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Understanding and targeting repetitive behaviors and restricted interests in autism spectrum disorder via high-definition transcranial direct current stimulation: a study-protocol

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Abstract

Background Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by persistent deficits in social interaction and repetitive behaviors (RBs). Therapies specifically targeting RBs have been underexplored despite advances in understanding their neurobiological basis. This study aims to evaluate whether high-definition transcranial direct current stimulation (HD-tDCS) can reduce dysfunctional RBs in autistic children and investigate whether improvements differ between lower-order and higher-order RBs based on the brain regions stimulated.

Methods The study entails a multi-session, sham-controlled, site-controlled, double-blind, and between-subjects design. The study will include participants with an ASD diagnosis (aged 8–13 years; IQ ≥ 70), who will undergo the HD-tDCS intervention for 10 sessions. Participants will be randomly assigned to three conditions: (1) Pre-Motor Active Group (active HD-tDCS over pre-SMA cortex); (2) Frontal Active Group (active HD-tDCS over dlPFC); (3) Placebo Control Group. In the active HD-tDCS conditions, the current will be delivered through a 4 × 1 montage; small circular electrodes will be used with the cathode placed centrally with a current intensity of 0.5 mA for a total of 20 min (30 s ramp up/down) per session. Participants during the sham condition will undergo the same procedures as those in the both active conditions actual placement of electrodes, and turning on the HD-tDCS equipment (30 s). The assessment will be completed at baseline (T0), immediately after the end of the intervention (T1) and 3 months after the end of the intervention (T2). The primary outcome measure will be the Total Score of the Repetitive Behavior Scale-Revised. The secondary outcomes measures will comprise ASD symptoms, sensory processing pattern, emotional/behavioral problems, sleep functioning, parental stress, neuropsychological features and High-Density EEG connectivity. We

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hypothesize that active HD-tDCS will lead to significant reduction in the total score of the primary outcome compared to Sham Group, with site-specific effects on lower-order and higher-order RBs.

Discussion HD-tDCS is an easy-to-deliver, time-efficient, neurobiologically-driven intervention that could be performed as add-on to reduce the time of conventional therapy for ASD. Given the inherent limitations of specific interventions for RBs, tDCS represents an important "third" treatment arm to address the burden of interventions for ASD.

Trial registration details The trial has been registered at ClinicalTrials.gov (ID: NCT06645587). Registered 17 October 2024.

Keywords Neuromodulation, Interventions, Sameness, Motor stereotypies, Pediatric age

Background

Autism spectrum disorder (ASD) is a lifelong, complex and heterogeneous neurodevelopmental disorder that reaches 1% of the worldwide population [1]. ASD is characterized by persistent deficits in two main domains: reduced social interaction abilities across multiple contexts and repetitive behaviors, interests or activities (hereafter Repetitive Behaviors, RBs). Regarding the first core symptom, autistic individuals usually exhibit impairments in social engagement, initiation, and maintenance. They often find it difficult to interpret social cues or maintain conversations, which consequently leads to lower quality of social relationships. Regarding the second area, multiple studies have reported two subgroups of RBs: lower-order RBs, comprising a heterogeneous group of behaviors such as motor mannerisms, sensory seeking behaviors, repetitive use of objects; and higher-order RBs, including restricted interests, sameness behaviors like compulsions, rituals and difficulties with changes in routine [2]. The manifestation of RBs in ASD (lower-order vs. higher-order) may vary according to the developmental stage: in particular, from the age of 2 years, autistic individuals usually start showing lower-level RBs, whereas in late childhood (> 11 years old), they often exhibit both lower- and higher-level RBs, such as ritualistic/sameness and compulsive behaviors [3].

Autistic individuals often exhibit comorbid psychiatric illnesses or conditions, which may include attention-deficit hyperactivity disorder (ADHD), anxiety, bipolar disorder, depression, and Tourette syndrome [4–6]. This results in increasing treatment costs and placing greater caregiver demands on the patients' families [7]. Remarkably, Horlin et al. (2014) found that the median family cost for ASD services was estimated to be € 21,4996/yr, and for each additional symptom reported, approximately € 862/yr in additional costs is incurred by the family. Given this high prevalence and societal burden, therapeutic interventions for ASD are urgently needed.

To date, a number of interventions for ASD have been developed to reduce deficits in social engagement, initiation, and maintenance [8, 9]. Promising evidence has documented improvements in social interaction and verbal communication in autistic individuals, including programs for children and adolescents that mostly focus on social communication deficits [10]. In contrast, treatment options for RBs have been less developed. Behavioral interventions targeting RBs symptoms include antecedent-based strategies, such as environmental enrichment and exercises, as well as consequence-based strategies, such as reinforcement and punishment procedures [10]. Notably, the majority of studies investigating behaviorally based interventions targeting RBs have employed single-subject designs, which inherently present challenges when attempting to generalize the findings [11].

All this suggests that RBs remain the "forgotten symptom" in ASD research [12], and treatment options for RBs are consequently very limited, with inconsistent evidence [12–14].

Neurocognitive correlates of RBs

At the neurobiological level, alterations in several neurotransmission systems underpinning RBs are linked with the excitatory/inhibitory (E/I) imbalance hypothesis of ASD [15, 16]. Briefly, the E/I balance refers to the equilibrium between excitatory and inhibitory synaptic inputs in local brain circuits. An imbalance can occur due to either increased glutamatergic signaling or decreased GABA signaling. Evidence obtained in toddlerhood, childhood, and adolescence has indicated an abnormal expression of GABA, the main inhibitory neurotransmitter in the brain. Low levels of GABA in the frontal lobe [17] and the first transverse temporal gyrus have been reported in autistic children [18]. Moreover, impairments in the dopamine system have been related to RBs. Dopamine modulates the connectivity of several brain areas such as the ventral tegmental area, substantia nigra, striatum, nucleus accumbens, caudate, anterior cingulate cortex, dorsal prefrontal cortex (dlPFC), globus pallidus, orbitofrontal cortex, putamen, subthalamic nucleus, thalamus, amygdala, and hippocampus [19]. These dopaminergic circuits modulate motor process [20], and alterations in dopamine projections from the substantia nigra pars

compacta to the striatum have been associated with RBs [21].

At a neuroanatomical level, RBs have been related with diffuse brain alterations involving two distinct cerebral loops: (i) a sensory-motor loop including the sensory-motor cortex (e.g., pre-SMA cortex) and its descending and ascending projections to the putamen; (ii) an associative loop including the dlPFC and its descending and ascending projections to the caudate [22]. Elevated RBs have also been associated with decreased volumes in several brain regions: left thalamus, right globus pallidus, left and right putamen, and right striatum [23]. Aberrant patterns of striatal connectivity have also been directly linked to RBs [24, 25].

At the cognitive level, one hypothesis explaining RBs in ASD is dysfunction in executive functions [26]. A recent meta-analysis of executive functions in ASD examined 235 studies (from 1980 to 2016), including 6,816 autistic participants and 7,265 controls [27]. The study confirms a broad executive dysfunction in autistic participants, relatively stable across development [27]. In particular, RBs are often associated with a range of deficits in executive functions, such as lack of inhibitory control - linked to the difficulties to suppress behaviors despite negative consequences [22] - and cognitive flexibility - linked to sameness behaviors [28].

Neurobiologically-driven interventions for RBs

Despite advances in understanding the neurobiological bases of RBs, brain-directed interventions specifically addressing RBs in ASD have been poorly investigated. Recently, promising evidence has emerged from the rapidly developing field of non-invasive transcranial electric stimulation (tES).

In recent years, there has been growing interest in the application of different tES tools – such as transcranial direct current stimulation (tDCS) – to induce neuroplasticity and to safely modulate cognition and behavior in paediatric populations [29–31].

tDCS is a non-invasive technique that operates by applying at least one electrode covered by a saline-soaked sponge (usually rectangular or circular with a size of 35 cm^2) positioned above target brain regions. By applying a weak current (usually ranging from 0.5 to 2 mA), tDCS can transiently modify neural excitability [32], via a subthreshold modulation of resting membrane potentials [33]. Its mechanism of action is polarity-dependent: anodal stimulation generally drives the neural resting membrane potential closer to the activation threshold, increasing excitability, whereas cathodal stimulation inhibits cell firing and decreases excitability [34]. The physiological mechanism underlying tDCS is related to long-term potentiation and long-term depression-like plasticity, primarily via a glutamatergic process involving N-methyl-D-aspartate receptors [35, 36]. tDCS is a safe, cost-effective, portable, and user-friendly intervention for paediatric population [37]. However, it is well-known that tDCS modulates cortical activity in a relatively larger area than that covered by the target electrode, reaching also distal brain areas [34]: therefore, its non-focality represents a major limitation [38]. An alternative approach is a high-definition tDCS (HD-tDCS), where small disc electrodes are arranged in a 4×1 configuration. As proposed by Datta and colleagues [39], the stimulation electrode is positioned at the center, surrounded by four reference electrodes arranged in a ring-like pattern. With this configuration, the current flow is confined primarily to the region directly beneath the electrodes, enhancing precision. This results in higher current densities primarily within the targeted area while minimizing the risk of side effects by limiting stimulation of non-target brain regions [40]. The transient effects of HD-tDCS on cortical excitability have already been demonstrated, with a peak of cortical excitability at 30 min post-stimulation up to 6 h [40].

There is encouraging evidence on the effect of tDCS in autistic youth [41, 42]. Improvements have been documented in core symptoms [43–46], social cognition [47–52], theory of mind [53, 54], language abilities [55], non-verbal intelligence [56], gross motor functions [57, 58], inhibitory control [59], and catatonic symptoms [60]. In addition, promising behavioral effects have been supported by changes in functional connectivity [61] and brain dynamics [51, 62–64] following tDCS interventions in autistic youth.

To date, only one study considered RBs as a clinical outcome (albeit not the main target) of a left anodal tDCS intervention over dlPFC in a group of autistic children [65], while the remaining research on neuromodulation has overlooked the effects of stimulation on reducing RBs and the investigation of possible site-specific effects (pre-SMA vs. dlPFC). Moreover, the majority of studies on ASD have focused on the application of conventional tDCS over the dlPFC [41, 42], while only one study has investigated the effects of HD-tDCS in autistic children [50]. In addition, to date, most of the study implemented anodal tDCS or bipolar montage (anodal/cathodal), while promising evidence also comes from the two studies which adopted cathodal tDCS in children and adolescents [51, 66].

We suppose that cathodal HD-tDCS may be effective in reducing the impact of RBs in autistic children by targeting the associated brain alterations and addressing the E/I imbalance. In particular, the high focality of HD-tDCS could help us disentangling the relative contributions of different brain loops (namely, sensory-motor and the associative loops) to RBs subtypes. If the proposed

treatment is found to be effective, it could be translated into novel and effective rehabilitation strategies for ASD.

Objectives

Building upon the reported evidence, the primary objective of this study is to determine whether the implementation of active HD-tDCS compared to sham HD-tDCS will contribute to reduce dysfunctional RBs. The secondary objectives are to investigate whether (i) Active HD-tDCS will lead to specific improvements on lower-order vs. higher-order RBs according to the different regions stimulated (pre-SMA vs. dlPFC cortex); (ii) Active Groups (i.e., Active HD-tDCS over dlPFC and pre-SMA) will significantly improve ASD-related clinical aspects (e.g., ASD symptoms, sensory processing pattern, emotional/behavioral problems, sleep functioning, and parenting stress) and neuropsychological features (inhibitory control, cognitive flexibility, and ecological executive functions), demonstrating significant correlations with RBs improvements; (iii) Active Groups will change EEG-connectivity, with significant associations between EEG-connectivity measures and neuropsychological features; (iv) Active HD-tDCS will be a safe and tolerable treatment for ASD.

Methods

Ethical committee

The local research ethics committee provided ethical approval for the study (process number GR-2021-12375413) and it was registered at ClinicalTrials.gov (ID: NCT06645587) on the 17Th October 2024. This study will be run following the Declaration of Helsinki. The protocol adheres to the SPIRIT guidelines (Standard Protocol Items: Recommendations for Interventional Trials, see Table S1 in Supplementary Materials).

Participants and clinical eligibility assessment

The study will be carried out at the Child and Adolescent Neuropsychiatry Unit of the Bambino Gesù Children's Hospital in Rome. Participants will be enrolled during the daily clinical activities by a team of psychologists and neuropsychiatrists with an expertise on the evaluation and diagnosis of ASD. Otherwise, electronic health records of patients referred to the Unit and assessed following the good clinical practices per international guidelines for neurodevelopmental disorders will be consulted for the recruitment. Research assistants will reach out families via phone and email to ensure their interest in joining project.

The principal investigator will fully explain the study procedures to participants and their parents in order to obtain their written consent and participation on a voluntary basis only. Since autistic children frequently display a specific language pattern profile with difficulties in both comprehension and expression [67], explaining the study in detail would be challenging for clinical researchers. Aiming to improve an inclusive and person-centered approach to brain stimulation research, the presentation of the study procedures will utilize the Augmentative and Alternative Communication (AAC) system. AAC enhances communication in both expression and comprehension, reducing misunderstandings during interactions and consequently minimizing challenging behaviors [68, 69]. For more details, see Passarini et al. [70].

Inclusion criteria are: (1) participants of both sexes with an ASD diagnosis according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition-Text Revision (DSM-5-TR) [1] and based on clinical evaluation and administration of "gold standard" instruments for ASD diagnosis; (2) an intelligence quotient (IQ) higher or equal to 70 (IQ ≥ 70); (3) age range from 8 years to 13 years and 11 months included.

Exclusion criteria include: (1) the presence of neurological/medical/genetic conditions (i.e., brain tumours or genetic syndromes); (2) personal or family history of epilepsy; (3) other primary psychiatric diagnoses (i.e., bipolar disorders, schizophrenia spectrum disorders, or adjustment disorder); (4) sensorimotor deficits; (5) the presence of peacemaker or other metal devices in the body; (6) ongoing CNS-active drug treatment; (7) receiving other cognitive-behavioral therapies specifically focused on RBs in the 3 months before the study.

Besides ASD diagnosis, the clinical eligibility assessment will include cognitive, adaptive and behavioral assessment, as listed below.

Cognitive assessment

Cognitive level will be assessed by using the Leiter International Performance Scale (Leiter-3) [71] or the Perceptual Reasoning Index of the Wechsler Intelligence Scale (WISC – IV) [72]. Intelligence quotient will be presented as composite scores (M = 100; SD = 15).

Adaptive behavior assessment

Adaptive behavior will be investigated by using Adaptive Behavior Assessment System Second Edition for Ages 5–21 (ABAS-II) [73]. The ABAS-II comprises 10 adaptive skills categorized into 3 domains: Conceptual (Communication, Preschool/School Skills, Self-Control); Social (Play/Leisure, Socialization); and Practical (Self-Care, Home/School Life, Environmental Use, Health and Safety, Work). Caregivers are required to complete 232 items rated on a four-point Likert scale. The ABAS-II embraces four composite scores, namely the Global Adaptive Composite, the Conceptual Adaptive Composite, the Social Adaptive Composite, and the Practical Adaptive Composite (M = 100; SD = 15).

ASD standardized diagnostic assessment

The diagnosis of ASD will be based on extensive clinical evaluation, observation and administration of "gold standard" instruments such as such as the Autism Diagnostic Observation Schedule-2 (ADOS-2) [74] and the Autism Diagnostic Interview-Revised (ADI-R) [75]. The ADOS-2 [74] is a standardized and semi-structured observational assessment. The tool comprises five modules, tailored to the individual's age and expressive language abilities. It provides for various tasks allowing the clinician to observe social and communicative behaviors and the presence of RBs. Specific items contribute to algorithms used to compute scores of the social-affect and RBs subscales, along with a total score, with a cut-off score to determine whether or not individuals meet diagnostic criteria for ASD. Algorithm scores for the two subscales and the total score can be converted into a Calibrated Severity Score (CSS), a measure of overall symptom severity, enabling comparisons across different modules [76]. The ADI-R [75] is a standardized and semi-structured interview for caregivers aiming to obtain a wide range of information for establishing a clinical diagnosis of ASD. To be administered, a minimum of 2 year-mental age of the child is mandatory. The interviewer collects certain and timely descriptions related to the individual's behaviors throughout the development. The ADI-R provides a diagnostic algorithm according to the ICD-10 and DSM-IV [77, 78] divided into three subdomains of ASD symptoms: qualitative impairments in reciprocal and social behavior; qualitative anomalies in communication; and restricted range of interests and/or stereotyped behaviors.

Psychopathological comorbidities screening

Emotional and behavioral problems will be assessed by using the Child Behavior Checklist/6–18 (CBCL/6–18) [79] and the Conners Behavior Rating Scale (CPRS) [80].

The CBCL [79] is a widely used parent-report questionnaire that contains 113-item evaluating the child's behaviors and emotions during the preceding 6 months on a three-point Likert scale. The CBCL encompasses several scales, as follows: (1) syndrome scales (Anxious/depressed, Withdrawn/depressed, Somatic complaints, Social problems, Thought problems, Attention problems, Rule-breaking behaviors, and Aggressive behaviors); (2) broadband scales (internalizing problems, which incorporates anxious/depressed, withdrawn/depressed, somatic complaints; externalizing problems, which incorporates rule-breaking behavior, and aggressive behavior; total problems); (3) DSM-oriented scales (Affective, Anxiety, Somatic, ADHD, Oppositional defiant problems, and Conduct problems); and (4) 2007 scales (Sluggish cognitive tempo, Obsessive-compulsive problems, and Post-traumatic stress problems). According to the cut-off thresholds of Achenbach and Rescorla (2001), T-scores > 69 are classified as clinically relevant, T-scores between 65 and 69 are classified as borderline, and T-scores < 65 indicate non-clinical symptoms. For the internalizing problems, externalizing problems, and total problems scales, T-scores > 63 are classified as clinically relevant, T-scores between 60 and 63 are classified as borderline, and T-scores < 60 indicate non-clinical symptoms.

The CPRS [80] is a parent report questionnaire addressing behaviors related to ADHD in children aged 3–17 years. The tool includes 80 items rate on a three-point Likert scale. The T-score cut-off for relevance is > 70 while T-scores from 60 to 70 are considered high average or elevated.

Only participants meeting the inclusion/exclusion criteria will be enrolled.

Study design, randomization and blinding

The study entails a multi-session, sham-controlled, site-controlled, double-blind, and between-subjects design.

After confirming clinical eligibility, the participants included in the study will be randomly assigned to three conditions: (1) Pre-Motor Active Group (active HD-tDCS over pre-SMA cortex); (2) Frontal Active Group (active HD-tDCS over dlPFC); (3) Placebo Control Group (sham HD-tDCS over pre-SMA cortex or dlPFC). The randomization will be stratified, based on IQ level (composite scores 70–90 and 90+). The randomization will use the minimal sufficient balancing method to prevent imbalances in baseline. A technician will perform the pseudo-randomization via a software.

After clinical eligibility evaluation, a baseline assessment will be completed on Day 1 (T0), before the interventions are administered. Participants will undergo the HD-tDCS intervention for 10 days (3 days per week for a total of four weeks). To minimize the influence of intra-circadian variations, participants will attend stimulation sessions each day at the same time. Participants will also complete an assessment at the end of the interventions (T1), and 3 months later (T2).

Both participants and experimenters will be blinded to the intervention conditions. At the end of whole study (at T2), participants and their parents as well as the experimenters will be asked to guess their stimulation condition. An independent researcher will maintain the randomization information until the data collection will be finalized. Only in the case of an emergency, such as a serious adverse event that requires knowledge of the interventions to manage the participant's condition, data will be accessed through an emergency code break envelope provided to the Principal Investigator.

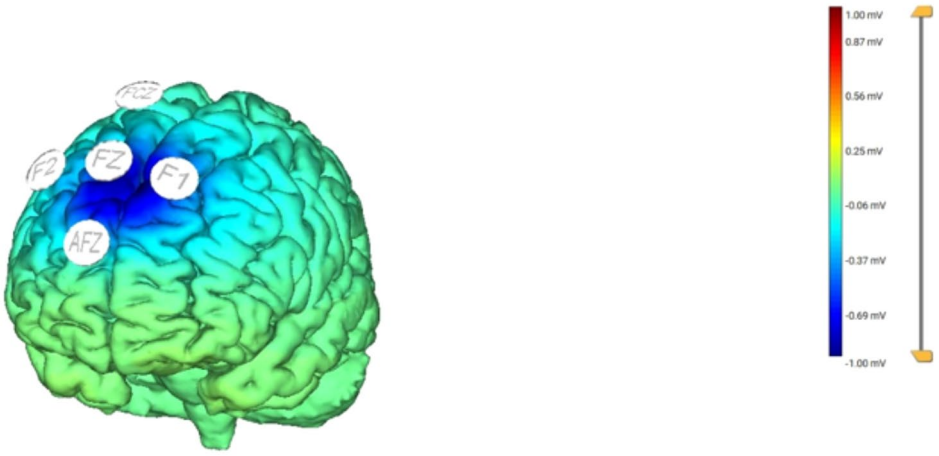

Fig. 1 Pre-SMA montage: map of electric field magnitudes in a male brain model viewed from the left-front perspective. The stimulating cathode electrode will be placed over FZ, targeting the pre-SMA, whereas the return anodal electrodes will be placed over F2, AFz, Fcz, and F1. The current intensity will be set at 0.5 mA for a total duration of 20 minutes.

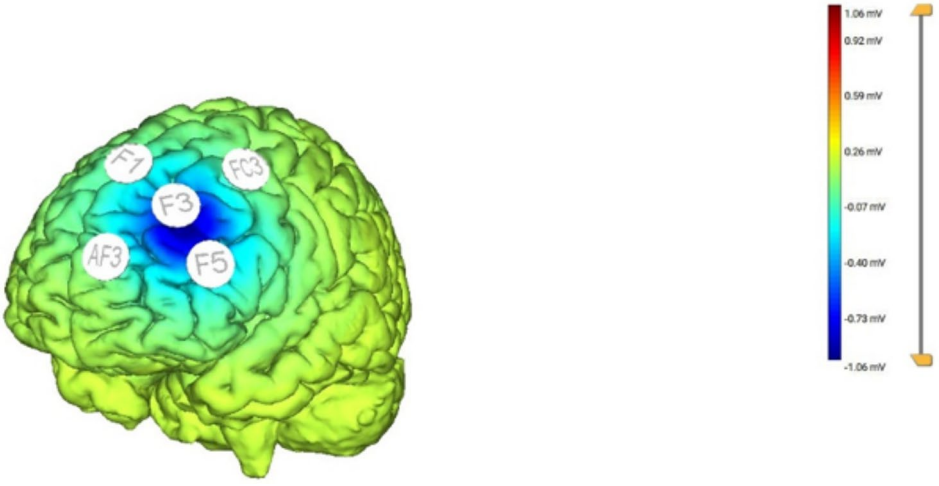

Fig. 2 dlPFC montage: map of electric field magnitudes in a male brain model viewed from the left-front perspective. The stimulating cathode electrode will be positioned over F3, targeting the left dlPFC, while the return anodal electrodes will be placed over AF3, F5, F1, and FC3. The current intensity will be set at 0.5 mA for a total duration of 20 minutes.

Intervention

High-definition transcranial direct current stimulation

The current will be delivered by Starstim 32 (Neuroelectrics Barcelona SLU). In the active HD-tDCS conditions, a 4 × 1 montage, small circular electrodes (diameter 12 mm, 3.14 cm^2) will be used with the cathode placed centrally with a current intensity of 0.5 mA for a total of 20 min (30 s ramp up/down) per session [81]. Hereby, the cathodal electrode modulates the excitability of the targeted area, whereas the other 4 electrodes return electrical currents that flow away from that area.

Based on literature, in the active HD-tDCS over pre-SMA, the cathode electrode will be placed over FZ [82–84], and the return electrodes will be positioned over F2, AFz, Fcz, F1 (spaced ~ 3 cm away) [81] according to the International 10–10 System (See Fig. 1). Based on literature and already published procedure, in the active HD-tDCS over left dlPFC, the cathode electrode will be placed over F3 [45, 51] and the return electrodes will be positioned over AF3, F5, F1, and FC3 (spaced ~ 3 cm away) [81, 85–87], according to the International 10–10 System (See Fig. 2). The impedance of the electrodes will be checked before and during the application of HD-tDCS to ensure that it remains below 10 kΩ.

To control for any placebo effect, participants during the sham condition will undergo the same procedures as those in the both active conditions, including the same localization of electrode placement, actual placement of electrodes, and turning on the HD-tDCS equipment (30 s). Other than this brief stimulation, participants during the sham condition will not receive active stimulation (0 mA) during the rest of the session.

To ensure protocol adherence and minimize variability, the experimenter responsible for delivering the interventions will complete a structured checklist before each stimulation session. This checklist will include participants' information, details of the procedures to be applied, and dose parameters. The checklist is adapted from Antal et al. [88].

During the stimulation, participants will be entertained by playing a simple computer task in which participants will pair stimuli according to their color, shape or letter following random rules.

Outcome measures

Each measure will be administered at T0, T1 and at T2, except for EEG measures that will be collected at T0 and T1. Participants will undergo evaluations in a quiet room to check for the fatigue effect (see Fig. 3).

Primary outcome

The primary outcome measure will be the Total Score of the Repetitive Behavior Scale-Revised (RBS-R) [89, 90]. It consists of a 43-item parent-report questionnaire evaluating the extent of RBs in autistic individuals.

The RBS-R encompasses the following six scales: Stereotyped Behavior (movement without an obvious purpose and repeated in a similar pattern), Self-injurious Behavior (actions that cause or have the potential to cause redness, bruising, or other injury to the body), Compulsive Behavior (behavior that is repeated and performed according to a rule or involves things being done "just so"), Routine Behavior (performing activities of daily living in a similar manner), Sameness Behavior (resistance to change, insisting that things stay the same), and Restricted Behavior (limited range of focus, interest, or activity). RBS-R items are rated on a 4-point scale (0-Behavior does not occur, 1-Behavior occurs and is a mild problem, 2-Behavior occurs and is a moderate problem, 3-Behavior occurs and is a severe problem); an overall total raw score and a total number of items score for each subscale are computed.

Examination of the psychometric properties of the RBS-R showed highly moderate internal consistency and good inter-rater reliability [90]. Cronbach's alphas for all of the subscales were satisfactorily high ranging from 0.78 for Restricted Interests subscale to 0.91 for Ritualistic/Sameness Behavior subscale, with a mean of 0.83. Alpha values over 0.80 are generally considered moderately high to high [90]. Inter-rater reliability, calculated using intraclass correlation coefficients (ICC), showed subscale correlations ranging from 0.57 to 0.73, with a mean of 0.66 [90]. ICC values are categorized as follows: 0.49–0.59 = fair; 0.60–0.79 = good; 0.75–1.00 = excellent [91].

Secondary outcomes

The secondary outcomes measures will comprise ASD symptoms, sensory processing pattern, emotional/behavioral problems, sleep functioning, parental stress, neuropsychological features and EEG (for more details see Table 1).

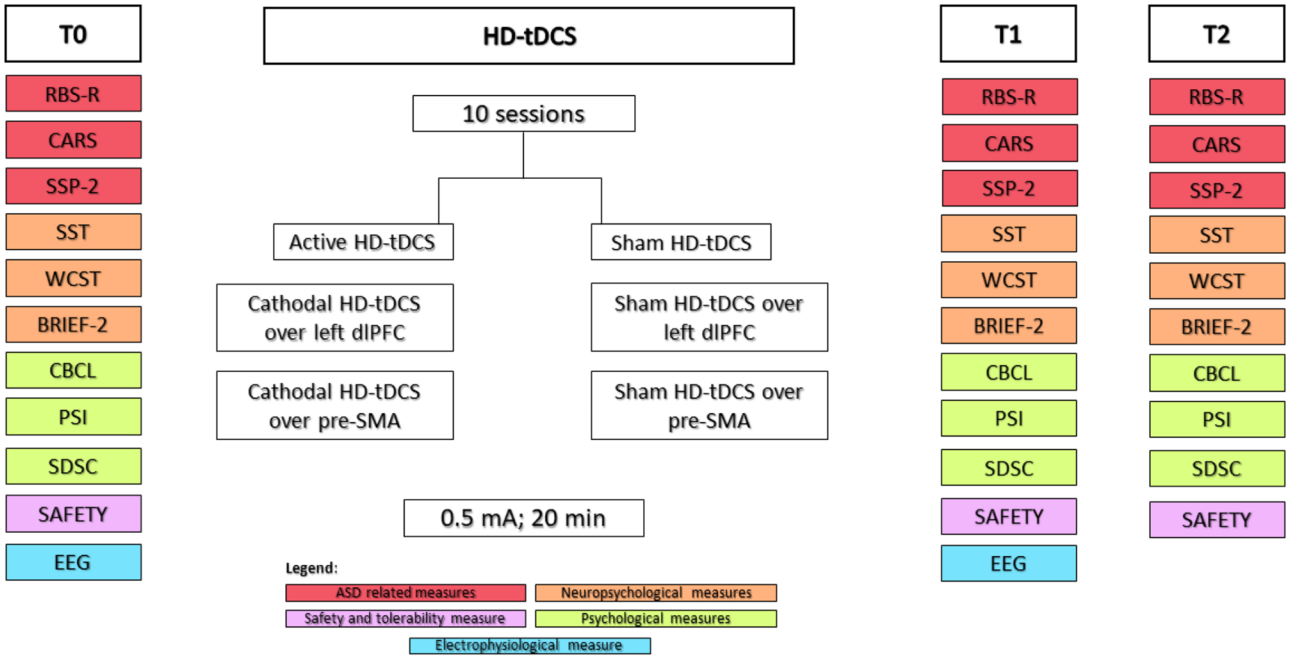

Fig. 3 Overview of the study design. T0, Baseline and before HD-tDCS intervention; T1, immediately after the end of the treatment; T2, 3 months after the end of the treatment.

Table 1 Detailed descriptions of secondary outcome measures.

Measure	Description
ASD related traits assessment	
CARS-2	A Rating scale for symptoms related to ASD in younger (from 2 to 6 years) or in autistic individuals and low functioning (IQ ≤ 79 and regardless the child's age) (Standard Form; CARS-ST), and autistic individuals and high functioning (IQ > 80) (High Functioning form; CARS-HF). Both versions contain 15 items rated on a four-point scale with higher scores revealing more severe symptoms related to ASD. The total raw score is converted into standard score within three severity ASD levels: no or minimum symptoms of ASD (15-29.5 or 15-27.5 with > 13 years for CARS-ST; 15-27.5 for CARS-HF) mild to moderate symptoms of ASD (30-30.6 or 28-34.5 with > 13 years for CARS-ST; 28-33.5 for CARS-HF), and moderate to severe symptoms of ASD (> 35 or > 37 with > 13 years for CARS-ST; >34 for CARS-HF).
Psychological assessment	
SSP2	A parent report questionnaire for evaluating the sensory processing pattern in children aged 3–14 years. It contains 34 items divided into 4 subscales: seeking/seeker, avoiding/avoider, sensitivity/ sensor, registration/bystander. SSP2 items are further divided into sensorial and behavioral domains resulting into sensory and behavioral total scores. Scores are assigned on a five-point Likert scale. Low scores are indicative of frequent dysfunctional behavior. Based on a bell curve normed distribution, the raw score total for each quadrant can be classified as "much less than others" (lower 2%), "less than others" (between 1 SD and 2 SD below the mean, accounting for 14% of the normative sample), "just like the majority of others" (± 1 SD from the mean and accounting for 68% of the normative sample), "more than others" (between 1 SD and 2 SD above the mean), and "much more than others" (upper 2%).
CBCL/6–18	A parent report questionnaire to evaluate behavioral and psychopathological problems of individuals aged 6–18 years.
SDSC	A parent report questionnaire for evaluating the sleep functioning of children and adolescents aged 6–16 years. It has been widely used in cohorts of children with various medical conditions (e.g. ASD, ADHD, cerebral palsy, epilepsy, and genetic syndromes). The SDSC investigates the occurrence of sleep disturbances in the previous six months throughout 26 items in a five-point Likert scale. It encompasses the following scales: difficulty in initiating and maintaining sleep, sleep-disordered breathing, disorders of arousal, sleep-wake disorders, disorders of excessive somnolence, and sleep hyperhidrosis. T scores of > 70 is clinically significant while T scores under 60 or ranged 61–69 are respectively in the average or borderline range.
Caregivers' psychopathological assessment	
PSI-SF	A self-report questionnaire to evaluate parenting stress levels through 36 items rated on a five-point Likert scale. Items encompass three subscales as follows, parental distress or the experienced distress in the role of being a parent (PD), difficult child (DC) linked to the child's behavioral problems, and parent–child dysfunctional interaction (P-CDI). The sum of all items results in the Total Stress score. The total raw score is converted into percentile score; percentile ≥ 85 is considered as clinically significant.
Neuropsychological assessment	
SST	A computerized task evaluating inhibitory control and consisting in randomly intermixed go and stop trials (75% and 25%, respectively). The task is structured in line with the consensus guide of SST [93] and it will be performed on PsychoPy® software (Open Science Tools Ltd., Nottingham, UK). Before the experimental session, participants will be familiarized with the task by performing approximately 10 trials of the go and no-stop task, and about 25 trials of the go no-go and the stop task. This familiarization ensures that all participants clearly understand the task requirements before data collection begins. All trials will begin with the presentation of a cross in the center of a computer screen and after 1500 ms, a stimulus target (go signal) will replace the cross. On go trials, children will be instructed to press the space bar as fast as possible after the go signal's appearance. In stop trials, after a variable delay (Stop-Signal Delay - SSD), a stop signal stimulus target will appear after the go signal. Children will be instructed to refrain from responding. The SSD duration will be controlled by a simple staircase procedure (50 ms step) to keep the probability of inhibition around 50% of trials. SSD will be increased or decreased by a single step after successful or unsuccessful stopping. The SST will yield the following measures: stop-signal reaction time (SSRT), calculated in milliseconds by subtracting a mean SSDs from the observed mean reaction times (RTs) in no-stop trials; go accuracy; go RTs; Stop Signal Delay. The task duration will be approximately 14 min.
WCST	The version of the Wisconsin Card Sorting Test for developmental stages evaluates executive functions. The Modified Card Sorting Test (MCST) [94] assesses executive functions in children aged 4–13 years. The tool requires assigning 48 cards, on which one to four symbols are printed in different colors and shapes. The sorting rule (number, shape, color) changes after six correct assignments. The participant must deduce the current rule from the own pattern of responses. The number of right and wrong assignments and the number of errors will be computed.
BRIEF-2	A parent report questionnaire for an ecological and comprehensive evaluation of executive functions in children aged 5–18 years. The tool encompasses 63 items evaluating inhibition, self-monitoring, shift, initiation, working memory, emotional control, planning, task-monitoring, and organization of materials. Items are further dived into 4 indices as follows, the Behavior Regulation Index (BRI), the Emotion Regulation Index (ERI), the Cognitive Regulation Index (CRI), and the Global Executive Composite (GEC). Raw scores of each scale and index are converted into T scores. For all BRIEF-2 clinical scales and indices, T scores from 60 to 64 and from 65 to 69 are considered respectively mildly elevated and potentially clinically elevated while T scores at or above 70 are clinically significant.

Table 1 (continued)

Measure	Description
Neurophysiological measure	
HD-EEG	HD-EEG recording sessions will be scheduled at baseline (T0) and following the HD-tDCS treatment (T1) to monitor any changes in HD-EEG connectivity induced by tDCS. Resting-state EEGs will be recorded in a sound-attenuated, electrically shielded room to minimize external noise and interference. Each session will include the presence of a caregiver and a dedicated research assistant to ensure the comfort of the child participants and to prevent any distress. EEG data acquisition will be conducted using the BRAIN QUICK® system (Micromed, Mogliano Veneto, Italy) equipped with a 256-channel, reusable pre-wired headcap system. Participants will be asked to sit comfortably and remain relaxed with their eyes closed during both the setup and the recording phases, with each session capturing a minimum of 8 min of EEG activity.

Legend. CARS-2: The Childhood Autism Rating Scale – 2nd ed [95].; SSP2: The Short Sensory Profile [96]; CLBCL/6–18: The Child Behavior Checklis/ 6–18 [79]; SDSC: The Sleep Disturbance Scale for Children [97]; PSI-SF: The Parenting Stress Index — Short Form [98]; SST: The Stop Signal Task [99]; WCST: The Wisconsin Card Sorting Test [100]; BRIEF-2: The Behavior Rating Inventory of Executive Function - Second Edition/ parent report [101]; EEG: Electroencephalography

Regarding safety and tolerability, possible symptoms and side effects will be evaluated after each HD-tDCS session by using the AAC version of the Adverse Effects Questionnaire by Brunoni et al. [92]. Briefly, the questionnaire lists possible adverse effects, such as headache, neck pain, scalp pain, tingling, itching, burning sensation, skin redness, sleepiness, trouble concentrating, and acute mood change. Participants will quantify the intensity of the symptoms or side effects related to HD-tDCS as follows, 1—absent; 2—mild; 3—moderate; 4—severe. The AAC safety questionnaire [70] depicts each side effect with a corresponding pictogram (image + word), aiming to enhance children comprehensions of quite abstract concepts, like sensations, by visualizing them. Additionally, it would assist clinical researchers in accurately verifying the tolerability of HD-tDCS procedures. For more details, see Passarini et al. [70]. Researchers will keep on monitoring any adverse effects that may arise during the treatment period even after the conclusion of the study, until the outcome is defined.

Protection of risks

To minimize risks associated with HD-tDCS, participants will be monitored throughout stimulation sessions and asked to report any discomfort. If the scalp sensation becomes uncomfortable or if a headache occurs, the stimulation will be stopped. All HD-tDCS sessions will be administered and continually supervised by a trained experimenter. tDCS side effects are minimal in children and adults, typically involving transient itching and reddening at the site of stimulation on some participants [29]. However, to avoid any chance of seizure, a prior history of neurological disorders and a personal or family history of epilepsy are exclusionary criteria for participating in the study.

Missed sessions and early termination of participation

Each participant's suspension or interruption during the study will be recorded. In the case of suspension during a testing session, data from that specific session will be excluded from the analyses. Nevertheless, clinical care will not be compromised.

Power and sample size

The sample size was calculated by a priori analysis in G * Power, version 3.1.9.7 (The G*Power Team, Düsseldorf, Germany). To be conservative, we calculated the expected effect size (f) to low and estimated it at 0.20 basing on previous literature [54, 66]. With an estimated f = 0.20, alpha value = 0.05 (i.e., probability of false positives of 5%), and ß = 0.20 (i.e., at least 80% power), the sample size that was required for repeated-measures analysis of variance (RM ANOVA) with 2 groups (Frontal Active Group + Pre-Motor Active Group vs. Sham Group) and 2 measurements (Time: T0 vs. T1) was 54 (i.e., 18 per group). Considering a 30% dropout rate in the follow-ups, we will plan to recruit a total of 78 participants (i.e., 26 per group).

Electrophysiological measures

Pre-processing

MATLAB software will be utilized for the preprocessing of EEG data. Initial steps will include the application of a Butterworth bandpass filter with cutoff frequencies between 0.5 and 45 Hz. Following filtering, EEG data will be normalized using z-score transformation to facilitate comparison across sessions and subjects by standardizing EEG amplitude distributions.

To enhance the quality of EEG data, visual inspection will be conducted to manually identify any artifacts. Furthermore, Independent Component Analysis will be implemented to systematically identify and remove components associated with common physiological and external artifacts, such as eye blinks, muscle contractions, and electrical noise.

All EEG data will be acquired in a monopolar configuration and then re-referenced to the common average reference to improve signal-to-noise ratio and overall data quality.

EEG connectivity analysis and features extraction

EEG data will be segmented into temporal windows vary between 1 and 4 s. Longer windows can provide better frequency resolution (useful for spectral analysis), while shorter ones may be preferable for capturing rapid dynamics. Spectral Analysis will be computed by calculating averaged power spectra for each epoch using the Fast Fourier Transform. Electrodes recording from the supplementary motor area (SMA) and thedlPFC will be identified. For each of these electrodes, EEG connectivity metrics will be extracted to explore neural dynamics and evaluate the effects induced by tDCS. Moreover, for each EEG electrode, we will extract the following features to comprehensively analyze the EEG connectivity and to quantify the EEG intrinsically and dynamical properties:

1. Coherence – According to Rosenberg et al. [102], coherence will be computed to assess the degree of co-activation between EEG channels over time, reflecting synchronous neural activities.
2. Granger Causality – This measure will be used to infer directional influences between neuronal populations, helping to elucidate the predictive relationships among EEG signals.
3. Phase Slope Index – This index will be calculated to measure the directed phase dynamics between signals, providing insight into the directed flow of neural information.

For each EEG electrode, we will extract the following features to comprehensively analyze the underlying neural dynamics:

1. Lyapunov Exponent: quantifies the rate of chaos in the system, providing insights into the chaotic nature of the EEG signals. A higher Lyapunov exponent suggests greater system chaos, indicative of more complex neural dynamics.
2. Hurst Exponent: is used to determine the long-term memory of time series data. In EEG analysis, a Hurst exponent greater than 0.5 indicates a persistent long-term positive autocorrelation, while a value less than 0.5 indicates a fading memory or anti-persistent behavior.
3. Power Density Spectrum: This analysis provides information on the distribution of power across various frequency bands within the EEG data. It is crucial for identifying dominant frequencies and assessing overall brain activity across different states of neurological conditions.
4. Entropy: quantifies the randomness or complexity in the EEG signal. Higher entropy values indicate more complexity and less predictability in the signal, which can be associated with higher cognitive processing or altered brain states.

Statistical analysis

The groups will be compared on demographic and categorical variables using Chi-Square analyses. Assumptions for ANOVA will be tested by Levene's test for homogeneity of variances and Shapiro-Wilk test for normal distribution. When data will not satisfy assumptions for ANOVA, non-parametric tests for comparisons between groups will be run or a Log- Transformation will be computed. Assessment measures will be analyzed by means of RM ANOVA with Group (Frontal Active Group vs. Pre-Motor Active Group vs. Sham Group) as between-factor and Time (T0 vs. T1 vs. T2) as within-factor. The effect size will be calculated by means of the partial eta squared value and the post hoc comparisons by means of Tukey's honest significance test.

Two batteries of analysis will be conducted. In order to preserve the benefit of randomization, intention-to-treat analysis will be performed, thus including all participants who are randomized in the statistical analysis and analysing according to the group they were originally assigned, regardless of what treatment (if any) they received. A per-protocol analysis will be also conducted, thus including who actually received the intervention assigned by the protocol.

A stimulation session (either real or sham) will be considered completed if the participant receives stimulation for the full 20 min provided.

For EEG data analysis, we will calculate the difference in each connectivity metric for each electrode between the post-tDCS (T1) and pre-tDCS (T0) recordings. This difference will be considered as the absolute connectivity parameter, capturing the impact of tDCS treatment on neural connectivity patterns. To determine the statistical significance of changes in connectivity metrics, the differences between the pre-SMA and the control group, as well as between the dlPFC and the control group, will be analyzed. An independent-samples t-test (or Mann-Whitney U test, if the data does not follow a normal distribution) will be utilized to compare the mean differences in connectivity metrics. This analysis aims to evaluate how tDCS modulate neural connectivity in these brain regions in comparison to normal conditions.

Expected results

We believe that active HD-tDCS will be effective in the amelioration of RBs in autistic children. We expect that:

1) Active HD-tDCS over pre-SMA and dlPFC will determine a significant reduction in the total score of RBS-R (primary outcome) compared to Sham Group at each time-point (T1, T2).

2) In an exploratory- fashion, the distribution of score changes (at T1 and T2 compared to T0) in the RBs subscales [Lower-Order RBs subscales (i.e., "stereotyped behaviors" and "self-injurious behaviors") vs. Higher- Order RBs subscales (i.e., "compulsive behaviors", "behavior inherent to routines", "insistence on sameness", "restricted interests and/or activities")] will vary across the Active Groups, with higher percentages of participants who improved in Lower-Order RBs subscales in the Pre-SMA Group compared to the Sham Group and higher percentages of participants who improved Higher-Order RBs in the Frontal Group compared to the Sham Group.
3) Active HD-tDCS over dlPFC and pre-SMA will improve ASD symptoms (i.e., lower mean total scores of CARS), sensory processing pattern (patterns classification), emotional/behavioral problems (lower mean scores of CBCL subscales), sleep functioning (lower mean scores of SDSC subscales), parental stress (lower percentiles of PSI Indices) and neuropsychological features (i.e., inhibitory control measured as SST output measures such as SSRT, go accuracy, go RTs, SSD); cognitive flexibility measured as higher levels achieved of MCST; ecological executive functions measured as lower mean scores of BRIEF-2 subscales) compared to Sham Group at each time-point (T1, T2).
4) Changes in ASD symptoms, emotional/behavioral problems, sleep functioning, parental stress, and neuropsychological features will significantly correlate with RBS-R changes at each time-point.
5) In an exploratory- fashion, the EEG-connectivity changes in Active Groups compared to Sham Group; changes in spontaneous EEG will serve as a non-invasive objective biomarker for HD-tDCS effects.
6) Changes in EEG-connectivity will correlate with neuropsychological changes.
7) Active Groups will report equal number of adverse effects as those reported by the Sham Group; thus HD-tDCS will be considered safe, tolerable and feasible from participants and their families.

Discussion

This is the first double-blind, sham-controlled, randomized clinical trial promoting a neurobiologically-based intervention for RBs in school-age autistic children. RBs have been reported as the most challenging symptom domain to manage, significantly impacting patients' well-being and family stress levels. These behaviors interfere with a child's functioning and learning opportunities, and they affect the ability to engage socially [103]. Despite the severe impact of RBs on both individual and family functioning, our knowledge on possible interventions remains very limited [12].

A unique facet of this study relies on its own primary objective, which is first targeting "lower-order "and "higher-order" RBs through HD-tDCS by addressing their neurobiological bases (sensory-motor loop vs. associative loop) [22]. HD-tDCS offers undoubtedly more precision compared to conventional tDCS [40], and is particularly recommended for hypothesis-driven clinical trials that depend on the engagement of site-specific brain functions, such as in the current study. Therefore, the present trial can greatly benefit from this more accurate method of stimulation, which can potentially prevent the interference of other brain regions.

An additional innovative feature of this study is that it applies cathodal stimulation over target brain regions, instead of anodal stimulation as most studies have done [41, 42]. The rationale for applying cathodal HD-tDCS comes from evidence of a higher E/I imbalance in ASD [104–106], which is linked to dysfunctional brain dynamics/connectivity and cognitive alterations underlying RBs. This E/I balance is crucial for maintaining neuronal homeostasis and stabilizing global brain dynamics [107], which optimizes information processing efficiency and flexibility – a key executive function associated with RBs [108, 109]. Disruptions in this balance can lead to reduced cognitive flexibility [28, 110]. The E/I imbalance seems to reflect hyperactivation of key hub regions related to ASD (e.g., left dlPFC) during cognitive tasks requiring inhibitory control and cognitive flexibility, as a recent neuroimaging meta-analysis documented [111]. In this context, both anodal and cathodal tDCS [112–114] can modulate the E/I balance by affecting glutamatergic and GABAergic signaling differently. Anodal tDCS enhances neuronal excitation by increasing glutamatergic signaling and reducing GABA concentrations in stimulated brain regions [35, 36, 115]. Conversely, cathodal tDCS promotes neuronal inhibition by decreasing local glutamate levels [116–118] and specifically modulating GABA [119]. Although cathodal tDCS also modulates these neurotransmitters, its effects in ASD have been less explored. Preliminary evidence suggests that cathodal tDCS coupled with cognitive training improves social functioning and cognitive processing speed in autistic children [51] and reduced core symptoms in autistic adolescents [66]. In addition, while in autistic population it has never been applied, encouraging results have been observed after cathodal tDCS over the pre-SMA in reducing RBs-like symptoms. These promising outcomes have been documented in studies on populations with Tourette syndrome [120–123] and Obsessive-Compulsive Disorder [124–126], where tics and obsessive-compulsive symptoms were significantly alleviated. Building upon the evidence that cathodal tDCS also modulates

glutamate and GABA, it is reasonable to assume that cathodal tDCS over brain circuits related to RBs may also play a role in modulating these symptoms and brain connectivity.

Concerning HD-tDCS parameters, current intensity has been chosen based on the few already published studies in children and adolescents with other neurodevelopmental disorders, such as ADHD [127–129]. Moreover, the montage electrodes for pre-SMA and dlPFC relies on already published procedure [81–83, 85–87]. To recruit targeted brain networks and achieve meaningful neural modifications [114, 130], HD-tDCS sessions are coupled with 10-min task. As suggested by current literature [49, 131], the rationale relies on task-facilitating functional connectivity changes.

Regarding the target population, it is worth highlighting that this study focuses on school-aged autistic children (aged 8–13 years), a specific age group that is often underrepresented in research on ASD. Specifically, there is a paucity of randomized clinical trials involving autistic scholars and focusing on interventions [132, 133].

The safety and feasibility of the current study is an aspect to be discussed. One possible critical aspect is related to the use of tDCS itself. The most commonly mentioned, non-specific side effects using tDCS can be local such as tingling, itching, local redness and burning sensation [134–136].

Of note, one significant barrier to inclusion in research may be linked to communication difficulties, which often affect autistic individuals and other neurodevelopmental disorders [137]. The fear of an unfamiliar research equipment in the presence of language anomalies may hinder the compliance with research procedures. This often results in challenging and uncooperative behaviors, which may lead to the exclusion of individuals with neurodevelopmental disorders from clinical trials [133, 138, 139]. Implementing strategies such as aided AAC may decrease communication challenges during research procedures [137], potentially mitigating non-compliant behaviors by educating, preparing, and anticipating steps in a simple and intuitive manner. Additionally, since AAC helps individuals in explaining their sensations and thoughts [70], the use of the AAC Safety Questionnaire [70] seems a valuable and inclusive practice to monitor potential adverse effects of tDCS.

One possible limitation of the current study is the inclusion of only high-functioning autistic individuals with an IQ of 70 or higher (IQ ≥ 70). However, the study did not exclude minimal verbal autistic children, a phenotype of autistic children often under investigated and excluded from clinical trials [140].

Conclusions

This easy-to-deliver, time-efficient, neurobiologically-driven intervention could be performed as add-on to reduce the time of conventional therapy for ASD: the potential to leverage combination therapy in a way that yields synergistic rather than additive effects is poorly explored for RBs in ASD. Given the inherent limitations of both pharmacotherapy and psychotherapy for RBs, tDCS represents an important "third" treatment arm to address the burden of interventions for ASD. Moreover, the project will be also relevant for ASD because it will provide crucial insights on the biological bases of RBs. The comparison between two different HD-tDCS protocols will allow us to discriminate the relative contribution of specific brain areas on different-order RBs, thus providing further insights into the neurobiology of RBs in ASD. Considering the heterogeneity of ASD manifestations, the possibility to act on targeted brain regions specifically associated with subgroups of symptoms would pave the road for personalized interventions. The evidence obtained with this project will have a high translational power since the study will provide for the application of a safe, low-cost intervention that is easily declinable in clinical settings. In light of these considerations, this project represents a crucial balance between scientific innovation and feasibility of application. This project could pave the way for implementing a short, innovative, and feasible intervention that offers benefits in terms of cost, time, and quality of care for autistic youth.

Abbreviations

ASD	Autism spectrum disorder
RBs	Repetitive Behaviors
tES	Transcranial electric stimulation
HD-tDCS	High-definition transcranial direct current stimulation
ADHD	Attention-deficit hyperactivity disorder
dlPFC	Dorsolateral prefrontal cortex
pre-SMA	Pre-supplementary motor area
AAC	Augmentative and Alternative Communication
ADOS-2	Autism Diagnostic Observation Schedule-2
ADI-R	Autism Diagnostic Interview-Revised
WISC – IV	Wechsler Intelligence Scale for Children – Fourth Edition
ABAS-II	Adaptive Behavior Assessment System Second Edition
CBCL	Child Behavior Checklist/6–18
CPRS	Conners Behavior Rating Scale —Italian Adaptation
RBS-R	Repetitive Behavior Scale-Revised
CARS-2	The Childhood Autism Rating Scale
SSP2	The Short Sensory Profile
SDSC	The Sleep Disturbance Scale for Children
PSI-SF	The Parenting Stress Index —Short Form
SST	The Stop Signal Task
WCST	The Wisconsin Card Sorting Test
BRIEF-2	The Behavior Rating Inventory of Executive Function - Second Edition/ parent report
EEG	Electroencephalography

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12888-025-06506-y.

Supplementary Material 1

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
The local research ethics committee (Ospedale Pediatrico Bambino Gesù, IRCCS) provided ethical approval for the study (process number GR-2021-12375413).

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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