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HAND-IN (hand function after neuromodulation and intensive training in children with cerebral palsy): study protocol for a randomized, triple-blind, controlled trial with embedded implementation and cost-effectiveness analyses

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CLINICAL TRIAL PROTOCOL

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HAND-IN (hand function after neuromodulation and intensive training in children with cerebral palsy): study protocol for a randomized, triple-blind, controlled trial with embedded implementation and cost-effectiveness analyses

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ABSTRACT

Aim: The following clinical trial protocol aims to investigate the additional effects of bilateral transcranial direct current stimulation (tDCS) combined with constraint-induced movement therapy (CIMT) compared to CIMT alone in children and adolescents with spastic hemiparetic cerebral palsy.

Methods: This randomized, triple-blind, controlled trial will enroll 32 participants aged 7–16 years with spastic hemiparetic cerebral palsy (MACS I–II). Participants will be allocated to CIMT with sham or active bilateral tDCS (C3-C4, 1 mA, 20 min), with electrode placement guided by transcranial magnetic stimulation mapping. The intervention will last 3 weeks (5 days/week, 3 h/day). Primary outcomes will assess upper limb use (PMAL/TMAL). Secondary outcomes include dexterity (Box and Block Test), strength (dynamometry), functional performance (PAFT), and participation (COPM, GAS). Assessments will occur post-intervention and at 1, 3, and 6 months. Implementation of outcomes and cost-effectiveness will also be evaluated. Once completed, the study team will perform intention-to-treat analyses using linear mixed-effects models.

Expected results: The HAND-IN trial will provide evidence on the clinical, implementation, and economic effects of combining CIMT with bilateral tDCS in children with spastic hemiparetic cerebral palsy. If effective, this approach may enhance the durability of upper limb functional gains and support the adoption of neuromodulation in pediatric neurorehabilitation.

Trial Registration Number (Brazilian Clinical Trials Record- REBEC): RBR-2fczbt2 (https://ensaiosclinicos.gov.br/rg/RBR-2fczbt2). Registration on January 15, 2026.

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Cerebral palsy; constraint-induced movement therapy; transcranial direct current stimulation; upper limb; Neurological Rehabilitation

1. Introduction

Cerebral Palsy (CP) describes a group of permanent movement and posture disorders attributed to a non-progressive disturbance that occurs during the development of the fetal or infant brain up to the second year of life [1]. Sensory, perceptual, visual, cognitive, and emotional impairments may also be present. Epidemiological studies conducted in developed countries have reported an incidence of CP of 1.5 per 1,000 live births, demonstrating that in these settings, both prevalence and severity have decreased due to public policies promoting healthy pregnancy and improved neonatal care [2]. Data from Brazil and other developing countries are inconsistent; however, mapping by the Institute for Health Metrics and Evaluation (IHME) indicates a prevalence of approximately 1.05 cases per 100 children under 5 years of age in Brazil [3,4].

Various classifications are used to categorize CP, including the type of tone, the distribution of motor involvement, and the level of independence. Spastic hemiparesis refers to the increased motor tonus and motor function of the contralateral hemibody to the lesion of the central nervous system. Children with hemiparesis are more functional and have less impact on motor function on participation, quality of life, and gait than children with other topographies [5]. Even though the patient may be highly functional in gross motor function, due to the pattern of encephalic involvement, the upper limb is usually significantly affected, with impairment of sensorimotor and interhemispheric pathways, which generate difficulties with unimanual and bimanual activities [6]. It is known that upper limb involvement affects an average of 83% of the population with CP, of whom 54% present moderate to severe difficulty in object manipulation [7].

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Article highlights

- This protocol evaluates a novel combination of bilateral transcranial direct current stimulation (tDCS) and constraint-induced movement therapy (CIMT) in pediatric cerebral palsy.
- The study uses a rigorous randomized, triple-blind, sham-controlled design, which is uncommon in pediatric neurorehabilitation trials.
- The intervention is grounded in a mechanistic model of interhemispheric modulation, aiming to enhance and sustain neuroplasticity.
- Individualized targeting using transcranial magnetic stimulation (TMS) increases precision and supports a personalized treatment approach.
- Primary outcomes focus on real-world upper limb use, complemented by measures of function, participation, and goal attainment.
- The protocol integrates implementation outcomes (acceptability, feasibility, appropriateness), addressing real-world applicability.
- A prospective cost-effectiveness analysis is included, strengthening translational and health system relevance.
- The study addresses a key limitation of CIMT: the limited durability of functional gains.
- Findings may support the development of scalable, low-cost neurorehabilitation strategies, particularly in resource-constrained settings.
- The results could also inform clinical guidelines and broader adoption of neuromodulation in pediatric neurorehabilitation.

Among the techniques for rehabilitation of the affected upper limb (AUL), Constraint-Induced Movement Therapy (CIMT) is considered one of the most evidence-supported interventions, with a solid level of evidence in rehabilitation, based on use-dependent cortical reorganization [8,9]. Pediatric CIMT is grounded on three pillars: intensive repetitive task-oriented training (through structured practice via shaping and task practice), the transfer of behavioral packages (behavioral strategies), and restraint of the less affected upper limb 24 h/day for 21 consecutive days [10]. Studies show that CIMT induces use-dependent cortical reorganization, as evidenced by neuroimaging and transcranial magnetic stimulation, and can promote volumetric gains in cerebral gray matter, specifically in the sensorimotor cortex, anterior motor areas, and bilateral hippocampus [11,12]. The challenge of this technique, as in numerous therapeutic interventions, is to propose ways to maintain cortical reorganization and prolong functional outcomes so that they become effective motor programs [11,13–16]. The Cochrane review shows evidence of substantial improvement in upper limb motor function at immediate follow-up; however, over time, some functions are lost [9]. Dissociated finger movements, grasp, wrist extension, grip strength, and bimanual activity were not maintained at follow-ups ranging from 2 weeks to 4 months, indicating that peak patient gains occur at immediate follow-up, with a considerable decline within the first 4 months after the end of the protocol [9]. In this context, noninvasive brain stimulation techniques have proven to be safe and feasible as potential instruments to improve upper limb function in children with CP and may enhance neuronal plasticity and the effectiveness of the applied intervention [17].

Transcranial Direct Current Stimulation (tDCS) is a noninvasive brain stimulation technique considered safe, applied by placing two electrodes, one with a positive charge (anode) and the other with a negative charge (cathode). The electrical current flows between these two poles and promotes chemical–biological changes in brain tissues. Even considering possible current dissipation, it is stated that sufficient current reaches cortical structures and modifies the action potential of the cell membrane, leading to depolarization or hyperpolarization depending on the direction of current flow relative to the direction of the axon [18]. This induces a physiological mechanism of plasticity, like long-term potentiation (LTP) and long-term depression (LTD), through a glutamatergic process that favors the release of N-methyl-D-aspartate (NMDA) receptors, which are involved in post-stimulation effects [19,20].

Currently, only a limited number of studies have analyzed the effectiveness of the original pediatric CIMT protocol combined with tDCS in individuals with CP [17,21,22]. A 2018 study used tDCS at 0.7 mA to inhibit the primary motor cortex in the non-affected hemisphere in 20 children with CP before the application of the local CIMT protocol for 100 min [22]. In this study, CIMT combined with tDCS did not show differences between the sham group and the active group, likely due to the low intensity applied, the small number of patients, the variability in corticospinal tract preservation, and the lack of association between the interventions, as tDCS was applied before CIMT [22]. In contrast, a 2017 review of tDCS as a tool in motor rehabilitation found that tDCS studies in CP focused on spasticity rather than functional training [21]. Studies in adult patients with post-stroke hemiparesis demonstrated that bilateral tDCS is a feasible and effective option to accelerate motor gains during the recovery period, as well as to promote greater retention of functional motor gains [23,24]. This effect appears to be modulated by intracortical inhibitory pathways in the contralesional primary motor cortex [23,24]. Similarly, Fleming et al. (2018), in their review of the role of tDCS in promoting motor function in children with cerebral palsy, adopted the interhemispheric imbalance model as the rationale for bilateral tDCS application [25]. The main purpose of the procedure is to decrease excitability of the contralesional primary motor cortex (M1) through cathodal stimulation while increasing excitability of the ipsilesional M1 through anodal stimulation [25]. However, the same review also reported that unilateral tDCS protocols, whether cathodal or anodal, have not demonstrated consistent improvements in upper limb function in children with cerebral palsy [25]. Evidence from another study suggests that the effectiveness of CIMT on hand function is not dependent on corticospinal projection patterns, as children with contralateral, ipsilateral, and bilateral projections all demonstrated functional improvements following the intervention [26]. A mini review on the application of tDCS in children with cerebral palsy (CP) reported limited evidence of improvements in upper limb function, although it highlighted the promising potential of this intervention [27]. Recent findings have demonstrated considerable interindividual variability in corticospinal excitability following tDCS, with no consistent clinical or neurophysiological predictors of responsiveness identified to date [28]. Therefore, no consensus currently exists regarding the optimal stimulation montage for this population.

In light of this knowledge gap, the objective of the present study is to compare the immediate, short-, and long-term effects of the combined bilateral tDCS + CIMT (intervention

group) with the control group (sham tDCS + CIMT) regarding frequency, quality, speed, movement dexterity, and spontaneous use of the more affected upper limb in an uncontrolled environment, and spontaneous use. Additionally, we will analyze the performance, satisfaction, and participation goals selected by the patient and the caregiver. Finally, we will carry out an implementation and cost-effectiveness analysis.

We propose that the addition of bilateral tDCS to CIMT will lead to more sustained and clinically relevant improvements in upper limb function in children with spastic hemiparetic cerebral palsy compared to CIMT alone. Additionally, we expect that this combined approach will be feasible to implement in clinical settings and will represent a cost-effectiveness intervention.

2. Methods

It is a prospective, randomized, controlled, triple-blind clinical trial. The study is being conducted in partnership with Universidade Cidade de São Paulo (UNICID) and the Associação de Assistência à Criança Deficiente (AACD) – Ibirapuera, São Paulo, Brazil, with collaborative support from Universidade Federal de São Paulo (UNIFESP-SP) on the electroencephalogram (EEG) and Transcranial Magnetic Stimulation (TMS) mapping apparatus. The study was approved by the Research Ethics Committees of both institutions (UNICID Approval No. 7.795.537 and AACD Approval No. 7.930.090). It was registered prospectively in the Brazilian Registry of Clinical Trials (ReBEC) under the number RBR-2fczbt2. If any modifications to the protocol are required, an addendum will be promptly submitted to the Ethics Committee and the clinical trial registry. This randomized clinical trial is being conducted and reported in accordance with the SPIRIT guideline for clinical trials protocols [29].

2.1. Sample size calculation

The study was designed to detect a clinically meaningful difference in the outcome related to the use of the more affected upper limb. For the PMAL, differences of 0.94 points for the amount of use and 0.74 points for the quality of movement were considered, with estimated standard deviations of 0.78 and 0.76, respectively [30]. An α of 0.05, a statistical power of 0.90, and an expected attrition rate of 15% during follow-up were considered. The calculated sample size was 16 children per group, for a total of 32 participants.

2.2. Eligibility criteria

Participants will be eligible to participate in the study if they have at least one cranial Magnetic Resonance Imaging (MRI) or Computed Tomography (CT) scan in to confirm the diagnosis and exclude structural brain malformations. Participants will undergo an EEG performed by a specialized medical team at UNIFESP-SP. EEG findings and clinical history will be evaluated by the specialist, who will provide an expert risk assessment for epileptic seizures. Only individuals with no identified contraindications will proceed to enroll in the study protocol.

2.3. Inclusion criteria

Eligible participants will be children and adolescents aged 7 to 16 years with a diagnosis of spastic hemiparetic cerebral palsy. Inclusion criteria are the following: sufficient cognitive ability to follow therapist instructions; ability to attend AACD Ibirapuera facility for 3 weeks, 3 h/day, 5 days/week; and being accompanied throughout the entire protocol by the same caregiver, who is actively involved in the participant's daily routine. From a motor standpoint, the participants must demonstrate active movement of the affected upper limb with at least 45 degrees of shoulder flexion and abduction, 20 degrees of elbow extension, 10 degrees of wrist extension, and movement of three fingers, including the thumb (corresponding to grades 2 and 3 on the CIMT Active Range of Motion Scale) [31]. Participants must be classified as levels I or II on the Manual Ability Classification System (MACS) [32] and have no history of seizures in the past 12 months. Prior to TMS HotSpot mapping procedure, completion and signing of the Safety Questionnaire will be required to confirm the absence of contraindications to the technique.

2.4. Exclusion criteria

Participants will be excluded from the study at screening if they present musculoskeletal deformities resulting in more than a 10-degree reduction in the range of motion of any joint in the affected upper limb (shoulder, elbow, or wrist); clinically significant neurological impairment that may interfere with participation in the intervention; hydrocephalus; received botulinum toxin within the last 6 months in the affected upper limb muscles; undergone corrective orthopedic surgery of the affected upper limb during the same period; presence of metallic implants in the cranial vault region or shunt valves with metallic components.

During the study, participants will be withdrawn if they experience a seizure during the Pediatric CIMT + tDCS protocol; if they are not cooperative with electrode placement, tDCS application, or CIMT procedures; or develop an adverse reaction to tDCS, such as pruritus, erythema, or headache persisting beyond 1 day after the first tDCS application. Any adverse reaction related to tDCS use will be reported to the Research Ethics Committee, and the necessity of protocol discontinuation will be evaluated.

2.5. Participant flow

Participants will be referred for CIMT evaluation via AACD–Ibirapuera internal referral pathway. Those indicated will undergo CIMT screening, which includes a motor assessment and an explanation of the protocol to caregivers. Participants deemed eligible to perform the CIMT protocol will then undergo tDCS screening. Before enrollment, participants receiving other rehabilitation therapies will be instructed to temporarily suspend these interventions and remain exclusively in the study protocol for the duration of the intervention period. Before participation, written informed consent will be obtained from the parents or legal guardians of all participants through the signing of the Informed Consent Form. In addition, all children and adolescents

will provide their assent by signing the Assent Form, in accordance with their age. Participants who meet the established criteria will be referred for an EEG at the UNIFESP–SP to evaluate the risk of seizure. Participants without contraindications will be referred for HotSpot mapping using Transcranial Magnetic Stimulation (TMS) at the Federal University of São Paulo (UNIFESP–SP), whose protocol will be described below. Following HotSpot mapping, participants will be invited to undergo a baseline assessment, during which sociodemographic and physical-functional data, past and current health history, and the standardized tests described below will be collected. All assessments will be conducted by a blinded evaluator. Participants will then be allocated to one of two groups (intervention or control) via randomization in blocks of 10, performed using R (version 4.5.2 [2025-10-31] — '[Not] Part in a Rumble'; Copyright © 2025, The R Foundation for Statistical Computing; platform: aarch64-apple-darwin20) [33]. All protocol treatment registrations will be made using REDCap software, allowing the authorized therapist to access the randomization. The therapists administering CIMT, as well as the participants and their caregivers, will be blinded to the participant's assigned group. The institution has a comprehensive manual detailing all aspects of the study conduct, including assessment protocols, treatment procedures, and all necessary information. On the first day of treatment, the caregivers will sign a commitment form to attend daily during the established period, without delays or absences, and to be present for all evaluations and follow-ups. Figure 1 presents the complete participant flow throughout the study.

2.6. Single-pulse TMS

For the HotSpot assessment, single-pulse TMS (Magventure MagPro Compact®, Magventure, Denmark) will be used to assess cortical excitability and circuitry (for diagnostic purposes, not as a neuromodulation technique). This is a safe and tolerable method for brain mapping in children with early brain injury [34]. The single-pulse TMS will be delivered using a hand-held figure-of-eight surface coil (Magventure CB-B60). HotSpot is defined as the optimal scalp location to elicit the largest motor evoked potential (MEP) with a single TMS pulse, using standardized coil positioning [35]. The Motor Threshold (MT) is defined as the minimum transcranial magnetic stimulation intensity applied over the motor cortex that is sufficient to elicit an MEP in the target muscle [36]. MT is

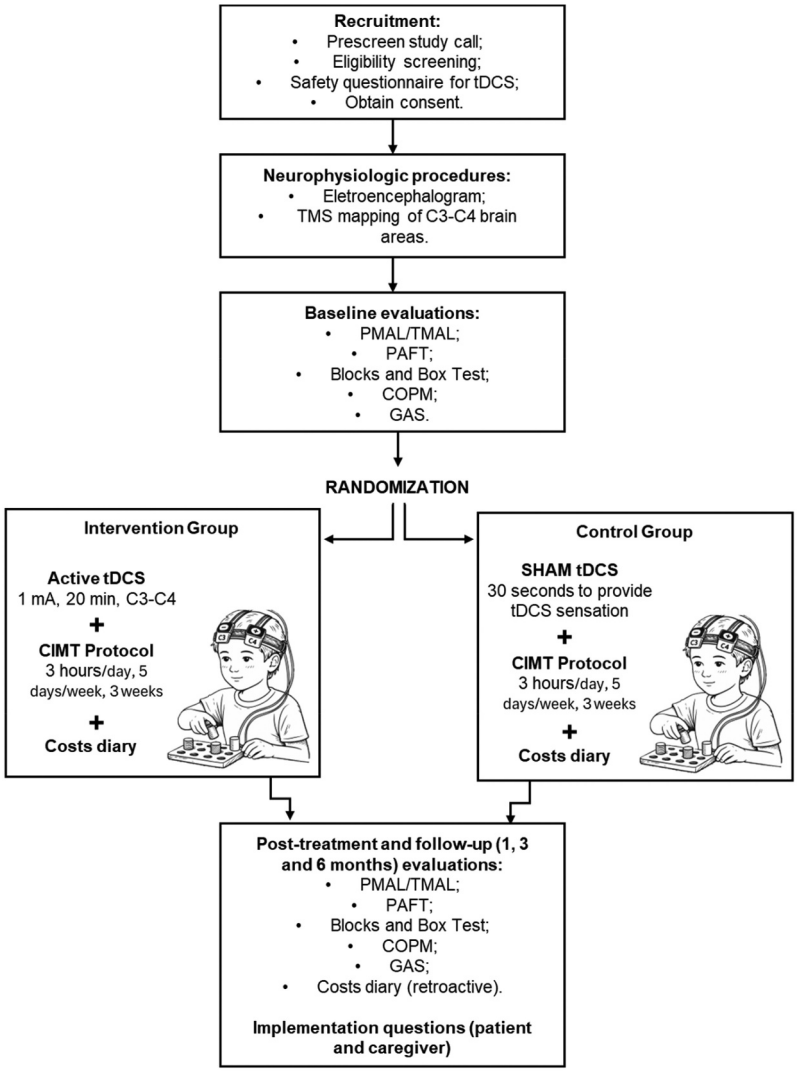


Figure 1. Flowchart of patient screening, inclusion, randomization, evaluation and treatment procedures.

ideally determined using EMG-recorded MEPs or, when EMG is unavailable, by visual detection of a consistent muscle twitch elicited by TMS stimulation [36]. The localization of brain targets using the international 10–20 electroencephalography system is commonly employed for mapping brain regions in healthy individuals [37]; however, there is low correspondence between these points and the upper limb motor cortex in children with cerebral palsy, in whom neuronal plasticity and compensatory processes are unpredictable [38]. Therefore, Hotspot localization will be performed through visual identification of the MT. Although this approach is a limitation compared with EMG-based MEP assessment, it provides an individualized functional reference of the target muscle representation and may offer a more precise guide for tDCS electrode placement compared to the 10–20 EEG system. Besides that, the primary objective of TMS in this protocol will be to functionally identify the motor hotspot for tDCS targeting rather than quantify corticospinal excitability. Participants will be seated in a comfortable position, with the upper limbs supported at 90º of elbow flexion, the forearm supinated, and the wrist in a neutral position, fully relaxed. A single magnetic stimulus will then be delivered, and motor responses will be assessed through visual observation of upper limb muscle contractions (abductor pollicis brevis and extensor digitorum), which is highly consistent and reliable in determining resting motor threshold over repeated attempts [39]. The stimulation intensity will gradually increase as needed, and pulses will be delivered with at least a 10-s interval between them to avoid any modulatory effects [40]. The mapped cortical locations will be bilaterally marked on an individualized cap, which will be carefully positioned using anatomical reference points to ensure consistent placement across sessions. The same cap will subsequently be used to guide tDCS electrode placement, maintaining alignment with the identified cortical targets. Participants who do not exhibit a reliable motor response despite stimulation at the maximum available TMS intensity will be considered unable to demonstrate a functional corticospinal response and will be excluded from the intervention protocol.

2.7. Outcome measures

All assessments described below will be used at pre-treatment, immediate post-treatment, and at 1-, 3-, and 6-month follow-up, and will be administered by the same trained and blind evaluator. At the end of data collection, all data management will be conducted entirely using REDCap, ensuring data security and maintaining blinding of assessors, therapists, and participants. To promote participant retention and complete follow-up, several strategies will be implemented, including regular communication with participants and caregivers, flexible scheduling of assessments, and reminders via phone or messaging.

2.7.1. Primary outcomes

2.7.1.1. Pediatric motor activity log revised (PMAL-R) or teenager motor activity log (TMAL).

The PMAL-R is a validated, semi-structured interview designed for caregivers or family members of children aged 2 to 8 years with hemiparesis. It assesses the real-world use of the AUL by capturing caregiver perceptions of the child's use during daily activities [41,42]. The instrument evaluates both the quality and frequency of AUL spontaneous movement on 22 functional activities, divided into basic and instrumental activities of daily living, performed unimanually or bimanually in an uncontrolled environment. Each activity is rated on a 6-point ordinal scale ranging from 0 (no use of the affected upper limb) to 5 (use equivalent to the non-affected upper limb). The TMAL keeps the same objective, structure, and scoring criteria as PMAL-R, adapted for adolescents aged 9 to 16 years [43]. The PMAL-R demonstrates a small measurement error (SEM ≈3%) and a minimum detectable change (MDC) of 8%, indicating that only changes exceeding these thresholds can be interpreted as real [41]. A potential limitation of both PMAL-R and TMAL is that they rely on caregiver- or self-reported perceptions rather than direct measures of upper-limb performance. Therefore, performance-based measures, described below, are included as secondary outcomes to provide objective information regarding upper limb performance and to complement the information obtained through subjective reports.

2.7.2. Secondary outcomes

2.7.2.1. Pediatric arm function test (PAFT).

The PAFT is an observational assessment for children and adolescents up to 16 years old. It evaluates the spontaneous use and qualitative functional ability of the AUL on 15 unimanual and seven bimanual activities [44]. Items 1–15 are initially administered once for unimanual tasks to assess spontaneous use of the affected upper limb. Items that are not performed spontaneous are then re-administered, focusing on their execution as unimanual tasks. The unimanual subtotal score is calculated as the sum of the first administration scores for items performed only once and the final administration scores for items administered more than once, divided by the total number of items (1–15) tested. The bilateral subtotal score is calculated in the same way for Items 16–22. The Functional Ability total score is obtained by averaging the unimanual and bilateral subtotal scores. The PAFT has demonstrated good psychometric properties, including test–retest reliability (ICC = 0.74), high internal consistency (Cronbach's $\alpha = 0.96$), and convergent validity with motor impairment severity ($r = -0.6$) in children with cerebral palsy [44]. However, no studies to date have established its minimal detectable change.

2.7.2.2. Box and blocks test (BBT).

The BBT is a validated test to assess gross manual dexterity in children with cerebral palsy [45]. It assesses the individuals' ability to manipulate objects using multi-finger grasp, pad-to-pad pinch, and/or tripod grasp. The test is initiated with the dominant hand (or the non-affected upper limb), then repeated with the non-dominant hand (or the affected upper limb) [46]. Participants have 15 s for practice, and the test is administered for 1 minute, timed by the examiner. The performance is measured as the number of blocks transferred from one compartment to the other [46]. The test is performed twice with each hand, and the final score is calculated as the average of the two trials. For children with unilateral cerebral palsy, 7 blocks of improvement on BBT can be interpreted as statistically

significant and clinically important, and the improvement is beyond measurement error [47].

2.7.2.3. Canadian occupational performance measure (COPM). The COPM is a validated self-perception measure of occupational performance and can be used in children from 8 years of age [48]. However, previous evidence has demonstrated the feasibility of using COPM in younger children with cerebral palsy when combined with caregiver involvement and complementary goal-based measures, such as the Goal Attainment Scaling (GAS) [49]. It consists of a five-step semi-structured interview conducted by a therapist and covers activities related to self-care, productivity, and leisure [50]. For each identified activity, the child rates their performance and satisfaction on a 10-point scale, with higher scores indicating greater ability or satisfaction [48]. This instrument tracks children's perception of their own needs and competencies, thereby promoting autonomy. A difference of 2 points on baseline and post treatment is considered clinically important [47].

2.7.2.4. Goal assessment scale (GAS). The GAS is a validated measure to assess rehabilitation progress in children with cerebral palsy. Individualized goals are collaboratively established with the patient prior to the intervention and rated post-intervention using a 5-point scale: the expected level of performance is defined as the central point, while scores above or below this level indicate outcomes that are better or worse than anticipated, respectively [51]. The scale demonstrates good interrater reliability [52]. For children with cerebral palsy, a minimal clinically meaningful improvement is defined as a score equal to or more than zero [53].

2.7.2.5. Dynamometry. The Palmar Grip Strength will be measured using a hydraulic hand dynamometer (Saehan, Korea), and Pinch Strength (PS) will be measured using a hydraulic pressure gauge (Jamar, USA). All measures will be performed with participants in a standardized position for children with Cerebral Palsy [54]. For each limb, three consecutive measurements will be taken, and the mean value will be used for analysis.

2.8. Intervention: original pediatric CIMT protocol – University of Alabama, Birmingham/USA

The intervention will follow the original CIMT protocol developed at the University of Alabama, which comprised four core components: 1) a behavioral transfer package, 2) restraint of the non-affected upper limb 24 h a day for 21 days, 3) intensive, repetitive, task-oriented training, and 4) structured practice using shaping and task practice [10].

The behavioral transfer package consists of a set of behavioral strategies composed of elements designed to transfer the gains achieved in the therapeutic environment to everyday life situations, including a behavioral contract, weekly and weekend activity schedules, a home diary, and the daily application of the PMAL-R/TMAL [13]. The restraint device (cast) will be applied during the pre-treatment phase and will be made of synthetic casting material, completely immobilizing the less-affected upper limb. It will have a dorsal opening and extend from the axilla to the fingers, with the elbow positioned at 90° of flexion to avoid compromising the patient's balance during gait. The therapist will remove the cast daily for hygiene purposes, which constitutes the first step of the daily treatment session. The device must be worn 24 h per day and should only be removed in cases of severe skin alterations reported by the patient and/or observed by caregivers at home. Intensive task-oriented training will be implemented through a combination of shaping and task practice. Shaping consisted of repetitive practice of functional tasks divided into progressively more challenging components, allowing motor goals to be addressed step by step and enabling gradual improvements in performance over time [55,56]. Task progression parameters will be predefined, and positive feedback will be provided after each attempt to maintain motivation and avoid frustration. Task practice involved less structured functional activities designed to resemble the participant's daily routines, thereby promoting the transfer of motor gains to real-life situations [55]. These activities will be performed concurrently with shaping and always while the participant wears the cast on the less-affected upper limb. All procedures will be standardized and administered by trained therapists in accordance with the original CIMT protocol developed at the University of Alabama.

2.9. Intervention: transcranial direct current stimulation protocol

A trained and certified evaluator will administer the transcranial direct current stimulation (tDCS) using the Microestim tDCS device (NKL, Brazil). The device is manufactured nationally and is certified by the Brazilian Health Regulatory Agency (ANVISA). Two nonmetallic sponge electrodes soaked in saline solution will be used, each containing rubber electrodes measuring 5×5 cm. Participants will be randomized and allocated into two groups, as previously described: the intervention group will receive active current stimulation, whereas the control group will be connected to the device in sham mode (30 s of current to provide the initial sensation, after which the device is turned off), to stimulate the primary motor cortex.

In this bilateral protocol, the anodal stimulation electrode will be positioned contralateral to the hemiparetic side impairment, over the C3 (left primary motor cortex) or C4 (right primary motor cortex) region, based on transcranial magnetic stimulation mapping [38,57]. The cathodal electrode will be placed over the opposite hemisphere, corresponding to the homologous motor cortex. This bilateral montage is a safe, feasible, and well-tolerated protocol for children with hemiparesis [58]. A current of 1 mA will be delivered for 20 min in each session, as the intensity of 1 mA has been demonstrated in a recent systematic review to be the most effective for the outcome of manual function [59]. The Microestim tDCS device includes a control knob that allows the therapist to regulate the stimulation intensity delivered to the participant; the current will gradually increase during the first 10 s of the session until reaching a maximum of 1 mA. The tDCS device will be programmed to

continuously monitor electrode impedance, ensuring that it does not exceed 40 kΩ throughout the stimulation. In the sham condition, the electrodes will be positioned in the same location, following identical procedures; the device will be activated during the first 30 s of the session to produce the initial mild tingling sensation generated by the current, after which no stimulation will be delivered for the remainder of the session. This sham protocol is widely accepted and has been demonstrated to effectively maintain participant blinding in tDCS clinical trials [60].

tDCS will be applied during all CIMT sessions in the first 2 weeks and on alternating days during the final week (gradual withdrawal of stimulation). Stimulation will be delivered during the second hour of the CIMT protocol, the most intense hour of active motor practice, and its effects are expected to persist for approximately one additional hour after the end of the application [61].

2.10. Adverse events monitoring

A recent systematic review on the use of tDCS in pediatric populations reported no serious adverse events, with the most described effects being mild tingling and itching at the stimulation site [59]. Less frequently reported symptoms include fatigue, burning sensation, headache, and difficulty concentrating [59]. A single seizure potentially associated with tDCS has been reported in the literature; however, in that case the participant was undergoing adjustment of antiepileptic medication [62]. To minimize the risk of adverse effects, the stimulation protocol will follow procedures recommended in the literature, including a gradual increase in stimulation intensity up to a maximum of 1 mA [17]. If participants report burning or pain at the stimulation site, stimulation will be immediately discontinued, and the skin will be inspected. Any complaint reported during the daily assessment that may be related to the stimulation administered on the previous day will prompt clinical reassessment and, if necessary, withdrawal from the study. If a serious adverse event happens, such as a seizure, the participant will receive immediate care according to the institution's emergency procedures, will be withdrawn from the study, and will be clinically monitored. The trial will be discontinued if three serious adverse events occur (corresponding to 10% of the planned sample). All adverse events will be documented and reported to the appropriate regulatory authority. The monitoring of patients will be carried out by regular phone contact and messages at the intervals of follow-up evaluations.

2.11. Exploratory analyses

The implementation and cost-effectiveness analyses are planned as secondary analyses and will be performed only if the HAND-IN trial demonstrates a significant clinical benefit of the intervention. Thus, conclusions regarding implementation feasibility and cost-effectiveness will be based on the clinical effectiveness results obtained from the randomized controlled trial.

2.11.1. Implementation analysis

Neuromodulation through tDCS has been increasingly recognized as a low-cost, safe, and effective technique. In this study, we aim to evaluate its efficacy in maintaining upper limb motor gains when applied in combination with the pediatric constraint-induced therapy (CIMT) protocol. Therefore, to support the incorporation of this technique into healthcare institutions, data will be collected to assess and provide insights regarding improvements and optimization within the implementation context. These data will be collected using the Weiner scale [63], translated and validated for Brazilian Portuguese. The scale assesses acceptability, appropriateness, and feasibility as implementation outcomes [64]. Acceptability refers to the level of patient satisfaction with the technique [63]. Appropriateness refers to the perceived relevance of this specific technique in relation to the treatment [63]. Feasibility evaluates the perceived success of implementing the technique within the context of the institution where it is applied [63]. These data will be analyzed from the perspectives of both the patient and the caregiver. Each domain is evaluated on a 5-point scale: strongly disagree (1 point), disagree (2 points), neither agree nor disagree (3 points), agree (4 points), and strongly agree (5 points). Additionally, we will add an open question to collect the opinion of both patients and caregivers about the tDCS intervention.

2.11.2. Cost-effectiveness analysis

The cost-effectiveness analysis will be conducted using an intention-to-treat approach. Effectiveness will be measured using the primary outcome of movement quality and frequency, assessed through the PMAL-R or TMAL, depending on the participant's age. Direct and indirect costs associated with the CIMT protocol and the application of tDCS will be collected and prospectively analyzed from an institutional perspective. Costs will be adjusted for inflation according to the reference year throughout the study period. Equipment depreciation will be calculated, and a 5% discount rate will be applied to costs. Subsequently, the incremental cost-effectiveness ratio (ICER) will be calculated [65].

In addition, costs from the patient's perspective will be collected through a cost diary. This diary will be completed daily during the intervention protocol and retrospectively during follow-up assessments. Furthermore, a REDCap link will be provided to caregivers to allow the recording of any additional costs related to the affected upper limb as they occur. The diary will capture medical costs (including clinician visits, medications, physiotherapy sessions, diagnostic exams, botulinum toxin injections, surgeries, emergency room visits, and other health services used for the affected upper limb care), whether paid by the health insurance/public health care system or out-of-pocket. It will also include hours of absence from paid and unpaid work by caregivers (lost productivity costs), hours of school absence by the children, transportation expenses, orthoses, assistive equipment devices, classroom aid, and informal care, including housekeeping, personal care, mobility support, and administrative tasks (patient/family-related costs).

2.12. Data analysis

Statistical analysis will be performed using an intention-to-treat approach. Missing data will be addressed following the intention-to-treat (ITT) principle, ensuring that all randomized participants are included in the analyses regardless

of adherence or protocol deviations. The pattern and mechanism of missingness will be explored to assess whether data are missing at random. Data normality will be assessed through inspection of histograms. Descriptive statistics will be used to characterize the groups. Differences between groups and their corresponding 95% confidence intervals will be calculated using mixed linear models, as all outcomes are continuous variables. This statistical approach inherently accounts for missing data. To account for multiple comparisons among the secondary outcomes, the Bonferroni correction will be applied. In addition to *p*-values, the interpretation of the findings will consider the corresponding 95% confidence intervals and the minimal clinically important change (MCIC) for each outcome measure to support the assessment of clinical relevance. The statistical package SPSS version 23.0 for Windows will be used for all analyses. All adverse events will be recorded, quantified, and analyzed.

3. Conclusion

The HAND-IN trial aims to provide high-quality evidence on the clinical, implementation, and economic effects of combining CIMT with bilateral tDCS in children with spastic hemiparetic cerebral palsy. If the intervention proves effective, this combined approach may represent a promising strategy to enhance the durability of upper limb functional gains and support the broader adoption of neuromodulation rehabilitation protocols in pediatric neurorehabilitation settings.

Ethics declaration

This study was approved by the Universidade Cidade de São Paulo (UNICID) Ethics Committee under protocol number 7.795.537 and by the Associação de Assistência à Criança com Deficiência (AACD) Ethics Committee under protocol number 7.930.090. Written informed consent will be obtained from the parents or legal guardians of all participants, and assents will be obtained from all children and adolescents.

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Declaration of interests

The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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