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Protocol

Transcranial Direct Current Stimulation as Adjuvant to Gamified Rehabilitation for Upper Limb Function in Paediatric Brain Damage (CHILDBOOST Project): A Study Protocol for a Triple-Blind Randomised Controlled Trial

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Featured Application: Paediatric brain damage leads to a broad spectrum of impairments that directly impact children's independence. Current neurorehabilitation approaches do not achieve a full recovery from the damage, leading to permanent disability. New techniques and protocols are needed to reduce the brain damage's sequelae and long-term disability. We propose a combined protocol of transcranial direct current stimulation and virtual reality to assess both motor and cognitive impairment in paediatric brain damage.

Abstract: (1) Background and objectives: Paediatric brain injuries can lead to motor and cognitive deficits. Effective rehabilitation is critical for enhancing independence. While virtual reality (VR) and transcranial direct current stimulation (tDCS) have independently demonstrated beneficial effects on motor and cognitive functions, their combined efficacy and its cognitive effects remain to be explored in this population. We aim to investigate the effects of integrating tDCS with VR training on upper limb (UL) functionality and cognitive outcomes through a triple-blind randomised trial. (2) Methods: Twenty-eight children with hemiparesis secondary to non-progressive brain damage will be randomly allocated into two groups: active anodal tDCS (2 mA) plus UL VR training, and sham tDCS with identical VR training. The tDCS will target M1 of the affected or most affected hemisphere for 20 min, simultaneous to VR training. The following four assessments will be carried out: pre-intervention, post-intervention, and three- and six-months follow-up. (3) Results: This study will explore motor and cognitive outcomes of a motor-based intervention in paediatric brain damage. We hypothesise that the experimental group will show significant improvements in UL function and cognition, enhancing their functional recovery. (4) Conclusions: We propose a multidisciplinary therapeutic approach combining neuromodulation and VR to potentiate functional recovery through enhancing motor and cognitive performance in paediatric brain damage.

Keywords: cerebral palsy; motor disorders; cognitive dysfunction; transcranial direct current stimulation; rehabilitation; virtual reality

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1. Introduction

Paediatric brain damage includes every brain injury that happens during gestation or early years of life to childhood and adolescence [1–3], and includes conditions such as cerebral palsy (CP) and paediatric acquired brain injury [1,4].

The sequelae of paediatric brain injuries manifest a broad spectrum of motor and cognitive deficits, adversely affecting a child's ability to perform everyday tasks [2]. Motor impairments compromise critical functions such as gait, posture, and the use of upper limbs (UL) [5]. Cognitive deficits have a direct impact on communication, social engagement, and participation [6–9]. Although motor and cognitive rehabilitation have traditionally been approached as separate entities, burgeoning evidence underscores the intricate interplay between cognitive and motor domains, highlighting their collective influence on motor planning and execution [10–12]. Notably, greater manual dexterity is associated with better cognitive function in children with CP [10]. The profound impact of UL motor impairments on the autonomy of children in daily living activities underscores the need for integrated neurorehabilitation strategies that address both motor and cognitive challenges [13].

Neuroplasticity plays a pivotal role in neurorehabilitation by driving the neural adaptations responsible for the development or restitution of function following brain injury [14]. Spontaneous neuroplastic changes often occur in the initial months post-injury, contributing to early symptomatic improvements. Interventions during the acute phase may amplify these inherent mechanisms. Despite the application of transdisciplinary rehabilitative approaches [15,16], a plateau in functional gains typically manifests during the chronic phase, where motor and cognitive deficits tend to persist. To overcome this plateau, strategies such as virtual reality (VR) and transcranial direct current stimulation (tDCS) have been deployed. These techniques have demonstrated efficacy in enhancing UL functionality across various stages of brain injury recovery [17–20].

VR allows the practice of repetitive tasks with immediate feedback on performance in an artificial environment similar to the real one, which is essential for learning processes. Specifically for children, game-based approaches add an extra motivation with task-related rewards and enlarge focused attentional span [17,21]. A good example is the Rehabilitation Gaming System (RGS) (Eodyne, Barcelona, Spain), which is a VR-based rehabilitation that considers both motor and cognitive aspects for UL rehabilitation with a wide range of task difficulty calibration. This program captures the specific features of the impaired limbs and adapts the task parameters to them [22]. Several studies have shown the effectiveness of VR in paediatric brain damage both in motor and cognitive skills [18,23–26]. Combined motor and cognitive RV protocols seem to yield better functioning results in both domains [25,27].

On the other hand, tDCS is one of the most used non-invasive brain stimulation techniques, as it has shown to be secure and effective [28] when applied in conjunction with other techniques, in motor [29] and cognitive outcomes [30,31] in paediatric brain damage. tDCS consists of applying a low intensity current (1–2 mA) to the skull [32] with two or more electrodes. There are several montages according to the aim of the stimulation application, which varies in electrode size, number of electrodes, and its placement. Bipolar tDCS is the most common montage nowadays, but high-definition tDCS, involving a greater number of electrodes, emerges as a tool for improving focality of the stimulation effects [33]. tDCS mechanism of action is based on changing the action potential threshold, either increasing it with anodal stimulation, or decreasing it with cathodal stimulation. The electrodes can be displayed stimulating one hemisphere or both of them in a bi-hemispheric approach [34]. Anodal stimulation over the affected hemisphere has shown good functional outcomes for UL rehabilitation in stroke patients [19,20]. Motor-centred intervention has been proven to influence cognition directly in post-stroke patients [35], but there is scarce evidence on the cognitive effects of tDCS used with motor protocols centred in M1 in paediatric brain damage, but current research, including anodal protocols, indicates promising potential for such combined applications [29–31,36].

This is the first protocol for a parallel triple-blind randomised controlled trial including VR training and anodal tDCS, evaluating the impact of both motor and cognitive effects in UL functionality in this population.

Our main hypothesis is that participants in the experimental group with active anodal tDCS will achieve greater significant improvement in UL functionality over the control group with sham tDCS. Improvements in cognitive-related functions are expected and it is believed that they will potentiate the impact of purely motor improvement to reach greater functional outcomes [37].

2. Materials and Methods

This protocol has been elaborated according to the Recommended Items for Interventional Trials (SPIRIT) 2013 checklist [38]. This protocol is registered in ClinicalTrials.gov with the following ID: NCT06214364.

2.1. Study Design

The study design is a parallel, randomised, controlled triple-blind experimental study with two groups. Triple-blind design was selected to reduce the potential biases related to knowing the participants' allocation in every step of the study, adding reliability, validity, and robustness to the study results.

Participants will be randomly allocated into groups with a ratio 1:1. Both groups will receive VR UL training with simultaneous tDCS; the experimental group will receive active anodal tDCS, whereas the control group will receive sham tDCS.

2.2. Participants

The participants will be recruited from the Paediatric Brain Damage Unit of the Beata Maria Ana Hospital of Madrid and referred from other collaborator centres or professionals, as well as self-referrals from trial information dissemination through social networks. The evaluations and the intervention will be conducted in the Paediatric Brain Damage Unit of the Beata Maria Ana Hospital of Madrid. The participants included will be evaluated by a neuropsychologist (B.G.A.) and a physical therapist (A.C.Z.). The included participants will be patients between 7 and 15 years of age with UL function impairment caused by a non-progressive brain injury with a minimum score of one in each task evaluated in the Melbourne Assessment 2 (MA-2) [39] and with a Z value equal or higher to -1 in comprehension of instructions of the NEPSY-II test [40]. The specific inclusion and exclusion criteria are exposed in Table 1. The following demographic data of participants will be collected: age, sex, affected or most affected side, lesion etiology and location and Manual Ability Classification System (MACS) [41].

Every participant's medical and rehabilitation treatment will be recorded, including drugs, type, and dose of conventional therapy (physical therapy, occupational therapy, neuropsychology, and speech therapy), and this cannot undergo any changes during the study participation.

Parents or caregivers will be signing the informed consent for all included procedures (therapies and outcomes measurement), approved by the ethics committee. In case the participant is 12 or older, he or she will also be signing the inform consent alongside their legal guardian. This study will follow the principles of the Declaration of Helsinki. All data obtained from the study will be registered separately, anonymised, and guarded according to current European data protection laws. Every participant will have an identification number to assure anonymisation. This information will only be accessible to an independent investigator (M.R.L.). Data will be secured and double checked in a database designed specifically for this purpose.

Regarding adherence strategies, sessions missed up will be restored the following week. Flexible therapy schedules will also be offered, and patients' families will be contacted directly by phone to confirm evaluation dates, thus reinforcing treatment adherence.

Information about the reason of the deviation from the intervention will be collected of any participant who did not complete the intervention and the evaluations of the study.

Table 1. Inclusion and exclusion criteria.

Inclusion Criteria	Exclusion Criteria
Patients between 7 and 15 years of age, with a Z value equal or higher to −1 in comprehension of instructions of the neuropsychological battery for children (NEPSY II)	Dermatological problems, cranial holes or fissures in the electrode application area (psoriasis, dermatitis on the scalp or face)
Ischemic or haemorrhagic stroke, traumatic brain injury, cerebral palsy, or other causes of non-progressive brain damage with a neuroimaging study test, susceptible to treatment with the established intervention	Ongoing brain damage such as oncologic processes and neurodegenerative diseases, and any neurological disease different from that described in the inclusion criteria
A 1-year evolution minimum since the injury, conducting a rehabilitation process	Pacemakers, medication pumps, stimulators (vagal, cerebral, transcutaneous), ventriculoperitoneal shunts, or aneurysm clips
Absence of previous brain injuries prior to the one prompting treatment	Presence of implants or metal pieces in the head excluding tooth fillings
Score between II and IV on the Manual Ability Classification System (MACS) scale for manual ability assessment	Significant language difficulties that restrict proper understanding of activities or severely limit expression
Signed informed consent	Moderate or severe mood disorders diagnosed by their paediatrician
Increased muscle tone according to the modified Ashworth scale ranging from 1 to 1+	Extreme hypotony or increased muscle tone above +1 in Modified Ashworth Scale (MAS) in UL muscles
Minimum score of 1 on each item assessed in the Melbourne Assessment-2 (MA-2)	Uncontrolled medical issues (acute phase pathologies without medical or pharmacological treatment with proven efficacy or life-threatening conditions)
Stable drug treatment, without changes during the participation	Having undergone surgical procedures involving the susceptible to treatment upper limb in the 3 months prior to the onset of the training sessions

2.2.1. Sample Size

Sample size was calculated based on precision with the presize R package (0.2.3. version) [42]. This tool is a precision-based calculator that obtains the sample size with different reference values (absolute or relative differences, correlation or diagnostic measures). The sample size calculation was conducted with mean difference value. The necessary data were extracted from the validation article of MA-2 of Wang et al. [43].

Taking a confidence interval of 8 points, which is coherent with the mean difference theorised and the minimal detectable change of each domain, we obtain a sample size of 22 participants. The sample will be increased by 20% to compensate for possible dropouts, leading to a total sample of 28 participants, with 14 in each group.

2.2.2. Randomisation

The participants will be randomly allocated into two groups in a 1:1 ratio. The experimental group will receive active anodal tDCS plus RGS, and the control group, sham tDCS plus RGS. Randomisation and allocation will be conducted using GraphPad software (GraphPad Software, San Diego, CA, USA) [44], from this site https://www.graphpad.com/quickcalcs/randomize1/ (3 July 2024), by an independent investigator (J.P.R.M.).

2.3. Intervention

2.3.1. Transcranial Direct Current Stimulation

Anodal tDCS in paediatric brain damage has shown positive benefits in functions like gait, balance, and attention [30,45,46]. Generally, studies addressing UL function applied cathodal stimulation protocols, which did not achieve significant changes between active and sham tDCS [47,48]. One study did apply an anodal program and showed an improvement in UL function associated to active tDCS [29]. In conjunction with the evidence that excitatory stimulations seem to be more adequate to improve UL function [19,20], the intervention of applying anodal tDCS is proposed.

tDCS will be administered by an experienced physical therapist (A.C.Z.) with the Starstim tCS® device (Neuroelectrics Inc., Barcelona, Spain) [49], with two saline-soaked

sponge electrodes of 25 cm^2 and a voltage of 15 V per electrode. Both groups (active and sham intervention) will have the same montage: the anodal electrode will be placed over C3/C4 (international 10–20 system of electrode placement) to stimulate the primary cortex motor of the affected or most affected hemisphere. The cathodal electrode will be placed in the supraorbital region (Fp1/Fp2) contralateral to the anode. In the experimental group with active anodal tDCS, the intensity of the current will be 2 mA and will be administered for 20 min, with a 30 s ramp-up and ramp-down. In the control group, with sham tDCS, intensity will only be applied for 30 s at the beginning and at the end of the stimulation to ensure the blinding [50,51].

2.3.2. Upper Limb Rehabilitation Gaming System

The RGS is a semi-immersive VR approach to UL impairment that has shown its benefits as a valid tool to provide sensorimotor training and feedback [22,52,53]. This system tracks arm and finger movements to translate them to an artificial environment, so the virtual limbs are controlled in a first-person perspective. The RGS set-up consists of a monitor integrated with a computer where games are displayed. Motion capture is tracked by a Kinect motion capture system (Microsoft, Redmond, WA, USA) and a Leap Motion device (Ultraleap, San Francisco, CA, USA) [54]. The Kinect motion capture system enables body tracking with a depth sensor, a matrix of microphones with a video camera and an orientation sensor. The Leap Motion controller is a hand tracking device composed of two cameras and some infrared LEDs. Exercises involving distal movements with wrists, hands, and fingers use a supplementary forearm support, so movement is correctly captured and posture during executive is correct. The body movements' recording is included in a gamified environment with several games involving the trunk, shoulder, elbow, wrist, hand, and fingers. The user's movements are captured and included in the virtual environment for achieving the specific objective depending on the selected game [22].

During the intervention, the participant will be seated in a comfortable position in front of the monitor where the VR will be displayed. The exercises will include reaching, grasping and realising, pronosupination, and fine motor skills. The VR training will be administered in 40 min sessions. The games included in the VR training are divided into UL training and hand-specific training. The UL training is conducted with the Kinect azure camera, and consists of the following games:

- Boat: the participant is asked to drive a boat moving laterally the trunk and to catch all the items during the exercise with both ULs. This exercise approaches reaching against gravity without support with flex–extension of the elbow and flex–extension and abduction of the shoulder, trunk control, and balance. Total duration: 4 min.
- Hockey: The participant is asked to hit the puck to reach the goal. This game exercises reaches with the table support, with flex–extension of the elbow and flex–extension and abduction of the shoulder. As the participant musts adapt to the return of the puck to hit it again, the reaction time and velocity are also trained. Total duration: 5 min
- Pinball: The participant is asked to reach a ball of a specific colour. This exercise trains reach the same way as the previous game. Total duration: 5 min
- Spheroids: The participant is asked to catch the balls and put them in the container of the same colour as the ball. This exercise trains reaches against gravity without support, with flex–extension of the elbow and flex–extension and abduction of the shoulder. Total duration: 5 min

The hand-specific training is conducted with the Leap Motion controller and the previously mentioned forearm support. This training consists of the following games:

- Robot: This exercise is conducted with a forearm support. The participant is asked to perform a thumb and index finger pinch to grab different objects to win points and facilitate the way to a kitten. This exercise aims to train fine motor skills. Total duration: 7 min

- Spaceship: This exercise is conducted with a forearm support. The participants are asked to turn the spaceship left or right to avoid asteroids and win points. This exercise trains the pronosupination of the forearm. Total duration: 7 min
- Monkey: The participant is asked to close the hand when the monkey reaches a branch and realise the hand grip to jump to the next one. This exercise trains the hand grip. Total duration: 7 min

Working memory, attention, executive functioning, and inhibition are trained across every game.

2.3.3. Procedure

A ten-session intervention will be conducted, during weekdays for two weeks. The VR training will be administered with the tDCS in an online paradigm (i.e., tDCS and VR training will be administered simultaneously within each session). After tDCS administration, the VR UL training will continue for another 20 min.

2.3.4. Blinding

Therapist, evaluators, participants, and caregivers will be blinded. The electrode disposition, as it will be the same in both control and experimental groups, allows for therapist, participants, and caregivers blinding. Therapist and evaluator in charge of the motor assessments (A.C.Z.) will be blinded to intervention allocation as the stimulation will be administered with the "double-blind" mode in the Starstim tCS® Software v2 1.3.2. (Neuroelectrics Inc., Barcelona, Spain) [49]. This mode permits a prior configuration of the tDCS device with the active and the sham tDCS by another investigator so the therapist can be blinded to the intervention. The same investigator in charge of the allocation and randomisation of the sample (J.P.R.M.) will conceal the interventions with the neutral numbers so the therapist will directly select the specific number, ignoring the corresponding protocol: sham or active anodal tDCS.

The investigator in charge of the allocation (J.P.R.M.) will place the number associated with the intervention in opaque sealed envelopes, which will be opened by the therapist (A.C.Z.), without knowing which code corresponds with each treatment. The neuropsychological assessments will be conducted in a separate room by another evaluator (B.G.A.), ignoring the participant intervention.

To evaluate the success of the blinding procedure, the children and caregivers will be asked what intervention they thought they had undergone at the end of the intervention.

All recollected data will be secured by recording them separately, anonymised and guarded following European data protection laws. Faces in video recordings will be pixeled to maintain anonymity.

2.3.5. Monitoring

Data monitoring will be conducted by two investigators of the group (F.S.C., Y.G.Z.), independent of this specific study.

To assess adverse effects, after each stimulation session a questionnaire will be completed, based on the one proposed in Gillick et al.'s study in 2015 [55]. This questionnaire includes headache, neck and scalp pain, tingling, itching, burning, sleepiness, mood and concentration change, skin signs, and other sensations. Moreover, before and after the daily intervention, the patient will be asked how they are feeling. If any adverse effect is detected in either group, it will be interpreted as being caused by the VR training.

A doctor will be notified of any adverse effect, in order to ensure correct management according to the severity. The protocol will be suspended for any patient with persistent adverse effects.

2.4. Outcome Measures

Evaluations will be carried out four different times for each participant: a pre-intervention assessment, a post-intervention assessment the following week after finishing the interven-

tion, and two follow-up assessments three months and six months after the intervention. The first three evaluations include a motor and a neuropsychological assessment (Figure 1). Motor assessments will be conducted in the affected or most affected side. Changes in the UL function of the non-stimulated side after an intervention with tDCS have been found [56]; therefore we will include the dexterity, the finger tapping task, and the strength measurements for both ULs. The six-month evaluation consists of questionnaires assessing affected UL use subjective experience and quality of life.

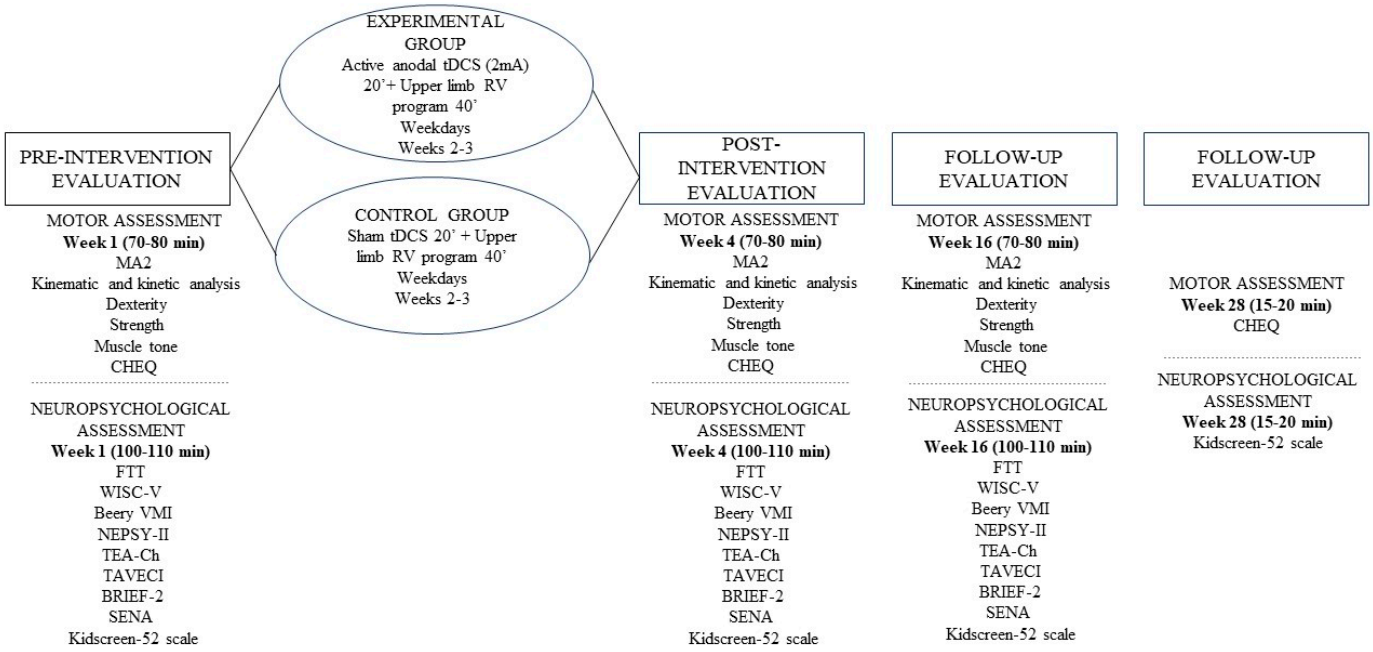

Figure 1. Schematic experimental procedures.

2.4.1. Primary Outcome

Melbourne Assessment-2 (MA-2)

This scale assesses UL function in children from 2.5 to 15 years of age with neurological impairment. It evaluates range of movement, target accuracy, fluency, grasp, accuracy of release, finger dexterity, and speed. These elements are scored separately based on the execution of 14 different activities, giving a 0 to 4 or 0 to 3 punctuations in 30 different items. Scores obtained were categorised into the following four different movement subscales: range of movement, accuracy, dexterity, and fluency [39]. The assessment will be conducted in the affected or the most affected side.

2.4.2. Secondary Outcomes

Kinematic Upper Limb Analysis

The activities included in the MA-2 and the box and block test (BBT) execution will be recorded with three different cameras: one in the frontal plane, another in the sagittal plane, and another for the transverse. The kinematic analysis will include velocity and peak velocity, acceleration, duration of the movement, time to target, and range of motion of the shoulder, elbow and wrist of the affected or the most affected side. The markers needed to register the movement will be place according to Wu et al. protocol [57] in sternocostoclavicular joints and xiphoid process for the trunk, trocanther for the femur, acromioclavicular joint for the shoulder, medial and lateral epicondyles for the elbow, radial and ulnar styloid processes for the wrist, and heads of the second and fourth metacarpals for the hand.

The analysis will be conducted with the Kinovea software 0.9.5® (Kinovea, France) [58].

Box and Block Test (BBT)

The BBT is designed to measure gross motor hand dexterity. It consists of translating the major number of cubes from one place to another in one minute. It is especially suitable for a paediatric population, as it is a short tool and easily understandable. It considers essential dominions of manual dexterity development such as grasping, holding, transferring, and releasing. It will be assessed in both ULs.

Hand Grip Strength

Isometric hand grip strength will be evaluated with the Jamar® Plus+ dynamometer (Performance Health Supply, Nottinghamshire, UK). Participants will be seated with both feet on the floor and the forearm resting on a table. Three measures will be taken with 1 min rest between them. The three measures mean will be considered. Patients will be asked to perform their maximal force output [59,60]. It will be assessed in both ULs.

Flexor Finger Muscle Groups Spasticity

Finger flexor muscles spasticity will be addressed with the AMADEO® device (Tyromotion, Graz, Austria) [61]. Participant's assessed hand is placed in the device while seated: each finger is individually attached to the device by magnets, allowing the muscle tone assessment of each of them separately. Spasticity measure is based on the Modified Ashworth Scale (MAS) and Tardieu scale, taking 3 different measurements at 3 different speeds [62–65]. It will be conducted in the affected or most affected side.

Children's Hand-Use Experience Questionnaire (CHEQ)

This questionnaire measures UL use in daily living activities and its subjective experience using the affected hand in activities where usually two hands are needed. This questionnaire can be answered by the children or their caregivers. It has 3 categories as follows: hand use, time needed to complete the action in comparison with their equals, and personal experience while conducting the action. It includes 27 different activities [66].

Finger Tapping Task (FTT)

The FTT is a measure of sensory–motor speed widely employed to detect both motor and cognitive impairments. It has also been used as a clinical neuropsychological test to evaluate controlled sequential responses. The participant will be seated comfortably in front of a computer and will be instructed to press with the index finger the spacebar as fast as possible repeatedly. The action will be executed 5 times for 10 **s** with both hands [67,68].

Wechsler Intelligence Scale for Children V (WISC-V)

It is a clinical instrument to assess intelligence in children from 6 to 16 years and 11 months of age [69]. It provides indices that reflect functioning in different cognitive areas: verbal comprehension, visuospatial ability, fluid reasoning, working memory, and processing speed. It also provides an overall intelligence score. Ten subtests will be administered: similarities, vocabulary, block design, visual puzzles, matrix reasoning, figure weights, digit span, picture span, coding, and symbol search.

Beery–Buktenica Developmental Test of Visual–Motor Integration (Beery VMI)

It is a visual perception test employed to assess visuomotor integration in individuals from 3 years to 17 years and 11 months of age [70]. The visual perception subtest will be administered.

Neuropsychological Battery for Children (NEPSY-II)

It is a tool for conducting specific cognitive assessment by domains, from 3 to 16 years of age, as it includes tests that assess attention and executive functions, language, memory and learning, sensorimotor functioning, visuospatial processing, and social perception [40].

Comprehension of instructions, word generation (semantic and initial letter), arrows, memory for face, and inhibition subtest will be applied.

Test for Everyday Attention for Children (TEA-Ch)

Designed to evaluate different types of attention (selective, divided, and sustained) in visual and auditive modality for children between 6 and 12 years of age [71]. Sustained auditory attention will be assessed by mean of the code transmission subtest.

Verbal Learning Test for Children Spain-Complutense (TAVECI)

This test is designed for evaluating memory and learning capacity in children between 3 and 16 years of age [72]. Total number of words recalled, and the long-term free recall will be considered in the present study.

Behaviour Rating Inventory for Executive Function 2 (BRIEF-2)

Considered for assessing executive functioning for children between 5 and 18 years of age [73]. Reports from parents, caregivers, and teachers will be registered. Behaviour regulation, emotion regulation, and cognitive regulation indexes will be considered.

Evaluation System for Children and Adolescents (SENA)

It assesses a wide spectrum of emotional and conduct problems for children from 3 to 18 years of age through information of their environment [74].

Kidscreen-52 Scale

It is a quality-of-life questionnaire that is completed both by the children and by their parents or caregivers. It includes several domains about situations and functions of daily living, answering the questions with a scale from 1 to 5. The final score is obtained by summing each value: higher values correlate with a good quality of life perception and lower punctuations correlate with a poor quality of life perception [75].

3. Results

3.1. Data Analysis

Statistical analysis will be carried out by a blinded statistician with the SPSS software package (version 29.00; SPSS Inc., Chicago, IL, USA) [76]. Summary statistics of continuous demographic and clinical variables will be reported as mean and standard deviation, median, and inter-quartile range. Categorial variables will be reported as relative frequencies (n and percentage).

For hypothesis testing, the primary end-point will be the differences between the groups at post-intervention, obtained as the average treatment effect (ATE). For this comparison, mean differences will be obtained by analysis of covariance (ANCOVA), adjusting for baseline values of each continuous outcome measure. All models will be of type y~Group + baseline. This allows us to increase the statistical precision by shrinking the standard error and is currently recommended for obtaining unbiased ATEs in randomised controlled trials. Statistical significance of between-group differences will be obtained via non-parametric tests (Mann–Whitney U) if the outcome measure does not follow a normal distribution, or via independent samples *t*-tests if it does. Before applying any statistical modelling, the distribution of all outcome measures will be screened via density plots and QQ plots, and if needed, kurtosis and asymmetry will be obtained. In addition, after modelling, normality of residuals will be screened by QQ plots. Corrections to the normality assumption being violated will include transformation of the outcome measure or full non-parametric ANCOVAs that do not make any assumptions on the distribution of the data. Other corrections include the use of beta regression for the outcome measures that have clear upper and lower bounds and/or where evidence of floor/ceiling effects is present. Should the trial yield inconclusive results, we will also consider the use of Bayesian analyses to evaluate the evidence in favour of the null hypothesis. As we acknowledge

that multiple comparisons will be made given that numerous outcome measures will be analysed, type I error rates will be corrected by the Holm method at each time point. Standardised effect sizes will be calculated by Hedges' g, given that this is recommended for small sample sizes.

Intention-to-treat analysis will be conducted if there is any drop-outs from the study. This will be performed by multiple imputation with m = 10 imputed samples and predictive mean matching. Sensitivity analyses will be carried out with other imputation methods to ensure the robustness of the results.

In all analyses, the confidence level will be 0.95 (i.e., alpha will be set at 0.05), and 95% confidence intervals will be obtained for parameter uncertainty.

3.2. Dissemination Plans

The findings from this study will be published in specialised scientific journals and made publicly accessible via our institutions' social media networks.

Authorship will be determined following the International Committee of Medical Journal Editors Guidelines (ICMJE) [77].

4. Discussion

The definition of specific intervention groups among a paediatric population is complex and it is of great importance considering that brain damage is an heterogeneous impairment itself. Traditionally, paediatric brain damage englobes both CP and acquired paediatric brain injury [78]. CP is defined as group of permanent disorders of movement and posture caused by a non-progressive brain injury, during the prenatal, natal, or perinatal period [1]. On the other hand, paediatric acquired brain injury includes injuries caused by external or internal factors starting from early childhood [2,3]. There has always been some controversy in whether the term of CP must be included in acquired brain injury, as it is in fact caused by a brain damage, and when to determine the time limit to make the differential diagnosis between the two terms [3]. Giving this lack of consensus, in order to include a wider population, our sample is determined to include children with non-progressive brain damage, whether it is titled as CP or acquired brain injury.

Paediatric brain damage causes a wide broad of manifestations, such as cognitive and motor impairments. One of the impairments with the highest impact in daily living functionality is UL function, as it is essential to execute bimanual activities and allow the child's daily living participation and environment exploration, allowing the acquisition and development of cognitive and motor skills [79,80].

Both VR and tDCS have shown benefits in UL function rehabilitation, but there is no evidence of the effects of these two techniques used in a combined protocol. An intervention combining VR and tDCS for UL function in paediatric brain damage is proposed.

VR was considered as one of the key elements of the protocol not only for its possibility to include the gamification aspect, so important in children, but also for the accumulated evidence supporting its effects on UL mobility and functional integration in daily living activities. Notably, gaming devices like the Nintendo® Wii device (Nintendo, Japan, Kyoto) have been utilised in research, yielding improvements in spasticity, grip strength, and hand function in children with CP, as demonstrated in studies by El-Shamy and El-Banna [81] and Sajan et al. [82], and summarised in Montoro-Cárdenas et al.'s review [83], which suggests that Nintendo Wii interventions can outperform conventional therapy in functional capacity and dexterity. Devices allowing a better integration of hand movements, such as the Leap Motion controller, have been associated with even more pronounced gains in grip and pinch strength, as stated in Tarakci et al.'s study [26].

This is the reason why the RGS (Eodyne, Barcelona, Spain) was selected for the protocol, as it is a VR approach that tracks the whole arm motion with a Kinect motion capture system (Microsoft, Redmond, WA, USA), and finger movements with the Leap Motion controller (Ultraleap, San Francisco, CA, USA) to translate them to an artificial environment. The virtual limbs are controlled in a first-person perspective, adding a better

embodiment experience. The games used require the use of the trunk, shoulder, elbow, wrist, hand, and fingers, allowing a wide UL training [22].

Our main intention was to develop and test a combined non-invasive neuromodulation protocol. The networks activated by VR rehabilitation are wide and include cognitive attentional areas as well as visuospatial and pre-motor areas; which seems a fairly good combination with the cortical stimulation with tDCS focused in M1 to achieve our objective. This combinated approach is initially focused on motor rehabilitation but, according to recent evidence on wide networks, involving motor areas may also enhance cognitive effects.

The two most used techniques among the non-invasive neuromodulation are repetitive transcranial magnetic stimulation (rTMS) and tDCS. Both techniques, although based on different principles of action, look for cortical stimulation or inhibition over a certain brain area. One of the most relevant differences between them both is their portability, as while rTMS requires that the subject stays still during the whole stimulation process, the tDCS allows freedom of movement and does not have any noise that may be disturbing when used with children [84–87].

Both techniques seems to have beneficial effects in improving and accelerating rehabilitation results, when used as an adjuvant therapy [28,32,86,88]. Specifically, tDCS has shown positive effects on paediatric brain damage in functions like balance, gait, and attention, when applied with an excitatory stimulation, with anodal tDCS [30,46,89]. tDCS's effects on UL function is still uncertain, as only two studies conducted a 10-session intervention with a cathodal approach, which achieved significant changes only in subjective UL function [47,48]. Studies in other populations like stroke have presented positive results with anodal tDCS stimulation for UL rehabilitation, which seems more beneficial for UL function and daily living performance [20]. Combined protocols of tDCS and VR have been employed also in stroke, finding better results in dexterity, motor impairment, and quality of life, versus an intervention based on VR exclusively [90–92].

The main UL function variable, which was used to calculate the sample of our study, is a widely validated scale such as MA-2, evaluating range of movement, accuracy, dexterity, and fluency. This is complemented with an objective kinematic UL evaluation that will allow for the analysis of the velocity and duration of the movement and range of motion of the shoulder, elbow, and wrist providing a wide evaluation of motor performance. Both measures are complemented with a widely validated a test as BBT.

One of the main goals of our study is to provide more evidence of the existing relation and functional connectivity between cognitive and motor brain networks and how protocols with direct influence in motor areas such as M1 may have direct cognitive effects that influence the functional improvement [37,93]. An exhaustive neuropsychological evaluation to assess potential changes in cognitive functions will be applied.

The Wechsler Intelligence Scale for Children V (WISC-V) [69] will serve as the cornerstone of our assessment, providing a detailed profile of intelligence across five cognitive domains: verbal comprehension, visuospatial ability, fluid reasoning, working memory, and processing speed. Complementing the WISC-V, the Beery–Buktenica Developmental Test of Visual–Motor Integration (Beery VMI) [70] will gauge visuomotor integration, a crucial skill in academic and daily activities, as the VR will be a key component of the rehabilitation program and might influence its performance. The neuropsychological battery for children (NEPSY-II) [40] will allow for domain-specific inquiries into attention, executive functions, language, and other cognitive faculties, facilitating a nuanced understanding of each child's cognitive profile and will allow for the identification of if there is a determinate profile that is more responsive to the therapy.

Attentional capacities will be further explored through the Test for Everyday Attention for Children (TEA-Ch) [71], which probes the various facets of attention crucial for learning and social interactions. Additionally, the Verbal learning test for children Spain-Complutense (TAVECI) [72] will measure memory and learning, vital for academic success and daily life navigation. The Behaviour Rating Inventory for Executive Function 2 (BRIEF-2) [73] will provide insights into executive functions from the perspective of

parents and teachers, offering a well-rounded view of the child's cognitive regulation in natural settings. To assess emotional and behavioural aspects, as our protocol may influence the frontal lobe and impact in emotional regulation, the use of the Evaluation System for children and adolescents (SENA) [74] will capture environmental feedback on a wide spectrum of emotional and conduct issues. Lastly, the Kidscreen-52 scale [75] will allow a child-centric perspective on quality of life, linking cognitive functioning and the changes in motor function with well-being in daily life contexts. The selection of these instruments is driven by their proven sensitivity and specificity for this age group, ensuring a robust and reliable assessment of cognitive function that can help to identify not only cognitive effects of the therapy but also the most responsive subjects.

This protocol will present some limitations: heterogeneity in pharmacological and rehabilitation treatment of the study's participants is expected, as their usual therapies will continue during their participation in the study. An exhaustive register about each participant therapies and drug prescription will be conducted, as their potential differences can influence the study's results, and further analysis will be implemented if this influence is confirmed. In addition, the sample will include children with different types of brain injury aetiology. This lack of homogeneity may impact the study's results but will assure the recruitment. Finally, including neurophysiological measures, such as electromyography or motor-evoked potentials, could be interesting for gathering objective information about the expected cortical changes, but was not possible due to equipment limitations.

5. Conclusions

The combined application of VR and anodal tDCS alongside comprehensive motor and cognitive assessments will provide valuable insights into the efficacy of combined interventions for UL rehabilitation in a paediatric population. We expect a major improvement in UL function after the intervention in the experimental group, with the active anodal tDCS and the VR training, compared to the control group, with the sham stimulation and the VR training.

Moreover, this approach will allow us to discern the extent to which cognitive improvements correlate with functional gains in the participants. As cognitive and motor functions are intimately related, we are expecting changes in the neuropsychology assessment, as a consequence of both the VR training and the specific tDCS stimulation over M1.

The findings from this novel approach could substantiate the interplay between motor and cognitive functions in neurorehabilitation, underscoring the imperative for multifaceted treatment strategies, including combined protocols, considering NIBS as a therapeutic tool in paediatric brain damage. Such strategies are essential for minimising long-term disability associated with paediatric brain damage.

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Institutional Review Board Statement: This protocol was approved by the ethics committee of the 12 de Octubre Hospital with the approval code: 23/489 on the 2nd November 2024. This work was developed following the guidelines of the Declaration of Helsinki. Trial registration in ClinicalTrials.gov with the ID number NCT06214364.

Informed Consent Statement: Informed consent will be obtained from all the legal guardians of the participants involved in the study, and the participants themselves if they are over 12.

Data Availability Statement: This protocol is registered in ClinicalTrials.gov with the following ID NCT06214364. Version 1.0. Any protocol modification will be notified in clinical trials protocol registration. The data obtained from the execution of this protocol will be available in a accessible repository and on request from the authors.

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