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THERAPEUTIC RESPONSE TO TRANSCRANIAL DIRECT CURRENT STIMULATION (TDCS) IN ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD): A STUDY PROTOCOL FOR A PARALLEL, RANDOMIZED, DOUBLE-BLINDED, SINGLE-CENTER TRIAL

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ABSTRACT

Attention-Deficit/Hyperactivity Disorder (ADHD) is a neurodevelopmental disorder characterized by deficits in attention regulation, hyperactivity, impulsivity and emotional self-control. Although psychostimulants are first-line treatments, their adverse effects and limited accessibility highlight the need for alternative therapies. Transcranial Direct Current Stimulation (tDCS) is a non-invasive neuromodulation technique that has shown promising results in improving ADHD-related cognitive functions. **Objective:** To evaluate the efficacy and safety of bifrontal tDCS in adults with ADHD, used as an alternative or add-on to lisdexamfetamine. **Methods:** This is a single-center, randomized, double-blind, placebo-controlled clinical trial involving 156 ADHD adults. Participants will be randomly assigned to the following groups: (1) active tDCS/lisdexamfetamine,(2) active tDCS/placebo, (3) sham tDCS/lisdexamfetamine, or (4) sham tDCS/ placebo. The intervention includes 20 sessions of bifrontal tDCS (anode F3, cathode F4) over 4 weeks, combined with lisdexamfetamine or placebo. ADHD symptoms will be assessed pre- and post-intervention using the Brazilian version of the ADHD Rating Scale for Adolescents and Adults (ETDAH-AD). **Primary Outcome:** Reduction in the severity of ADHD symptoms across five domains (inattention, hyperactivity, impulsivity, emotional aspects, and self-regulation) from baseline to post-treatment. **Expected Results:** It is hypothesized that active tDCS—especially when add-on therapy—will lead to greater clinical improvements compared to other intervention arms. *Trial Registration:* The Trial was registered on April 24, 2025 on the Registro Brasileiro de Ensaios Clínicos (Brazilian Clinical Trials Registry - ReBEC under the number RBR-10nbjgb9

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INTRODUCTION

Attention- Deficit/ Hyperactivity Disorder (ADHD) is considered a neurodevelopmental condition and, as such, manifests with signs and symptoms from childhood. It manifests through symptoms that may indicate dysfunction in the prefrontal cortex, including difficulties with attention, and impulsive and/or hyperactive behaviors[1]. Typically, individuals with the disorder exhibit distinct or combined behavioral patterns, such as: the inattentive type, which may involve wandering off during tasks, lack of persistence, difficulty maintaining focus, and disorganization; the hyperactive type, characterized by excessive motor activity when inappropriate or excessive talking; and/or the impulsive type, which is associated with hasty actions that carry a high potential for harm, inability to delay gratification, and a strong desire for immediate rewards[2].

Neuroimaging studies conducted on individuals with ADHD indicate changes in the frontal cortex and its connections [3]. These alterations may impair frontal executive functions such as inhibition, working memory, emotional regulation, and attention, leading to difficulties in attentional processing and inhibitory responses [4]. This can affect self-control, which is essential for emotional regulation, and compromise the ability to maintain attention on a task for extended periods (sustained attention). Research involving neurotransmitters and neuroimaging suggests that catecholamines — particularly dopamine and norepinephrine — are involved in the pathophysiology of ADHD. Genes encoding transporters and receptors of the dopaminergic, noradrenergic, and serotonergic systems are also implicated [5,6,7,8,9]. The neural circuits most frequently affected in ADHD are those that regulate attention, motor control, emotional regulation (including motivation), and the reward system.

This suggests that the causes of ADHD are complex and multifactorial, involving the interaction of environmental factors, genetic predispositions, and/or structural and neurochemical brain deficits. Environmental factors may act as a nonspecific trigger, leading to the manifestation of ADHD symptoms [10,111]. ADHD has an estimated global prevalence of 5.2% in school-aged children and 2.5% in adults, with approximately two million cases in Brazil. Adults with ADHD face significant challenges, including difficulties with attention, impaired impulse inhibition, problems resisting distractions, poor emotional control, and often, a lack of self-regulation and self-discipline. Managing daily responsibilities, coping with the demands of adult life, and dealing with the consequences of symptoms can be especially difficult, given the increased responsibilities and obligations faced in adulthood [12,13].

Currently available pharmacological treatments have limitations, such as high cost and significant adverse effects, which can restrict their clinical applicability [14,15,16]. In this context, the development of new therapeutic approaches that are safe, effective, and accessible becomes essential. Various electrical stimulation techniques have been tested in neuropsychiatric disorders with positive results, including Transcranial Direct Current Stimulation (tDCS) [17]. tDCS is a non-invasive brain stimulation technique that uses low-intensity electrical current to induce neuromodulation and neuroplasticity in specific brain regions. Neuromodulation refers to the process of modifying neural activity using electrical or chemical stimulation. This modulation enables the regulation of the central, peripheral, or autonomic nervous system for therapeutic purposes by inhibiting or stimulating targeted neural activity [17,18]. Although tDCS does not directly induce neuronal action potentials, it can alter cortical activity in the region beneath the electrodes by modulating the activity of sodium and calcium ion channels on neuronal membranes, as well as by influencing the efficiency of postsynaptic receptors such as N-methyl-D- aspartate (NMDA). These effects are thought to be influenced by several neuromodulators, including serotonin, dopamine, adrenaline, gamma- aminobutyric acid (GABA), and acetylcholine.

Thus, stimulation of a single area may lead to improvements in adjacent regions as well [19,20,21]. tDCS has the potential to produce lasting effects on brain activity even after the stimulation period ends, with results that may persist for several hours or even weeks, depending on parameters such as current intensity, electrode placement, distance between electrodes, duration of stimulation, number of sessions, and the interval between them.[22] According to the most recent guidelines, tDCS is considered safe, with no serious adverse events or irreversible injuries reported across more than 33,000 sessions conducted with conventional protocols (sessions lasting less than 40 minutes and using currents below 4 mA) [23]. The tDCS device allows for both active and sham stimulation. In active stimulation, the current is gradually increased (ramp-up) at a rate of approximately 100 μA/s until the desired intensity is reached, which is then maintained throughout the session, followed by a gradual decrease (ramp- down) at the end. In sham stimulation, the ramp-up occurs, but the current is then reduced and the device is deactivated. During this procedure, the individual typically experiences a mild tingling sensation at the electrode site, but no effective stimulation occurs [18]. Several studies using tDCS as an intervention in areas associated with executive control functions have demonstrated improvements in cognitive deficits characteristic of ADHD, including attention, working memory or short- term memory, and executive functions [24,25,26,27]. Additionally, increased brain connectivity and processing speed have been observed following treatment. The stimulated area (anodal stimulation) in most studies corresponds to the left dorsolateral prefrontal cortex (left DLPFC - F3 in the 10-20 EEG system), with the cathode positioned in the right dorsolateral prefrontal cortex (right DLPFC - F4) or in the contralateral supraorbital region [21,27,28]. In a recent Brazilian study, daily treatment with a home-based tDCS device over 4 weeks improved attention in adult patients with ADHD who were not taking stimulant medication[28].

Other studies show the same results, with predominantly positive results regarding attention, with almost no results in the field of hyperactivity/impulsivity. This discrepancy in treatment response has implications for understanding the neurobiological mechanisms of ADHD[29]. Given some evidence of clinical and cognitive improvement with tDCS, the main objective of this clinical trial is to evaluate the therapeutic response of Transcranial Direct Current Stimulation (tDCS) in Attention Deficit Hyperactivity Disorder (ADHD), comparing results when used as an alternative or add-on therapy with medication.

DESIGN AND METHODS: This prospective study is designed as single-center, randomized, double-blind clinical trial and aims to evaluate the therapeutic response of Transcranial Direct Current Stimulation (tDCS) in Attention Deficit Hyperactivity Disorder (ADHD). Altogether, 156 patients will be randomly assigned to one of four parallel groups in a 1:1:1:1: allocation ratio. Patients will be distributed into the following interventions: 1. tDCS plus psychostimulant; 2. tDCS plus placebo pill; 3. sham- tDCS plus psychostimulant; 4. sham-tDCS plus placebo pill.

All participants will undergo 20 daily sessions (Monday through Friday for 4 weeks) of bifrontal tDCS or sham-tDCS with anode over left DLPFC (F3) and the cathode over right DLPFC (F4) lasting 20 minutes, associated with the use of 30mg of lisdexamfetamine or placebo.

Study population: The clinical trial will include patients aged from 18 to 50 years with a primary diagnosis of adult ADHD according to the DSM-5-TR criteria. Experienced study investigators will perform a clinical interview based on the Diagnostic and Statistical Manual of Mental Disorders 5th Edition- Text Revision (DSM-5-TR) [1] Table 1 contains all inclusion and exclusion criteria for the present study.

Table 1. Inclusion and exclusion criteria of the trial

Inclusion Criteria	• Primary diagnosis of ADHD according to DSM-5-TR diagnostic criteria • Age between 18 and 50 years • Written informed consent • Availability for daily tDCS sessions • If previous diagnosis of ADHD, provided the participant is not undergoing pharmacological treatment within 30 days prior to randomization (minimum washout period: 30 days)
Exclusion criteria	• Acute severe depression episode (defined as Beck Depression Inventory with scores≥ 21) • Moderate to severe anxiety (defined as Beck Anxiety Inventory with scores ≥ 21) • Diagnosis of bipolar disorder with an episode of mania or depression in the last year • Schizophrenia or other psychotic disorder • Diagnosis of autism spectrum disorder • Positive screening for substance use disorder such alcohol, tobacco and other psychoactive substance, using the ASSIST scale (Alcohol, Smoking and Substance Involvement Screening Test) • Severe neurological and organic comorbidities (e.g., history of brain surgery, epilepsy, significant brain malformation or neoplasm, head injury, stroke, neurodegenerative disorders). • Severe somatic comorbidities • Current use/washing out of psychotropic medication (e.g. antidepressants, antipsychotics, anticonvulsants, lithium) • Pregnant or nursing females • Contraindications for tDCS (e.g. metallic plates or electronic implants in th brain or skull, skull defects and skin lesions on the scalp, history of epileptic seizure, cardiac pacemaker or defibrillator) • Contraindications for lisdexanfetamine (cardiac arrhythmias and family history of sudden death before age 50)

Study center and recruitment: The present study will be conducted at the Quality Multidisciplinary Clinic, located in the municipality of Jequié, in the southwestern region of Bahia, 370.6 km from Salvador. The municipality has a territorial area of 2,969,039 km², an estimated

population of 156,277 inhabitants, and a Municipal Human Development Index (MHDI) of 0.66532. This center has the appropriate technical equipment and experienced staff specializing in the diagnosis and treatment of adult ADHD patients as well as the application of tDCS in psychiatric conditions. During the pre-screening period, a trained study investigator will give comprehensive verbal and written information about trial- related objectives, procedures, and possible risks to each patient. All patients will have the opportunity to ask questions and will have enough time to consider whether they want to participate in the study. Before any study-specific measures are administered, an informed consent form must be signed. The consent to participate in the trial can be withdrawn at any given time during the study and without the necessity to provide a reason for withdrawal. Participants will be recruited through digital platforms between October 2025 and May 2026, until the target sample size is reached. A digital form will be distributed via WhatsApp, Facebook, and Instagram groups, presenting all eligibility criteria.

Study timeline: The trial comprises a pre-treatment phase and a treatment phase of 4-weeks duration. The flow chart (figure 1) gives an overview of the study timeline.

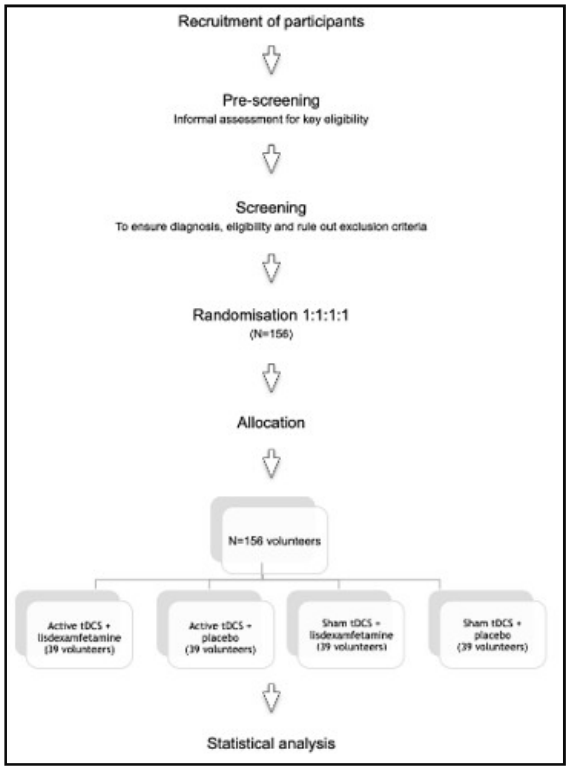

Figure 1. Study time line

In the context of a pre-screening, the most important inclusion and exclusion criteria are informally checked. If pre-screening examination confirms a suspected adult ADHD diagnosis, an appointment for screening will be offered to the patient concerned. Patients will receive the study information and consent in advance, allowing sufficient time for the consent form to be studied before it is being signed after a final discussion with the investigators. Eligible volunteers will undergo psychiatric evaluation for clinical data collection and a semistructured interview based on DSM-V TR criteria for diagnostic confirmation and ADHD subtype, as well as other inclusion criteria. Furthermore, several psychiatric, somatic and neurological concomitant diseases will be excluded. Finally, all participants will be required to undergo an electrocardiogram to assess potential contraindications for the use of psychostimulants, such as cardiac arrhythmias. It is expected that some volunteers may require more than one evaluation session for diagnostic confirmation. Patients who meet the inclusion and exclusion criteria will complete all pre-treatment assessments comprising the baseline visit and will then be randomized to the four parallel treatment arms. During the treatment phase, each patient will receive one active/sham tDCS session per day on twenty days (monday through friday for 4 weeks, with a break on weekends) combined with a psychostimulant/placebo. Possible adverse reactions related to the psychostimulant or tDCS will be formally evaluated on days 10 and 20 of treatment, but checked daily. Major protocol violations such as missing one (or more) intended stimulations or an overall duration of treatment longer than 4 weeks will result in exclusion from per- protocol analysis**.**

ASSESSMENT

Clinical measures: The assessment and the procedure performed during the pre-screening, screening, baseline and treatment period are summarized in Table 2. In the context of the pre-screening, the digital form will recruit participants with signs and symptoms of ADHD present since childhood, in addition to informally checking inclusion and exclusion criteria.

Table 2. Schedule of assessments and procedures

Study period	Pre-treatment		Treatment		
Visit	PS	SV	1	10	20
Week	-8	-4	1		
Day			1	10	20
Assessment	Screening and consent				
• Informed consent for pre-screening	✓				
• Informed consent for clinical trial		✓			
• In-/exclusion criteria		✓			
• SCID-5-CV		✓			
• BDI-II		✓			
• BAI		✓			
• ASSIST		✓			
• Functional level rating scale		✓			
• Physical and neurological exam		✓			
• Medical and psychiatric history		✓			
• Electrocardiogram		✓			
• Beta hCG test (female)		✓			
• Randomization		✓			
			Intervention		
Active/sham tDCS			✓✓✓✓✓✓✓✓✓✓✓✓✓✓		
Lisdexamfetamine/placebo			✓✓✓✓✓✓✓✓✓✓✓✓✓✓		
			Efficacy		
ETDAH-AD			✓		✓
			Safety		
(S) AE				✓	✓
			Other		
Blinding check				✓	✓
Demographics		✓			

PS: Pre-Screening; SV: Screening Visit; SCID-5-CV: Structured Clinical Interview for DSM-5 Disorders-Clinical Version; BDI- II: Beck's Depression Inventory-II; BAI: Beck Anxiety Inventory; ASSIST: Alcool, Smoking and Substance Test; ETDAH-AD: Attention Deficit Hyperactivity Disorder Rating Scale, Adolescent and Adult Score; (S) AE: Adverse Effects

The screening visit includes the signing of the informed consent for clinical trial, the registration of the sociodemographic characteristics, the collection of the medical and psychiatric history, a physical-neurological examination, including electrocardiogram and a beta-hCG test to rule out pregnancy. In addition, a detailed psychopathological examination is carried out with the clinician version of the Structured Clinical Interview for DSM-5 Disorders-Clinical Version (SCID-5-CV)[30]. In addition, the participants fill out the following questionnaires: Beck Depression Inventory-II (BDI-II)[31,32], Beck Anxiety Inventory (BAI)[32] and Alcohol, Smoking and Substance Involvement Screening Test

(ASSIST) [33,34]. At the baseline visit, and prior to the first active/sham tDCS combined with lisdexanfetamine/placebo, all participants will undergo assessment with the standardized scale for Attention Deficit Hyperactivity Disorder, Adolescent and Adult version (ETDAH-AD) developed for the Brazilian population [35,36]. This scale has 69 items and assesses five factors: 1) Inattention; 2) Impulsivity; 3) Emotional Aspects; 4) Self-regulation of Attention, Motivation and Action; and 5) Impulsivity. Each item allows the person being evaluated to choose the following responses: Never (0); Very Rarely (1); Rarely (2); Usually (3); Frequently (4); Very Frequently (5). The same scale will be answered at the end of the study for comparative purposes. All participants will be asked about adverse events involving tDCS and psychostimulant at visits on days 10 and 20 of the study. They will be asked about headache, neck pain, tingling and itching at the site of tDCS application, drowsiness during stimulation, metallic taste in the mouth, fatigue, difficulty concentrating, mood swings, palpitations, loss of appetite, insomnia, dry mouth, among others. Additionally in the same days, all participants will be asked whether they believe they received active or sham stimulation, as well as lisdexanfetamine or placebo ("blinding check").

Randomization and Blinding: A stratified randomization procedure will be implemented to ensure balanced allocation of participants across four intervention groups, within each of the three ADHD subtypes: predominantly inattentive presentation, predominantly hyperactive/impulsive presentation, and combined presentation. The randomization sequence will be generated using the online tool *Randomizer* [37]. Separate randomization lists will be created for each stratum (ADHD subtype), with participants randomized in a 1:1:1:1 ratio to one of the four intervention arms. Block randomization will be used within each stratum to maintain group balance and reduce the risk of allocation bias. The randomization list for each stratum will include a series of randomly generated identification codes, each pre-assigned to one of the four intervention groups. These codes will be stored in a password-protected file and will not be accessible to the investigators responsible for recruitment or data collection. Allocation concealment will be maintained through the involvement of an independent researcher, who will not be engaged in any aspect of participant recruitment, assessment, or intervention. Upon enrollment and stratification of each participant, the independent researcher will be contacted to reveal the group assignment based on the pre-generated list, ensuring that both the allocation process and group assignments will remain blinded to the core research team.

INTERVENTION

Stimulation: The tDCS sessions will be carried out over 20 days, from Monday to Friday, with a break on weekends (Saturdays and Sundays). The 20 minutes stimulation will be administered using a battery-driven constant-current stimulator (Model 1×1 tDCS, Soterix Medical Inc., New York, NY, USA). Two saline-soaked sponge electrodes (5 × 7 cm; Soterix Medical Inc.) will be positioned according to the international 10–20 EEG system, with the anode placed over on the left dorsolateral prefrontal cortex (F3) and the cathode over the right dorsolateral prefrontal cortex (F4). The anatomical location of these regions will be defined daily using the 10-20 electroencephalographic method. To estimate brain locations, measurements are taken from the individual's skull, collecting the tragus-tragus distance, nasion-inion distance, and head circumference. Subsequently, online software [38] estimates the region corresponding to the study areas. After locating the target regions, the electrodes are attached using a silicone headband. A constant current of 2mA (current density=0.0571 mA/cm^2) will be applied in verum tDCS. Current will be ramped up/down for 30s at the beginning /end of the session to avoid fast transients enabling subjects to distinguish between real and sham stimulations. Output current, output voltage, and impedance are monitored continuously. The Save-Stop mode prevents an uncomfortable and sometimes even painful "current jump" by slowing down the present current to 0mA when stimulation is manual or automatic stopped.

Sham stimulation: In contrast to the active tDCS condition, current for the sham intervention will be ramped up to 2mA for 30s followed by a 30s fade out at the beginning and end of each session to mimic the experience of mild itching and tingling that is commonly reported during the active stimulation, but no effective stimulation will occur for the remaining duration of the intervention. The induced sensory impression of being stimulated serves to improve the blinding.

Technical devices: For active and sham tDCS, the stimulation apparatus will consist of a battery- powered stimulator (Model 1×1 tDCS, Soterix Medical Inc., New York, NY, USA) specifically designed for transcranial direct current stimulation applications. The device delivers a monophasic, direct electrical current with programmable intensity and duration, and incorporates continuous impedance monitoring and an automatic current shut-off feature for safety. Stimulation is delivered via two independent electrode leads, each terminating in a reusable carbon–rubber electrode (surface area: 35 cm²) inserted into a saline-soaked sponge housing. Each sponge is constructed of synthetic, non-abrasive material with high porosity to ensure uniform saline distribution and consistent current density across the contact surface. Electrodes are positioned within the sponge pocket immediately prior to application to maintain optimal hydration and conductivity. The sponge–electrode assemblies are affixed to the scalp using elastic head straps fabricated from conductive, stretchable material, allowing stable electrode placement without excessive pressure. The strap system permits adjustable tension and accommodates variations in head circumference while minimizing displacement during stimulation. Electrical contact between the electrode and skin is maintained through the saline interface, reducing skin impedance and preventing focal current hotspots. All components are non- ferromagnetic and conform to IEC 60601-1 safety standards for medical electrical equipment

Psychostimulant: The active pharmacological intervention will consist of a single oral dose of lisdexamfetamine dimesylate (30 mg), administered once daily in the morning. The medication will be administered directly by a trained study applicator, who will have no involvement in any other stage of the trial, including participant allocation, randomization procedures, or data analysis, in order to preserve the integrity of the double-blind design. Lisdexamfetamine is a pharmacologically inactive prodrug of dextroamphetamine, in which dextroamphetamine is covalently bound to the essential amino acid L-lysine. Following oral ingestion, lisdexamfetamine is rapidly absorbed from the gastrointestinal tract and enzymatically hydrolyzed primarily in red blood cells to release the active moiety, dextroamphetamine [39]. The liberated dextroamphetamine exerts its central nervous system (CNS) stimulant effects by promoting the release of dopamine and norepinephrine from presynaptic storage vesicles and inhibiting their reuptake via dopamine transporter (DAT) and norepinephrine transporter (NET) blockade. This leads to increased synaptic concentrations of these catecholamines, particularly in the prefrontal cortex, striatum, and other regions implicated in attention and executive function [40]. Pharmacokinetic parameters for lisdexamfetamine 30 mg in adults indicate a median time to peak plasma concentration (Tmax) of approximately 3.5 hours for dextroamphetamine, with an elimination half-life of 10–13 hours. The prodrug formulation confers a gradual onset of action and prolonged duration of effect, reducing the potential for rapid fluctuations in plasma concentrations and lowering abuse liability compared with immediate-release amphetamine formulations.[40] Capsules will be sourced from a single manufacturing batch to ensure dosing consistency and will be indistinguishable in appearance from placebo capsules to maintain study blinding.

Placebo: Participants randomized to the placebo arm will receive an inert capsule containing a non-cognitive-enhancing compound intended solely to mimic the peripheral sensory experience of the active drug and maintain blinding integrity. The placebo will consist of beta-alanine (800 mg), an amino acid commonly found in sports pre-workout supplements, known to induce transient peripheral paresthesia (tingling sensation) through cutaneous nerve fiber

activation without exerting central cognitive effects at the administered dose[41].

Blinding: To maintain rigorous double-blinding, participants randomized to the sham stimulation arm will undergo the same electrode placement, duration, and ramp- up/down procedures as those receiving active tDCS. The sham protocol will consist of a brief period of current application (e.g., 30 seconds) mimicking the initial sensation of stimulation, followed by no current delivery for the remainder of the session, ensuring participant blinding to stimulation condition. Similarly, placebo capsules will be indistinguishable from active medication capsules in terms of weight, size, shape, color, and odor. Both active and placebo capsules will be manufactured to identical specifications to prevent unblinding via sensory cues. All interventions, including stimulation and capsule administration, will be conducted by trained personnel who are uninvolved in randomization, allocation concealment, or outcome assessments to preserve study integrity.

STUDY ENDPOINTS

Primary outcome measure: The primary outcome measure is the efficacy of active tDCS in reducing ADHD symptoms. It is expected to find a statistical difference between the groups regarding the cognitive domains evaluated (attention, hyperactivity, impulsivity, emotional aspects and self-regulation of attention/motivation/action) using a validated scale (ETDAH-AD), applied at the beginning and at the end of the study

Secondary outcome measure: As secondary outcomes, safety assessments will be analyzed between groups through acceptability and tolerability. To this end, a scale for the incidence of clinically relevant side effects will be applied on days 10 and 20 of the study.

Sample size calculation: To ensure adequate statistical power and minimize the risk of type II errors, a sample size calculation was performed. The *G*Power 3.1 software*, widely recognized for its ability to calculate sample size for various research designs was used[42]. A mixed ANOVA will be used to compare the mean ADHD-AD scores between the four groups over time. A significance level (α) of 0.05 and a statistical power (β) of 80% were established, values commonly adopted in health research[43]. Effect size is a crucial parameter in calculating sample size. It represents the magnitude of the difference between the groups to be detected. In this study, considering the existing literature and the nature of the intervention, a moderate effect size (f=0.25) was estimated, following Cohen's conventions[44]. Based on these parameters (k=4 groups, f=0.25, α=0.05, 1-β=0.80), G*Power indicated a sample size of 34 participants per group. Considering a possible 15% dropout rate, frequently observed in longitudinal studies of ADHD, it was considered best to increase the sample size by 15%, resulting in approximately 39 participants per group. Therefore, the study anticipated the inclusion of 156 participants, equally distributed among the four groups. This rigorous sample size calculation procedure aimed to ensure the robustness of the results and the study's ability to detect clinically meaningful differences between the proposed interventions.

Statistical analysis: Statistical analysis will be performed using the Statistical Package for the Social Sciences (SPSS Chicago – IL, version 25). Normality of data distribution will be assessed using descriptive statistics, graphical analysis, and the *Shapiro-Wilk Test*. Normal data will be subjected to multiple ANOVA. If variables are non-normal, they will be assessed using non-parametric tests— the *Friedman Test*, followed by the *Mann-Whitney Test*. Data will be expressed as mean and standard deviation or median and interquartile range. If the analysis of variance results in a significant F-value, a post hoc test will be performed for multiple analyses and definition of the means that differ from each other. The *Bonferroni method* will be applied in this study. In all cases, significance will be set at $p<0.05$. All missing or invalid data will be imputed to the mean of the data present in the corresponding parameters. In the event of a violation of the assumptions of homogeneity of variance, the corrected Welch, Brown, and Forsythe, or Greenhouse and Geisser hypothesis tests will be considered. To interpret the effect size of the difference between means, *Cohen's d* statistic and its equivalent version calculated from the F statistic of the mixed ANOVA will be used. $d<0.20$ indicates a small effect, $0.50<d<0.80$ a moderate effect, and $d>0.80$ a strong effect. To assess the integrity of the participant's blinding, a questionnaire will be administered asking participants to choose whether they are in the active tDCS group, the placebo group, or if they don't know the answer. The results regarding the belief that they will have received active treatment will be analyzed using the chi-square test, with the aim of quantitatively assessing the relationship between the study results and the distribution of the sample into groups, thus assessing the integrity of the study's blinding.

Safety aspects and data safety monitoring board: Exclusion criteria for this trial include all contraindications for the application of tDCS (e.g., metallic plates or electronic implants in the brain or skull, skull defects, history of epileptic seizures, cardiac pacemaker) and use of amphetamine psychostimulant (severe cardiac arrhythmias, family history of sudden death). Information on adverse events (AEs) and serious adverse events (SAEs) will be collected during the treatment period. (S)AE will be followed up until complete recovery and/or patient's status is stable.

Ethical aspects: This study received approval from the Research Ethics Committee of the State University of Southwest Bahia (Universidade Estadual do Sudoeste da Bahia – UESB), under protocol number CAAE: 81802524.3.0000.0055, on September 22, 2024. Additionally, authorization was obtained from Quality – Multidisciplinary Clinic for conducting data collection within its facilities. All participants will provide written informed consent via the Informed Consent Form (ICF). For illiterate participants, consent will be provided through fingerprint. The ICF was designed in adherence to the principles of bioethics— respect for autonomy, non-maleficence, beneficence, justice, and equity— aiming to safeguard the rights and responsibilities of participants, the scientific community, and the State, in accordance with Brazilian Resolution CNS No. 466/2012. Participants will be fully informed about the study's objectives, intervention procedures, and potential risks and side effects associated with both psychostimulant treatment and neuromodulation procedures. They will also be explicitly instructed that their participation is voluntary and that they can withdraw from the study at any time without any penalty.

DISCUSSION

We report on the design and rationale of a clinical trial conceived to investigate the efficacy of tDCS in reducing ADHD symptoms as an alternative or add-on therapy to stable ongoing treatment compared to sham stimulation and the amphetamine psychostimulant. There is a lot of evidence that tDCS can lead to an improvement in cognitive symptoms in a variety of neuropsychiatric conditions, and recent research show improving in ADHD symptoms. However it is unclear how it can be used in routine clinical practice. Clinical trials available to date have only compared tDCS with sham stimulation, without expanding the comparison with amphetamine psychostimulants, considered first-line treatment for ADHD. To our knowledge, this study represents the first attempt to compare tDCS with sham stimulation and psychostimulant in a four-arm study. Over the last years, several small studies with heterogeneous designs have been conducted in patients with ADHD. The majority of these studies have been conducted in pediatric ADHD patients, presumably due to the tolerability and relatively low side effect profile of tDCS. Therefore, clinical trials with adults are still scarce in the literature. Almost all authors of reviews and meta-analyses on the use of tDCS in ADHD also conclude that the efficacy of tDCS, and especially its clinical benefit on ADHD symptoms, cannot yet be conclusively assessed and further studies with optimized designs are warranted. A substantial number of those studies have compared tDCS with sham stimulation,

and all clinical trials excluded individuals using psychostimulants. With our study, we aim to contribute to gathering more robust data on this. In summary, positive results of this parallel, randomized and double- blinded trial would expand the treatment option for adult ADHD patients with an alternative or add-on therapy to psychostimulants with a low risk for side effects.

Limitations of the Study and Future Directions: This study protocol, while methodologically rigorous, has several inherent limitations that warrant consideration. The single-center design, situated in a specific urban area in Bahia, Brazil, may restrict the external validity and generalizability of our findings to other populations. Furthermore, the reliance on digital platforms for participant recruitment could introduce a selection bias, potentially enrolling individuals who are more technologically literate or actively seeking novel therapeutic approaches, thus affecting the representativeness of the sample. A key limitation of this trial is its focus on short-term outcomes, as the four-week treatment period does not allow for the assessment of long-term therapeutic effects. Consequently, the persistence of clinical benefits, tolerability, and the need for maintenance therapy remain important questions to be addressed by future studies. While our sample size calculation, based on a moderate effect size, ensures adequate power for the primary outcome, the study may be underpowered to detect smaller, yet clinically meaningful, differences. Additionally, although stratified randomization by ADHD subtype was implemented to ensure group balance, the sample size may not be sufficient to conduct definitive, well-powered subgroup analyses to determine whether the efficacy of tDCS varies across different clinical presentations. Therefore, any findings related to subtype-specific effects should be considered exploratory. These limitations, however, do not diminish the value of this protocol, which is designed to provide robust data on the efficacy of tDCS in a context that directly addresses critical gaps in the existing literature.

Conflict of Interest: The authors declare that the research will be conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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