHD treatment and provide new strategies. Repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS) are the most widely applied NIBS techniques, and their efficacy has been validated in clinical trials for various neurodevelopmental disorders(13, 14). Studies have already shown that rTMS-tDCS combined therapy can effectively improve psychiatric symptoms associated with Alzheimer's disease(15) and insomnia(16). However, the multimodal stimulation approach of rTMS-tDCS in pediatric ADHD research is being attempted for the first time. Given the serious societal impact of

ADHD and the challenges in its treatment, neurostimulation holds great potential as a novel therapeutic approach. Therefore, this study aims to explore the enhanced synergistic effects of rTMS-tDCS combined therapy and its impact on improving core symptoms associated with ADHD, providing clinical evidence for the development of personalized and precise neurostimulation treatment protocols for ADHD, and promoting the enhancement of its therapeutic effects.

Objectives {7}

(1) To prospectively monitor adverse events through periodic follow-up visits and assess the safety and tolerability profiles of multi-modal neuromodulation (rTMS-tDCS) in children with ADHD.

(2) To explore preliminary evidence regarding the intervention efficacy of multi-modal neuromodulation on core ADHD symptoms, with exploratory subgroup analyses addressing ADHD heterogeneity to examine moderating effects of baseline functional levels and gender.

(3) To investigate the neural mechanisms underlying neuromodulation using fNIRS technology, by quantifying hemodynamic changes to characterize treatment effects on neurophysiology, and establishing associations between neural activation patterns and clinical phenotypes to identify potential ADHD-related neural biomarkers.

Trial design {8}

This study is a randomized, double-blind (participants and operators blinded), sham-controlled trial designed to recruit 88 children with ADHD who meet the inclusion criteria. Participants will be randomly assigned to one of four groups: the active rTMS-tDCS group, the rTMS-only group, the tDCS-only group, and the sham group. Each group will undergo a 4-week neurostimulation

intervention, with 5 sessions per week, totaling 20 sessions.

Methods: participants, interventions and outcomes

Study setting {9}

This single-center, prospective randomized controlled trial will be conducted from March 2025 to December 2027 at West China Second University Hospital of Sichuan University, a tertiary maternal and child specialty hospital in China. The study site is equipped with neuromodulation devices: rTMS and tDCS, as well as the fNIRS. Participants will be recruited through referrals from the child developmental behavior clinic, focusing on children aged 6-12 years diagnosed with ADHD according to DSM-5 criteria. The protocol has been approved by the medical ethics review board of west China second university hospital, Sichuan university (Approval No. 2024-319).

Patient and Public Involvement and Population Equity, Diversity, and Inclusion (PRO EDI)

In accordance with the Population, Research Equity, Diversity, and Inclusion (PRO EDI) framework, the anticipated characteristics of the study population are summarized in Table 1. The six core characteristics considered include age, sex, gender, race/ethnicity/ancestry, socioeconomic status, and geographic location.

This study will recruit children with attention-deficit/hyperactivity disorder (ADHD) from the Child Developmental and Behavioral Clinic and existing ADHD follow-up databases at West China Second University Hospital, Sichuan University, Chengdu, China. The eligibility criteria specify an age range of 5–12 years. Sex will be considered in the randomization procedure and statistical analyses. Gender identity, race/ethnicity/ancestry, and socioeconomic characteristics are not explicitly specified as data collection variables in the current study protocol. No restrictions based

on these characteristics are specified in the eligibility criteria. The single-center recruitment setting and the characteristics of the available clinical population may influence the representativeness and generalizability of the findings. These considerations are presented transparently in Table 1.

Table 1. Expected demographic and equity-related characteristics of the trial population (PRO EDI)

Core characteristic	Anticipated characteristics of the study population	Rationale and considerations
Age	Children aged 5–12 years (subject to confirmation against the final eligibility criteria).	The study focuses on children diagnosed with ADHD. The target age range is determined by the diagnostic criteria and study eligibility requirements.
Sex	Eligible participants of either sex.	Sex is considered a balancing factor in the randomization procedure and is included as a covariate in the statistical analyses.
Gender	Gender identity is not explicitly specified as a data collection variable in the current protocol.	The current protocol primarily addresses biological sex and does not specify the collection of gender identity information. Sex and gender are therefore considered distinct characteristics.

Race/ethnicity/ancestry	Participants will be recruited at a single clinical site in Chengdu, Sichuan Province, China. The specific racial, ethnic, and ancestral composition of the study population is not specified.	The protocol does not specify restrictions on recruitment based on race, ethnicity, or ancestry, nor does it explicitly describe the collection of these characteristics.
Socioeconomic status	Socioeconomic characteristics of the anticipated study population are not specified in the current protocol.	Household income, parental educational attainment, and other socioeconomic indicators are not currently specified as data collection variables.
Geographic location	This is a single-center study. Participants will be recruited West China Second University Hospital, Sichuan University, Chengdu, Sichuan Province, China.	through referrals from the Child Developmental and Behavioral Clinic and existing ADHD follow-up databases at the study hospital.

141 **Abbreviations:** ADHD, attention-deficit/hyperactivity disorder; PRO EDI, Population, Research
142 Equity, Diversity, and Inclusion.

143

144 **Eligibility criteria {10}**

145 Inclusion criteria: 1) aged 5 to 12 years; 2) meets the diagnostic criteria for ADHD as outlined in

the 5th edition of the diagnostic and statistical manual of mental disorders (DSM-5); 3) full scale IQ ⩾80, as measured by the Wechsler intelligence scale for children (WISC); 4) no prior history of non-invasive brain stimulation treatment.

Exclusion criteria: 1) history of seizures (including febrile seizures); 2) current use of benzodiazepines (equivalent to lorazepam ⩾2mg) or anticonvulsant medications; 3) history of significant medical or neurological conditions; 4) diagnosis of idiopathic autism spectrum disorder (e.g., fragile x syndrome, tuberous sclerosis); 5) history of severe head injury; 6) presence of metallic implants in the brain; 7) diagnosis of pervasive developmental disorder (PDD), as PDD is considered an exclusion diagnosis for ADHD according to the DSM-IV.

Who will take informed consent? {26a}

Informed consent will be obtained by GCP-certified child psychiatrists. Parents or legal guardians of children with ADHD will receive informed consent documents approved by the ethics committee, which will outline the study's objectives, interventions, potential risks and benefits, and privacy protections. For children aged ⩾8 years, age-appropriate assent forms, illustrated with cartoons, will be used to obtain verbal assent after guardian consent. Participants and their guardians may withdraw from the study at any time without affecting the provision of routine clinical care. Signed consent forms will be retained in duplicate, with originals stored by the hospital's research department and copies provided to the guardians.

Additional consent provisions for collection and use of participant data and biological specimens {26b}

Not applicable. We will not collect any biological specimens from participants, and we are not currently considering the use of these data for ancillary studies.

Interventions

Explanation for the choice of comparators {6b}

This four-arm parallel design includes four groups: the active rTMS-tDCS group, the rTMS-only group, the tDCS-only group, and the sham group. This structure allows the independent evaluation of the effects of rTMS and tDCS compared with sham stimulation, while also enabling exploratory examination of their combined effects. rTMS sham coil producing equivalent acoustic artifacts without magnetic pulses, and tDCS 30-second ramp-up/down phase maintaining skin sensation with 0 mA sustained current. This design controls for nonspecific effects while maintaining blinding integrity. By including both active and sham groups, the study aims to rigorously evaluate the efficacy of multimodal neurostimulation and its components, while minimizing bias and ensuring the reliability of results. A similar multi-arm design has been applied in patients with Alzheimer’s disease and has been shown to be feasible(15).

Intervention description {11a}

All groups receiving a 4-week intervention (1 session per day, monday to friday, for a total of 20 sessions). Assessments will be conducted at baseline, post-intervention, and at the 4-week follow-up (including the BRIEF-2 executive function scale, conners’ third edition, IVA-CPT attention test, Achenbach child behavior checklist, and fNIRS test). Weekly visits and monitoring of adverse events will also be conducted.

Intervention Parameters

rTMS Protocol (Fig.1a)

Equipment: the Magneuro CCY-100 system (Yiruide Medical Technology Co., Ltd., Wuhan, China) equipped with an 8-shaped coil (outer diameter 90 mm).

Localization: the right dorsolateral prefrontal cortex (r-DLPFC) was targeted, with the initial site placed at the F4 position of the 10-10 EEG system. The resting motor threshold (RMT) was determined over the left abductor pollicis brevis motor cortex, and after that, the coil was moved 5 cm anteriorly along the sagittal midline for verification.

Parameters:

Frequency: 10 Hz

Intensity: 100% RMT, the resting motor threshold (RMT) is defined as the minimum stimulation intensity required to elicit motor evoked potentials (MEPs) exceeding 50 μV in the primary motor cortex using five consecutive single-pulse stimuli.

Pulse duration: 4 seconds

Inter-stimulus interval: 26 seconds

Single session duration: 20 minutes (1600 pulses)

tDCS Protocol (Fig.1b)

Equipment: high-precision tDCS system (Keyue Co., Ltd., Xi'an, China), with a 4×1 ring electrode array.

Localization: based on the SimNIBS v4.0 electric field simulation(17), the anode was placed at the F4 position (10-10 system). The cathodes were placed at F6, F2, FC4, and FC6, equidistant from each other

with a 3 cm spacing, arranged in a ring around the anode.

Parameters:

Current: 2 mA

Ramp-up/ramp-down: 30 seconds

Stimulation duration: 20 minutes

Sham Stimulation

Sham rTMS: a sham coil was used, with magnetic field output <5%, providing the same auditory and visual feedback as the active stimulation. The sham coil has the same appearance as the active coil and mimics its operational procedures and sensory experience, while delivering only negligible magnetic stimulation. This approach preserves the sensory characteristics of stimulation while preventing meaningful cortical activation, thereby maintaining blinding for both participants and operators.

Sham tDCS: under the sham stimulation condition, the current was ramped up from 0 mA to 2 mA over the first 30 seconds, maintained for 30 seconds, and then immediately decreased to 0 mA. The sham stimulation mimicked the tingling and itching sensations associated with real stimulation but did not produce any physiological effects. This procedure mimics the initial tingling and itching sensations associated with active stimulation while delivering no sustained current. The process was automatically controlled by the stimulator, making it difficult for participants to distinguish between active and sham stimulation. The device programming personnel (unblinded) and clinical operators (blinded) were separated to ensure proper blinding during the procedure.

Criteria for discontinuing or modifying allocated interventions {11b}

Immediate termination of stimulation if a participant experiences severe adverse events (e.g., seizures, syncope, or intolerable pain). Temporary suspension for moderate adverse events (e.g., scalp irritation, headache) until resolution, with resumption upon participant consent. Participants or guardians may voluntarily withdraw at any time without providing a reason.

Modification or exclusion will occur if participants engage in additional rehabilitation therapies or undergo any changes in their medication regimen during the 4-week neurostimulation period. A 30-day washout period will be required for re-enrollment.

Strategies to improve adherence to interventions {11c}

Participants missing two consecutive sessions will receive WeChat reminders within 24 hours, followed by a guardian phone call if unresolved. A third-party auditor will cross-check 20% of session logs against video recordings to detect protocol violations.

Participants completing $\geqslant$18/20 sessions will receive a certificate of participation and a small gift (e.g., educational toy). Participants will receive a cartoon calendar to track progress, with stickers awarded post-session. A dedicated hotline will address guardian concerns about side effects or scheduling. Protocol rescue measures: 1) missed sessions due to illness/emergencies can be rescheduled within 7 days; 2) if device malfunction occurs mid-session, the full protocol will be repeated at no cost to the participant.

Relevant concomitant care permitted or prohibited during the trial {11d}

Participants are permitted to continue stable pharmacological treatments for ADHD (e.g.,

methylphenidate, atomoxetine) if doses remain unchanged throughout the trial, but dose adjustments or initiation of new ADHD medications will require exclusion from per-protocol analyses. Concurrent NIBS therapies (e.g., EEG neurofeedback), structured behavioral interventions (e.g., cognitive-behavioral therapy, occupational therapy), and experimental rehabilitation programs are prohibited during the 4-week intervention period to avoid confounding treatment effects. Emergency medical care for unrelated conditions (e.g., infections, injuries) is permitted and must be reported to the trial team within 48 hours. All concomitant therapies will be documented weekly via guardian-completed logs and cross-verified against electronic medical records.

Provisions for post-trial care {30}

Participants experiencing trial-related adverse events will receive free medical care until resolution. Those with worsened ADHD symptoms will be prioritized for clinical follow-up. The sham group participants may opt for open-label active stimulation if ethically approved.

Outcomes {12}

Primary outcome:

fNIRS HbO2

Prior to fNIRS recording, participants were seated in a sound-attenuated, dimly lit laboratory and instructed to remain motionless for 10 minutes to stabilize physiological parameters, including heart rate and blood pressure. After this stabilization period, participants performed a computerized N-back task synchronized with fNIRS acquisition (Fig. 2). The task comprised three conditions: in the 0-back condition, participants pressed "A" for the target stimulus "X" and "L" for non-targets; in the

1-back condition, they pressed "A" if the current letter matched the immediately preceding one; and in the 2-back condition, they pressed "A" if the current letter was identical to the letter presented two trials earlier. Each block consisted of 15 trials (5 targets, 10 non-targets) with precise temporal parameters: a stimulus presentation of 1,000 ms, an inter-stimulus interval of 2,000 ms (with a centered fixation cross), and a block duration of 30 s. The task structure involved 4 repetitions per condition (totaling 12 blocks) that were fully randomized in condition order across participants to counterbalance potential fatigue effects, resulting in a total acquisition time of 6.7 ± 0.3 minutes. Visual instructions specifying task demands were displayed for 5 s preceding each block, and behavioral responses (accuracy and reaction time) were recorded via E-Prime 3.0 (Psychology Software Tools, USA).

Hemodynamic signals were acquired using the fNIRS system (NirSmart-6000B, Danyang Huichuang Medical Equipment Co., Ltd.), configured with 29 LEDs emitting dual wavelengths (730 nm and 850 nm) and 30 photodiodes operating at a sampling rate of 10 Hz. The system maintained a source-detector distance of 30 mm, and utilized a channel configuration comprising 79 measurement channels. Probe placement was achieved with a midline reference at Fpz (according to the international 10-20 EEG system) and an inferior row oriented toward T3/T4.

Secondary outcome:

1) behavior rating inventory of executive function, second edition (BRIEF-2) score change;

The BRIEF-2 Parent Form was administered to evaluate children's executive functioning. This standardized tool comprises 63 items across nine subscales (e.g., inhibit, working memory, emotional control), with parents rating their child's daily behaviors over the preceding six months using a 3-point Likert scale (1="never" to 3="often").

2) conners' rating scales score change;

The Conners was utilized to assess behavioral symptoms, particularly ADHD-related manifestations, in children and adolescents. Both parent- and teacher-report forms were administered, with respondents rating the frequency and severity of behaviors over the preceding month using a 4-point Likert scale (0="not true at all" to 3="very much true"). Raw scores were converted to age- and gender-adjusted T-scores, with elevated scores indicating clinically significant concerns.

3) integrated visual and auditory continuous performance test (IVA-CPT) score change;

The IVA-CPT is a computerized dual-modality assessment tool designed to evaluate sustained and divided attention. Participants respond to target stimuli presented in visual or auditory modalities by pressing a designated button, while withholding responses to non-targets. Key metrics include reaction time variability, commission errors, and omission errors, which collectively quantify attentional deficits.

4) child behavior checklist score change (CBCL);

The CBCL, a core component of the Achenbach system, was administered to evaluate behavioral and emotional problems in children aged 6 − 18 years. Both parent- and teacher-report forms (112 items each) assess symptom frequency over the preceding six months using a 3-point Likert scale (0="not true" to 2="very true"). The CBCL yields two broad domains: internalizing problems (e.g., anxiety, depression) and externalizing problems (e.g., aggression, attention deficits).

Participant timeline {13}

The figure 3 outlines the timing and evaluation of the study (Fig. 3).

Sample size {14}

The sample size was determined based on the primary outcome (prefrontal HbO2 changes) and a synergistic effect size anticipated for combined rTMS-tDCS stimulation, derived from Lu et al.'s tDCS – fNIRS study (d = 0.72)(18) and Zhuo et al(4), using G*Power (v3.1)

We assumed a moderate-to-large effect ($f \approx 0.30$; approx. Cohen's $d \approx 0.60 - 0.70$ for pairwise contrasts commonly observed in small neuromodulation – fNIRS studies). Under a 2×2 factorial ANOVA framework ($\alpha = 0.05$, $1 - \beta = 0.90$), this yielded an initial estimate of approximately 19 participants per arm (total $N \approx 76$). Given the higher variance (medication status, ADHD type) and lower detectability typical of pediatric fNIRS measures, as well as the uncertainty surrounding interaction effects, we increased the planned sample size to accommodate repeated measures and potential attrition and applied a 20% attrition allowance. After these adjustments the planned recruitment target is 88 participants (22 per group). This target preserves adequate power for the primary (main-effect) analyses while treating any factorial interaction tests as secondary or exploratory.

Recruitment {15}

Participants will be recruited from the child developmental behavior clinic outpatient department and existing ADHD follow-up databases at West China Second University Hospital, Sichuan University, between March 2025 and December 2027.

Assignment of interventions: allocation

Sequence generation {16a}

Randomization

Participants will be randomly assigned to one of four groups using stratified block randomization via the BiAS software (https://www,bias-online,de/). Allocation sequences were generated by an independent statistician blinded to clinical data. The randomization list will be embedded in the electronic Case Report Form (eCRF) system. After baseline assessments, group assignment will be automatically revealed through the eCRF.

Concealment mechanism {16b}

Allocation concealment is achieved through preloaded coded stimulation protocols managed by an independent programmer. rTMS and tDCS devices utilize stimulation templates labeled with codes (e.g., "Protocol_A1", "Protocol_B2") that are stored in a password-protected repository. fNIRS and behavioral data are anonymized using participant IDs. Blinded evaluators analyze neuroimaging and clinical scores using the NirSmart and SPSS platforms, respectively, while statisticians process only anonymized datasets without group labels until the final analysis.

Implementation {16c}

Randomization will be implemented through a centralized web-based system. After eligibility confirmation and completion of baseline assessments, participants will be stratified by ADHD subtype (inattentive / hyperactive-impulsive / combined) as the primary stratification factor. Secondary covariates, including sex and current medication use, will be balanced using a computerized minimization procedure. A computer-generated randomization sequence incorporating both stratification and minimization is sent as encrypted codes directly to the rTMS

and tDCS devices, ensuring clinicians cannot modify or view them. Following allocation, anonymized data are uploaded to a blinded server accessible to outcome assessors and statisticians via unique participant IDs, maintaining blinding integrity throughout the trial.

Assignment of interventions: blinding

Who will be blinded {17a}

This is a double-blind trial in which participants, treating clinicians, outcome assessors, and data analysts will remain blinded to treatment allocation (active or sham rTMS－tDCS). To maintain blinding: (1) Participants will receive sham interventions designed to mimic the sensory experience of active rTMS or tDCS (e.g., high-performance sham coil, brief ramp-up/ramp-down currents, and consistent device panel indicators). Environmental interactions and reassurance will be standardized across all groups. (2) Treating clinicians are blinded by separating programming personnel (non-blinded) from clinical operators (blinded). Operators only initiate encrypted protocols automatically delivered to devices and cannot view or modify treatment parameters. (3) Blinding assessment will be conducted at multiple time points using Bang’ s Blinding Index for participants, guardians, and clinicians, with results reported in supplementary materials. Sensitivity analyses will account for any significant blinding breaches.

Procedure for unblinding if needed {17b}

Unblinding is allowed only in medical emergencies. Requests must be submitted via an encrypted portal to the Independent Unblinding Committee (IUC), which solely holds the randomization codes. Once approved, the IUC will notify the treating physician of the group assignment, recording the

rationale and timestamp. After database lock, full unblinding will occur and group assignments will be disclosed in the final report.

Data collection and management

Plans for assessment and collection of outcomes {18a}

Outcome assessments will be conducted at baseline, post-intervention (4 weeks), and at a 4-week follow-up, including neurophysiological measures, clinical scales, neurocognitive tests, and safety monitoring. All outcome assessments will be performed by trained evaluators who remain blinded to group allocation to minimize assessment bias. At the first, sixth, and final sessions, participants (if age/understanding allows), their guardians, and operators will complete brief blinding questionnaires. Specifically, neurophysiological measures involve assessing hemodynamic changes via fNIRS during the N-back task. Clinical scales include the BRIEF-2 (executive function), Conners 3rd Edition (ADHD symptoms), IVA-CPT (attention/impulsivity), and the CBCL (behavioral problems). Safety monitoring entails recording adverse events weekly.

Plans to promote participant retention and complete follow-up {18b}

To minimize attrition, several measures will be implemented: child-friendly engagement strategies such as sticker rewards after each session and cartoon-themed progress trackers will be provided; guardians will receive automated SMS/WeChat reminders 24 hours before visits and follow-up phone calls after two missed sessions; and flexible scheduling options will be offered. Participants who discontinue interventions will remain in follow-up for intention-to-treat (ITT) analyses.

Data management {19}

Management will be encrypted data entry, storage, and audit trail logging. Access control is maintained through role-based permissions. Daily encrypted backups will be made to Sichuan University's secure servers, with disaster recovery protocols in place.

Confidentiality {27}

Participant confidentiality is ensured by replacing personal information with unique IDs, and all staff are bound by signed confidentiality agreements. All data access and modifications are tracked via access logs. Additionally, raw data will be retained for 10 years post-trial, with physical records shredded and electronic data cryptographically erased.

Plans for collection, laboratory evaluation and storage of biological specimens for genetic or molecular analysis in this trial/future use {33}

No biological specimens will be collected in this trial.

Statistical methods

Statistical methods for primary and secondary outcomes {20a}

Preprocessing: fNIRS data will be preprocessed using the Homer2 or NIRS-SPM toolboxes in MATLAB 2023a. Custom scripts will convert raw light intensity data into hemoglobin concentration changes (HbO and HbR) while correcting for motion artifacts and baseline drift. For each channel, the oxy-hemoglobin (oxy-Hb) signal will be detrended using a first-order polynomial fit and a high-pass filter (cut-off frequency: 0.01 Hz) to eliminate baseline drift, followed by a low-pass filter at

0.8 Hz to remove cardiac pulsations.

Primary fNIRS analysis:

Hemodynamic changes (HbO and HbR) in pre-specified regions of interest will be analyzed using linear mixed-effects models (LMMs) to account for repeated measurements and nested channel/time structures. Fixed effects in the models will include the main effects of rTMS and tDCS, as well as their interaction, which will be interpreted exploratorily to assess potential state-dependent or metaplasticity modulation. Additional covariates will include session number (time point), ADHD subtype (inattentive, hyperactive-impulsive, or combined), medication status (yes/no), medication type and weight-adjusted dose (mg/kg or low/medium/high), baseline HbO_2, and sex. fNIRS multi-channel data will be analyzed according to a priori ROI partitions, with primary results reported for prefrontal ROIs, and multiple comparisons will be corrected using Bonferroni or false discovery rate procedures. Contrast values for each block will be computed between target (4 – 24 s post-block onset) and baseline periods (14 – 24 s pre-block onset).

Behavioral analysis:

Baseline and post-intervention behavioral measures will include N-back accuracy/reaction time, BRIEF-2, Conners 3rd Edition, IVA-CPT, and CBCL scores. Mixed-design ANOVA or LMMs will be applied, with time (baseline, post-intervention, follow-up) and treatment group as factors, while controlling for ADHD subtype and medication as covariates. Pairwise between-group comparisons (rTMS-tDCS vs single rTMS, single tDCS, sham) and within-group comparisons (baseline vs post-intervention, follow-up) will be conducted. Bonferroni correction will be applied for multiple comparisons (between-group $P < 0.017$, within-group $P < 0.025$), with effect sizes reported as partial eta squared. Sensitivity analyses will be performed by excluding participants with recent medication

changes or analyzing only medication-free participants.

Correlation and network analysis:

Pearson correlations will examine the relationship between behavioral scores and fNIRS signals. Functional brain networks will be constructed from fNIRS data, with metrics such as synchrony and local efficiency evaluated. Exploratory analyses will assess whether tDCS modulates rTMS effects in a state-dependent manner, based on time/space patterns of HbO_2 changes across channels.

Interim analyses {21b}

No interim analyses are planned in the trial.

Methods for additional analyses (e.g., subgroup analyses) {20b}

Subgroup analyses will be conducted to explore potential moderators of treatment response, with ADHD subtype (inattentive, hyperactive-impulsive, or combined) designated as the primary stratification factor. Sex and medication status will be included as secondary covariates and balanced across groups using dynamic minimization to avoid cell fragmentation and maintain statistical efficiency. Linear mixed-effects models will include fixed effects for treatment (rTMS-tDCS vs. sham), time points, ADHD subtype, sex, and medication status, with random intercepts for subjects to account for repeated measurements. Post hoc contrasts will be adjusted for multiple comparisons using the Holm-Bonferroni method, and fNIRS analyses will be guided by predefined ROI-based channels. Sensitivity analyses will exclude participants with comorbid conditions (e.g., ASD, learning disabilities) and/or recent medication changes to isolate ADHD-specific effects. Exploratory analyses will examine neural-behavioral correlations within subgroups (e.g., prefrontal

HbO changes vs. BRIEF-2 scores) using partial least squares regression, with findings considered hypothesis-generating.

Methods in analysis to handle protocol non-adherence and any statistical methods to handle missing data {20c}

Participants deviating from the intervention protocol (e.g., missing >20% sessions or receiving concurrent therapies) will be excluded from per-protocol analyses but retained in the ITT population. Missing fNIRS or behavioral data will be addressed using multiple imputation. For participants lost to follow-up, baseline characteristics will be compared between completers and non-completers to assess potential bias. If >10% data are missing, pattern-mixture models will evaluate the robustness of findings under different missingness assumptions.

Plans to give access to the full protocol, participant-level data and statistical code {31c}

This protocol is publicly available and the data sets generated/anal analyzed during the current study are available from the corresponding authors on reasonable request.

Oversight and monitoring

Composition of the coordinating center and trial steering committee {5d}

The coordinating center, located at west China second university hospital, sichuan university, will manage trial operations, including recruitment, data collection, and protocol adherence. The trial steering committee, an independent body, comprises a chair, a biostatistician, an ethicist, and a patient advocate.

Composition of the data monitoring committee, its role and reporting structure {21a}

The data monitoring committee, independent of the sponsor and investigators, includes a senior clinical trial methodologist, a pediatric psychiatrist, a neuroimaging expert, and a biostatistician. The data monitoring committee monitors safety data and conducts blinded interim analyses at 25%, 50%, and 75% enrollment to assess futility or safety concerns.

Adverse event reporting and harms {22}

Adverse events are defined as any untoward medical occurrence during the trial, with serious adverse events including death, life-threatening conditions, hospitalization, or persistent disability. Serious adverse events are reported to the ethics board and regulatory authorities within 24 hours. Severe adverse events (e.g., seizures) result in immediate stimulation suspension, with free medical care provided.

Frequency and plans for auditing trial conduct {23}

Audit is not planned in this trial.

Plans for communicating important protocol amendments to relevant parties (e.g., trial participants, ethical committees) {25}

Substantial protocol amendments will be submitted to the ethics committee for approval prior to implementation. Approved changes will be communicated to participants/guardians via revised consent forms. Public registries (ClinicalTrials.gov) will be updated within 30 days.

Dissemination plans {31a}

The results of this trial will be communicated through conference presentation and publication of peer-reviewed research article.

Discussion

This randomized, double-blind, sham-controlled trial is designed to evaluate the feasibility and preliminary efficacy of combined rTMS-tDCS neuromodulation for treating children with ADHD, while investigating the potential of fNIRS as a biomarker for monitoring treatment-induced neurophysiological changes. Utilizing a factorial design targeting the r-DLPFC, this study aims to address the core pathological mechanism of executive dysfunction in ADHD, with the goal of shifting from symptom-oriented to neurophysiology-guided intervention paradigms. The protocol will enable precise assessment of synergistic effects between rTMS and tDCS, although such interactions are considered exploratory and hypothesis-generating rather than confirmatory.

A meta-analysis(19) demonstrated that tDCS applied to the DLPFC can partially improve cognitive functions, including attention/alertness, working memory, executive function, processing speed, verbal fluency, verbal learning, and social cognition. Notably, a recent randomized controlled trial employing unimodal tDCS intervention demonstrated that anodal stimulation over the right inferior frontal gyrus significantly enhanced interference control as assessed by the flanker task(20). Additionally, other studies have shown that tDCS also enhances certain cognitive subdomains in patients with schizophrenia (21) and Alzheimer's disease(22). This provides a precise intervention pathway for disorders such as ADHD, which are characterized by core deficits in cognitive control.

A key focus and challenge in current clinical research lies in accelerating the onset of therapeutic effects. The combined rTMS-tDCS intervention may produce additive or synergistic effects, with mechanisms potentially related to tDCS-mediated membrane polarization enhancing cortical excitability and rTMS-induced long-term potentiation (LTP) promoting lasting synaptic plasticity(23, 24). The temporally coordinated application of both modalities can generate additive effects, operating in accordance with homeostatic plasticity mechanisms.

Temporally coordinated application of both modalities could facilitate plasticity in accordance with homeostatic mechanisms, but these effects remain theoretical and will be explored using fNIRS-derived neurophysiological measures. At the molecular level, multimodal neuromodulation might further enhance synaptic plasticity—and consequently accelerate behavioral improvements—through modulation of neurotransmitter/receptor expression, intrinsic/extrinsic neuronal properties, and neurotrophic factor activation(25)(26)(27). These mechanistic insights are intended to guide exploratory analyses and interpretation, rather than to provide definitive causal conclusions.

Limitation

This study has several limitations. First, the single-center design may restrict the generalizability of the findings, necessitating multicenter studies to validate its applicability across diverse populations. Second, while the 4-week intervention period was sufficient to detect acute effects, it could not assess long-term efficacy. Future studies should incorporate extended follow-up periods to evaluate the durability of effects and potential delayed benefits. Third, despite the use of standardized sham stimulation protocols, operational measures to assess blinding integrity, and strict separation of device programmers from clinical operators, achieving complete blinding in pediatric

neuromodulation trials remains inherently challenging, particularly given potential sensory differences between active and sham stimulation. The impact of any residual unblinding will be evaluated through sensitivity analyses. Fourth, while the sample size was estimated based on effect sizes from comparable pediatric fNIRS studies and incorporated blinded sample size reassessment to account for data variability, the exploratory nature of the interaction analysis between rTMS and tDCS may be underpowered. Therefore, interaction effects will be interpreted as hypothesis-generating rather than confirmatory. Fifth, although medication status was systematically recorded and incorporated as a covariate in the primary mixed-effects models, and sensitivity analyses excluding participants with recent medication changes or those on polypharmacy are planned, residual confounding due to concomitant pharmacotherapy cannot be entirely excluded.

Trial status

This trial is currently in the active recruitment phase, following prospective registration at Chinese Clinical Trial Registry (ChiCTR2500096754) on 6 February 2025 and ethical approval (No. 2024-319) granted by the Medical Ethics Review Board of West China Second University Hospital, Sichuan University on 13 November 2024. The study protocol (Version 1.0, 6 September 2024) commenced participant recruitment on 1 March 2025, with an anticipated completion date of 31 December 2027.

Abbreviations

ADHD

Attention Deficit Hyperactivity Disorder

586 rTMS

587 repetitive Transcranial Magnetic Stimulation

588 tDCS

589 transcranial Direct Current Stimulation

590 fNIRS

591 functional Near-Infrared Spectroscopy

592 DLPFC

593 Dorsolateral Prefrontal Cortex

594 r-DLPFC

595 right Dorsolateral Prefrontal Cortex

596 NIBS

597 Non-invasive Brain Stimulation

598 LTP

599 Long-Term Potentiation

600 RMT

601 Resting Motor Threshold

602 MEP

603 Motor Evoked Potential

604 BRIEF-2

605 Behavior Rating Inventory of Executive Function, Second Edition

606 IVA-CPT

607 Integrated Visual and Auditory Continuous Performance Test

608 CBCL

609 Child Behavior Checklist

610 DSM-5

611 Diagnostic and Statistical Manual of Mental Disorders, 5th Edition

612 WISC

613 Wechsler Intelligence Scale for Children

614 NMPA

615 National Medical Products Administration

616 eCRF

617 electronic Case Report Form

618 ITT

619 Intention-to-Treat

620 HbO

621 Oxy-hemoglobin

622 HbR

623 Deoxy-hemoglobin

624 EEG

625 Electroencephalogram

626 PDD

627 Pervasive Developmental Disorder

628 ASD

629 Autism Spectrum Disorder

MCID

Minimal Clinically Important Difference

Declarations

Acknowledgements

The investigators gratefully acknowledge the children and their families who participated in this trial. We extend our sincere appreciation to the clinical staff at West China Second University Hospital, Sichuan University, for their operational support in participant recruitment and intervention delivery. Special thanks to the Child Developmental Behavior Clinic team for their expertise in diagnostic assessments. Technical assistance provided by Danyang Huichuang Medical Equipment Co., Ltd. in fNIRS device calibration is also acknowledged.

Authors' contributions

Zhuoru Zhou was responsible for conceptualizing the study design, developing the experimental protocol, securing funding support, and drafting the initial manuscript; Xinping Du led the sample size calculation and design of the randomization procedure, and completed the methodological validation; Xiaoqin Hu coordinated the participant recruitment process, conducted the fNIRS neurophysiological assessments, and monitored adverse events; Min Li administered the behavioral assessments, ensured protocol compliance, and coordinated the ethical review process; Dewei Zheng optimized the parameters of the multimodal neuromodulation devices, established the quality control standards for sham stimulation, and managed data normalization; the corresponding author, Yurong Wen and Qiu Wang, provided comprehensive academic guidance, elucidated the

652 neurobehavioral mechanisms, and performed critical manuscript revisions and final approval. All
653 authors contributed to the interpretation of the results, reviewed, and approved the final manuscript.
654
655 **Funding**
656 This work was supported by the Sichuan Provincial Health Commission Scientific Research Project
657 (Grant No. 24CXTD17), titled "Multimodal Data Modeling and Evaluation of Developmental
658 Dyscalculia and Development of the 'Nine-Grid Mathematics' Intelligent Training System", and
659 the Key Research and Development Program of the Science and Technology Department of the
660 Tibet Autonomous Region (Grant No. XZ202501ZY0116), titled "Chronobiological Study of Lung
661 Development Adaptation in a Plateau Infant Cohort."
662
663 **Availability of data and material**
664 The data sets generated and analyzed during the current study are available from the corresponding
665 authors on reasonable request.
666
667 **Ethics approval and consent to participate**
668 The study protocol is approved by the Medical Ethics Review Board of West China Second
669 University Hospital, Sichuan University (No. 2024-319). All participants provided written informed
670 consent.
671
672 **Consent for publication**
673 Not applicable.

Competing interests

The authors declare that they have no competing interests.

Footnotes

Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

References

1. Chalabianloo F, Fadnes LT, Mordal J, Spigset O, Loberg EM, Halmoy A, et al. Impact of dextroamphetamine substitution on the use of illicit amphetamines in adults with amphetamine dependence: a study protocol for the multicentre double blind randomised controlled trial ATLAS4Dependence. BMJ OPEN. 2025;15(10).

2. Posner J, Polanczyk GV, Sonuga-Barke E. Attention-deficit hyperactivity disorder. Lancet. 2020;395(10222):450–62.

3. Liu A, Xu Y, Yan Q, Tong L. The Prevalence of Attention Deficit/Hyperactivity Disorder among Chinese Children and Adolescents. Sci Rep. 2018;8(1):11169.

4. Zhuo L, Zhao X, Zhai Y, Zhao B, Tian L, Zhang Y, et al. Transcutaneous electrical acupoint stimulation for children with attention-deficit/hyperactivity disorder: a randomized clinical trial. Transl Psychiatry. 2022;12(1):165.

5. Kessler RC, Adler LA, Berglund P, Green JG, McLaughlin KA, Fayyad J, et al. The effects of

696 temporally secondary co-morbid mental disorders on the associations of DSM-IV ADHD with adverse
697 outcomes in the US National Comorbidity Survey Replication Adolescent Supplement (NCS-A). Psychol
698 Med. 2014;44(8):1779–92.
699 6. Kittel-Schneider S, Arteaga-Henriquez G, Vasquez AA, Asherson P, Banaschewski T, Brikell I, et
700 al. Non-mental diseases associated with ADHD across the lifespan: Fidgety Philipp and Pippi
701 Longstocking at risk of multimorbidity? Neurosci Biobehav Rev. 2022;132:1157–80.
702 7. Greenhill LL, Swanson JM, Hechtman L, Waxmonsky J, Arnold LE, Molina BSG, et al. Trajectories
703 of Growth Associated With Long-Term Stimulant Medication in the Multimodal Treatment Study of
704 Attention-Deficit/Hyperactivity Disorder. J Am Acad Child Adolesc Psychiatry. 2020;59(8):978–89.
705 8. Faraone SV, Biederman J, Morley CP, Spencer TJ. Effect of stimulants on height and weight: a
706 review of the literature. J Am Acad Child Adolesc Psychiatry. 2008;47(9):994–1009.
707 9. Wright N, Moldavsky M, Schneider J, Chakrabarti I, Coates J, Daley D, et al. Practitioner Review:
708 Pathways to care for ADHD - a systematic review of barriers and facilitators. J Child Psychol Psychiatry.
709 2015;56(6):598–617.
710 10. Crippa A, Salvatore C, Molteni E, Mauri M, Salandi A, Trabattoni S, et al. The Utility of a
711 Computerized Algorithm Based on a Multi-Domain Profile of Measures for the Diagnosis of Attention
712 Deficit/Hyperactivity Disorder. Front Psychiatry. 2017;8:189.
713 11. Gu Y, Miao S, Han J, Liang Z, Ouyang G, Yang J, et al. Identifying ADHD children using
714 hemodynamic responses during a working memory task measured by functional near-infrared
715 spectroscopy. J Neural Eng. 2018;15(3):035005.
716 12. Miao S, Han J, Gu Y, Wang X, Song W, Li D, et al. Reduced prefrontal cortex activation in children
717 with attention-deficit/hyperactivity disorder during go/no-go task: a functional near-infrared

718 spectroscopy study. Frontiers in Neuroscience. 2017;11:367.

719 13. Camacho-Conde JA, Gonzalez-Bermudez MDR, Carretero-Rey M, Khan ZU. Brain stimulation: a

720 therapeutic approach for the treatment of neurological disorders. CNS Neurosci Ther. 2022;28(1):5–18.

721 14. Westwood SJ, Radua J, Rubia K. Noninvasive brain stimulation in children and adults with

722 attention-deficit/hyperactivity disorder: a systematic review and meta-analysis. J Psychiatry Neurosci.

723 2021;46(1):E14–e33.

724 15. Hu Y, Jia Y, Sun Y, Ding Y, Huang Z, Liu C, et al. Efficacy and safety of simultaneous rTMS-tDCS

725 over bilateral angular gyrus on neuropsychiatric symptoms in patients with moderate Alzheimer's disease:

726 A prospective, randomized, sham-controlled pilot study. Brain Stimul. 2022;15(6):1530–7.

727 16. Zhou Q, Liu Z, Yu C, Wang Q, Zhuang W, Tang Y, et al. Effect of combined treatment with

728 transcranial direct current stimulation and repetitive transcranial magnetic stimulation compared to

729 monotherapy for the treatment of chronic insomnia: a randomised, double-blind, parallel-group,

730 controlled trial. BMC Med. 2024;22(1):538.

731 17. Thielscher A, Antunes A, Saturnino GB. Field modeling for transcranial magnetic stimulation: A

732 useful tool to understand the physiological effects of TMS? Annu Int Conf IEEE Eng Med Biol Soc.

733 2015;2015:222–5.

734 18. Lu H, Zhang Y, Qiu H, Zhang Z, Tan X, Huang P, et al. A new perspective for evaluating the efficacy

735 of tACS and tDCS in improving executive functions: A combined tES and fNIRS study. Hum Brain

736 Mapp. 2024;45(1):e26559.

737 19. Dedoncker J, Brunoni AR, Baeken C, Vanderhasselt MA. The effect of the interval-between-

738 sessions on prefrontal transcranial direct current stimulation (tDCS) on cognitive outcomes: a systematic

739 review and meta-analysis. J Neural Transm (Vienna). 2016;123(10):1159–72.

20. Krauel K, Brauer H, Breitling-Ziegler C, Freitag CM, Luckhardt C, Mühlherr A, et al. Prefrontal Transcranial Direct Current Stimulation in Pediatric Attention-Deficit/Hyperactivity Disorder: A Randomized Clinical Trial. JAMA Netw Open. 2025;8(2):e2460477.

21. Boudewyn MA, Scangos K, Ranganath C, Carter CS. Using prefrontal transcranial direct current stimulation (tDCS) to enhance proactive cognitive control in schizophrenia. Neuropsychopharmacology. 2020;45(11):1877–83.

22. Li X, Chen L, Yu K, Zhuang W, Zhu H, Xu W, et al. Impact of twice-a-day transcranial direct current stimulation intervention on cognitive function and motor cortex plasticity in patients with Alzheimer's disease. Gen Psychiatr. 2023;36(6):e101166.

23. Lang N, Siebner HR, Ernst D, Nitsche MA, Paulus W, Lemon RN, et al. Preconditioning with transcranial direct current stimulation sensitizes the motor cortex to rapid-rate transcranial magnetic stimulation and controls the direction of after-effects. Biol Psychiatry. 2004;56(9):634–9.

24. von Papen M, Fisse M, Sarfeld AS, Fink GR, Nowak DA. The effects of 1 Hz rTMS preconditioned by tDCS on gait kinematics in Parkinson's disease. J Neural Transm (Vienna). 2014;121(7):743–54.

25. Siebner HR, Lang N, Rizzo V, Nitsche MA, Paulus W, Lemon RN, et al. Preconditioning of low-frequency repetitive transcranial magnetic stimulation with transcranial direct current stimulation: evidence for homeostatic plasticity in the human motor cortex. J Neurosci. 2004;24(13):3379–85.

26. Lefaucheur JP, Antal A, Ayache SS, Benninger DH, Brunelin J, Cogiamanian F, et al. Evidence-based guidelines on the therapeutic use of transcranial direct current stimulation (tDCS). Clin Neurophysiol. 2017;128(1):56–92.

27. Global burden of 369 diseases and injuries in 204 countries and territories, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. Lancet. 2020;396(10258):1204–22.

762

763

764

765

766

767

768

769

770

771

772

773

774

775

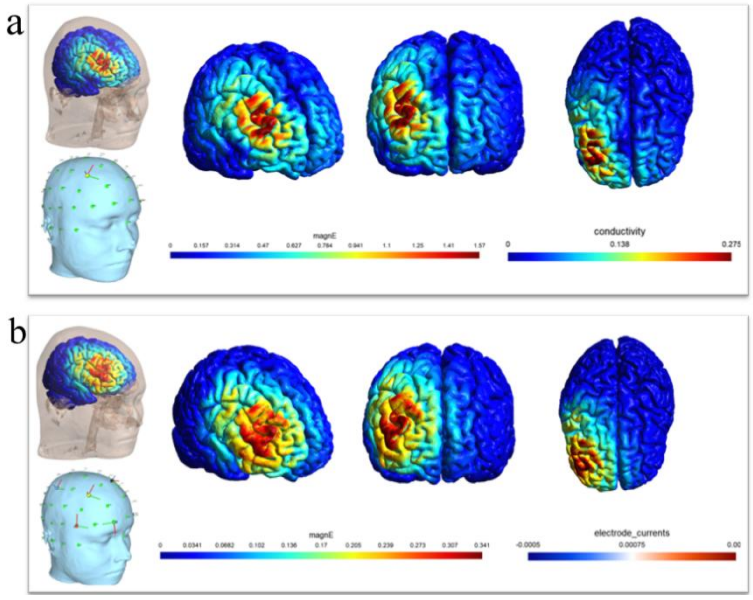
776

777

778

779

780



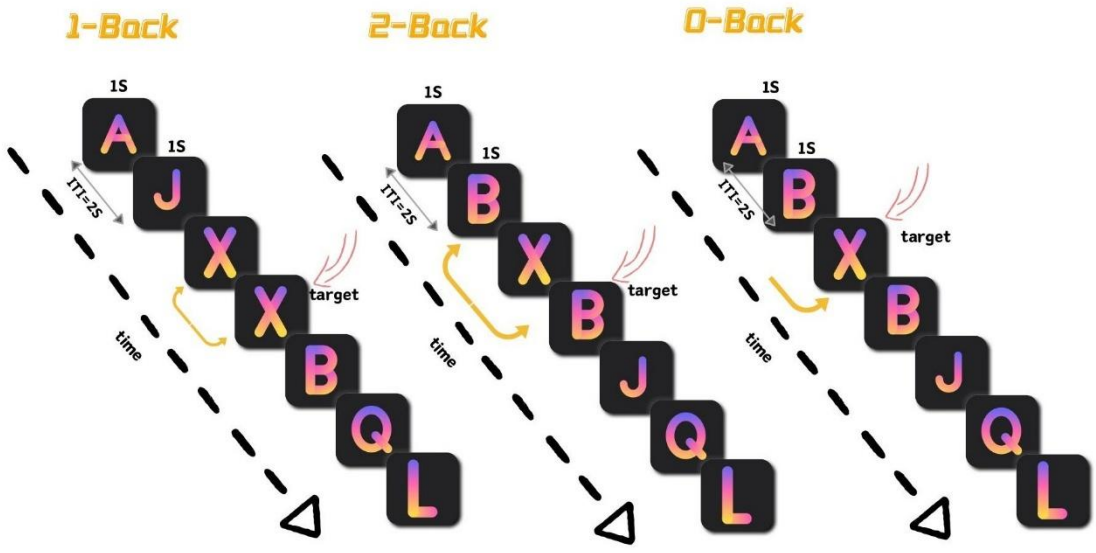
781 Fig.1. Computational modeling of cortical electric fields induced by (a) repetitive transcranial
782 magnetic stimulation (rTMS) and (b) transcranial direct current stimulation (tDCS) using the
783 SimNIBS software platform.

784

785

786

787



788

789 Fig. 2. Schematic representation of the N-back task protocol synchronized with fNIRS acquisition.

	STUDY PERIOD						
	Enrolment	Allocation	Post-allocation				Close-out
TIMEPOINT**	$-t_1$	0	t_1 week1	t_2 week2	t_3 week3	t_4 week4	t_5 week8
ENROLMENT:							
Eligibility screen	√						
Informed consent	√						
Allocation		√					
WISC	√						
Demographic	√						
INTERVENTIONS:							
active rTMS + active tDCS			♦—	—	—	—♦	
active rTMS + sham tDCS			♦—	—	—	—♦	
sham rTMS + active tDCS			♦—	—	—	—♦	
sham rTMS + sham tDCS			♦—	—	—	—♦	
ASSESSMENTS:							
fNIRS	√	√				√	√
BRIEF-2		√				√	√
Conners		√				√	√
IVA-CPT		√				√	√
CBCL		√				√	√
Adverse Events			√	√	√	√	√
Medication Logs		√	√	√	√	√	√

790

791 Fig. 3. Schedule of enrolment, interventions, and assessments. NOTE: WISC, wechsler intelligence
792 scale for children; fNIRS, functional near-infrared spectroscopy; BRIEF-2, behavior rating
793 inventory of executive function, second edition; Conners, Conners 3rd edition rating scales; IVA-
794 CPT, integrated visual and auditory continuous performance test; CBCL, child behavior checklist;
795 rTMS, repetitive transcranial magnetic stimulation; tDCS, transcranial direct current stimulation.

Supplementary Files

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

- AppendixBlindingQuestionnaire.docx
- samplesize.docx
- SPIRIT2025checklistfilledpagenumbers.docx