



OPEN ACCESS

EDITED BY

Andrea Perrottelli,
University of Campania "Luigi Vanvitelli", Italy

REVIEWED BY

Jacopo Lisoni,
Asst Spedali Civili di Brescia, Italy
Rebecca Kazinka,
University of Minnesota, United States

*CORRESPONDENCE

Chuansheng Wang
✉ chuansongwang@126.com

RECEIVED 09 November 2025

REVISED 20 January 2026

ACCEPTED 21 January 2026

PUBLISHED 24 February 2026

CITATION

Wei Y, Shen Z, Luo P, He S, Su H, Liu R, Wu Y, Wang J, Zhang J, Ji G, Wang F and Wang C (2026) Efficacy and mechanisms underlying MRI-guided HD-tDCS combined with aerobic exercise to ameliorate cognitive impairment associated with schizophrenia. *Front. Psychiatry* 17:1742634. doi: 10.3389/fpsy.2026.1742634

COPYRIGHT

© 2026 Wei, Shen, Luo, He, Su, Liu, Wu, Wang, Zhang, Ji, Wang and Wang. This is an open-access article distributed under the terms of the [Creative Commons Attribution License \(CC BY\)](https://creativecommons.org/licenses/by/4.0/). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

Efficacy and mechanisms underlying MRI-guided HD-tDCS combined with aerobic exercise to ameliorate cognitive impairment associated with schizophrenia

Yange Wei^{1,2}, Zengyuan Shen¹, Peng Luo¹, Shanyuan He¹, Hanshuo Su¹, Rongxun Liu^{1,3}, Yanran Wu¹, Juan Wang¹, Jingdan Zhang¹, Guangjun Ji¹, Fei Wang^{4,5} and Chuansheng Wang^{1*}

¹Department of Early Intervention, Mental Health and Artificial Intelligence Research Center, The Second Affiliated Hospital of Xinxiang Medical University, Henan Mental Hospital, Xinxiang, China, ²NHC Key Laboratory of Mental Health (Peking University), Peking University Sixth Hospital, Peking University Institute of Mental Health, National Clinical Research Center for Mental Disorders (Peking University Sixth Hospital), Beijing, China, ³School of Public Health, Xinxiang Medical University, Xinxiang, China, ⁴Unit of Early Intervention, The Affiliated Brain Hospital of Nanjing Medical University, Nanjing, China, ⁵Department of Psychiatry, Yale School of Medicine, New Haven, CT, United States

Background: The primary treatment for schizophrenia currently relies on medication. Nevertheless, the efficacy of medication for Cognitive Impairment Associated with Schizophrenia (CIAS) is constrained, and it is also accompanied by side effects. Consequently, the investigation of novel non-pharmacological strategies is essential. High-definition transcranial direct current stimulation (HD-tDCS) and aerobic exercise (AE) have emerged as promising approaches for cognitive enhancement in individuals with schizophrenia. This study aims to evaluate the efficacy of integrating HD-tDCS with AE for CIAS and to elucidate the underlying mechanisms of this synergistic intervention.

Methods: A randomized, double-blind, controlled trial will be conducted. The CIAS will be randomly allocated to one of four groups: MRI-guided HD-tDCS + AE, MRI-guided HD-tDCS alone, AE alone, and a control group. Structural magnetic resonance imaging (MRI) data will be obtained to determine the optimal electrode placement. The central electrode will be positioned over the medial prefrontal cortex (mPFC). Both HD-tDCS and AE will be administered five times per week over a four-week period, resulting in a total of 20 sessions. The primary outcome measure will be the change in cognitive function, evaluated using the MATRICS Consensus Cognitive Battery. Secondary outcomes will include changes assessed by the Repeatable Battery for the Assessment of Neuropsychological Status and the Wisconsin Card Sorting Test which are designed to evaluate global and executive functions. The Facial Emotion Perception Test and the Voice Emotion Perception Test will be utilized to assess social cognition. The severity of clinical symptoms will be quantified through the Positive and Negative Syndrome Scale and the Brief Psychiatric Rating Scale. This study will incorporate functional near-infrared spectroscopy, MRI, electroencephalography, P300 event-related potential, eye movement

examination and plasma brain-derived neurotrophic factor (BDNF) levels to investigate the underlying mechanisms. Assessments will be evaluated at baseline (T0), after 2 weeks (T1), after 4 weeks (T2), and after 6 months (T3).

Discussion: The integration of MRI-guided HD-tDCS targeting the mPFC and AE presents an efficacious and individualized treatment strategy for CIAS. This proof-of-concept study may provide a multi-dimensional view of biological mechanisms underlying HD-tDCS combined with AE in precision psychiatry.

Trial registration details: The study is registered with <https://www.chictr.org.cn/> protocol registration number ChiCTR2500106980 (date of registration: 1. August. 2025). It was approved by the Research Ethics Committee of the Second Affiliated Hospital of Xinxiang Medical University (Approval Code: XYEFYLL-2025-16, Approval Date: 17 February 2025). Recruitment began in December 2025.

KEYWORDS

aerobic exercise, cognitive impairment associated with schizophrenia, high-definition transcranial direct current stimulation, schizophrenia, study protocol

Background

Cognitive Impairment Associated with Schizophrenia (CIAS) is a core symptom of schizophrenia, and its severity directly affects patients' social functioning, activities of daily living, and long-term prognosis (1, 2). The extent of cognitive function improvement is a key prognostic indicator for patients with schizophrenia (3). Current antipsychotic medications primarily target the dopamine system and effectively alleviate positive symptoms but have limited impact for CIAS (4). Cognitive abilities of individuals with schizophrenia do not necessarily enhance with the remission of psychotic symptoms (5, 6). Although several potential cognitive-enhancing agents have advanced to Phase III trials as adjuncts to antipsychotic treatment, none have yet demonstrated sufficient efficacy to secure FDA approval for schizophrenia (7). Furthermore, variability in individual responses and adherence to therapy pose additional challenges (8). Consequently, the exploration of novel non-pharmacological strategies is critically important.

High-definition transcranial direct current stimulation (HD-tDCS) is a non-invasive intervention technique that utilizes a constant direct current to modulate cortical neuron activity. Compared to conventional tDCS, HD-tDCS provides more precise cortical stimulation targeting, enhanced cortical penetration, and the potential for targeted neuromodulation, which can lead to specific symptomatic changes (9, 10). Multiple randomized controlled trials have indicated that tDCS targeting regions such as the prefrontal cortex significantly enhances working memory and executive functions in patients (11, 12). Research has demonstrated that HD-tDCS can improve the integrity of specific white matter tracts in individuals with chronic schizophrenia,

which is associated with enhanced attentional function (13). A recent meta-analysis further substantiates that HD-tDCS exerts a moderate effect on overall cognitive function in schizophrenia (14). Mechanistically, HD-tDCS may enhance cognition by modulating cortical neuronal excitability, promoting synaptic plasticity, and influencing associated neurotransmitter systems (15). Overall, HD-tDCS exhibits clear potential and value for CIAS. Concerning the selection of stimulation sites, previous studies have demonstrated that cognitive impairments, such as deficits in episodic and working memory and challenges in emotional regulation, are associated with dysfunction in the medial prefrontal cortex (mPFC) and altered connectivity with subcortical regions (16). Furthermore, dysregulation of dopaminergic activity in the mPFC is associated with the progression of schizophrenia (17, 18). Delayed dopamine release in the medial prefrontal cortex (mPFC) is a defining characteristic of the pathophysiology of schizophrenia (19). A deficiency in the dopamine transporter leads to reduced spine density in mPFC pyramidal neurons, resulting in mPFC dysfunction and potentially contributing to behavioral abnormalities in schizophrenia. The primary manifestations are abnormalities in attention (e.g., poor concentration), memory (especially working memory), and executive functions (e.g., deficits in planning, decision-making, and cognitive flexibility) (20). Postmortem studies and schizophrenia mouse models, induced by neonatal basolateral amygdala lesions, also demonstrate reduced dendritic spine density in mPFC pyramidal neurons (21, 22). Consequently, the mPFC has been selected as the target in this study. Research utilizing HD-tDCS targeting the mPFC in schizophrenia remain limited. Further, individual anatomical variations can substantially affect the outcomes of HD-tDCS altering the distribution of electrical currents within

the cortical regions, thereby impacting therapeutic efficacy (23, 24). The use of MRI-guided HD-tDCS interventions enables the identification of optimal electrode placements tailored to each individual, thereby reducing the impact of structural brain differences and enhancing the effectiveness of HD-tDCS (25, 26). Consequently, this study will utilize MRI to obtain anatomical data for each participant, and develop appropriate therapeutic target for individualized precision therapy for CIAS.

Aerobic exercise (AE) is one of the psychosocial interventions with most robust evidence for CIAS (27). AE exerts its effects through multiple mechanisms. It has been demonstrated to influence brain neuroplasticity via neurogenesis and structural alterations (28, 29). Furthermore, AE can mitigate age-related cognitive decline by altering brain metabolism, structure, and connectivity (30). Additionally, AE significantly enhances the activity of mPFC and improves cognitive function within this region (31, 32). Accumulating evidence suggests that structured AE programs can lead to improvements in executive function, attention, and memory in patients with schizophrenia, possibly through mechanisms involving enhanced prefrontal oxygenation and neurotrophic support (33). HD-tDCS has demonstrated promising results in disease intervention, recent studies indicate that its therapeutic effects may be further enhanced when combined with AE intervention methods (34, 35). Consequently, this research aims to examine the synergistic effects of combined HD-tDCS with AE for CIAS.

This study employed a simultaneous intervention approach utilizing HD-tDCS and AE, based on the evidence of the temporal effect of combined intervention. A comprehensive review suggests that integrating neuroregulation with psychosocial methods yields superior outcomes in enhancing cognitive function and alleviating negative symptoms in individuals with schizophrenia, compared to singular interventions; it also highlights the critical role of intervention timing in determining efficacy (36). Furthermore, a randomized controlled trial further confirmed that the concurrent application of neuroregulation and psychosocial strategies significantly ameliorates cognitive deficits and negative symptoms in schizophrenia patients (37). Consequently, the synchronous research design is underpinned by a sound theoretical and empirical rationale. In terms of the therapeutic mechanism, HD-tDCS and AE may exert their effects through a multi-level synergies: AE enhances the secretion of brain-derived neurotrophic factor (BDNF), thereby promoting synaptic plasticity (38, 39), BDNF is not only a key factor for the survival and functional maintenance of neurons, but also regulates synaptic structure and function, especially in the prefrontal cortex, where it supports the long-term potentiation effect, which is the neural basis for learning and memory formation (40). HD-tDCS can regulate the excitability of cortical neurons through direct current, and it supports the neuroplastic mechanism mediated by BDNF, thereby forming a bidirectional synergistic enhancement effect (41). Secondly, AE improves the blood flow to the brain, reduces oxidative stress responses, and enhances mitochondrial function and metabolic efficiency, thereby providing a more favorable

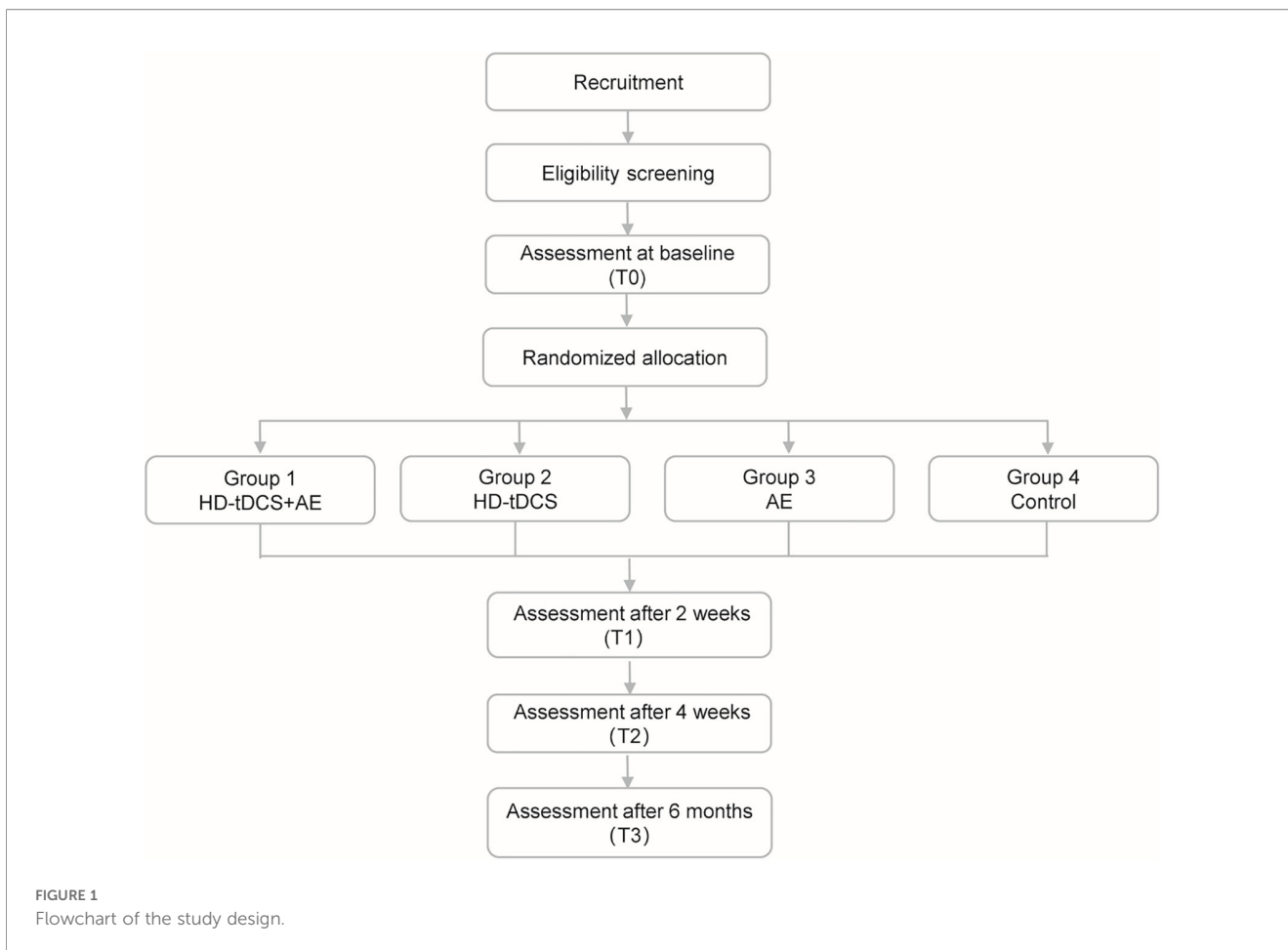
physiological environment for the brain (42). Concurrently, HD-tDCS directly modulates the excitability of the mPFC, enhancing the metabolic improvement such as reduced oxidative stress and increased cerebral blood flow induced by AE, thus facilitating cognitive enhancement (43). The combination of the two can promote the increase of blood flow and oxygenation levels in the mPFC area, thereby enhancing its role in executive functions, working memory, and emotional processing. Exploring this integrated intervention approach could offer a novel and effective intervention option for CIAS.

This study aims to investigate three principal aspects. The primary objective of this study is to evaluate the efficacy of the combined intervention of HD-tDCS and AE in enhancing cognitive function at the individual level. Additionally, we aim to assess the long-term impact of this intervention over a six-month period, focusing on changes in cognitive function, clinical symptoms—measured by the Positive and Negative Syndrome Scale (PANSS) and Brief Psychiatric Rating Scale (BPRS), social function—measured by Social Disability Screening Schedule (SDSS), and Schizophrenia Quality of Life Scale (SQLS). Furthermore, the study seeks to elucidate the biological mechanisms of MRI-guided HD-tDCS and AE from a multi-dimensional perspective. By evaluating the feasibility and safety of this precision approach, the study aims to provide biological insights into individualized treatment strategies for CIAS.

Methods

Study design

This randomized, double-blind, controlled clinical trial evaluates the efficacy of combining HD-tDCS with AE to improve cognitive function in individuals with CIAS. Eligible participants will be randomly assigned to one of four groups in equal proportions (1:1:1:1): MRI-guided HD-tDCS +AE (Group 1), MRI-guided HD-tDCS alone (Group 2), AE alone (Group 3), and a control group (Group 4). Assessments will be conducted at baseline (T0), at 2 weeks (T1), at 4 weeks (T2), and at 6 months post-intervention (T3). The specific intervention measures for each group are delineated as follows: the MRI-guided HD-tDCS + AE group first undertakes a 15-minute warm-up exercise. Subsequently, HD-tDCS and AE treatments are administered concurrently for a duration of 30 minutes. The HD-tDCS group receives 30 minutes of electrical stimulation per session. The AE group's intervention comprises a 15-minute warm-up followed by a 30-minute formal AE stage, amounting to a total of 45 minutes. The control group does not receive HD-tDCS or AE but instead is provided with routine psychiatric care, including regular psychiatric follow-ups, medication management, and general health guidance, but no experimental interventions. Each intervention for the aforementioned groups is conducted once daily, five days a week, over a period of four weeks, culminating in a total of 20 sessions. The study design is illustrated in Figure 1.



Recruitment

Participants will be recruited from the Department of Psychiatry at the Second Affiliated Hospital of Xinxiang Medical University. The trial will be publicized via the hospital’s official website and various media outlets. Information leaflets will be distributed within the Department of Psychiatry, where psychiatrists will provide an overview of the study. Potential participants will receive both oral and written information regarding the research procedures, along with their potential benefits and risks. All participants and their legal guardians, will sign informed consent forms. In accordance with the Helsinki Declaration on Ethical Principles for Medical Research Involving Human Subjects, this study received approval from the Research Ethics Committee of the Second Affiliated Hospital of Xinxiang Medical University (Approval Number: XYEFYLL-2025-16, Approval Date: February 17, 2025) and has been registered with the Chinese Clinical Trial Center (Registration Number: ChiCTR250010698). The trial will take place at the Second Affiliated Hospital of Xinxiang Medical University. This research protocol adheres to the 2013 Standard Protocol Items: Recommendations for Intervention Trials (SPIRIT) Statement Guidelines (44).

Eligibility criteria

Eligible individuals must meet the following inclusion criteria (1): The current episode of the patient aligns with the diagnostic criteria for schizophrenia according to the Diagnostic and Statistical Manual of Mental Disorders-5 (DSM-5) (2). patients who achieved the stable period through oral antipsychotic drug treatment, as judged by the following criteria: delusion, hallucinatory behaviors, exaggeration, and suspicion/victimization items in the positive and negative symptom scale (PANSS), abnormal thought content scores of ≤ 5 in the general psychopathology scale, and PANSS conceptual disorganization scores of ≤ 4 , if all the aforementioned criteria were met, the patient was considered to be in a stable period of schizophrenia (45) (3). Patient must be undergoing treatment with atypical antipsychotic medications, with equivalent doses calculated using the defined daily dose method (4). To minimize study population heterogeneity only Han ethnic participants will be enrolled (5). Aged between 18 and 55 years (6). Written informed consent must be obtained from the patient. Exclusion criteria (1): Individuals with organic brain lesions, intellectual disabilities, or other physical ailments (2). Those experiencing intracranial hypertension (3). Frequent or persistent migraines (4). Individuals with a personal history of epilepsy or a familial

history of epilepsy (5). Patients possessing metallic implants within their bodies (6). Severe substance use disorder (7). Pregnant women or those who are breastfeeding (8). Subjects currently displaying significant abnormalities in laboratory tests (i.e. blood routine, liver and kidney function, electrolytes, and thyroid function. Results that exceed the normal range and are recognized by the attending psychiatrist as having clinical significance, such as severe anemia, acute liver/kidney function disorders) (9). Patients undergoing modified electroconvulsive therapy (10). Individuals with a history of limb disability or leg injury. Participants will be evaluated based on the inclusion and exclusion criteria outlined in Table 1.

Randomization

The randomization process will be conducted by an independent researcher who is not involved in the experiment. This researcher will utilize a random number table to randomly allocate participants into four distinct groups, labeled as “1, 2, 3, and 4.” Specifically, the group coding is as follows: Group 1 corresponds to the HD-tDCS combined with AE group, Group 2 to the HD-tDCS group, Group 3 to the AE group, and Group 4 to the control group. The random allocation process will be implemented using Microsoft Excel 2019. Upon the recruitment of all 48 eligible participants, each individual will be assigned a unique identifier and paired with a randomly generated value using Excel’s “=RAND ()” function. The “Paste Special” function will then be employed to convert these random numbers into fixed values. Subsequently, the list of participants will be sorted in descending order based on the random values, with participants allocated to groups 1 to 4, each comprising 12 individuals, according to their ranking positions. Once the randomization scheme is established, it will be sealed within an opaque envelope, which will be opened sequentially in accordance with the order of subject enrolment. The allocation scheme contained within each envelope will dictate the group assignment for the corresponding participant. This approach ensures that researchers are unable to access the randomization scheme in advance, thereby safeguarding the integrity of the randomization process.

Blinding

All participants and researchers will remain blinded throughout the research process. During the entire research process, the designated stimulus conditions will be kept strictly confidential and will only be disclosed to the principal researcher. Four distinct groups will be tasked with administering the treatment, with strict measures in place to prevent inter-group communication regarding the particulars of each treatment. Each group will be informed only of its own treatment protocol and will remain unaware of the grouping details or the treatment plans of the other groups. The principal investigator will assign specific measures to each group, which will then implement the experimental treatment for their

respective patient cohorts. Patients will remain unaware of their group allocation and will be instructed not to discuss the grouping, the treatment received, the completion of questionnaires, or any other aspects of the experimental protocol. During the phase of result measurement, personnel involved in data collection and analysis will also be blinded to the grouping information and specific measures. Subsequently, the principal investigator will conduct two unblinding procedures: the first will occur before data locking, and the second will follow data analysis. The initial unblinding will occur after data locking, organizing the data into groups 1–4 without disclosing the actual correspondence between these groups and their respective identities. The second unblinding will take place after the data analysis, explicitly revealing the specific identities of groups 1–4. Furthermore, to ensure that participants are unaware of their group assignments, the intervention activities will be conducted in designated rooms. Although the researchers will be aware of the group assignments, they must not disclose this information to the participants and will not be involved in the evaluation or analysis of the study. Additionally, the evaluators and data analysts will remain unaware of the intervention group’s situation throughout the entire research process.

All researchers involved in data management and statistical analysis will remain blinded to the grouping information throughout the entire process. Specifically, data will be analyzed using coded group identifiers (e.g., Group A, B, and C), and the blinding code will remain undisclosed until the completion of the statistical analysis and the locking of the database. This procedure aligns with the principle of the blind method for minimizing assessment bias, as outlined in clinical trial protocols (46).

A Blinding Integrity (BI) assessment will be conducted following the final intervention session. Participants will be required to specify their perceived group allocation via a forced-choice questionnaire, asking: “Which intervention do you believe you received?” The response options will include (1): Combined HD-tDCS and AE (2), HD-tDCS alone (3), AE alone (4), Control, or (5) Unsure. To rigorously assess the blinding effect, Bang’s Blinding Index (BI) will be calculated for each group. This index allows for the distinction between genuine unblinding and random guessing. The BI is the primary tool for quantitatively evaluating the effectiveness of blinding implementation in clinical trials. By calculating the BI separately for each group, we can accurately assess the maintenance of blinding across different intervention groups (47).

Unlike drug trials, these trials—such as those involving surgery, rehabilitation, psychological, and physical therapy—cannot physically blind the “treatment itself” (48). During the informed consent process, we informed participants that the study was designed to investigate the effects of non-pharmacological interventions on cognitive function of individuals with schizophrenia. In the informed consent form, all intervention measures were described as “interventions with potential benefits,” without disclosing which group was the experimental group and which was the control group. The language used in the informed consent form was intentionally general to avoid revealing specific differences between groups, thereby minimizing the

TABLE 1 World Health Organization trial registration data set related to this study.

Data category	Information
Primary Registry and Trial Identifying Number	ChiCTR2500106980
Date of Registration in Primary Registry	1. August. 2025
Secondary Identifying Numbers	N/A
Source(s) of Monetary or Material Support	National Natural Science Foundation of China (grant number 82301689); Medical Science and Technique Foundation of Henan Province (SBGJ202403043)
Primary Sponsor	Yange Wei, MD. Ph.D., The Second Affiliated Hospital of Xinxiang Medical University, Henan Mental Hospital, 207 Qianjin Road, Xinxiang 453002, Henan. China
Secondary Sponsor(s)	N/A
Contact for Public Queries	Zengyuan Shen, The Second Affiliated Hospital of Xinxiang Medical University, Henan Mental Hospital, 50250101154@stu.xmu.edu.cn
Contact for Scientific Queries	Yange Wei, MD. Ph.D., The Second Affiliated Hospital of Xinxiang Medical University, Henan Mental Hospital, weiyange@xxmu.edu.cn
Public Title	Efficacy and mechanisms underlying MRI-guided HD-tDCS combined with aerobic exercise to ameliorate cognitive impairment associated with schizophrenia
Scientific Title	Efficacy and mechanisms underlying MRI-guided HD-tDCS combined with aerobic exercise to ameliorate cognitive impairment associated with schizophrenia
Countries of Recruitment	China
Health Condition(s) or Problem(s) Studied	Schizophrenia
Intervention(s)	High-definition transcranial direct current stimulation combined with aerobic exercise
Key Inclusion and Exclusion Criteria	<p>Inclusion criteria:</p> <ol style="list-style-type: none"> 1. The current episode of the patient aligns with the diagnostic criteria for schizophrenia according to the Diagnostic and Statistical Manual of Mental Disorders-5 (DSM-5). 2. patients who achieved the stable period through oral antipsychotic drug treatment, as judged by the following criteria: delusion, hallucinatory behaviors, exaggeration, and suspicion/victimization items in the positive and negative symptom scale (PANSS), abnormal thought content scores of ≤ 5 in the general psychopathology scale, and PANSS conceptual disorganization scores of ≤ 4, if all the aforementioned criteria were met, the patient was considered to be in a stable period of schizophrenia (45). 3. Patient must be undergoing treatment with atypical antipsychotic medications, with equivalent doses calculated using the defined daily dose method. 4. To minimize study population heterogeneity only Han ethnic participants will be enrolled. 5. Aged between 18 and 55 years. 6. Written informed consent must be obtained from the patient. <p>Exclusion criteria:</p> <ol style="list-style-type: none"> 1. Individuals with organic brain lesions, intellectual disabilities, or other physical ailments. 2. Those experiencing intracranial hypertension. 3. Frequent or persistent migraines. 4. Individuals with a personal history of epilepsy or a familial history of epilepsy. 5. Patients possessing metallic implants within their bodies. 6. Severe substance uses disorder. 7. Pregnant women or those who are breastfeeding. 8. Subjects currently displaying significant abnormalities in laboratory tests (i.e. blood routine, liver and kidney function, electrolytes, and thyroid function. Results that exceed the normal range and are recognized by the attending psychiatrist as having clinical significance, such as severe anemia, acute liver/kidney function disorders). 9. Patients undergoing modified electroconvulsive therapy. 10. Individuals with a history of limb disability or leg injury.
Study Type	Interventional Allocation: randomized Masked: double blind Primary purpose: schizophrenia intervention
Date of First Enrollment	December 2025
Sample Size	48
Recruitment Status	Pending
Primary Outcome(s)	Changes in The Chinese version of the MATRICS Consensus Cognitive Battery (MCCB)

(Continued)

TABLE 1 Continued

Data category	Information
Key Secondary Outcomes	Changes in Repeatable Battery for the Assessment of Neuropsychological Status (RBANS), Wisconsin Card Sorting Test (WCST), Facial Emotion Perception Test (FEPT), the Voice Emotion Perception Test (VEPT), Brief Psychiatric Rating Scale (BPRS), Positive and Negative Syndrome Scale (PANSS), Social Disability Screening Schedule (SDSS) and the Schizophrenia Quality of Life Scale (SQLS)
Ethics Review	Approved (Approval Number: XYEFYLL-2025-16) Approval Date: 17 February 2025 The Second Affiliated Hospital of Xinxiang Medical University, xyefyll@126.com, +86 0373-3373500
Completion date	Pending
Summary Results	Pending
IPD sharing statement	N/A

expectancy effect. Upon completion of the study, it is imperative to fully disclose the actual research design and the group assignments to all participants.

MRI-guided high-definition transcranial direct current stimulation intervention

To construct precise and anatomically accurate head models, T1- and T2-weighted MRI data will be collected to optimize electrode placement and account for individual anatomical variations. These models will be developed and simulated using SimNIBS software to estimate the electric field distributions resulting from HD-tDCS stimulation. Eight distinct 4*1 montages centered on the mPFC will be used to simulate 280 the E-field for each brain. The finite element method will be utilized to compute the normal component of the induced electric field. The head models, derived from individual MRI data will differentiate among five tissue types: skin, skull, cerebrospinal fluid, gray matter, and white matter. The mPFC will be delineated in each participant's brain according to the Ranta atlas. The study will utilize an MRI-guided HD-tDCS device (MxN-9-9002A, Soterix Medical, New York, USA). We used five small circular electrodes (1x1 cm each) with a small area for high-precision electrode arrangement, concentrating the stimulation current on the target brain region. Specifically, the central electrode (anode) will be placed in the mPFC (fz) according to international 10–20 system, while the four surrounding cathodes will be directly located in front of Fp1, Fp2, F7, and F8, thus forming a circular current circuit. The current intensity will be maintained at 2 mA. Each HD-tDCS session will involve the delivery of a 2mA direct current for a duration of 30 minutes, with ramp-up and ramp-down periods of 30 seconds each. HD-tDCS will be administered once daily for 30 minutes, five times a week over a total duration of 4 weeks, culminating in 20 treatment sessions.

Aerobic exercise

AE training will be administered using a stationary bicycle. The training sessions will be characterized by moderate to low intensity

and will include both a warm-up phase and a formal AE phase. Each session is customized according to each individual's maximum heart rate (HRmax), which is calculated using the formula: $HR_{max} = (220 - \text{Age}) \times 0.7$. (34). Each session will last for 45 minutes, comprising a 15-minute warm-up and a 30-minute formal AE phase. During the warm-up, participants' heart rates are expected to remain between 55% and 60% of HRmax. In the formal AE phase, heart rates should be maintained between 60% and 70% of HRmax (34). A portable monitor will be utilized to record heart rates throughout the training, ensuring participants maintain an appropriate level of physical exertion. Blood pressure measurements will be taken both before and after the sessions. The intervention will occur once daily, 5 days per week, over a period of 4 weeks, culminating in 20 treatment sessions.

Multimodal neuroimaging acquisitions and analyses

Structural T1-weighted MRI images will be acquired using a three-dimensional magnetization-prepared rapid gradient-echo (3D MPRAGE) sequence with the following parameters: repetition time (TR)/echo time (TE)/inversion time (TI) = 240/2.14/100 ms, flip angle = 8 degrees, field of view (FOV) = 224 x 224 mm, voxel size = 0.7 mm isotropic, bandwidth = 210 Hz/pixel, integrated parallel acquisition techniques (iPAT) = 2, and an acquisition time of 7 minutes and 40 seconds. T2-weighted images will be acquired using a 3D T2 sampling perfection with application-optimized contrasts using different flip angle evolutions (T2-SPACE) sequence, with parameters: TR/TE = 320/565 ms, variable flip angle, FOV = 224 x 224 mm, voxel size = 0.7 mm isotropic, bandwidth = 755 Hz/pixel, iPAT = 2, and an acquisition time of 8 minutes and 24 seconds. The total duration for structural imaging acquisition will be 16 minutes and 4 seconds. Resting-state functional MRI (fMRI) images will be acquired with the following specifications: TR/TE = 720/33.1 ms, flip angle = 52 degrees, FOV = 208 x 180 mm, matrix size = 104 x 90, slice thickness = 2.0 mm, 72 slices, 2.0 mm isotropic voxels, multiband factor = 8, echo spacing = 0.58 ms, and bandwidth = 229 Hz/pixel. The acquisition of resting-state functional images will require 14 minutes and 33 seconds.

A 48-channel functional near-infrared spectroscopy (fNIRS) device (NirScan model from Danyang Huichuang Medical Equipment Co. Ltd in China) will be employed in this study. The fNIRS data will be collected during the administration of The Chinese version of the Verbal Fluency Test (VFT) serves to evaluate verbal fluency, working memory, verbal recall, attention, and retrieval capabilities. The VFT task is structured into three distinct phases: a 30-second pre-task baseline period, a 60-second task period, and a 70-second post-task period. The baseline phase is characterized by the absence of VFT task performance. During the 30-second pre-task baseline phase, participants are instructed to count repeatedly from one to five until the commencement of the task period. In the subsequent 60-second VFT task period, participants are required to generate as many phrases as possible using simple words such as “white,” “north,” and “big.” Following the completion of the phrase generation task, participants are instructed to resume counting from one to five repeatedly throughout the 70-second post-task period. Fifteen light source probes and sixteen light detector probes will be positioned on the bilateral frontotemporal cortex, with a distance of 3 cm maintained between each light source and detector probe. In accordance with the 10/20 electrode placement system, the central probe will be positioned at FPz, while the lower boundary of the probe array will extend from Fp1 to Fp2. Hemodynamic changes will be assessed through measurements of oxyhemoglobin, deoxyhemoglobin, and total hemoglobin. Resting-state and task-state fNIRS data acquisitions will be performed for all participants in this study. The raw fNIRS data will be preprocessed utilizing the MATLAB Home 3 toolkit. Five statistical metrics—mean, variance, skewness, kurtosis, and peak value—will be calculated for changes in oxy-Hb signals, based on the spatial average across all 48 channels. This methodology will generate a total of 240 independent features for each subject.

The resting-state EEG data were recorded utilizing a PN-NET multichannel electroencephalogram device with 64 scalp electrodes, 1 reference electrode on the nose tip, and 2 electro-ocular electrodes positioned at the right eye corner and beneath the left eye. Data collection transpired in a tranquil examination room by a consistent researcher. Subjects were instructed to maintain stillness, wakefulness, and relaxation, minimize bodily and ocular movements, and abstain from specific tasks. Electrode impedance was maintained below 5 k Ω to ensure data fidelity during collection. A sampling rate of 1,024 Hz was employed, capturing EEG data with closed eyes over a 5-minute interval.

Biological assessment

Participants will undergo a fasting anterior elbow vein puncture to collect a 5 ml blood sample, which will be transferred to an anticoagulant tube and centrifuged at 300 rpm for 10 minutes. The supernatant and sedimented blood cells will be separately transferred into two Eppendorf tubes. Subsequently, the centrifuge tube will be placed in a freezing centrifuge for further centrifugation. The supernatant will be aspirated, and its protein

concentration will be quantified using the BCA kit. Subsequently, equal volumes of samples and molecular weight standards will be subjected to Tris-SDS-PAGE electrophoresis, followed by transfer onto a PVDF membrane. The membrane will be incubated in a 5% skimmed milk solution for blocking for a duration of 2 hours. After a washing step, primary antibodies specific to BDNF and β -actin, diluted at a ratio of 1:500, will be applied and incubated overnight at 4°C. Thereafter, secondary antibodies, also diluted at a ratio of 1:500, will be introduced and incubated at room temperature for 2 hours. The PVDF membrane containing the target protein will then be immersed in a developing solution for analysis using a chemiluminescence imaging analyzer. The exposure time will be adjusted based on the protein's abundance, and the expression levels of BDNF will be quantitatively assessed using ImageJ software.

Outcomes

The primary outcome measure will be the change in scores on the Chinese version of the Food and Drug Administration utilizes the MATRICS Consensus Cognitive Battery (MCCB). Assessments will be conducted at baseline (T0), at 2 weeks (T1), at 4 weeks (T2), and at 6 months post-intervention (T3). The MCCB consists of 10 cognitive tests (3), it covers a total of seven different cognitive domains, including speed of processing, attention/vigilance, working memory, verbal learning, social cognition, reasoning and problem-solving (49). MCCB provides a comprehensive evaluation of specific cognitive domains associated with schizophrenia. Assessments will be conducted at baseline (T0), at 2 weeks (T1), at 4 weeks (T2), and at 6 months post-intervention (T3).

For the assessment of secondary outcomes, this study employed the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) and the Wisconsin Card Sorting Test (WCST) to evaluate global and executive functions. Simultaneously, the Facial Emotion Perception Test (FEPT) and the Voice Emotion Perception Test (VEPT) were utilized to assess emotion perception abilities within the domain of social cognition. The severity of clinical symptoms and overall changes were quantified using the Positive and Negative Syndrome Scale (PANSS) and the Brief Psychiatric Rating Scale (BPRS). Furthermore, improvements in social functioning and quality of life were evaluated using the Social Disability Screening Schedule (SDSS) and the Schizophrenia Quality of Life Scale (SQLS). The RBANS comprises five components: immediate memory, visuospatial skills, language, attention, and delayed memory. Its notable features include ease of administration, brief administration time, and robust reliability and validity. The RBANS is effective for detecting cognitive impairment and can also be used to assess changes in cognitive function following treatment or intervention (50). The WCST is a widely utilized standardized tool in neuropsychological research and clinical cognitive assessment, primarily crafted to assess cognitive flexibility and abstract thinking within executive functions. Participants must discern classification rules based on evolving feedback (e.g., color, shape, or number) and adapt their

strategies accordingly. This assessment effectively mirrors the operation of the prefrontal cortex and is frequently employed to pinpoint executive function impairments linked to psychiatric disorders, brain injuries, and ageing (51). The FEPT is predominantly employed to gauge an individual's capacity to perceive and comprehend the emotions conveyed in the facial expressions of others. This evaluation presents a sequence of standardized facial expression images (e.g., happiness, sadness, anger, fear, etc.), requiring participants to recognize the type or intensity of emotion (52). The VEPT is employed to assess an individual's ability to perceive emotional nuances in others' voices. Participants listen to voice samples (neutral or expressing emotions like joy, sadness, anger, etc.) and must identify the specific emotion conveyed (53). The BPRS is utilized to gauge the intensity of psychiatric symptoms, with higher scores indicating more pronounced symptom severity (54). The PANSS is a widely used standardized tool in psychiatric clinical and research settings, primarily crafted to evaluate symptom severity in individuals with schizophrenia (55). It consists of the Positive Symptom Scale and the Negative Symptom Scale, each comprising 7 items, alongside a general psychopathology scale with 16 items, totaling 30 items. The SDSS is employed to quantitatively evaluate social functioning impairment in patients, encompassing crucial aspects such as work and social interactions. It is user-friendly and suitable for rehabilitation assessments (56). The QLS assesses patients' quality of life using various indicators that mirror their subjective experiences, offering a benchmark for evaluating effectiveness (57).

To explore the underlying mechanisms, the study adopted a multimodal assessment framework. MRI and fNIRS were utilized to investigate changes in brain activity, structure, and functional connectivity. EEG and P300 were employed to capture the neurophysiological dynamics of electrical brain activity. EM served as an objective behavioral-physiological marker of cognitive processing. Additionally, plasma BDNF levels were measured to evaluate the molecular correlates of neurotrophic support and plasticity. This integrated approach aims to elucidate the therapeutic effects of MRI-guided HD-tDCS combined with AE for CIAS and to uncover the neurobiological mechanisms underlying these effects. The procedure for the site visit is outlined in Table 2.

Sample size calculation

We performed the necessary calculations using G*Power software (version 3.1.9.7). Under the following command, test family: F tests; Statistical test: ANOVA: Repeated measures, within-between interaction (58). The research parameters were defined as follows: a Type I error rate of 0.05, a statistical power of 80%, and an effect size of 0.25. Utilizing a repeated measures ANOVA model and considering a potential participant dropout rate of 20%, we determined that the required sample size is 48 patients, with 12 patients assigned to each group. In preliminary studies where prior sample size data are unavailable, a group size of 12 subjects is deemed appropriate. We will justify the rationale for

selecting a sample size of 12 per group from three perspectives: feasibility, improved precision in estimating means and variances, and adherence to regulatory requirements (59). This sample size is expected to provide adequate statistical power to address the study objectives.

Date management

The evaluation of cognitive function and the severity of psychiatric symptoms will be conducted by two psychiatrists, who will remain blinded to the group assignments. All demographic information and scale-related data will be recorded in electronic Case Report Forms (eCRFs) and stored on a designated website. Access to the securely stored eCRFs will be restricted to the project leader and the principal investigator. To maintain confidentiality, anonymization will be implemented during data entry by substituting patients' actual names with unique identification numbers. The independent data monitoring committee will be established to monitor safety, the occurrence of adverse events, and advise on trial design decisions.

Statistical methods

The Shapiro-Wilk test will be employed to determine whether the quantitative data conform to a normal distribution. When the quantitative data are normally distributed, they will be described using the mean and standard deviation. If the data deviate from a normal distribution, the median and interquartile range will be utilized for presentation. Categorical data will be presented as counts and percentages. To evaluate differences in baseline characteristics among groups, appropriate statistical tests such as t-tests, nonparametric tests, chi-square tests, Mann-Whitney U tests, or ANOVA will be selected based on the type and distribution of the data. Additionally, Fisher's exact test or chi-square test will be used to compare adverse reactions between groups.

This study will adhere to the CONSORT guidelines and perform data analysis based on the intention-to-treat principle, ensuring that all participants are evaluated according to their initial randomization assignments. To assess differences in primary and secondary outcomes both between and within groups over time, generalized linear mixed models and repeated-measures ANOVA will be employed as appropriate. A stepwise model selection approach will be implemented to derive a succinct multivariate regression model. Age, gender, and the Defined Daily Dose (DDD) of antipsychotic medications will be included as covariates in all models. The treatment effect will be evaluated using the likelihood ratio test to ascertain whether the coefficients for treatment and the interaction between time and treatment are both zero. To correct for multiple comparisons across time points, the Bonferroni correction method will be applied to adjust the p-values. All statistical analyses will be conducted using SPSS version 20.0, with a significance threshold

TABLE 2 Time schedule of screening, interventions and assessments.

Item	Recruitment	Assessment time point			
		T0	T1	T2	T3
Prescreening for eligibility, consenting, and clinical interview					
Recruitment					
Eligibility screening	✓				
Informed consent	✓				
Allocation	✓				
Primary outcome assessment					
MCCB		✓	✓	✓	✓
Second outcome assessment					
RBANS		✓	✓	✓	✓
BPRS		✓	✓	✓	✓
SQLS		✓	✓	✓	✓
SDSS		✓	✓	✓	✓
PEPT		✓	✓	✓	✓
VEPT		✓	✓	✓	✓
WCST		✓	✓	✓	✓
Biological assessment					
fNIRS		✓	✓	✓	✓
EEG		✓	✓	✓	✓
EM		✓	✓	✓	✓
P300		✓	✓	✓	✓
MRI		✓	✓	✓	✓
Plasma BDNF		✓	✓	✓	✓
Safety					
ARS			✓	✓	✓

A checkmark (✓) indicates the time point at which each assessment is carried out. ARS, Adverse Reaction Scale; BPRS, Brief Psychiatric Rating Scale; EEG, Electroencephalography; EM, Eye Movements; fNIRS, Functional Near-Infrared Spectroscopy; MCCB, MATRICS Consensus Cognitive Battery; MRI, Magnetic Resonance Imaging; PANSS, Positive and Negative Syndrome Scale; PEPT, Facial Emotion Perception Test; P300, P300 Event-Related Potential; RBANS, Repeatable Battery for the Assessment of Neuropsychological Status; SDSS, Social Dysfunction Screening Scale; SQLS, Schizophrenia Quality of Life Scale; VEPT, Voice Emotion Perception Test; WCST, Wisconsin Card Sorting Test.
T0: baseline, T1: after 2 weeks, T2: after 4 weeks, T3: after 6 months.

set at $P < 0.05$ to denote statistical significance. Research framework is illustrated in Figure 2.

Data monitoring

Despite being deemed low-risk for participants, the Institutional Review Board of the Second Affiliated Hospital of Xinxiang Medical University opted to form a data monitoring committee for the ensuing experiments to safeguard data quality and participant well-being.

Harms

To evaluate the safety and potential adverse effects of HD-tDCS, this study will thoroughly investigate both severe and mild adverse events. All participants will be required to complete the HD-tDCS Adverse Reaction Scale (ARS), which encompasses common side effects such as tingling, mild redness, itching, and discomfort at the stimulation site. Participants will rate their adverse reactions on a scale from 0 to 5, with all occurrences documented in the CRFs. The HD-tDCS equipment will be operated by trained therapists proficient in its use, aiming to minimize the risk of participants encountering any significant health hazards or adverse effects. In the event of a severe adverse reaction, the participant will be withdrawn from the study, and the incident will be promptly reported to the ethics committee.

Auditing

To ensure data quality, a dual verification system will be implemented throughout the study, covering both the treatment phase and the 6-month follow-up period. The lead researcher will conduct weekly evaluations of CRFs and estimation forms. Additionally, a bi-weekly comparison between hard copy and electronic records will be performed to verify consistency. Any discrepancies will be documented and discussed in team meetings to facilitate prompt corrective actions.

Protocol modifications

The procedure for implementing substantial protocol modifications requires submitting all changes to the Ethics Review Committee of the Second Affiliated Hospital of Xinxiang Medical University for approval. Upon receiving approval, the research team will formally notify all relevant stakeholders in writing. Subsequently, the approved amendments will be promptly recorded on the Chinese Clinical Trial Registry platform.

Dissemination policy

Prior to enrolling any participants, the research team will register and disclose the trial details on the Chinese Clinical Trial Registry. Furthermore, there is a commitment to publicly release the complete study outcomes. The dissemination of results will be achieved through presentations at international conferences and submissions for peer-reviewed publication in scientific journals.

Confidentiality

Regarding confidentiality, all study personnel have received training and certification in human subjects' research protections

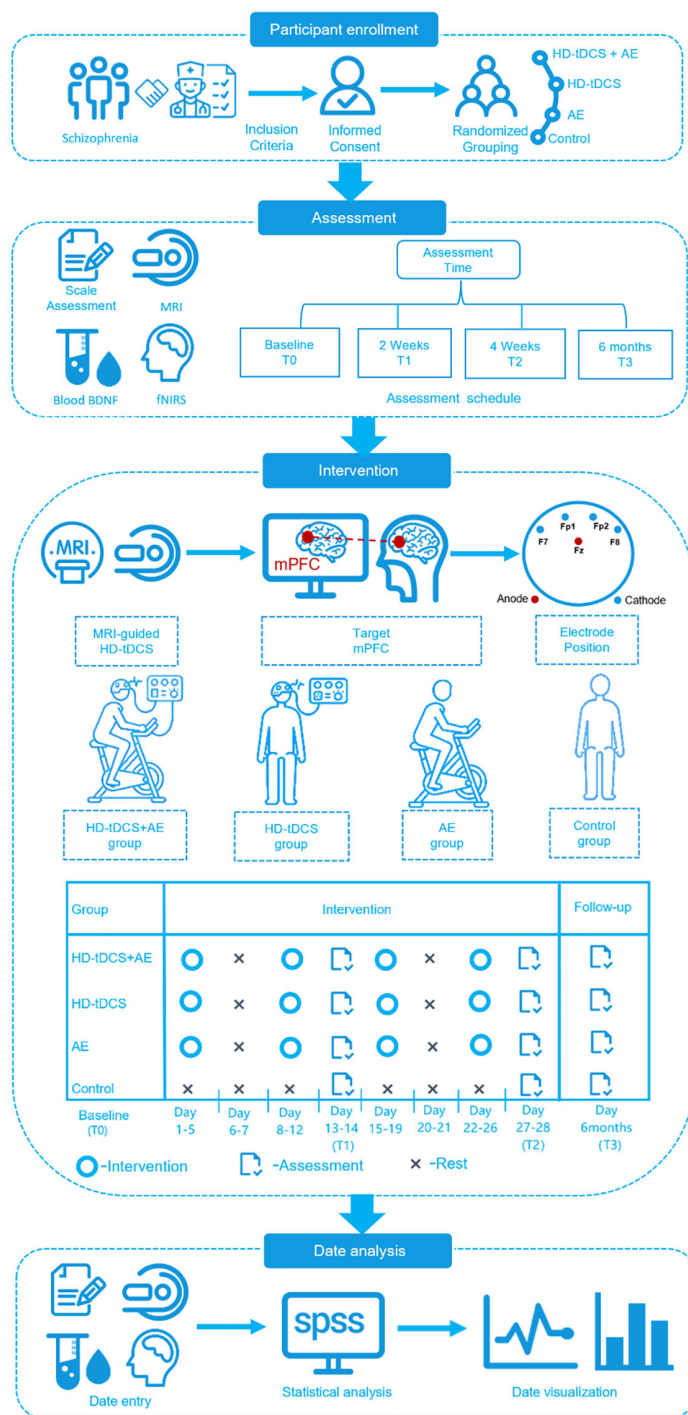


FIGURE 2 Study schedule for the participants in this randomized, double-blind, controlled trial. AE, Aerobic Exercise; fNIRS, Functional Near-Infrared Spectroscopy; HD-tDCS, High-definition transcranial direct current stimulation; MRI, magnetic resonance imaging.

through the Second Affiliated Hospital of Xinxiang Medical University Training Program. The Principal Investigator provides ongoing training and oversight to the evaluation coordinator to maintain the confidentiality and privacy of all participants and their data.

Data sharing

Raw data will be generated at the Second Affiliated Hospital of Xinxiang Medical University. Derived data supporting the findings

of this study will be accessible upon request from the corresponding author.

Discussion

To the best of our knowledge, this may represent the first randomized, double-blind, controlled clinical trial investigating the potential of combining MRI-guided HD-tDCS with AE to enhance cognitive function for CIAS at the individual level. Most non-pharmacological interventions focus exclusively on either HD-tDCS or AE. HD-tDCS has been demonstrated to enhance executive function and working memory by modulating neuronal excitability in the mPFC (60). Meanwhile, AE influences brain plasticity, metabolism, structure, and connectivity by promoting neurogenesis and structural changes, thereby improving cognitive function (28, 61). Here in, we aim to integrate these two non-pharmacological approaches to examine their synergistic effect on cognitive enhancement for CIAS. This synergistic intervention strategy may break through the limitations of single intervention and provide a multi-dimensional view of cognitive improvement. This could eventually provide individualized precision treatment strategies to increase treatment effectiveness.

This prospective, randomized, double-blind, controlled study will utilize MRI-guided HD-tDCS targeting mPFC to improve cognitive function for CIAS. Considering the significant impact of inter-individual neuroanatomical differences on HD-tDCS outcomes, MRI was employed to precisely identify and localize the target region for each participant. This customized approach ensured accurate electrode positioning, thereby enhancing stimulation precision and efficacy. Previous HD-tDCS research has demonstrated significant improvements in cognitive symptoms, particularly in executive functions (13, 62, 63). Given its role in advanced cognitive regulation, decision-making, working memory, and emotion control (64), the mPFC is a crucial brain region involved in the pathophysiology of schizophrenia. Its functional abnormalities are associated with CIAS, including impairments in working memory and attention control (65). Autopsy studies have demonstrated a significant reduction in the density of dendritic spines within the mPFC neurons of patients with schizophrenia (21). Studies utilizing animal models have revealed that abnormal dopaminergic regulation of the mPFC contributes to cognitive impairment (19). Investigations employing conventional HD-tDCS have indicated that stimulation of the mPFC can enhance language fluency and working memory in patients (66). Consequently, the mPFC may serve as a potential target for CIAS.

AE as an adjunctive intervention for chronic schizophrenia, may improve cognitive functions across five domains: information processing speed, working memory, problem-solving skills, verbal learning and memory, and visual learning and memory, consistent with previous research findings (33). Learning and memory functions are associated with the mPFC and hippocampus (67). Individuals with schizophrenia exhibit irregularities in neural growth and neurotransmitter release in mPFC (40), as well as

alterations in hippocampal volume and morphology (68, 69). AE has been shown to improve mitochondrial structure and function in the mPFC, increase the release of neurotrophic factors such as BDNF (38), enhances aerobic metabolism (70), and mitigates hypoxia and inflammation (43, 71). AE interventions contribute to increased hippocampal volume in individuals with schizophrenia (72, 73), as well as elevated levels of oxygenated hemoglobin in the mPFC, which are closely linked to improved executive function (28). Animal studies using schizophrenia models further confirmed that exercise enhances hippocampal volume and cognitive abilities (73). Collectively, these findings imply that AE may improve cognition by modulating brain function and neurotransmitter release in the mPFC, which are critical for cognitive processes.

This study explores the integration of MRI-guided HD-tDCS with AE to enhance cognitive function in individuals with CIAS. This combined approach holds potential for mitigating adverse drug reactions, such as extrapyramidal symptoms and endocrine disorders, thereby improving patients' overall quality of life. In other words, this approach provides a scalable non-pharmacological intervention, particularly advantageous for patients who experience limited drug efficacy or intolerable side effects. AE could simultaneously enhance cerebral blood flow and elevate neurotrophic levels, and achieve a synergistic effect when combined with electrical stimulation. This application could amplify therapeutic outcomes through a synergistic process. HD-tDCS can be safely administered in domestic settings, eliminating the need for frequent hospital visits and thereby reducing time and transportation costs. The flexibility of AE allows patients to select exercise methods tailored to their individual conditions, potentially improving adherence to interventions among individuals with CIAS and facilitating long-term treatment possibilities. In comparison to more complex neuroregulation techniques such as transcranial magnetic stimulation, this integrated strategy may overcome the limitations of single interventions. In the long term, it demonstrates high cost-effectiveness and is particularly suitable for implementation in community settings and low-income regions.

In this study, we will employ multi-dimensional measures to investigate the biological mechanisms of HD-tDCS combined with AE in individuals with CIAS. With the progress in individualized precision medicine, researchers are seeking biomarkers to guide therapy or assess patient outcomes in schizophrenia. MRI data will be utilized to determine the optimal electrode placement, accounting for individual anatomical variations, and to evaluate alterations in brain structure and function. The HD-tDCS will target the mPFC to modulate neuronal excitability, with MRI employed to assess potential morphological enhancements in this region following the intervention, thereby providing structural-level support for cognitive enhancement. fNIRS will be used as a direct measure of neural activity to evaluate both local and network effects (74–76). Due to its high temporal resolution, robust resistance to motion artifacts, and cost-effectiveness (77), fNIRS is well-suited for the dynamic assessment of changes in brain function during interventions. Previous research has demonstrated a significant reduction in oxygenated hemoglobin signals within the mPFC during VFT in individuals with schizophrenia, which was

negatively associated with cognitive performance (78). This study will utilize fNIRS to quantitatively evaluate the activation patterns of the mPFC, thereby providing objective insights into the neural mechanisms underlying a combined intervention. Previous research has demonstrated that AE can increase BDNF levels (38). Furthermore, P300, and EEG will be employed as objective measures to deliver a more comprehensive and systematic analysis of the neural mechanisms involved in the combined intervention. We hypothesize that the combined strategy may induce significant changes in mPFC activity and BDNF levels. We also hypothesize that these changes will correlate with improvements in cognitive function. If so, the study will provide objective evidence supporting the efficacy of HD-tDCS combined with AE, underscoring its potential as an individualized therapeutic strategy for addressing CIAS at the biological level.

This study presents some limitations. Firstly, the lack of a “sham” exercise or “sham” HD-tDCS compromises the complete blinding of participants, which may enhance the “expectancy effect” within the combined group. Although this study primarily investigates the synergistic feasibility of the two active interventions, future research should incorporate Sham-tDCS and an Active Control condition (such as stretching or low-intensity tasks) to balance “attention time” and “treatment expectation” across all participant groups. Secondly, cognitive tasks during treatment were not included in this study. Future research should incorporate cognitive tasks (such as N-back) concurrently with the intervention measures to enhance the magnitude and specificity of cognitive improvement. Thirdly, the sample size is relatively small, potentially compromising statistical power. Fourthly, the study lacks an analysis of various parameters of AE. Consequently, future research should focus on enlarging the sample size, and investigating optimal AE parameters. Fifthly, this study is the single center design, which may have a center effect and a selection bias. Further larger, prospective, multicenter studies are worthwhile.

This randomized, double-blind, controlled clinical design incorporated a multi-dimensional assessment will provide biological insights for the synergistic effect of HD-tDCS and AE on cognitive improvement. The integration of MRI-guided HD-tDCS targeting the mPFC with AE constitutes a promising avenue for cognitive rehabilitation in schizophrenia. This approach holds significant translational and clinical potential in precision psychiatry. Implementing these individualized therapeutic strategies may yield substantial clinical and economic benefits in the management of CIAS.

Ethics statement

The studies involving humans were approved by The Research Ethics Committee of the The Second Affiliated Hospital of Xinxiang Medical University. The studies will be conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation in this study will be obtained by the participants' legal guardians/next of kin.

Author contributions

YW: Conceptualization, Formal analysis, Resources, Visualization, Funding acquisition, Data curation, Project administration, Validation, Software, Writing – review & editing, Methodology, Supervision, Investigation, Writing – original draft. ZS: Visualization, Writing – review & editing, Writing – original draft. PL: Formal analysis, Writing – original draft, Visualization, Resources, Funding acquisition, Project administration, Software, Data curation, Methodology, Writing – review & editing, Conceptualization, Validation, Supervision, Investigation. SH: Supervision, Methodology, Validation, Project administration, Conceptualization, Investigation, Data curation, Funding acquisition, Writing – review & editing, Resources, Writing – original draft, Formal analysis, Software, Visualization. HS: Methodology, Formal analysis, Supervision, Writing – review & editing, Project administration, Writing – original draft, Data curation, Software, Investigation, Visualization, Conceptualization, Resources, Funding acquisition, Validation. RL: Formal analysis, Supervision, Project administration, Validation, Methodology, Writing – review & editing, Visualization, Investigation, Writing – original draft, Software, Data curation, Conceptualization, Funding acquisition, Resources. YRW: Investigation, Visualization, Resources, Formal analysis, Data curation, Validation, Writing – review & editing, Software, Project administration, Methodology, Writing – original draft, Supervision, Conceptualization, Funding acquisition. JW: Resources, Funding acquisition, Writing – review & editing, Software, Formal analysis, Data curation, Methodology, Writing – original draft, Validation, Conceptualization, Project administration, Investigation, Visualization, Supervision. JZ: Supervision, Methodology, Writing – review & editing, Formal analysis, Writing – original draft, Data curation, Software, Validation, Funding acquisition, Conceptualization, Resources, Visualization, Investigation, Project administration. GJ: Supervision, Formal analysis, Writing – review & editing, Project administration, Methodology, Writing – original draft, Resources, Data curation, Software, Investigation, Visualization, Conceptualization, Validation, Funding acquisition. FW: Writing – review & editing, Funding acquisition, Conceptualization, Investigation, Resources, Writing – original draft, Software, Supervision, Project administration, Validation, Visualization, Methodology, Data curation, Formal analysis. CW: Software, Methodology, Writing – original draft, Visualization, Investigation, Data curation, Funding acquisition, Validation, Conceptualization, Resources, Supervision, Writing – review & editing, Project administration, Formal analysis.

Funding

The author(s) declared that financial support was received for this work and/or its publication. This research was supported by the National Natural Science Foundation of China (grant number 82301689 to YW), Medical Science and Technique Foundation of Henan Province (grant number SBJ202403043 to YW), Young and Middle-aged Health Science and Technology Innovation Talents

Project of Henan province (grant number JQRC2025014 to YW), Proof-of-Concept Project for Medical Scientific and Translational Achievements in Henan Province (grant number 2025-G-010 to YW), Joint Fund of Science and Technology Development Program of Henan Province (grant number 232301420103 to YW), Graduate Education Reform Project of Henan Province (grant numbers 2023SJGLX063Y to YW and 2023SJGLX010Y to GJ), General Project of Henan Province Education Science (grant number 2023YB0135 to YW), Henan Provincial University Humanities and Social Science Research General Project (grant number 2025-ZZJH-317 to RL), Postgraduate Education Reform and Quality Improvement Project of Henan Province (grant number YJS2025GZZ23 to RL) and the 111 Project (D20036, China).

Acknowledgments

The authors thank all the members of Mental Health and Artificial Intelligence Research Center.

Conflict of interest

The author(s) declared that this work was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

References

- Javitt DC. Cognitive impairment associated with schizophrenia: from pathophysiology to treatment. *Annu Rev Pharmacol Toxicology*. (2023) 63:119–41. doi: 10.1146/annurev-pharmtox-051921-093250
- Xu Y, Cai Z, Fang C, Zheng J, Shan J, Yang Y. Impact of aerobic exercise on cognitive function in patients with schizophrenia during daily care: A meta-analysis. *Psychiatry Res*. (2022) 312:114560. doi: 10.1016/j.psychres.2022.114560
- Nuechterlein KH, Green MF, Kern RS, Baade LE, Barch DM, Cohen JD, et al. The MATRICS Consensus Cognitive Battery, part 1: test selection, reliability, and validity. *Am J Psychiatry*. (2008) 165:203–13. doi: 10.1176/appi.ajp.2007.07010042
- Harvey PD, Keefe RS. Studies of cognitive change in patients with schizophrenia following novel antipsychotic treatment. *Am J Psychiatry*. (2001) 158:176–84. doi: 10.1176/appi.ajp.158.2.176
- Zanelli J, Mollon J, Sandin S, Morgan C, Dazzan P, Pilecka I, et al. Cognitive change in schizophrenia and other psychoses in the decade following the first episode. *Am J Psychiatry*. (2019) 176:811–9. doi: 10.1176/appi.ajp.2019.18091088
- McCleery A, Nuechterlein KH. Cognitive impairment in psychotic illness: prevalence, profile of impairment, developmental course, and treatment considerations. *Dialogues Clin Neurosci*. (2019) 21:239–48. doi: 10.31887/DCNS.2019.21.3/amccleery
- Keefe RSE. Why are there no approved treatments for cognitive impairment in schizophrenia? *World Psychiatry*. (2019) 18:167–8. doi: 10.1002/wps.20648
- Leucht S, Priller J, Davis JM. Antipsychotic drugs: A concise review of history, classification, indications, mechanism, efficacy, side effects, dosing, and clinical application. *Am J Psychiatry*. (2024) 181:865–78. doi: 10.1176/appi.ajp.20240738
- Jacquemin L, Shekhawat GS, Van de Heyning P, Mertens G, Franssen E, Van Rompaey V, et al. Effects of electrical stimulation in tinnitus patients: conventional versus high-definition tDCS. *Neurorehabil Neural Repair*. (2018) 32:714–23. doi: 10.1177/1545968318787916
- Parlikar R, Vanteemar SS, Shivakumar V, Narayanaswamy CJ, Rao PN, Ganesan V. High definition transcranial direct current stimulation (HD-tDCS): A systematic review on the treatment of neuropsychiatric disorders. *Asian J Psychiatr*. (2021) 56:102542. doi: 10.1016/j.ajp.2020.102542
- García-Fernández L, Romero-Ferreiro V, Padilla S, Wynn R, Pérez-Gálvez B, Álvarez-Mon M, et al. Transcranial direct current stimulation (tDCS) enhances

Generative AI statement

The author(s) declared that generative AI was not used in the creation of this manuscript.

Any alternative text (alt text) provided alongside figures in this article has been generated by Frontiers with the support of artificial intelligence and reasonable efforts have been made to ensure accuracy, including review by the authors wherever possible. If you identify any issues, please contact us.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Supplementary material

The Supplementary Material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fpsy.2026.1742634/full#supplementary-material>

cognitive function in schizophrenia: A randomized double-blind sham-controlled trial. *Psychiatry Res*. (2025) 344:116308. doi: 10.1016/j.psychres.2024.116308

12. Boudewyn MA, Scangos K, Ranganath C, Carter CS. Using prefrontal transcranial direct current stimulation (tDCS) to enhance proactive cognitive control in schizophrenia. *Neuropsychopharmacology*. (2020) 45:1877–83. doi: 10.1038/s41386-020-0750-8

13. Xu H, Zhou Y, Wang J, Liang Z, Wang Y, Wu W, et al. Effect of HD-tDCS on white matter integrity and associated cognitive function in chronic schizophrenia: A double-blind, sham-controlled randomized trial. *Psychiatry Res*. (2023) 324:115183. doi: 10.1016/j.psychres.2023.115183

14. Cheng PWC, Louie LLC, Wong YL, Wong SMC, Leung WY, Nitsche MA, et al. The effects of transcranial direct current stimulation (tDCS) on clinical symptoms in schizophrenia: A systematic review and meta-analysis. *Asian J Psychiatr*. (2020) 53:102392. doi: 10.1016/j.ajp.2020.102392

15. Fritsch B, Reis J, Martinowich K, Schambra HM, Ji Y, Cohen LG, et al. Direct current stimulation promotes BDNF-dependent synaptic plasticity: potential implications for motor learning. *Neuron*. (2010) 66:198–204. doi: 10.1016/j.neuron.2010.03.035

16. Euston DR, Gruber AJ, McNaughton BL. The role of medial prefrontal cortex in memory and decision making. *Neuron*. (2012) 76:1057–70. doi: 10.1016/j.neuron.2012.12.002

17. Howes OD, Shatalina E. Integrating the neurodevelopmental and dopamine hypotheses of schizophrenia and the role of cortical excitation-inhibition balance. *Biol Psychiatry*. (2022) 92:501–13. doi: 10.1016/j.biopsych.2022.06.017

18. Weinstein JJ, Chohan MO, Slifstein M, Kegeles LS, Moore H, Abi-Dargham A. Pathway-specific dopamine abnormalities in schizophrenia. *Biol Psychiatry*. (2017) 81:31–42. doi: 10.1016/j.biopsych.2016.03.2104

19. Kasahara Y, Arime Y, Hall FS, Uhl GR, Sora I. Region-specific dendritic spine loss of pyramidal neurons in dopamine transporter knockout mice. *Curr Mol Med*. (2015) 15:237–44. doi: 10.2174/1566524015666150330143613

20. Yang KC, Yang BH, Liu MN, Liou YJ, Chou YH. Cognitive impairment in schizophrenia is associated with prefrontal-striatal functional hypoconnectivity and striatal dopaminergic abnormalities. *J Psychopharmacol*. (2024) 38:515–25. doi: 10.1177/02698811241257877

21. Glantz LA, Lewis DA. Decreased dendritic spine density on prefrontal cortical pyramidal neurons in schizophrenia. *Arch Gen Psychiatry*. (2000) 57:65–73. doi: 10.1001/archpsyc.57.1.65
22. Solis O, Vázquez-Roque RA, Camacho-Abrego I, Gamboa C, de la Cruz F, Zamudio S, et al. Decreased dendritic spine density of neurons of the prefrontal cortex and nucleus accumbens and enhanced amphetamine sensitivity in postpubertal rats after a neonatal amygdala lesion. *Synapse*. (2009) 63:1143–53. doi: 10.1002/syn.20697
23. Opitz A, Paulus W, Will S, Antunes A, Thielscher A. Determinants of the electric field during transcranial direct current stimulation. *Neuroimage*. (2015) 109:140–50. doi: 10.1016/j.neuroimage.2015.01.033
24. Datta A, Truong D, Minhas P, Parra LC, Bikson M. Inter-individual variation during transcranial direct current stimulation and normalization of dose using MRI-derived computational models. *Front Psychiatry*. (2012) 3:91. doi: 10.3389/fpsy.2012.00091
25. Datta A, Zhou X, Su Y, Parra LC, Bikson M. Validation of finite element model of transcranial electrical stimulation using scalp potentials: implications for clinical dose. *J Neural Eng*. (2013) 10:036018. doi: 10.1088/1741-2560/10/3/036018
26. Laakso I, Tanaka S, Koyama S, De Santis V, Hirata A. Inter-subject variability in electric fields of motor cortical tDCS. *Brain Stimul*. (2015) 8:906–13. doi: 10.1016/j.brs.2015.05.002
27. Vita A, Gaebel W, Mucci A, Sachs G, Barlati S, Giordano GM, et al. European Psychiatric Association guidance on treatment of cognitive impairment in schizophrenia. *Eur Psychiatry*. (2022) 65:e57. doi: 10.1192/j.eurpsy.2022.2315
28. Firth J, Stubbs B, Rosenbaum S, Vancampfort D, Malchow B, Schuch F, et al. Aerobic exercise improves cognitive functioning in people with schizophrenia: A systematic review and meta-analysis. *Schizophr Bull*. (2017) 43:546–56. doi: 10.1093/schbul/sbw115
29. de Sousa Fernandes MS, Ordóño TF, Santos GCJ, Santos LER, Calazans CT, Gomes DA, et al. Effects of physical exercise on neuroplasticity and brain function: A systematic review in human and animal studies. *Neural Plast*. (2020) 2020:8856621. doi: 10.1155/2020/8856621
30. Mandolesi L, Polverino A, Montuori S, Foti F, Ferraioli G, Sorrentino P, et al. Effects of physical exercise on cognitive functioning and wellbeing: biological and psychological benefits. *Front Psychol*. (2018) 9:509. doi: 10.3389/fpsyg.2018.00509
31. Kelly NA, Wood KH, Allendorfer JB, Ford MP, Bickel CS, Marstrand J, et al. High-intensity exercise acutely increases substantia nigra and prefrontal brain activity in parkinson's disease. *Med Sci Monit*. (2017) 23:6064–71. doi: 10.12659/MSM.906179
32. Faulkner J, Lambrick D, Kaufmann S, Stoner L. Effects of upright and recumbent cycling on executive function and prefrontal cortex oxygenation in young healthy men. *J Phys Act Health*. (2016) 13:882–7. doi: 10.1123/jpah.2015-0454
33. Shimada T, Ito S, Makabe A, Yamanushi A, Takenaka A, Kawano K, et al. Aerobic exercise and cognitive functioning in schizophrenia: An updated systematic review and meta-analysis. *Psychiatry Res*. (2022) 314:114656. doi: 10.1016/j.psychres.2022.114656
34. Ji Y, Ni X, Zheng K, Jiang Y, Ren C, Zhu H, et al. Combined effects of transcranial direct current stimulation and aerobic exercise on inhibitory control function in healthy young adults: An event-related potential study. *Brain Cogn*. (2023) 173:106090. doi: 10.1016/j.bandc.2023.106090
35. da Silva VCC, da Silva Arêas FZ, Lopes A, de Almeida EVFF, da Costa AG, Dos Santos JCC, et al. Anodal transcranial direct current stimulation associated with aerobic exercise on the functional and physical capacity of patients with heart failure with reduced ejection fraction: ELETRIC study protocol. *Trials*. (2023) 24:738. doi: 10.21203/rs.3.rs-3206508/v1
36. Lisoni J, Nibbio G, Baglioni A, Dini S, Manera B, Maccari A, et al. Is it possible to combine non-invasive brain stimulation and evidence-based psychosocial interventions in schizophrenia? A critical review. *Brain Sci*. (2024) 14:1067. doi: 10.3390/brainsci14111067
37. Li X, Yuan X, Kang Y, Pang L, Liu Y, Zhu Q, et al. A synergistic effect between family intervention and rTMS improves cognitive and negative symptoms in schizophrenia: A randomized controlled trial. *J Psychiatr Res*. (2020) 126:81–91. doi: 10.1016/j.jpsychires.2020.04.009
38. Cotman CW, Berchtold NC. Exercise: a behavioral intervention to enhance brain health and plasticity. *Trends Neurosci*. (2002) 25:295–301. doi: 10.1016/S0166-2236(02)02143-4
39. van Praag H, Kempermann G, Gage FH. Running increases cell proliferation and neurogenesis in the adult mouse dentate gyrus. *Nat Neurosci*. (1999) 2:266–70. doi: 10.1038/6368
40. Lu H, Cheng PL, Lim BK, Khoshnevisrad N, Poo MM. Elevated BDNF after cocaine withdrawal facilitates LTP in medial prefrontal cortex by suppressing GABA inhibition. *Neuron*. (2010) 67:821–33. doi: 10.1016/j.neuron.2010.08.01
41. Aberna AS, Wang R, Grill WM, Peterchev AV. Multi-scale model of axonal and dendritic polarization by transcranial direct current stimulation in realistic head geometry. *Brain Stimul*. (2023) 16:1776–91. doi: 10.1016/j.brs.2023.11.018
42. Abdullahi A, Wong TW, Ng SS. Understanding the mechanisms of disease modifying effects of aerobic exercise in people with Alzheimer's disease. *Ageing Res Rev*. (2024) 94:102202. doi: 10.1016/j.arr.2024.102202
43. Broadhouse KM, Singh MF, Suo C, Gates N, Wen W, Brodaty H, et al. Hippocampal plasticity underpins long-term cognitive gains from resistance exercise in MCI. *NeuroImage: Clin*. (2020) 25:102182. doi: 10.1016/j.nicl.2020.102182
44. Chan AW, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K. SPIRIT 2013 statement: defining standard protocol items for clinical trials. *Ann Intern Med*. (2013) 158:200–7. doi: 10.7326/0003-4819-158-3-201302050-00583
45. Sun Y, Jiang W, Yu H, Zhang J, Zhou Y, Yin F, et al. Construction and verification of aggressive behavior risk prediction model in stable patients with schizophrenia. *BMC Psychiatry*. (2023) 23:800. doi: 10.1186/s12888-023-05296-5
46. Schulz KF, Grimes DA. Blinding in randomised trials: hiding who got what. *Lancet*. (2002) 359:696–700. doi: 10.1016/S0140-6736(02)07816-9
47. Haq R, Molteni L, Huneke NTM. The relationship between blinding integrity and medication efficacy in randomised-controlled trials in patients with anxiety disorders: A systematic review and meta-analysis. *Acta Psychiatr Scand*. (2024) 150:187–97. doi: 10.1111/acps.13741
48. Boutron I, Guitte L, Estellat C, Moher D, Hróbjartsson A, Ravaud P. Reporting methods of blinding in randomized trials assessing nonpharmacological treatments. *PLoS Med*. (2007) 4:e61. doi: 10.1371/journal.pmed.0040061
49. Shi C, Kang L, Yao S, Ma Y, Li T, Liang Y, et al. The MATRICS consensus cognitive battery (MCCB): co-norming and standardization in China. *Schizophr Res*. (2015) 169:109–15. doi: 10.1016/j.schres.2015.09.003
50. Gold JM, Queern C, Iannone VN, Buchanan RW. Repeatable battery for the assessment of neuropsychological status as a screening test in schizophrenia I: sensitivity, reliability, and validity. *Am J Psychiatry*. (1999) 156:1944–50. doi: 10.1176/ajp.156.12.1944
51. Miles S, Howlett CA, Berryman C, Nedeljkovic M, Moseley GL, Phillipou A. Considerations for using the Wisconsin Card Sorting Test to assess cognitive flexibility. *Behav Res Methods*. (2021) 53:2083–91. doi: 10.3758/s13428-021-01551-3
52. Kohler CG, Turner TH, Bilker WB, Brensinger CM, Siegel SJ, Kanesh SJ, et al. Facial emotion recognition in schizophrenia: intensity effects and error pattern. *Am J Psychiatry*. (2003) 160:1768–74. doi: 10.1176/appi.ajp.160.10.1768
53. Zhao W, Zhang Q, An H, Yun Y, Fan N, Yan S, et al. Vocal emotion perception in schizophrenia and its diagnostic significance. *BMC Psychiatry*. (2023) 23:760. doi: 10.1186/s12888-023-05110-2
54. Hofmann AB, Schmid HM, Jabat M, Brackmann N, Noboa V, Bobes J, et al. Utility and validity of the Brief Psychiatric Rating Scale (BPRS) as a transdiagnostic scale. *Psychiatry Res*. (2022) 314:114659. doi: 10.1016/j.psychres.2022.114659
55. Kay SR, Fiszbein A, Opler LA. The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophr Bull*. (1987) 13:261–76. doi: 10.1093/schbul/13.2.261
56. Luo R, Fan N, Dou Y, Wang Y, Wang M, Yang X, et al. Relationship between cognitive function and functional outcomes in remitted major depression. *BMC Psychiatry*. (2024) 24:311. doi: 10.1186/s12888-024-05675-6
57. Wilkinson G, Hesdon B, Wild D, Cookson R, Farina C, Sharma V, et al. Self-report quality of life measure for people with schizophrenia: the SQLS. *Br J Psychiatry*. (2000) 177:42–6. doi: 10.1192/bjp.177.1.42
58. Alipouri M, Amiri E, Hoseini R, Hezarkhani LA. Effects of eight weeks of aerobic exercise and vitamin D supplementation on psychiatric comorbidities in men with migraine and vitamin D insufficiency: A randomized controlled clinical trial. *J Affect Disord*. (2023) 334:12–20. doi: 10.1016/j.jad.2023.04.108
59. Julious SA. Sample size of 12 per group rule of thumb for a pilot study. *Pharm Statistics*. (2005) 4:287–91. doi: 10.1002/pst.185
60. Orlov ND, Muqtadir SA, Oroojeni H, Averbeck B, Rothwell J, Shergill SS. Stimulating learning: A functional MRI and behavioral investigation of the effects of transcranial direct current stimulation on stochastic learning in schizophrenia. *Psychiatry Res*. (2022) 317:114908. doi: 10.1016/j.psychres.2022.114908
61. Falkai P, Malchow B, Schmitt A. Aerobic exercise and its effects on cognition in schizophrenia. *Curr Opin Psychiatry*. (2017) 30:171–5. doi: 10.1097/YCO.0000000000000326
62. Rezakhani S, Amiri M, Hassani A, Esmailpour K, Sheibani V. Anodal HD-tDCS on the dominant anterior temporal lobe and dorsolateral prefrontal cortex: clinical results in patients with mild cognitive impairment. *Alzheimers Res Ther*. (2024) 16:27. doi: 10.1186/s13195-023-01370-y
63. Chua EF, Ahmed R, Garcia SM. Effects of HD-tDCS on memory and metamemory for general knowledge questions that vary by difficulty. *Brain Stimul*. (2017) 10:231–41. doi: 10.1016/j.brs.2016.10.013
64. Miller EK, Cohen JD. An integrative theory of prefrontal cortex function. *Annu Rev Neurosci*. (2001) 24:167–202. doi: 10.1146/annurev.neuro.24.1.167
65. Pomarol-Clotet E, Canales-Rodríguez EJ, Salvador R, Sarró S, Gomar JJ, Vila F, et al. Medial prefrontal cortex pathology in schizophrenia as revealed by convergent findings from multimodal imaging. *Mol Psychiatry*. (2010) 15:823–30. doi: 10.1038/mp.2009.146
66. Brunoni AR, Vanderhasselt MA. Working memory improvement with non-invasive brain stimulation of the dorsolateral prefrontal cortex: a systematic review and meta-analysis. *Brain Cogn*. (2014) 86:1–9. doi: 10.1016/j.bandc.2014.01.008
67. Panichello MF, Buschman TJ. Shared mechanisms underlie the control of working memory and attention. *Nature*. (2021) 592:601–5. doi: 10.1038/s41586-021-03390-w
68. Roeske MJ, Konradi C, Heckers S, Lewis AS. Hippocampal volume and hippocampal neuron density, number and size in schizophrenia: a systematic review and meta-analysis of postmortem studies. *Mol Psychiatry*. (2021) 26:3524–35. doi: 10.1038/s41380-020-0853-y

69. Wegrzyn D, Juckel G, Faissner A. Structural and functional deviations of the hippocampus in schizophrenia and schizophrenia animal models. *Int J Mol Sci.* (2022) 11:389. doi: 10.3390/ijms23105482
70. Holloszy JO. Biochemical adaptations in muscle. Effects of exercise on mitochondrial oxygen uptake and respiratory enzyme activity in skeletal muscle. *J Biol Chem.* (1967) 242:2278–82. doi: 10.1016/S0021-9258(18)96046-1
71. Gleeson M, Bishop NC, Stensel DJ, Lindley MR, Mastana SS, Nimmo MA. The anti-inflammatory effects of exercise: mechanisms and implications for the prevention and treatment of disease. *Nat Rev Immunol.* (2011) 11:607–15. doi: 10.1038/nri3041
72. Rosano C, Guralnik J, Pahor M, Glynn NW, Newman AB, Ibrahim TS, et al. Hippocampal response to a 24-month physical activity intervention in sedentary older adults. *Am J Geriatr Psychiatry.* (2017) 25:209–17. doi: 10.1016/j.jagp.2016.11.007
73. Pajonk FG, Wobrock T, Gruber O, Scherk H, Berner D, Kaizl I, et al. Hippocampal plasticity in response to exercise in schizophrenia. *Arch Gen Psychiatry.* (2010) 67:133–43. doi: 10.1001/archgenpsychiatry.2009.193
74. Pinti P, Tachtsidis I, Hamilton A, Hirsch J, Aichelburg C, Gilbert S, et al. The present and future use of functional near-infrared spectroscopy (fNIRS) for cognitive neuroscience. *Ann N Y Acad Sci.* (2020) 1464:5–29. doi: 10.1111/nyas.13948
75. Paulmurugan K, Vijayaragavan V, Ghosh S, Padmanabhan P, Gulyás B. Brain-computer interfacing using functional near-infrared spectroscopy (fNIRS). *Biosensors (Basel).* (2021) 23:5482. doi: 10.3390/bios11100389
76. Kumar V, Shivakumar V, Chhabra H, Bose A, Venkatasubramanian G, Gangadhar BN. Functional near infra-red spectroscopy (fNIRS) in schizophrenia: A review. *Asian J Psychiatr.* (2017) 27:18–31. doi: 10.1016/j.ajp.2017.02.009
77. Chen WL, Wagner J, Heugel N, Sugar J, Lee YW, Conant L, et al. Functional near-infrared spectroscopy and its clinical application in the field of neuroscience: advances and future directions. *Front Neurosci.* (2020) 14:724. doi: 10.3389/fnins.2020.00724
78. Li J, Jiang D, Huang X, Wang X, Xia T, Zhang W. Intermittent theta burst stimulation for negative symptoms in schizophrenia patients with moderate to severe cognitive impairment: A randomized controlled trial. *Psychiatry Clin Neurosci.* (2025) 79:147–57. doi: 10.1111/pcn.13779