BMJ Open

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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-052409
Article Type:	Protocol
Date Submitted by the Author:	14-Apr-2021
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Keywords:	NEUROLOGY, NEUROPHYSIOLOGY, Paediatric neurology < NEUROLOGY

HABIT + tDCS: Study protocol of a randomized controlled trial (RCT) investigating the synergistic efficacy of Hand-arm bimanual intensive therapy (HABIT) plus targeted non-invasive brain stimulation to improve upper extremity function in school-age children with unilateral cerebral palsy

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Word count: 3921

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Keywords: hemiplegia, hand, motor cortex, corticospinal tract, bimanual training, physical rehabilitation, non-invasive brain stimulation, transcranial direct current stimulation, transcranial magnetic stimulation (TMS), pediatric stroke

Abstract

Introduction: Unilateral spastic cerebral palsy (USCP) is characterized by movement deficits primarily on one body side. The best available upper extremity (UE) therapies are costly and intensive. Thus, there is an urgent need for better, more efficient, and thus more accessible. Transcranial direct current stimulation (tDCS) is a type of non-invasive brain stimulation that influences excitability of motor brain areas which may enhance physical rehabilitation approaches. The aim of this study is to determine whether tDCS targeted to the hemisphere with corticospinal tract (CST) connectivity enhances the efficacy of UE training in children with USCP. Our central hypothesis is that Hand-arm bimanual intensive therapy (HABIT) combined with a tDCS montage targeting the hemisphere with CST connectivity to the impaired UE muscles will improve UE function more than HABIT plus sham stimulation. We will test this by conducting a randomized clinical trial with clinical and motor cortex physiology outcomes.

Methods and analyses: 81 children, age 6-17 years, will be randomized to receive 2mA anodal tDCS targeted to the affected UE motor map, 2mA cathodal tDCS to the contralesional motor cortex, or sham tDCS, each paired with HABIT (10 hrs; 2 hrs per day for 5 days). Primary outcomes will be Box and Blocks Test, Assisting Hand Assessment, and motor cortex excitability, determined with single-pulse transcranial magnetic stimulation. Secondary outcomes include ABILHAND-Kids, Canadian Occupational Performance Measure, Cooper Stereognosis, Dimension of Mastery Questionnaire and Participation and Environment Measure - Children and Youth. A group x test session mixed ANOVA will test differences among groups on all measures.

Ethics and dissemination: The study has been approved by the BRANY Institutional Review Board (#18-10-285-512). We will leverage our patient and family relationships to maximize dissemination. The study results will be shared with the academic and patient/family advocacy groups.

Trial registration number NCT03402854

Strengths and limitations of this study

- This study will determine how best to target tDCS to a child with USCP based on corticospinal tract (CST) connectivity.
- The results will identify which targeted tDCS strategies lead to strongest expansion of motor maps.
- The determination of the synergistic effects of HABIT+tDCS will provide strong justification for their continued development as an effective intervention for children with USCP that is more efficient in time and financial cost than the best available present therapies.
- The findings will dissect the interactions between CST laterality, non-invasive brain stimulation, and motor training in children with USCP and examine them using an integrated approach.
- We do not expect to obtain equal sample sizes for each CST connectivity pattern, and may not be able to fully determine interactions if a group is underpowered.

Introduction

Background

Unilateral spastic cerebral palsy (USCP) is characterized by movement deficits, particularly upper extremity (UE) impairments, on one side of the body. Although significant strides to develop rehabilitation approaches to improve UE function in children with USCP have occurred,[1] the best available UE therapies fail result in limited improvements in UE function, are costly, and require large amounts of treatment time (i.e., 4-6 hours per day for 2-3 weeks). Few families, particularly families of lower socio-economic status, have the ability to engage their children in these intensive therapies[2 3] and the high intensity is a limiting factor for more widespread implementation.[4] There is an urgent need for therapies that can deliver enhanced improvements, but are more cost-efficient and accessible.

Transcranial direct current stimulation (tDCS) is a non-invasive, low-risk method of delivering low levels of energy to the brain via saline-soaked sponge electrodes placed over the scalp. TDCS is portable, affordable, and well-tolerated in pediatric populations, making it an ideal strategy to combine with UE training.[5] Typically, neurons stimulated by the anodal electrode are depolarized whereas neurons stimulated by the cathodal electrode are hyperpolarized.[6] Repeated sessions of motor training of desired motor behaviors with concurrent anodal tDCS targeted to motor cortex of healthy adults facilitates learning through enhancement of consolidation.[7]

A consensus group in neurology[8] hypothesized that tDCS may increase the rate of motor learning in healthy adults. Enhanced motor learning was seen in typically developing children following contralateral anodal tDCS stimulation.[9 10] A recent meta-analysis in adults with stroke suggested that tDCS was beneficial in improving activities of daily living, with contralesional cathodal stimulation likely targeting impaired interhemispheric inhibition (IHI) being most effective. [11] Others have questioned whether IHI is the main driver of impaired UE function.[12]

Although promising, the results of tDCS studies in limited samples of children with USCP have yielded equivocal differences between stimulation and sham groups,[13-17] possibly due to underdosing the tDCS and over-dosing the paired motor skill training, with the latter washing out the additional effects of tDCS. Furthermore, tDCS was not always specifically targeted to the motor map of the affected UE. Thus, the montage may result in different outcomes depending on whether the lesioned hemisphere maintains contralateral corticospinal tract (CST) connectivity to the affected hand's muscles or the connectivity pattern has been reorganized, with the contralesional hemisphere controlling both hands.

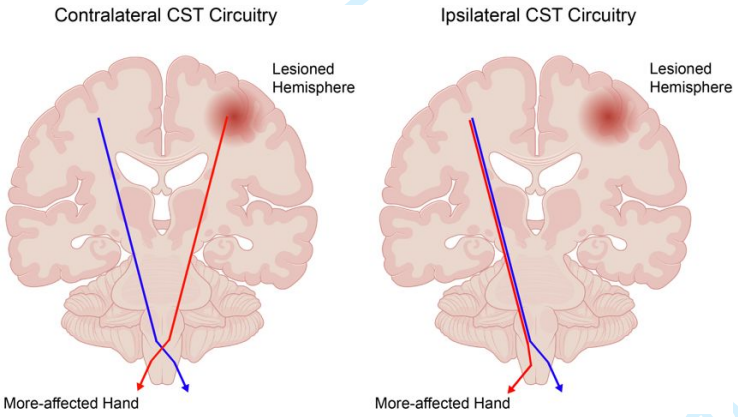

Fig. 1. Corticospinal tract (CST) connectivity patterns. Left – CST connectivity is maintained from lesioned hemisphere to affected hand. Right – CST connectivity is lost from lesioned hemisphere, and shifted to the ipsilateral hemisphere.

Objectives

The overall objective of this project is to determine how to optimally target tDCS to enhance the efficacy of UE training in children with USCP. Our central hypothesis is that combined Hand-arm bimanual intensive therapy (HABIT) and an individualized tDCS montage targeting the hemisphere with CST connectivity to the impaired UE muscles will improve UE function more than HABIT plus sham stimulation. We will also determine interactions between HABIT+tDCS and motor cortex physiology. We hypothesize that children who receive anodal tDCS targeted to the individual's hemisphere containing CST connections to the affected UE will show the most robust changes in motor cortex physiology after therapy, which will correlate with changes in hand function.

Methods and Analysis

Public/patient involvement statement

Pilot data were collected on 20 children (age 10.8±2.6y, range 7-18y). Parents and participants provided ongoing daily feedback on the feasibility and acceptability of tDCS. Two study personnel have cerebral palsy and have been instrumental in the design of the study from its conception.

Overall Study Design: We will conduct a single-blinded randomized controlled trial (RCT) to determine whether efficacy of HABIT+tDCS depends on the targeting of tDCS to the locus of motor control of the impaired UE. Three types of tDCS will be compared: anodal tDCS targeted to either the affected UE motor map, cathodal tDCS targeted to the or unaffected UE motor map and sham tDCS. In all groups, tDCS will be paired with HABIT (10 hrs; 2 hrs per day for 5 days).

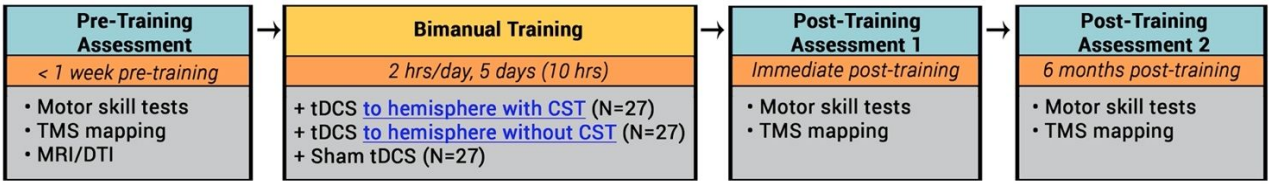

Fig. 2. Participant flow through the study.

Participants

Eighty-one children with unilateral spastic cerebral palsy (USCP), age 6-17 years, will be enrolled (Fig. 2). Participants will be recruited by advertising at our respective institutions, mailings, local clinics/hospitals, our existing database of more than 800 eligible individuals, and social media.

When a child and their family express interest in enrollment, we will send them a health survey via a HIPAA-secure, NIH-supported clinical database (REDCap). The primary exclusion criteria (Table 1) pertain to risks associated with magnetic resonance imaging (MRI), single-pulse

transcranial magnetic stimulation (TMS), and tDCS. We will discuss the study, risks, and the child's health history in detail with families to confirm eligibility. Eligible children and caregivers will be invited to our facilities for consent, review of study, and testing and intervention.

Table 1: Inclusion and Exclusion Criteria

Criterion	Method of Ascertainment	Justification
Inclusion Criteria:		
1. Age 6-17 years	Medical records	Children < 6 yrs of age may have difficulty tolerating procedures and may have small head size
2. Diagnosis of unilateral CP	Physical health screening and examination of neurological reports	Target population of the trial
3. Parent/guardian willing to provide informed consent	Meeting with PI to discuss study, signing consent form in presence of PI	Required
4. Participant willing to provide informed assent	Meeting with PI to discuss study, signing assent form in presence of PI	Required
5. Ability to pick up, hold and release a light object with affected hand	Pre-intervention screening measures and score under the maximum JTTHF ceiling of 1080s.	Intervention may be too challenging for the child
Exclusion Criteria:		
1. Current medical illness unrelated to CP	Medical history, physical examination	May impair child's ability to comply with trial, may affect study results
2. Seizure beyond age 2, use of anti-seizure medication, history of epilepsy, cranial metal implants, structural brain lesion, devices that may be affected by tDCS or TMS (pacemaker,	Medical records, interview with participant and parent(s), use of a checklist	TMS and tDCS may increase risk of seizure in subjects prone to seizures

medication pump, cochlear implant, implanted brain stimulator)		
3. Cognitive deficits	Pre-intervention screening measures; Kaufman Brief Intelligence Test, score ± 1 SD from normal	Child needs to understand study assent and instructions related to the testing and intervention
4. High motor ability in affected arm	Pre-intervention screening measures; Motor activity log, score > 2.5 (> slight-to-moderate)	Child may not benefit from further interventions
5. Severe spasticity	Pre-intervention screening measures; Modified Ashworth test, score > 3 (> moderate)	May confound ability to drive changes in motor control quality
6. Lack of asymmetry in hand function	Pre-intervention screening measures; Jebsen-Taylor score < 50%	May suggest bilateral CP
7. Orthopedic surgery in affected arm in last 12 months	Medical records, interview with participant and parent(s)	Recovery may confound study results
8. Botulinum toxin therapy in either upper extremity during last 6 months, or planned during study period	Medical records, interview with participant and parent(s)	Change in tone may confound study results
9. Currently receiving intrathecal baclofen	Medical records, interview with participant and parent(s)	Change in tone may confound study results
10. True positive response on the Transcranial Magnetic Stimulation & TDCS Safety Screen	Interview with participant and parent(s)	Would indicate an increased risk of seizure
11. Current use of medications known to lower the seizure threshold	Medical records, interview with participant and parent(s)	Underlying condition may pose risk of seizure and medication may influence TMS results
12. Previous episode of unprovoked neurocardiogenic syncope	Medical records, interview with participant and parent(s)	Could be exacerbated by TMS
13. Indwelling metal or incompatible medical devices	Medical records, interview with participant and parent(s)	Metallic objects in body may shift during MRI, posing risk of injury

14. Centrally-acting medications including anti-seizure medications	Medical records, interview with participant and parent(s)	Underlying condition may pose risk of seizure and medication may influence TMS results
15. Evidence of scalp disease or skin abnormalities	Medical records, interview with participant and parent(s)	tDCS may exacerbate the skin condition or increase discomfort

Number of participants: The primary clinical outcomes are Box and Blocks Test (BB) for unimanual dexterity and the Assisting Hand Assessment (AHA) for bimanual function. The estimated effect size from previous studies[14 15 18] and pilot data is estimated to be 0.35 (BB change 3 SD=10.2 blocks, AHA change 2, SD=9.3 AHA units, alpha=0.05 (two-tailed), and beta=0.8). We estimate that 22 subjects will be needed per group. We will recruit 20% more children than needed for the primary analyses, to account for children whose affected UE is controlled by both hemispheres and dropouts. Thus, 81 children (27 children/group) will be recruited.

Randomization Procedure: We will use a computer-generated blocked randomization stratified by CST connectivity, age and gender with concealed allocation for prospective allocation to the 3 groups. We will follow intention-to-treat principles. Randomization occurs after baseline assessments to allow CST connectivity determination.

Blinding: Children and their families, study personnel, clinical evaluators and AHA scorers will be blinded to treatment (active vs sham tDCS) allocation. One PI will not be blinded as it is critical for one person to monitor the quality and settings of the tDCS devices, to optimize safety and protocol adherence and fidelity. TMS and DTI data analysis will be performed using coded file names.

General Methods

Bimanual training

All participants will receive HABIT for 2 hrs/day on 5 consecutive days (10 hrs). This duration was chosen as changes in most clinical outcomes following bimanual training alone have been shown to require at >30 hours,[19 20] and thus the dose will be subthreshold such that findings won't be washed out with the addition of tDCS. Nonetheless, our pilot data suggests that children will improve on goal performance (Canadian Occupational Performance Measure, COPM) even with HABIT alone (sham), thus providing some potential benefits for all participants. HABIT will be conducted at either Teachers College (TC), Columbia University, New York, NY, USA or Burke Neurological Institute (BNI), White Plains, NY, USA. HABIT relies on principles of motor learning and plasticity[21-28] and largely parallels Constraint Induced Movement Therapy (CIMT).[26 28 29] Each child will be assigned to an interventionist to maintain at least a 1:1 ratio. Children can work individually with their interventionist or with other children. Our study, funded before the COVID pandemic began, proposed to conduct the intervention in groups of 4-6 children to allow for social interaction, peer-modeling and encouragement. Given ongoing COVID precautions, we may need to reduce our group size to 2-3 children (plus each child's interventionist and supervisors), spread children out across rooms and limit and/or maintain social distancing for group activities. Example activities for HABIT+tDCS include playing cards, building with blocks, throwing and catching a ball, arts and crafts, and functional tasks such as buttoning.[21]

Task Selection: We have identified age-appropriate fine and gross motor activities that require use of both hands[21]. Activities are selected by considering the role of the involved limb increasing in complexity from passive assist to active manipulator. Both positive reinforcement and knowledge of results provide motivation and reinforce target movements.[30] Instructions are given to the child before the start of each task reminding children how each hand will be used during the activity,[31] although problem-solving is highly encouraged.

Whole Task Practice involves performing repetitive practice of targeted movements embedded in a play activity. An example is a card game. The motor components of play involve holding cards in one hand, and picking up and placing down cards with the other hand.

Part Task Practice involves isolating a single component of the activity and performing it repeatedly. For example, after playing a card game, the child may be asked to flip cards over simultaneously with each hand, using a supination movement, as quickly as possible. The interventionist records the number of cards the child can turn in 30 seconds and the procedure is repeated several times.

Grading task difficulty: Depending on the child's motor capabilities and designated target movements, playing can be structured to grade the difficulty of a specific movement. Skill progression,[32] where we use part and whole practice to drive performance and scaffold the environment to facilitate success and grade difficulty, has been shown to be the essential ingredient to enhance performance[32 33] and drive motor map expansion.[18] These outcomes are independent of CST laterality.[34,35] In the context of a card game, cards can be placed farther away from the child to encourage elbow extension, or on an elevated surface, to encourage wrist extension.

Training and supervision of intervention providers: Interventionists are students in the Kinesiology or Neuroscience & Education program at Teachers College and local universities. Interventionists are trained with a standardized protocol. Interventionists are supervised by experienced physical and occupational therapists to ensure consistent approaches are used and treatment adherence and fidelity are maintained. Throughout each session, the supervisor will oversee each child's activities and progress. The supervisor and study PIs will meet daily with interventionists to discuss the progress of each child and serve to identify key goals for the following day. The high ratio of interventionist to child and supervisor to interventionist enable treatment consistency, adherence and fidelity.

Determination of CST laterality: We will determine CST laterality in two ways. 1) TMS (primary measure): We will determine which hemisphere evokes movement of the affected hand when TMS is applied (within a latency of 40ms, to rule out indirect motor pathways); 2) DTI (secondary measure): We will use DTI to visualize the affected CST in cases where laterality cannot be determined by TMS. There is high concordance between these approaches ($p<0.001$, sensitivity 93%, specificity 85%).[36]

Transcranial Direct Current Stimulation (tDCS)

A 2mA current will be delivered using surface rubber-carbon electrodes (35cm2) embedded in saline soaked sponges (0.9% NaCl) by a battery driven, constant current stimulator (Soterix LTE). 2mA tDCS has been shown to improve dexterity in typically developing children more than 1mA without increased side effects.[37] Participants randomized to receive tDCS will receive stimulation during the first 20 min of HABIT while seated, with the anode either over motor hotspot of the side containing CST connectivity for the first dorsal interosseous (FDI) as identified using TMS or the anode over the side without CST connectivity. Participants randomized to receive tDCS will receive stimulation during the first 20 min of HABIT while seated, For one group, the anode will be placed over the motor hotspot of the side containing CST connectivity for the first dorsal interosseous (FDI) as identified using TMS, and the cathode will be placed on the supraorbital area contralateral to the anode. For the second group, the cathode will be placed over the contralesional motor cortex, and the anode will be placed on the supraorbital area contralateral to the cathode. A 20 min duration was chosen as it has been safely tested in several studies with children with USCP.[5 13 16 37-39] For participants randomized to receive the Sham tDCS, a comparable preparation will be performed and will include a 30 sec real current ramping to 2mA at commencement, followed by a 5 sec slow decrease, with no

current sustained during the 20mins.[13 37 38] We will record the amount of saline used and electrode contact quality (measured by the device). The tDCS will be performed by one study PI who is not blinded to the type of stimulation. This person will monitor contact quality ensure fidelity is maintained. Study personnel will also measure blood pressure before and after tDCS, as well as any side effects.

Measures of Hand Function

Assessments were chosen to capture changes in 1) unimanual dexterity, 2) bimanual performance, and 3) functional use of the affected hand. Tests will be performed and videoed by an evaluator blinded to the child's CST laterality and treatment group before, immediately after, and six months after treatment. The assessments will occur at the location HABIT was provided (BNI or TC).

Two primary outcome measures will quantify bimanual performance and unimanual capacity under the Activity domain of the International Classification of Functioning, Disability, and Health (ICF).[40]

1) Assisting Hand Assessment (AHA): The AHA[41 42] measures and describes the effectiveness with which a child with a unilateral disability makes use of his/her affected (assisting) hand in performance of bimanual activities. The AHA is conducted through scoring of observable performance skills exposed during meaningful occupational performance (play). AHA is a standardized and criterion referenced test for children with unimanual motor impairments; test validity for all items; 99% confidence interval[41] and excellent reliability (0.97 interrater and 0.99 intrarater).[43] It is sensitive to change in USCP.[44] A functionally meaningful score change is 4 logit points.[43]

2) Box & Blocks Test (BB): Children will sit at a table in front of rectangular box divided into two compartments. One compartment contains 150 wooden 2.5cm^3 blocks.[45] Children will be asked to

move blocks, one at a time, with one hand, from one compartment to the other. The number of blocks moved in 60 sec is recorded for each hand. (Inter-rater reliability 0.95, reliable, and responsive to change.[46]). A functionally meaningful score change is 1.9 blocks on the more affected hand, 3.0 blocks on the less affected hand.[46]

Assessment	Measurement	Outcome Measure	Test Duration	Equipment
Primary Measures:				
Transcranial Magnetic Stimulation	CST laterality	Which hemisphere evokes movement of the affected hand when TMS is applied	90 minutes	TMS device, Neuroconn system, EMG electrodes
Box and Blocks Test	Unimanual movement speed	# of 2.5cm³ blocks moved from one box, over a barrier, into adjacent box in 1 min	30 minutes	BBT test kit – box, blocks, blindfold, nitrile gloves
Assisting Hand Assessment	Bimanual UE use	Effectiveness with which child uses affected UE in bimanual activities (AHA Units)	20 minutes	AHA test kit – board game, toys
Secondary Measures:				
Structural MRI, Diffusion Tensor Imaging	CST laterality	Which hemisphere shows visualization of the affected CST	1 hour	MRI scanner, DTI Studio software
Cooper Stereognosis	Ability to identify objects using only touch	# of objects identified correctly (out of 16), time taken to identify each object	20 minutes	16 standardized objects & shapes for child to identify
ABILHAND-Kids	UE impairments in children	Parent/caregiver report of child's ability to perform 21 specific motor tasks	5 minutes	Questionnaire form (parent/caregiver)
Canadian Occupational Performance Measure	Assess outcome relating to goals for self-care	Parent/caregiver report of child's performance of up to 5 parent- or child-selected self-care goals, as well as satisfaction	5 minutes	Questionnaire form (parent/caregiver)
Participation and Environment Measure-Children and Youth	Assess participation in the home, school and community settings	Parent/caregiver report of child's participation in 3 settings, alongside environmental factors (20 questions)	5 minutes	Questionnaire form (parent/caregiver)
Dimensions of Mastery Questionnaire	Assess child's mastery-related behaviors	Parent/caregiver report of child's levels of mastery motivation (41 questions)	5 minutes	Questionnaire form (parent/caregiver)

Secondary measures will be used across the 3 ICF domains:

1) ABILHAND-Kids measures the ability of a child to perform specific motor tasks, regardless of strategy. It has been validated for children with CP. A caregiver completes the survey about the child's abilities. It has a strong reliability (R=0.94) and reproducibility (R=0.91).[47]

2) Canadian Occupational Performance Measure (COPM) was designed to identify and measure, by means of interview, changes in functional problems clients consider to be relevant in the areas of self-care, productivity, and leisure performance. The client or caregiver defines the most relevant functional goals, ranks their importance, and rates their child's performance and their own satisfaction level.[48-50] It is valid and reliable for use with parents[50], and provides outcomes relevant to children and their families.[51 52]

3) Cooper Stereognosis[53] measures the ability of a child to identify sixteen small objects and shapes using only tactile input. The child will sit at a table, blindfolded. Objects will be placed

individually and the child must feel the object with one hand and identify it. Each hand will be tested separately and the number of objects correctly identified is recorded. Its inter-rater reliability is 0.85.[53]

4) Dimensions of Mastery Questionnaire (DMQ-18)[54] will be used to assess the level of motivation in mastering challenging tasks. The parent-report questionnaire assesses instrumental (persistence at object-related tasks, social activities with adults and peers, and gross motor tasks) and expressive (behavioral indicators of positive affect and negative reaction to failure) motivation. Subscale scores will be used to determine whether motivation impacts gains in functional motor skills. It has good reliability (0.84) and discriminate and concurrent validity are supported.[55]

5) Participation and Environment Measure - Children and Youth (PEM-CY) evaluates participation in the home, school, and in the community, alongside environmental factors within these settings. The PEM-CY can be used for children 5-17 years old, with or without disabilities. Internal consistency and reliability: moderate to good.[56]

Expected Outcome: We predict that all groups will show improved goal performance, and that there will be a significant interaction between stimulation type and improvement in dexterity and *quality* of bimanual performance, with children receiving stimulation targeted to the motor map of the affected UE showing greater improvements than children receiving other tDCS conditions.

We will assess changes in motor cortex excitability measures using TMS associated with HABIT+tDCS.

Transcranial Magnetic Stimulation

TMS will be conducted at Burke Neurological Institute for all participants making the process as child friendly as possible.[35]

Resting motor threshold (rMT): Resting MT is a measure of excitability of the motor cortex. The rMT is the minimum stimulator output required to evoke an MEP over 50μV in the FDI muscle in 6 of 10 trials while children have relaxed their arms.[57]

Active motor threshold (aMT): Active MT is a measure of excitability of the motor cortex. The aMT is the minimum stimulator output required to evoke an FDI MEP over 50μV in 6 of 10 trials during low-level squeeze of the tips of the thumb and index finger.[57]

Recruitment curve (RC): RCs quantify changes in MEP over different stimulus intensities. Ten TMS pulses will be delivered at <0.1 Hz at each of the following stimulation levels: 90%, 110%, 120%, 130%, and 150% rMT. RCs will be done at hotspots for each FDI. Stimuli will be delivered in a pseudorandomized order. RCs will be performed up to 150% rMT or maximum stimulator output, whichever is lower.

Motor evoked potential (MEP) amplitude: MEP is a measure of the strength of motor response to TMS. EMG will be exported to MATLAB for filtering and processing. The MEP for each muscle at each stimulation site will be defined as the peak-to-peak amplitude of the EMG response. Trials will be excluded if the child was not relaxed before the TMS pulse. MEPs will be averaged for stimuli delivered at the same site.

Bilateral TMS mapping of motor cortex: Muscle activity will be recorded using surface EMG electrodes. A multi-channel recording system (NeuroConn, Germany) will be used to simultaneously record EMG activity bilaterally in the first dorsal interosseous (FDI), wrist flexor and extensor muscles. The TMS device will trigger the recording system such that EMG activity is recorded at 4000 Hz 400ms before and 400ms after each TMS pulse is delivered. The position of each stimulation point over the scalp will be recorded in 3D and overlaid on the child's MRI using neuronavigation software (Brainsight Frameless, Rogue Research, Montreal, Canada).

Stimulation will begin in a medial portion of the affected motor cortex (M1). The coil will be progressed laterally until a motor evoked potential (MEP) for the affected FDI is obtained. If an MEP is found, a rectangular grid of 1cm-spaced sites will be generated in Brainsight, centered around the point of strongest activation of the affected FDI ("hotspot"). The coil will be moved along the grid M1 until responses are no longer found for any recorded muscles. Both hemispheres will be mapped.

Area of motor map: If the average MEP is greater than 50 μV for a muscle at one site, that site will be categorized as controlling that muscle. Total area enclosing digit and wrist sites for each hand will be measured. This measure serves as the primary measure.

Expected Outcome:. We predict that changes in cortical excitability will have been largest when tDCS is targeted to the cortex controlling movement of the affected hand. We further expect to have determined that changes will be larger in response to targeted HABIT+tDCS compared to sham HABIT+tDCS.

Magnetic Resonance Imaging

Each child will receive a structural MR scan and diffusion tensor imaging scan without sedation on a Siemens MRI tDCS Study Protocol at the Citigroup Biomedical Imaging Center, at Weill Cornell Medicine, New York, NY, USA. The structural MRI will be used to co-register TMS stimulation targets with specific brain landmarks for TMS neuronavigation. For TMS localization, there is normal variability in brain topography relative to scalp landmarks. For structural scans, 165-slice images will be taken at a resolution of 256 x 256 px. The structural MRI will be also used to identify the lesion type and extent. The DTI scan will be performed during the same

session using a 65-direction protocol, 75 slices per direction at a resolution of 112 x 112 px each.

Classification of CP etiology: Each child's structural MRI will be used to identify and measure type, location, and extent of lesion or brain malformation by a neuroradiologist. We will use the open-source program Horos to measure the extent of a lesion/brain malformation.

Diffusion tensor tractography: DT images will be imported into DTI Studio software (V3, Johns Hopkins U., Baltimore, MD) for processing and analyses. Image series for each participant will be screened for movement artifact, and slices showing artifact will be removed. Since we will obtain images using 65 gradients and will perform duplicate scans, up to 30% of slices can be removed without compromising feasibility of tract reconstruction. After screening for movement artifact, color maps of fractional anisotropy will be constructed, showing the integrity of different neural pathways. To visualize fiber streams, seeds will be placed in the internal capsule and cerebral peduncle.

Expected Outcome: We predict that changes will have been largest when tDCS is targeted to the cortex controlling movement of the affected hand. We further expect to have determined that changes will be larger in response to targeted HABIT+tDCS compared to sham HABIT+tDCS.

Statistical Analysis Plans

For both aims we will use a group x test session ANOVA with repeated measures on test session to examine differences among groups on each primary and secondary measure of hand function. If data are missing we will use a mixed linear model analysis. We will also add in covariates including gender, age, side of impairment, lesion type, lesion size, CST connectivity,

CST fractional anisotropy and number of streamlines (determined by DTI), and baseline hand function.

Procedure for Handling Missing Data: Intention-to-treat analysis will be used. To account for children who miss assessments, we will analyze data using a mixed linear model regression, which accounts for unequal time points among individuals. Mixed linear models on test sessions will be performed for all clinical outcomes with time as a fixed factorial factor to see improvements over time. Mixed linear models allow the estimation of interindividual variability and intraindividual patterns of change over time, while accounting for missing data.

Data Management

All data will be stored for 3 years study completion. Data analysis will be conducted in collaboration with statisticians. Data will be stored on an online, HIPAA-compliant database (REDCap). All study-related electronic files will be accessible only by key personnel, and all computers will be password protected. All subjects will be given a unique identifier at the time of enrollment that will be used for all study-related documentation. Paper case report forms and study files will be kept in the study coordinator's locked cabinet in a secure office.

Resource sharing plan

We have made a commitment to publish, in a timely manner, all the relevant scientific information that they will derive during this project. Unpublished information could be made available to interested parties via a request to the Principal Investigator. All study data also will

be made available via the Data and Specimen Hub (DASH), a data sharing platform of the Eunice Kennedy Shriver National Institute of Child Health and Development.

Ethics and dissemination

The study has been approved by the BRANY Institutional Review Board (# 18-10-285-512) and is registered with Clinicaltrials.gov (NCT03402854). The study will be conducted according to the principles of the Declaration of Helsinki. The results of this RCT will be published in open access, peer-reviewed scientific journals and presented at national and international meetings. We will leverage our patient and family relationships to maximize dissemination. The study results will be shared with the academic and stakeholder community, including dissemination of training tools through patient associations and patient/family advocacy groups. Participants will receive a plain language report at the end of the study.

Acknowledgments

We thank the children and families who participated in the pilot study and the volunteers who worked with the participants. We thank Bernadette Gillick for assistance with tDCS application in children with USCP and Talita Campos, Grace-Anne Herard, Lindsey Soles, Orit Herzberg-Keller, Ellen Osei, Genni Hester, and Amanda Sarafian for clinical evaluations.

Contributors: AMG and KMF are the study Principal Investigators. CLF and MTR assisted with collection and analysis of pilot data. KC was responsible for ethics applications and reporting and summarizing preliminary data. MB analyzed pilot AHA videos and supervised interventions. KMF and AMG will take the lead roles on preparation for publication of the clinical outcomes. AMG and KMF drafted the final version of this manuscript. All authors have contributed to the writing and critical review of the manuscript and have approved the final version.

Funding: This work is supported by the National Institutes of Health (2R01 HD076436-06) to KMF and AMG. MTR was supported by a Postdoctoral training award from Fonds de Recherche en Santé du Québec. CLF was supported by NIH/NCATS Grant #TL1-TR-002386.

Competing interests: None declared.

Patient and public involvement: Patients were involved in the design, conduct, reporting, and dissemination plans of this research.

Patient consent for publication: Not required.

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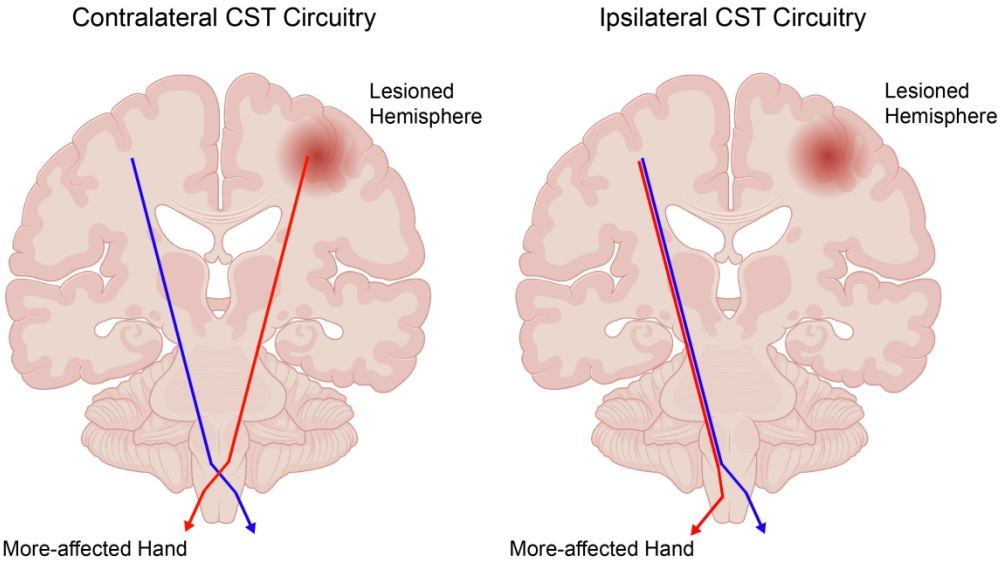

Fig. 1. Corticospinal tract (CST) connectivity patterns. Left – CST connectivity is maintained from lesioned hemisphere to affected hand. Right – CST connectivity is lost from lesioned hemisphere, and shifted to the ipsilateral hemisphere.

Assessment	Measurement	Outcome Measure	Test Duration	Equipment
Primary Measures:				
Transcranial Magnetic Stimulation	CST laterality	Which hemisphere evokes movement of the affected hand when TMS is applied	90 minutes	TMS device, Neuroconn system, EMG electrodes
Box and Blocks Test	Unimanual movement speed	# of 2.5cm³ blocks moved from one box, over a barrier, into adjacent box in 1 min	30 minutes	BBT test kit – box, blocks, blindfold, nitrile gloves
Assisting Hand Assessment	Bimanual UE use	Effectiveness with which child uses affected UE in bimanual activities (AHA Units)	20 minutes	AHA test kit – board game, toys
Secondary Measures:				
Structural MRI, Diffusion Tensor Imaging	CST laterality	Which hemisphere shows visualization of the affected CST	1 hour	MRI scanner, DTI Studio software
Cooper Stereognosis	Ability to identify objects using only touch	# of objects identified correctly (out of 16), time taken to identify each object	20 minutes	16 standardized objects & shapes for child to identify
ABILHAND-Kids	UE impairments in children	Parent/caregiver report of child's ability to perform 21 specific motor tasks	5 minutes	Questionnaire form (parent/caregiver)
Canadian Occupational Performance Measure	Assess outcome relating to goals for self-care	Parent/caregiver report of child's performance of up to 5 parent- or child-selected self-care goals, as well as satisfaction	5 minutes	Questionnaire form (parent/caregiver)
Participation and Environment Measure-Children and Youth	Assess participation in the home, school and community settings	Parent/caregiver report of child's participation in 3 settings, alongside environmental factors (20 questions)	5 minutes	Questionnaire form (parent/caregiver)
Dimensions of Mastery Questionnaire	Assess child's mastery-related behaviors	Parent/caregiver report of child's levels of mastery motivation (41 questions)	5 minutes	Questionnaire form (parent/caregiver)

Fig. 2. Participant flow through the study.

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description
Administrative information		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry
	2b	All items from the World Health Organization Trial Registration Data Set
Protocol version	3	Date and version identifier
Funding	4	Sources and types of financial, material, and other support
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors
	5b	Name and contact information for the trial sponsor
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)
Introduction		
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention
	6b	Explanation for choice of comparators
Objectives	7	Specific objectives or hypotheses
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)

Methods: Participants, interventions, and outcomes

Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size

Methods: Assignment of interventions (for controlled trials)

Allocation:

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions

Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial
Methods: Data collection, management, and analysis		
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)
Methods: Monitoring		
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed

	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor

Ethics and dissemination

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions
	31b	Authorship eligibility guidelines and any intended use of professional writers
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code

Appendices

Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

HABIT + tDCS: Study protocol of a randomized controlled trial (RCT) investigating the synergistic efficacy of Hand-arm bimanual intensive therapy (HABIT) plus targeted non-invasive brain stimulation to improve upper extremity function in school-age children with unilateral cerebral palsy

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-052409.R1
Article Type:	Protocol
Date Submitted by the Author:	23-Oct-2021
Complete List of Authors:	Gordon, Andrew; Columbia University Ferre, Claudio; Burke Neurological Institute; Boston University, Dept. of Occupational Therapy Robert, Maxime; Laval University Chin, Karen; Columbia University, Teachers College; Burke Neurological Institute Brandao, Marina; Universidade Federal de Minas Gerais Friel, Kathleen M.; Burke Neurological Institute
Primary Subject Heading:	Rehabilitation medicine
Secondary Subject Heading:	Neurology
Keywords:	NEUROLOGY, NEUROPHYSIOLOGY, Paediatric neurology < NEUROLOGY

HABIT + tDCS: Study protocol of a randomized controlled trial (RCT) investigating the synergistic efficacy of Hand-arm bimanual intensive therapy (HABIT) plus targeted non-invasive brain stimulation to improve upper extremity function in school-age children with unilateral cerebral palsy

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Word count: 4,120

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Keywords: hemiplegia, hand, motor cortex, corticospinal tract, bimanual training, physical rehabilitation, non-invasive brain stimulation, transcranial direct current stimulation, transcranial magnetic stimulation (TMS), pediatric stroke

Abstract

Introduction: Unilateral spastic cerebral palsy (USCP) is characterized by movement deficits primarily on one body side. The best available upper extremity (UE) therapies are costly and intensive. Thus, there is an urgent need for better, more efficient, and thus more accessible therapies. Transcranial direct current stimulation (tDCS) is non-invasive and may enhance physical rehabilitation approaches. The aim of this study is to determine whether tDCS targeted to the hemisphere with corticospinal tract (CST) connectivity enhances the efficacy of UE training in children with USCP. Our central hypothesis is that Hand-arm bimanual intensive therapy (HABIT) combined with a tDCS montage targeting the hemisphere with CST connectivity to the impaired UE muscles will improve UE function more than HABIT plus sham stimulation. We will test this by conducting a randomized clinical trial with clinical and motor cortex physiology outcomes.

Methods and analyses: 81 children, age 6-17 years, will be randomized to receive 2mA anodal tDCS targeted to the affected UE motor map, 2mA cathodal tDCS to the contralesional motor cortex, or sham tDCS during the first 20 minutes of each HABIT session (10 hrs; 2 hrs per day for 5 days). Primary outcomes will be Box and Blocks Test, Assisting Hand Assessment, and motor cortex excitability, determined with single-pulse transcranial magnetic stimulation. Secondary outcomes include ABILHAND-Kids, Canadian Occupational Performance Measure, Cooper Stereognosis, Dimension of Mastery Questionnaire and Participation and Environment Measure - Children and Youth. All measures will be collected before, immediately and 6 months after treatment. A group x test session mixed ANOVA will test differences among groups on all measures.

Ethics and dissemination: The study has been approved by the BRANY Institutional Review Board (#18-10-285-512). We will leverage our patient and family relationships to maximize dissemination and share results with the academic and patient/family advocacy groups.

Trial registration number NCT03402854

Strengths and limitations of this study

- This study will determine how best to target tDCS to a child with USCP based on corticospinal tract (CST) connectivity.
- The results will identify which targeted tDCS strategies lead to strongest expansion of motor maps.
- The determination of the synergistic effects of HABIT+tDCS will provide strong justification for their continued development as an effective intervention for children with USCP that is more efficient in time and financial cost than the best available present therapies.
- The findings will dissect the interactions between CST laterality, non-invasive brain stimulation, and motor training in children with USCP and examine them using an integrated approach.
- We do not expect to obtain equal sample sizes for each CST connectivity pattern, and may not be able to fully determine interactions if a group is underpowered.

Introduction

Background

Unilateral spastic cerebral palsy (USCP) is characterized by movement deficits, particularly upper extremity (UE) impairments, on one side of the body. Although significant strides to develop rehabilitation approaches to improve UE function in children with USCP have occurred,[1] the best available UE therapies result in limited improvements in UE function, are costly, and require large amounts of treatment time (i.e., 4-6 hours per day for 2-3 weeks). Few families, particularly families of lower socio-economic status, have the ability to engage their children in these intensive therapies[2 3] and the time required to achieve the high intensity is a limiting factor for more widespread implementation.[4] There is an urgent need for therapies that can deliver enhanced improvements, but are more cost-efficient and accessible.

Transcranial direct current stimulation (tDCS) is a non-invasive, low-risk method of delivering low levels of energy to the brain via saline-soaked sponge electrodes placed over the scalp. tDCS is portable, affordable, and well-tolerated in pediatric populations, making it an ideal strategy to combine with UE training.[5] Typically, neurons stimulated by the anodal electrode are depolarized whereas neurons stimulated by the cathodal electrode are hyperpolarized.[6] Repeated sessions of motor training of desired motor behaviors with concurrent anodal tDCS targeted to motor cortex of healthy adults facilitates learning through enhancement or consolidation.[7]

A consensus group in neurology[8] hypothesized that tDCS may increase the rate of motor learning in healthy adults. Enhanced motor learning was seen in typically developing children following contralateral anodal tDCS stimulation.[9 10] A recent meta-analysis in adults with stroke suggested that tDCS was beneficial in improving activities of daily living, with contralesional cathodal stimulation likely targeting impaired interhemispheric inhibition (IHI) being most effective. [11] Others have questioned whether IHI is the main driver of impaired UE function.[12]

Although promising, the results of tDCS studies in limited samples of children with USCP have yielded equivocal differences between stimulation and sham groups,[13-17] possibly due to underdosing the tDCS and over-dosing the paired motor skill training, with the latter washing out the additional effects of tDCS. Furthermore, tDCS studies have not specifically targeted the motor map of the affected UE. Thus, the montage may result in different outcomes depending on whether the lesioned hemisphere maintains contralateral corticospinal tract (CST) connectivity to the affected hand's muscles or the connectivity pattern has been reorganized, with the contralesional hemisphere controlling both hands (Fig. 1).

Objectives

The overall objective of this project is to determine how to optimally target tDCS to enhance the efficacy of UE training in children with USCP. Our central hypothesis is that combined Hand-arm bimanual intensive therapy (HABIT) and an individualized tDCS montage targeting the hemisphere with CST connectivity to the impaired UE muscles will improve UE function more than HABIT plus sham stimulation. We will also determine interactions between HABIT+tDCS and motor cortex physiology. We hypothesize that children who receive anodal tDCS targeted to the individual's hemisphere containing CST connections to the affected UE will show the most robust changes in motor cortex physiology after therapy, which will correlate with changes in hand function.

Methods and Analysis

Public/patient involvement statement

Pilot data were collected on 20 children (age 10.8±2.6y, range 7-18y). Parents and participants provided ongoing daily feedback on the feasibility and acceptability of tDCS. Two study

personnel have cerebral palsy and have been instrumental in the design of the study from its conception.

Overall Study Design: We will conduct a single-blinded randomized controlled trial (RCT) with stratification based on CST connectivity, age and gender to determine whether efficacy of HABIT+tDCS depends on the targeting of tDCS to the locus of motor control of the impaired UE. We will compare 3 types of tDCS: 1) anodal tDCS targeted to either the affected UE motor map, 2) cathodal tDCS targeted to the unaffected UE motor map and 3) sham tDCS. In all groups, tDCS will be paired with HABIT (10 hrs; 2 hrs per day for 5 days)(Fig. 2).

Participants

Eighty-one children with unilateral spastic cerebral palsy (USCP), age 6-17 years, will be enrolled (Fig. 2). Participants will be recruited by advertising at our respective institutions, mailings, local clinics/hospitals, our existing database of more than 800 eligible individuals, and social media.

When a child and their family express interest in enrollment, we will send them a health survey via a HIPAA-secure, NIH-supported clinical database (REDCap). The primary exclusion criteria (Table 1) pertain to risks associated with magnetic resonance imaging (MRI), single-pulse transcranial magnetic stimulation (TMS), and tDCS. We will discuss the study, risks, and the child's health history in detail with families to confirm eligibility. Eligible children and caregivers will be invited to our facilities for consent, review of study, and testing and intervention.

Table 1: Inclusion and Exclusion Criteria

Criterion	Method of Ascertainment	Justification

Inclusion Criteria:		
1. Age 6-17 years	Medical records	Children < 6 yrs of age may have difficulty tolerating procedures and may have small head size
2. Diagnosis of unilateral CP	Physical health screening and examination of neurological reports	Target population of the trial
3. Parent/guardian willing to provide informed consent	Meeting with PI to discuss study, signing consent form in presence of PI	Required
4. Participant willing to provide informed assent	Meeting with PI to discuss study, signing assent form in presence of PI	Required
5. Ability to pick up, hold and release a light object with affected hand	Pre-intervention screening measures and score under the maximum JTTHF ceiling of 1080s.	Intervention may be too challenging for the child
Exclusion Criteria:		
1. Current medical illness unrelated to CP	Medical history, physical examination	May impair child's ability to comply with trial, may affect study results
2. Seizure beyond age 2, use of anti-seizure medication, history of epilepsy, cranial metal implants, structural brain lesion, devices that may be affected by tDCS or TMS (pacemaker, medication pump, cochlear implant, implanted brain stimulator)	Medical records, interview with participant and parent(s), use of a checklist	TMS and tDCS may increase risk of seizure in subjects prone to seizures
3. Cognitive deficits	Pre-intervention screening measures; Kaufman Brief Intelligence Test, score ± 1 SD from normal	Child needs to understand study assent and instructions related to the testing and intervention
4. High motor ability in affected arm	Jebsen-Taylor score of < 50% differences between the two hands or score <100 secs	Child may not benefit from interventions due to mild hand function or extremely

		limited use of the affected hand
5. Severe spasticity	Pre-intervention screening measures; Modified Ashworth test score > 3 (> moderate)	May confound ability to drive changes in motor control quality
6. Lack of asymmetry in hand function	Pre-intervention screening measures; Jebsen-Taylor score of < 50% differences between the two hands	May suggest bilateral CP
7. Orthopedic surgery in affected arm in last 12 months	Medical records, interview with participant and parent(s)	Recovery may confound study results
8. Botulinum toxin therapy in either upper extremity during last 6 months, or planned during study period	Medical records, interview with participant and parent(s)	Change in tone may confound study results
9. Currently receiving intrathecal baclofen	Medical records, interview with participant and parent(s)	Change in tone may confound study results
10. True positive response on the Transcranial Magnetic Stimulation & TDCS Safety Screen	Interview with participant and parent(s)	Would indicate an increased risk of seizure
11. Current use of medications known to lower the seizure threshold	Medical records, interview with participant and parent(s)	Underlying condition may pose risk of seizure and medication may influence TMS results
12. Previous episode of unprovoked neurocardiogenic syncope	Medical records, interview with participant and parent(s)	Could be exacerbated by TMS
13. Indwelling metal or incompatible medical devices	Medical records, interview with participant and parent(s)	Metallic objects in body may shift during MRI, posing risk of injury
14. Centrally-acting medications including anti-seizure medications	Medical records, interview with participant and parent(s)	Underlying condition may pose risk of seizure and medication may influence TMS results
15. Evidence of scalp disease or skin abnormalities	Medical records, interview with participant and parent(s)	tDCS may exacerbate the skin condition or increase discomfort

Number of participants: The primary clinical outcomes are Box and Blocks Test (BB) for unimanual dexterity and the Assisting Hand Assessment (AHA) for bimanual function. The estimated effect size from previous studies[14 15 18] and pilot data is estimated to be 0.35 (BB change 3 SD=10.2 blocks, AHA change 2, SD=9.3 AHA units, alpha=0.05 (two-tailed), and beta=0.8). We estimate that 22 subjects will be needed per group. We will recruit 20% more children than needed for the primary analyses, to account for children whose affected UE is controlled by both hemispheres and dropouts. Thus, 81 children (27 children/group) will be recruited.

Randomization Procedure: We will use a computer-generated blocked randomization stratified by CST connectivity (determined with TMS), age and gender with concealed allocation for prospective allocation to the 3 groups: targeted tDCS, untargeted tDCS, and sham tDCS. We will follow intention-to-treat principles. Randomization occurs after baseline assessments to allow CST connectivity determination.

Blinding: Children and their families, study personnel, clinical evaluators and AHA scorers will be blinded to treatment (active vs sham tDCS) allocation. One PI will not be blinded as it is critical for one person to monitor the quality and settings of the tDCS devices, to optimize safety and protocol adherence and fidelity. TMS and DTI data analysis will be performed using coded file names.

General Methods

Bimanual training

All participants will receive HABIT for 2 hrs/day on 5 consecutive days (10 hrs). This duration was chosen as changes in most clinical outcomes following bimanual training alone have been shown to require at least 30 hours,[19 20] and thus the dose will be subthreshold such that findings

won't be washed out with the addition of tDCS. Nonetheless, our pilot data suggests that children will improve on goal performance (Canadian Occupational Performance Measure, COPM) even with HABIT alone (sham), thus providing some potential benefits for all participants. HABIT will be conducted at either Teachers College (TC), Columbia University, New York, NY, USA or Burke Neurological Institute (BNI), White Plains, NY, USA. HABIT relies on principles of motor learning and plasticity[21-28] and largely parallels Constraint Induced Movement Therapy (CIMT).[26 28 29] Each child will be assigned to an interventionist to maintain at least a 1:1 ratio. Children can work individually with their interventionist or with other children. Our study, funded before the COVID pandemic began, proposed to conduct the intervention in groups of 4-6 children to allow for social interaction, peer-modeling and encouragement. Given ongoing COVID precautions, we may need to reduce our group size to 2-3 children (plus each child's interventionist and supervisors), spread children out across rooms and limit and/or maintain social distancing for group activities. Example activities for HABIT+tDCS include playing cards, building with blocks, throwing and catching a ball, arts and crafts, and functional tasks such as buttoning.[21]

Task Selection: We have identified age-appropriate fine and gross motor activities that require use of both hands[21]. Activities are selected by considering the role of the involved limb increasing in complexity from passive assist to active manipulator. Both positive reinforcement and knowledge of results provide motivation and reinforce target movements.[30] Instructions are given to the child before the start of each task reminding children how each hand will be used during the activity,[31] although problem-solving is highly encouraged.

Whole Task Practice involves performing repetitive practice of targeted movements embedded in a play activity. An example is a card game. The motor components of play involve holding cards in one hand, and picking up and placing down cards with the other hand.

Part Task Practice involves isolating a single component of the activity and performing it repeatedly. For example, after playing a card game, the child may be asked to flip cards over simultaneously with each hand, using a supination movement, as quickly as possible. The interventionist records the number of cards the child can turn in 30 seconds and the procedure is repeated several times.

Grading task difficulty: Depending on the child's motor capabilities and designated target movements, playing can be structured to grade the difficulty of a specific movement. Skill progression,[32] where we use part and whole practice to drive performance and scaffold the environment to facilitate success and grade difficulty, has been shown to be the essential ingredient to enhance performance[32 33] and drive motor map expansion.[18] These outcomes are independent of CST laterality.[34,35] In the context of a card game, cards can be placed farther away from the child to encourage elbow extension, or on an elevated surface, to encourage wrist extension.

Training and supervision of intervention providers: Interventionists are students in the Kinesiology or Neuroscience & Education program at Teachers College and local universities. Interventionists are trained with a standardized protocol. Interventionists are supervised by experienced physical and occupational therapists to ensure consistent approaches are used and treatment adherence and fidelity are maintained. Throughout each session, the supervisor (who will train all interventionists and be present at both sites) will oversee each child's activities and progress, and will rotate through each participant-interventionist pair to provide modeling and feedback and ensure treatment fidelity. The supervisor and study PIs will meet daily with interventionists to discuss the progress of each child, problem-solve and serve to identify key goals for the following day. The high ratio of interventionist to child and supervisor to interventionist further enables treatment consistency, adherence and fidelity.

Determination of CST laterality: We will determine CST laterality in two ways. 1) TMS map side (primary measure): We will determine which hemisphere evokes movement of the affected hand when TMS is applied (within a latency of 40ms, to rule out indirect motor pathways). If both hemispheres elicit MEPs (bilateral CST connectivity), the side with the greatest area (# of sites) will be used to denote the dominant side; 2) DTI (secondary measure): We will use DTI to visualize the affected CST in cases where laterality cannot be determined by TMS. There is high concordance between these approaches ($p<0.001$, sensitivity 93%, specificity 85%).[36]

Transcranial Direct Current Stimulation (tDCS)

A 2mA current will be delivered using surface rubber-carbon electrodes (35cm2) embedded in saline soaked sponges (0.9% NaCl) by a battery driven, constant current stimulator (Soterix LTE). 2mA tDCS has been shown to improve dexterity in typically developing children more than 1mA without increased side effects.[37] Participants randomized to receive tDCS will receive stimulation during the first 20 min of HABIT while seated, with the anode either over motor hotspot of the side containing CST connectivity for the first dorsal interosseous (FDI) of the more affected hand as identified using TMS (targeted tDCS) or the cathode over the contralesional hemisphere (untargeted tDCS, Figure 1). For the targeted tDCS group, the anode will be placed over the motor hotspot of the side containing CST connectivity for the first dorsal interosseous (FDI) as identified using TMS, and the cathode will be placed on the supraorbital area contralateral to the anode. The targeted hemisphere will depend on whether the affected CST has a contralateral or ipsilateral organization pattern. For the untargeted tDCS group, the cathode will be placed over the contralesional motor cortex, and the anode will be placed on the supraorbital area contralateral to the cathode. A 20 min duration overlapping physical training was chosen as it has been safely tested in several studies with children with USCP.[5 13 16 37-39] For participants randomized to receive sham tDCS, a comparable preparation will be performed

and will include a 30 sec real current ramping to 2mA at commencement, followed by a 5 sec slow decrease, with no current sustained during the 20mins.[13 37 38] We will record the amount of saline used and electrode contact quality (measured by the device). The tDCS will be performed by one study PI who is not blinded to the type of stimulation. This person will monitor contact quality and ensure fidelity is maintained. Study personnel will also measure blood pressure before and after tDCS, as well as any side effects.

Measures of Hand Function

Assessments were chosen to capture changes in 1) unimanual dexterity, 2) bimanual performance, and 3) functional use of the affected hand (Figure 3). Tests will be performed and videoed by an evaluator blinded to the child's CST laterality and treatment group before, immediately after, and six months after treatment. The assessments will occur at the location HABIT was provided (BNI or TC) before, immediately and 6 months after treatment by the same assessor at each time point and caregivers will complete questionnaires during the child's evaluation.

Two primary outcome measures will quantify bimanual performance and unimanual capacity under the Activity domain of the International Classification of Functioning, Disability, and Health (ICF).[40] This domain is most relevant the targeted upper extremity function.

1) Assisting Hand Assessment (AHA): The AHA[41 42] measures and describes the effectiveness with which a child with a unilateral disability makes use of his/her affected (assisting) hand in performance of bimanual activities. The AHA is conducted through scoring of observable performance skills exposed during meaningful occupational performance (play). AHA is a standardized and criterion referenced test for children with unimanual motor impairments; test validity for all items; 99% confidence interval[41] and excellent reliability (0.97 interrater and 0.99

intrarater).[43] It is sensitive to change in USCP.[44] A functionally meaningful score change is 4 logit points.[43]

2) Box & Blocks Test (BB): Children will sit at a table in front of rectangular box divided into two compartments. One compartment contains 150 wooden 2.5cm^3 blocks.[45] Children will be asked to move blocks, one at a time, with one hand, from one compartment to the other. The number of blocks moved in 60 sec is recorded for each hand. (Inter-rater reliability 0.95, reliable, and responsive to change.[46]). A functionally meaningful score change is 1.9 blocks on the more affected hand, 3.0 blocks on the less affected hand.[46]

Secondary measures will be used across the 3 ICF domains:

1) ABILHAND-Kids (ICF activity domain) measures the ability of a child to perform specific motor tasks, regardless of strategy. A caregiver completes the survey about the child's abilities. It has been validated for children with CP, has a strong reliability (R=0.94) and reproducibility (R=0.91).[47]

2) Canadian Occupational Performance Measure (COPM) (ICF activity domain) was designed to identify and measure, by means of interview, changes in functional problems clients consider to be relevant in the areas of self-care, productivity, and leisure performance. The client or caregiver defines the most relevant functional goals, ranks their importance, and rates their child's performance and their own satisfaction level.[48-50] It is valid and reliable for use with parents[50], and provides outcomes relevant to children and their families.[51 52]

3) Cooper Stereognosis[53] (ICF body structure and function domain) measures the ability of a child to identify sixteen small objects and shapes using only tactile input. The child will sit at a table, blindfolded. Objects will be placed individually and the child must feel the object with one hand and identify it. Each hand will be tested separately and the number of objects correctly identified is recorded. Its inter-rater reliability is 0.85.[53]

4) Dimensions of Mastery Questionnaire (DMQ-18)[54] (ICF activity domain) will be used to assess the level of motivation in mastering challenging tasks. The parent-report questionnaire assesses instrumental (persistence at object-related tasks, social activities with adults and peers, and gross motor tasks) and expressive (behavioral indicators of positive affect and negative reaction to failure) motivation. Subscale scores will be used to determine whether motivation impacts gains in functional motor skills. It has good reliability (0.84) and discriminate and concurrent validity are supported.[55]

5) Participation and Environment Measure - Children and Youth (PEM-CY) (ICF participation domain) evaluates participation in the home, school, and in the community, alongside environmental factors within these settings. The PEM-CY can be used for children 5-17 years old, with or without disabilities. Internal consistency and reliability: moderate to good.[56]

Expected Outcome: We predict that all groups will show improved goal performance, and that there will be a significant interaction between stimulation type and improvement in dexterity and *quality* of bimanual performance, with children receiving stimulation targeted to the motor map of the affected UE showing greater improvements than children receiving other tDCS conditions immediately after treatment and maintained at the 6 month followup.

We will assess changes in motor cortex excitability measures using TMS associated with HABIT+tDCS.

Transcranial Magnetic Stimulation

TMS will be conducted at Burke Neurological Institute for all participants making the process as child friendly as possible.[35]

Resting motor threshold (rMT): Resting MT is a measure of excitability of the motor cortex. The rMT is the minimum stimulator output required to evoke an MEP over 50μV in the FDI muscle in 6 of 10 trials while children have relaxed their arms.[57]

Active motor threshold (aMT): Active MT is a measure of excitability of the motor cortex. The aMT is the minimum stimulator output required to evoke an FDI MEP over 50μV in 6 of 10 trials during low-level squeeze of the tips of the thumb and index finger.[57]

Recruitment curve (RC): RCs quantify changes in MEP over different stimulus intensities. Ten TMS pulses will be delivered at <0.1 Hz at each of the following stimulation levels: 90%, 110%, 120%, 130%, and 150% rMT. RCs will be done at hotspots for each FDI. Stimuli will be delivered in an order unpredictable to subjects. RCs will be performed up to 150% rMT or maximum stimulator output, whichever is lower.

Motor evoked potential (MEP) amplitude: MEP is a measure of the strength of motor response to TMS. EMG will be exported to MATLAB for filtering and processing. The MEP for each muscle at each stimulation site will be defined as the peak-to-peak amplitude of the EMG response. Trials will be excluded if the child was not relaxed before the TMS pulse. MEPs will be averaged for stimuli delivered at the same site.

Bilateral TMS mapping of motor cortex: Muscle activity will be recorded using surface EMG electrodes. A multi-channel recording system (NeuroConn, Germany) will be used to simultaneously record EMG activity bilaterally in the first dorsal interosseous (FDI), wrist flexor and extensor muscles. The TMS device will trigger the recording system such that EMG activity is recorded at 4000 Hz 400ms before and 400ms after each TMS pulse is delivered. The position of each stimulation point over the scalp will be recorded in 3D and overlaid on the child's MRI using neuronavigation software (Brainsight Frameless, Rogue Research, Montreal, Canada).

Stimulation will begin in a medial portion of the affected motor cortex (M1). The coil will be progressed laterally until a motor evoked potential (MEP) for the affected FDI is obtained. If an MEP is found, a rectangular grid of 1cm-spaced sites will be generated in Brainsight, centered around the point of strongest activation of the affected FDI ("hotspot"). This site will be marked for subsequent use of the tDCS. The coil will be moved along the grid M1 until responses are no longer found for any recorded muscles. Both hemispheres will be mapped.

Area of motor map: If the average MEP is greater than 50 μV for a muscle at one site, that site will be categorized as controlling that muscle. The total number of sites will constitute the area of digit and wrist maps for each hand. This measure serves as the primary measure of motor cortical physiology.

Expected Outcome: We predict that changes in motor map size and cortical excitability will be largest when tDCS is targeted to the cortex controlling movement of the affected hand. We further expect to have determined that changes will be larger in response to HABIT+ targeted tDCS compared to HABIT+ untargeted tDCS and HABIT+ sham tDCS.

Magnetic Resonance Imaging

Each child will undergo a structural MR scan and diffusion tensor imaging scan without sedation on a Siemens MRI tDCS Study Protocol at the Citigroup Biomedical Imaging Center, at Weill Cornell Medicine, New York, NY, USA. The structural MRI will be used to co-register TMS stimulation targets with specific brain landmarks for TMS neuronavigation. For TMS localization, there is normal variability in brain topography relative to scalp landmarks. For structural scans, 165-slice images will be taken at a resolution of 256 x 256 px. The structural MRI will also be

used to identify the lesion type and extent. The DTI scan will be performed during the same session using a 65-direction protocol, 75 slices per direction at a resolution of 112 x 112 px each.

Classification of CP etiology: Each child's medical history (in particular the neurological report) will be used to determine their diagnosis, and this will be confirmed by the child's physical or occupational therapist and during the screening process.

Diffusion tensor tractography: DT images will be imported into DTI Studio software (V3, Johns Hopkins U., Baltimore, MD) for processing and analyses. Image series for each participant will be screened for movement artifact, and slices showing artifact will be removed. Since we will obtain images using 65 gradients and will perform duplicate scans, up to 30% of slices can be removed without compromising feasibility of tract reconstruction. After screening for movement artifact, color maps of fractional anisotropy will be constructed, showing the integrity of different neural pathways. To visualize fiber streams, seeds will be placed in the internal capsule and cerebral peduncle.

Statistical Analysis Plans

The accuracy of all data will be verified by two researchers. For both aims a statistician blinded to treatment group will use a group x test session ANOVA with repeated measures on test session and Tukey posthoc tests corrected for multiple comparisons to examine differences among groups on each primary and secondary measure of hand function. The interaction will determine differential group effects, whereas a lack of an interaction will indicate statistically similar outcomes irrespective of treatment group. If data are missing we will use a mixed linear model analysis. We will also add in (stepwise) covariates including gender, age, side of impairment, lesion type, lesion size, CST connectivity, CST fractional anisotropy and number of

streamlines (determined by DTI), and baseline hand function. If the data are not normally distributed we will use nonparametric statistics.

Procedure for Handling Missing Data: Intention-to-treat analysis will be used. To account for children who miss assessments, we will analyze data using a mixed linear model regression, which accounts for unequal time points among individuals. Mixed linear models on test sessions will be performed for all clinical outcomes with time as a fixed factorial factor to see improvements over time. Mixed linear models allow the estimation of interindividual variability and intraindividual patterns of change over time, while accounting for missing data.

Data Management

All data will be stored for 3 years after study completion. Data analysis will be conducted in collaboration with a statistician. Data will be stored on an online, HIPAA-compliant database (REDCap). All study-related electronic files will be accessible only by key personnel, and all computers will be password protected. All subjects will be given a unique identifier at the time of enrollment that will be used for all study-related documentation. Paper case report forms and study files will be kept in the study coordinator's locked cabinet in a secure office.

Resource sharing plan

We have made a commitment to publish, in a timely manner, all the relevant scientific information that they will derive during this project. Unpublished information could be made available to interested parties via a request to the Principal Investigator. Anonymized data will

be made available via the Data and Specimen Hub (DASH) at the Eunice Kennedy Shriver National Institute of Child Health and Development.

Ethics and dissemination

The study has been approved by the BRANY Institutional Review Board (# 18-10-285-512) and is registered with Clinicaltrials.gov (NCT03402854). The study will be conducted according to the principles of the Declaration of Helsinki. The results of this RCT will be published in open access, peer-reviewed scientific journals and presented at national and international meetings. We will leverage our patient and family relationships to maximize dissemination. The study results will be shared with the academic and stakeholder community, including dissemination of training tools through patient associations and patient/family advocacy groups. Participants will receive a plain language report at the end of the study.

Acknowledgments

We thank the children and families who participated in the pilot study and the volunteers who worked with the participants. We thank Bernadette Gillick for assistance with tDCS application in children with USCP and Talita Campos, Grace-Anne Herard, Lindsey Soles, Orit Herzberg-Keller, Ellen Osei, Genni Hester, and Amanda Sarafian for clinical evaluations.

Contributors: AMG and KMF are the study Principal Investigators. CLF and MTR assisted with collection and analysis of pilot data. KC was responsible for ethics applications and reporting and summarizing preliminary data. MB analyzed pilot AHA videos and supervised interventions. KMF and AMG will take the lead roles on preparation for publication of the clinical outcomes. AMG and KMF drafted the final version of this manuscript. All authors have contributed to the writing and critical review of the manuscript and have approved the final version.

Funding: This work is supported by the National Institutes of Health (2R01 HD076436-06) to KMF and AMG. MTR was supported by a Postdoctoral training award from Fonds de Recherche en Santé du Québec. CLF was supported by NIH/NCATS Grant #TL1-TR-002386.

Competing interests: None declared.

Patient and public involvement: Patients were involved in the design, conduct, reporting, and dissemination plans of this research.

Patient consent for publication: Not required.

Figure Legends

Fig. 1. Corticospinal tract (CST) connectivity patterns and tDCS montages.. Top row – CST connectivity is maintained from lesioned hemisphere to affected hand. Targeted tDCS – anode placed over motor map of affected UE in affected hemisphere. Untargeted tDCS – cathode placed over less-affected hemisphere. Bottom row – CST connectivity is lost from lesioned hemisphere, and shifted to the ipsilateral hemisphere Targeted tDCS – anode placed over motor map of affected UE in less-affected hemisphere. Untargeted tDCS – cathode placed over less-affected hemisphere. For all tDCS montage, the second electrode will be placed on the forehead contralateral to the first electrode.

Fig. 2. Experimental design.

Fig. 3 Assessments.

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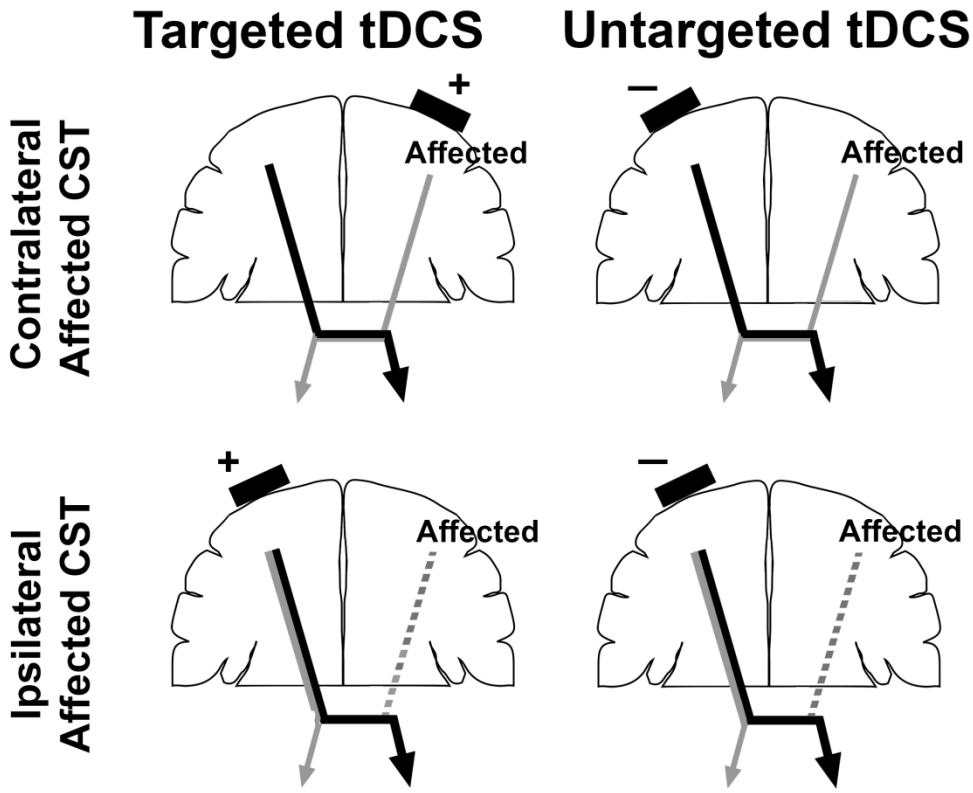

Fig. 1. Corticospinal tract (CST) connectivity patterns and tDCS montages.. Top row – CST connectivity is maintained from lesioned hemisphere to affected hand. Targeted tDCS – anode placed over motor map of affected UE in affected hemisphere. Untargeted tDCS – cathode placed over less-affected hemisphere. Bottom row – CST connectivity is lost from lesioned hemisphere, and shifted to the ipsilateral hemisphere Targeted tDCS – anode placed over motor map of affected UE in less-affected hemisphere. Untargeted tDCS – cathode placed over less-affected hemisphere. For all tDCS montage, the second electrode will be placed on the forehead contralateral to the first electrode.

860x714mm (72 x 72 DPI)

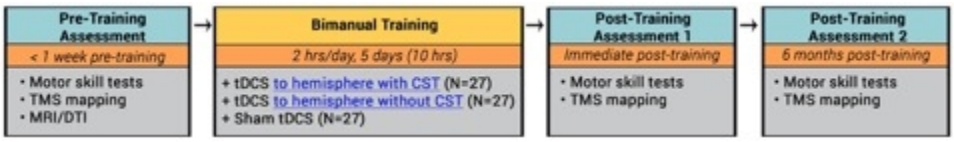

Fig. 2. Experimental design.

168x24mm (72 x 72 DPI)

Assessment	Measurement	Outcome Measure	Test Duration	Equipment
Primary Measures:				
Transcranial Magnetic Stimulation	CST laterality	Which hemisphere evokes movement of the affected hand when TMS is applied	90 minutes	TMS device, Neuroconn system, EMG electrodes
Box and Blocks Test	Unimanual movement speed	# of 2.5cm³ blocks moved from one box, over a barrier, into adjacent box in 1 min	30 minutes	BBT test kit – box, blocks, blindfold, nitrile gloves
Assisting Hand Assessment	Bimanual UE use	Effectiveness with which child uses affected UE in bimanual activities (AHA Units)	20 minutes	AHA test kit – board game, toys
Secondary Measures:				
Structural MRI, Diffusion Tensor Imaging	CST laterality	Which hemisphere shows visualization of the affected CST	1 hour	MRI scanner, DTI Studio software
Cooper Stereognosis	Ability to identify objects using only touch	# of objects identified correctly (out of 16), time taken to identify each object	20 minutes	16 standardized objects & shapes for child to identify
ABILHAND-Kids	UE impairments in children	Parent/caregiver report of child's ability to perform 21 specific motor tasks	5 minutes	Questionnaire form (parent/caregiver)
Canadian Occupational Performance Measure	Assess outcome relating to goals for self-care	Parent/caregiver report of child's performance of up to 5 parent- or child-selected self-care goals, as well as satisfaction	5 minutes	Questionnaire form (parent/caregiver)
Participation and Environment Measure-Children and Youth	Assess participation in the home, school and community settings	Parent/caregiver report of child's participation in 3 settings, alongside environmental factors (20 questions)	5 minutes	Questionnaire form (parent/caregiver)
Dimensions of Mastery Questionnaire	Assess child's mastery-related behaviors	Parent/caregiver report of child's levels of mastery motivation (41 questions)	5 minutes	Questionnaire form (parent/caregiver)

Fig. 3 Assessments

Post Brain Stim Symptoms Checklist

Study ID _____

Date of Brain Stimulation: _____

Which Type of Brain Stim?
☐ TMS
☐ tDCS

Post TMS1 Blood pressure: _____

Post TMS1 Heart rate: _____

Post TMS1: Is the participant currently experiencing...?

	None	Mild	Moderate	Severe
Headache	○	○	○	○
Neck pain	○	○	○	○
Scalp pain	○	○	○	○
Itchy scalp	○	○	○	○
Tingling on scalp	○	○	○	○
Hearing difficulties	○	○	○	○
Skin irritation	○	○	○	○
Body ache	○	○	○	○
Unusual mood	○	○	○	○

Post tDCS

Post tDCS blood pressure: _____

Post tDCS heart rate: _____

Post tDCS: Is the participant currently experiencing...?

	None	Mild	Moderate	Severe
Headache	○	○	○	○
Neck pain	○	○	○	○
Scalp pain	○	○	○	○
Itchy scalp	○	○	○	○
Tingling on scalp	○	○	○	○

Hearing difficulties	○	○	○	○
Skin irritation	○	○	○	○
Body ache	○	○	○	○
Unusual mood	○	○	○	○

Post TMS2: Is the participant currently experiencing...?

	None	Mild	Moderate	Severe
Headache	○	○	○	○
Neck pain	○	○	○	○
Scalp pain	○	○	○	○
Itchy scalp	○	○	○	○
Tingling on scalp	○	○	○	○
Hearing difficulties	○	○	○	○
Skin irritation	○	○	○	○
Body ache	○	○	○	○
Unusual mood	○	○	○	○

Notes

Notes about any present symptoms

_____

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description
Administrative information		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry
	2b	All items from the World Health Organization Trial Registration Data Set
Protocol version	3	Date and version identifier
Funding	4	Sources and types of financial, material, and other support
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors
	5b	Name and contact information for the trial sponsor
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)
Introduction		
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention
	6b	Explanation for choice of comparators
Objectives	7	Specific objectives or hypotheses
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)

Methods: Participants, interventions, and outcomes

Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size

Methods: Assignment of interventions (for controlled trials)

Allocation:

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions

Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial
Methods: Data collection, management, and analysis		
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)
Methods: Monitoring		
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed

	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor

Ethics and dissemination

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions
	31b	Authorship eligibility guidelines and any intended use of professional writers
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code

Appendices

Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

HABIT + tDCS: Study protocol of a randomized controlled trial (RCT) investigating the synergistic efficacy of Hand-arm bimanual intensive therapy (HABIT) plus targeted non-invasive brain stimulation to improve upper extremity function in school-age children with unilateral cerebral palsy

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-052409.R2
Article Type:	Protocol
Date Submitted by the Author:	21-Jan-2022
Complete List of Authors:	Gordon, Andrew; Columbia University Ferre, Claudio; Burke Neurological Institute; Boston University, Dept. of Occupational Therapy Robert, Maxime; Laval University Chin, Karen; Columbia University, Teachers College; Burke Neurological Institute Brandao, Marina; Universidade Federal de Minas Gerais Friel, Kathleen M.; Burke Neurological Institute
Primary Subject Heading:	Rehabilitation medicine
Secondary Subject Heading:	Neurology
Keywords:	NEUROLOGY, NEUROPHYSIOLOGY, Paediatric neurology < NEUROLOGY

HABIT + tDCS: Study protocol of a randomized controlled trial (RCT) investigating the synergistic efficacy of Hand-arm bimanual intensive therapy (HABIT) plus targeted non-invasive brain stimulation to improve upper extremity function in school-age children with unilateral cerebral palsy

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Word count: 4,120

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Keywords: hemiplegia, hand, motor cortex, corticospinal tract, bimanual training, physical rehabilitation, non-invasive brain stimulation, transcranial direct current stimulation, transcranial magnetic stimulation (TMS), pediatric stroke

Abstract

Introduction: Unilateral spastic cerebral palsy (USCP) is characterized by movement deficits primarily on one body side. The best available upper extremity (UE) therapies are costly and intensive. Thus, there is an urgent need for better, more efficient, and thus more accessible therapies. Transcranial direct current stimulation (tDCS) is non-invasive and may enhance physical rehabilitation approaches. The aim of this study is to determine whether tDCS targeted to the hemisphere with corticospinal tract (CST) connectivity enhances the efficacy of UE training in children with USCP. Our central hypothesis is that Hand-arm bimanual intensive therapy (HABIT) combined with a tDCS montage targeting the hemisphere with CST connectivity to the impaired UE muscles will improve UE function more than HABIT plus sham stimulation. We will test this by conducting a randomized clinical trial with clinical and motor cortex physiology outcomes.

Methods and analyses: 81 children, age 6-17 years, will be randomized to receive 2mA anodal tDCS targeted to the affected UE motor map, 2mA cathodal tDCS to the contralesional motor cortex, or sham tDCS during the first 20 minutes of each HABIT session (10 hrs; 2 hrs per day for 5 days). Primary outcomes will be Box and Blocks Test, Assisting Hand Assessment, and motor cortex excitability, determined with single-pulse transcranial magnetic stimulation. Secondary outcomes include ABILHAND-Kids, Canadian Occupational Performance Measure, Cooper Stereognosis, Dimension of Mastery Questionnaire and Participation and Environment Measure - Children and Youth. All measures will be collected before, immediately and 6 months after treatment. A group x test session mixed ANOVA will test differences among groups on all measures.

Ethics and dissemination: The study has been approved by the BRANY Institutional Review Board (#18-10-285-512). We will leverage our patient and family relationships to maximize dissemination and share results with the academic and patient/family advocacy groups.

Trial registration number NCT03402854

Strengths and limitations of this study

- This study will determine whether targeting tDCS based on corticospinal tract (CST) connectivity has a synergistic effect with bimanual training in children with USCP.
- The approach will identify which targeted tDCS strategies lead to strongest expansion of motor maps.
- The study will dissect the interactions between CST laterality, non-invasive brain stimulation, and motor training in children with USCP and examine them using an integrated approach.
- We do not expect to obtain equal sample sizes for each CST connectivity pattern, and may not be able to fully determine interactions if a group is underpowered.
- It is possible that anodal and cathodal tDCS polarity affect cortical excitability differently in children with USCP than their typical effects in adults.

Introduction

Background

Unilateral spastic cerebral palsy (USCP) is characterized by movement deficits, particularly upper extremity (UE) impairments, on one side of the body. Although significant strides to develop rehabilitation approaches to improve UE function in children with USCP have occurred,[1] the best available UE therapies result in limited improvements in UE function, are costly, and require large amounts of treatment time (i.e., 4-6 hours per day for 2-3 weeks). Few families, particularly families of lower socio-economic status, have the ability to engage their children in these intensive therapies[2 3] and the time required to achieve the high intensity is a limiting factor for more widespread implementation.[4] There is an urgent need for therapies that can deliver enhanced improvements, but are more cost-efficient and accessible.

Transcranial direct current stimulation (tDCS) is a non-invasive, low-risk method of delivering low levels of energy to the brain via saline-soaked sponge electrodes placed over the scalp. tDCS is portable, affordable, and well-tolerated in pediatric populations, making it an ideal strategy to combine with UE training.[5] Typically, neurons stimulated by the anodal electrode are depolarized whereas neurons stimulated by the cathodal electrode are hyperpolarized.[6] Repeated sessions of motor training of desired motor behaviors with concurrent anodal tDCS targeted to motor cortex of healthy adults facilitates learning through enhancement or consolidation.[7]

A consensus group in neurology[8] hypothesized that tDCS may increase the rate of motor learning in healthy adults. Enhanced motor learning was seen in typically developing children following contralateral anodal tDCS stimulation.[9 10] A recent meta-analysis in adults with stroke suggested that tDCS was beneficial in improving activities of daily living, with contralesional cathodal stimulation likely targeting impaired interhemispheric inhibition (IHI) being most effective. [11] Others have questioned whether IHI is the main driver of impaired UE function.[12]

Although promising, the results of tDCS studies in limited samples of children with USCP have yielded equivocal differences between stimulation and sham groups,[13-17] possibly due to underdosing the tDCS and over-dosing the paired motor skill training, with the latter washing out the additional effects of tDCS. Furthermore, tDCS studies have not specifically targeted the motor map of the affected UE. Thus, the montage may result in different outcomes depending on whether the lesioned hemisphere maintains contralateral corticospinal tract (CST) connectivity to the affected hand's muscles or the connectivity pattern has been reorganized, with the contralesional hemisphere controlling both hands (Fig. 1).

Objectives

The overall objective of this project is to determine how to optimally target tDCS to enhance the efficacy of UE training in children with USCP. Our central hypothesis is that combined Hand-arm bimanual intensive therapy (HABIT) and an individualized tDCS montage targeting the hemisphere with CST connectivity to the impaired UE muscles will improve UE function more than HABIT plus sham stimulation. We will also determine interactions between HABIT+tDCS and motor cortex physiology. We hypothesize that children who receive anodal tDCS targeted to the individual's hemisphere containing CST connections to the affected UE will show the most robust changes in motor cortex physiology after therapy, which will correlate with changes in hand function.

Methods and Analysis

Public/patient involvement statement

Pilot data were collected on 20 children (age 10.8±2.6y, range 7-18y). Parents and participants provided ongoing daily feedback on the feasibility and acceptability of tDCS. Two study

personnel have cerebral palsy and have been instrumental in the design of the study from its conception.

Overall Study Design: We will conduct a single-blinded randomized controlled trial (RCT) with stratification based on CST connectivity, age and gender to determine whether efficacy of HABIT+tDCS depends on the targeting of tDCS to the locus of motor control of the impaired UE. We will compare 3 types of tDCS: 1) anodal tDCS targeted to either the affected UE motor map, 2) cathodal tDCS targeted to the unaffected UE motor map and 3) sham tDCS. In all groups, tDCS will be paired with HABIT (10 hrs; 2 hrs per day for 5 days)(Fig. 2).

Participants

Eighty-one children with unilateral spastic cerebral palsy (USCP), age 6-17 years, will be enrolled (Fig. 2). Participants will be recruited by advertising at our respective institutions, mailings, local clinics/hospitals, our existing database of more than 800 eligible individuals, and social media.

When a child and their family express interest in enrollment, we will send them a health survey via a HIPAA-secure, NIH-supported clinical database (REDCap). The primary exclusion criteria (Table 1) pertain to risks associated with magnetic resonance imaging (MRI), single-pulse transcranial magnetic stimulation (TMS), and tDCS. We will discuss the study, risks, and the child's health history in detail with families to confirm eligibility. Eligible children and caregivers will be invited to our facilities for consent, review of study, and testing and intervention by the study coordinator.

Table 1: Inclusion and Exclusion Criteria

Criterion	Method of Ascertainment	Justification
Inclusion Criteria:		
1. Age 6-17 years	Medical records	Children < 6 yrs of age may have difficulty tolerating procedures and may have small head size
2. Diagnosis of unilateral CP	Physical health screening and examination of neurological reports	Target population of the trial
3. Parent/guardian willing to provide informed consent	Meeting with PI to discuss study, signing consent form in presence of PI	Required
4. Participant willing to provide informed assent	Meeting with PI to discuss study, signing assent form in presence of PI	Required
5. Ability to pick up, hold and release a light object with affected hand	Pre-intervention screening measures and score under the maximum JTTHF ceiling of 1080s.	Intervention may be too challenging for the child
Exclusion Criteria:		
1. Current medical illness unrelated to CP	Medical history, physical examination	May impair child's ability to comply with trial, may affect study results
2. Seizure beyond age 2, use of anti-seizure medication, history of epilepsy, cranial metal implants, structural brain lesion, devices that may be affected by tDCS or TMS (pacemaker, medication pump, cochlear implant, implanted brain stimulator)	Medical records, interview with participant and parent(s), use of a checklist	TMS and tDCS may increase risk of seizure in subjects prone to seizures
3. Cognitive deficits	Pre-intervention screening measures; Kaufman Brief Intelligence Test, score ± 1 SD from normal	Child needs to understand study assent and instructions related to the testing and intervention
4. High motor ability in affected arm	Jebsen-Taylor score of < 50% differences between	Child may not benefit from interventions due to mild hand function or extremely

	the two hands or score <100 secs	limited use of the affected hand
5. Severe spasticity	Pre-intervention screening measures; Modified Ashworth test score > 3 (> moderate)	May confound ability to drive changes in motor control quality
6. Lack of asymmetry in hand function	Pre-intervention screening measures; Jebsen-Taylor score of < 50% differences between the two hands	May suggest bilateral CP
7. Orthopedic surgery in affected arm in last 12 months	Medical records, interview with participant and parent(s)	Recovery may confound study results
8. Botulinum toxin therapy in either upper extremity during last 6 months, or planned during study period	Medical records, interview with participant and parent(s)	Change in tone may confound study results
9. Currently receiving intrathecal baclofen	Medical records, interview with participant and parent(s)	Change in tone may confound study results
10. True positive response on the Transcranial Magnetic Stimulation & TDCS Safety Screen	Interview with participant and parent(s)	Would indicate an increased risk of seizure
11. Current use of medications known to lower the seizure threshold	Medical records, interview with participant and parent(s)	Underlying condition may pose risk of seizure and medication may influence TMS results
12. Previous episode of unprovoked neurocardiogenic syncope	Medical records, interview with participant and parent(s)	Could be exacerbated by TMS
13. Indwelling metal or incompatible medical devices	Medical records, interview with participant and parent(s)	Metallic objects in body may shift during MRI, posing risk of injury
14. Centrally-acting medications including anti-seizure medications	Medical records, interview with participant and parent(s)	Underlying condition may pose risk of seizure and medication may influence TMS results
15. Evidence of scalp disease or skin abnormalities	Medical records, interview with participant and parent(s)	tDCS may exacerbate the skin condition or increase discomfort

Number of participants: The primary clinical outcomes are Box and Blocks Test (BB) for unimanual dexterity and the Assisting Hand Assessment (AHA) for bimanual function. The estimated effect size from previous studies[14 15 18] and pilot data is estimated to be 0.35 (BB change 3 SD=10.2 blocks, AHA change 2, SD=9.3 AHA units, alpha=0.05 (two-tailed), and beta=0.8). We estimate that 22 subjects will be needed per group. We will recruit 20% more children than needed for the primary analyses, to account for children whose affected UE is controlled by both hemispheres and dropouts. Thus, 81 children (27 children/group) will be recruited.

Randomization Procedure: We will use a computer-generated blocked randomization stratified by CST connectivity (determined with TMS), age and gender with concealed allocation for prospective allocation to the 3 groups: targeted tDCS, untargeted tDCS, and sham tDCS. We will follow intention-to-treat principles. Randomization occurs after baseline assessments to allow CST connectivity determination.

Blinding: Children and their families, study personnel, clinical evaluators and AHA scorers will be blinded to treatment (active vs sham tDCS) allocation. One PI will not be blinded as it is critical for one person to monitor the quality and settings of the tDCS devices, to optimize safety and protocol adherence and fidelity. TMS and DTI data analysis will be performed using coded file names.

General Methods

Bimanual training

All participants will receive HABIT for 2 hrs/day on 5 consecutive days (10 hrs). This duration was chosen as changes in most clinical outcomes following bimanual training alone have been shown to require at least 30 hours,[19 20] and thus the dose will be subthreshold such that findings

won't be washed out with the addition of tDCS. Nonetheless, our pilot data suggests that children will improve on goal performance (Canadian Occupational Performance Measure, COPM) even with HABIT alone (sham), thus providing some potential benefits for all participants. Participants will not receive other treatments during the 5 days of treatment but may continue ongoing care during the 6 month of followup. HABIT will be conducted at either Teachers College (TC), Columbia University, New York, NY, USA or Burke Neurological Institute (BNI), White Plains, NY, USA. HABIT relies on principles of motor learning and plasticity[21-28] and largely parallels Constraint Induced Movement Therapy (CIMT).[26 28 29] Each child will be assigned to an interventionist to maintain at least a 1:1 ratio. Children can work individually with their interventionist or with other children. Our study, funded before the COVID pandemic began, proposed to conduct the intervention in groups of 4-6 children to allow for social interaction, peer-modeling and encouragement. Given ongoing COVID precautions, we may need to reduce our group size to 2-3 children (plus each child's interventionist and supervisors), spread children out across rooms and limit and/or maintain social distancing for group activities. Example activities for HABIT+tDCS include playing cards, building with blocks, throwing and catching a ball, arts and crafts, and functional tasks such as buttoning.[21]

Task Selection: We have identified age-appropriate fine and gross motor activities that require use of both hands[21]. Activities are selected by considering the role of the involved limb increasing in complexity from passive assist to active manipulator. Both positive reinforcement and knowledge of results provide motivation and reinforce target movements.[30] Instructions are given to the child before the start of each task reminding children how each hand will be used during the activity,[31] although problem-solving is highly encouraged.

Whole Task Practice involves performing repetitive practice of targeted movements embedded in a play activity. An example is a card game. The motor components of play involve holding cards in one hand, and picking up and placing down cards with the other hand.

Part Task Practice involves isolating a single component of the activity and performing it repeatedly. For example, after playing a card game, the child may be asked to flip cards over simultaneously with each hand, using a supination movement, as quickly as possible. The interventionist records the number of cards the child can turn in 30 seconds and the procedure is repeated several times.

Grading task difficulty: Depending on the child's motor capabilities and designated target movements, playing can be structured to grade the difficulty of a specific movement. Skill progression,[32] where we use part and whole practice to drive performance and scaffold the environment to facilitate success and grade difficulty, has been shown to be the essential ingredient to enhance performance[32 33] and drive motor map expansion.[18] These outcomes are independent of CST laterality.[34,35] In the context of a card game, cards can be placed farther away from the child to encourage elbow extension, or on an elevated surface, to encourage wrist extension.

Training and supervision of intervention providers: Interventionists are students in the Kinesiology or Neuroscience & Education program at Teachers College and local universities. Interventionists are trained with a standardized protocol. Interventionists are supervised by experienced physical and occupational therapists to ensure consistent approaches are used and treatment adherence and fidelity are maintained. Throughout each session, the supervisor (who will train all interventionists and be present at both sites) will oversee each child's activities and progress, and will rotate through each participant-interventionist pair to provide modeling and feedback and ensure treatment fidelity. The supervisor and study PIs will meet daily with interventionists to discuss the progress of each child, problem-solve and serve to identify key goals for the following day. The high ratio of interventionist to child and supervisor to interventionist further enables treatment consistency, adherence and fidelity.

Determination of CST laterality: We will determine CST laterality in two ways. 1) TMS map side (primary measure): We will determine which hemisphere evokes movement of the affected hand when TMS is applied (within a latency of 40ms, to rule out indirect motor pathways). If both hemispheres elicit MEPs (bilateral CST connectivity), the side with the greatest area (# of sites) will be used to denote the dominant side; 2) DTI (secondary measure): We will use DTI to visualize the affected CST in cases where laterality cannot be determined by TMS. There is high concordance between these approaches ($p<0.001$, sensitivity 93%, specificity 85%).[36]

Transcranial Direct Current Stimulation (tDCS)

A 2mA current will be delivered using surface rubber-carbon electrodes (35cm2) embedded in saline soaked sponges (0.9% NaCl) by a battery driven, constant current stimulator (Soterix LTE). 2mA tDCS has been shown to improve dexterity in typically developing children more than 1mA without increased side effects.[37] Participants randomized to receive tDCS will receive stimulation during the first 20 min of HABIT while seated, with the anode either over motor hotspot of the side containing CST connectivity for the first dorsal interosseous (FDI) of the more affected hand as identified using TMS (targeted tDCS) or the cathode over the contralesional hemisphere (untargeted tDCS, Figure 1). For the targeted tDCS group, the anode will be placed over the motor hotspot of the side containing CST connectivity for the first dorsal interosseous (FDI) as identified using TMS, and the cathode will be placed on the supraorbital area contralateral to the anode. The targeted hemisphere will depend on whether the affected CST has a contralateral or ipsilateral organization pattern. For the untargeted tDCS group, the cathode will be placed over the contralesional motor cortex, and the anode will be placed on the supraorbital area contralateral to the cathode. A 20 min duration overlapping physical training was chosen as it has been safely tested in several studies with children with USCP.[5 13 16 37-39] For participants randomized to receive sham tDCS, a comparable preparation will be performed

and will include a 30 sec real current ramping to 2mA at commencement, followed by a 5 sec slow decrease, with no current sustained during the 20mins.[13 37 38] We will record the amount of saline used and electrode contact quality (measured by the device). The tDCS will be performed by one study PI who is not blinded to the type of stimulation. This person will monitor contact quality and ensure fidelity is maintained. Study personnel will also measure blood pressure before and after tDCS, as well as any side effects using a Post Brain Stimulation Symptoms Checklist (see supplementary file).

Measures of Hand Function

Assessments were chosen to capture changes in 1) unimanual dexterity, 2) bimanual performance, and 3) functional use of the affected hand (Figure 3). Tests will be performed and videoed by an evaluator blinded to the child's CST laterality and treatment group before, immediately after, and six months after treatment. The assessments will occur at the location HABIT was provided (BNI or TC) before, immediately and 6 months after treatment by the same assessor at each time point and caregivers will complete questionnaires during the child's evaluation.

Two primary outcome measures will quantify bimanual performance and unimanual capacity under the Activity domain of the International Classification of Functioning, Disability, and Health (ICF).[40] This domain is most relevant the targeted upper extremity function.

1) Assisting Hand Assessment (AHA): The AHA[41 42] measures and describes the effectiveness with which a child with a unilateral disability makes use of his/her affected (assisting) hand in performance of bimanual activities. The AHA is conducted through scoring of observable performance skills exposed during meaningful occupational performance (play). AHA is a standardized and criterion referenced test for children with unimanual motor impairments; test

validity for all items; 99% confidence interval[41] and excellent reliability (0.97 interrater and 0.99 intrarater).[43] It is sensitive to change in USCP.[44] A functionally meaningful score change is 4 logit points.[43]

2) Box & Blocks Test (BB): Children will sit at a table in front of rectangular box divided into two compartments. One compartment contains 150 wooden 2.5cm^3 blocks.[45] Children will be asked to move blocks, one at a time, with one hand, from one compartment to the other. The number of blocks moved in 60 sec is recorded for each hand. (Inter-rater reliability 0.95, reliable, and responsive to change.[46]). A functionally meaningful score change is 1.9 blocks on the more affected hand, 3.0 blocks on the less affected hand.[46]

Secondary measures will be used across the 3 ICF domains:

1) ABILHAND-Kids (ICF activity domain) measures the ability of a child to perform specific motor tasks, regardless of strategy. A caregiver completes the survey about the child's abilities. It has been validated for children with CP, has a strong reliability (R=0.94) and reproducibility (R=0.91).[47]

2) Canadian Occupational Performance Measure (COPM) (ICF activity domain) was designed to identify and measure, by means of interview, changes in functional problems clients consider to be relevant in the areas of self-care, productivity, and leisure performance. The client or caregiver defines the most relevant functional goals, ranks their importance, and rates their child's performance and their own satisfaction level.[48-50] It is valid and reliable for use with parents[50], and provides outcomes relevant to children and their families.[51 52]

3) Cooper Stereognosis[53] (ICF body structure and function domain) measures the ability of a child to identify sixteen small objects and shapes using only tactile input. The child will sit at a table, blindfolded. Objects will be placed individually and the child must feel the object with one hand and

identify it. Each hand will be tested separately and the number of objects correctly identified is recorded. Its inter-rater reliability is 0.85.[53]

4) Dimensions of Mastery Questionnaire (DMQ-18)[54] (ICF activity domain) will be used to assess the level of motivation in mastering challenging tasks. The parent-report questionnaire assesses instrumental (persistence at object-related tasks, social activities with adults and peers, and gross motor tasks) and expressive (behavioral indicators of positive affect and negative reaction to failure) motivation. Subscale scores will be used to determine whether motivation impacts gains in functional motor skills. It has good reliability (0.84) and discriminate and concurrent validity are supported.[55]

5) Participation and Environment Measure - Children and Youth (PEM-CY) (ICF participation domain) evaluates participation in the home, school, and in the community, alongside environmental factors within these settings. The PEM-CY can be used for children 5-17 years old, with or without disabilities. Internal consistency and reliability: moderate to good.[56]

Expected Outcome: We predict that all groups will show improved goal performance, and that there will be a significant interaction between stimulation type and improvement in dexterity and *quality* of bimanual performance, with children receiving stimulation targeted to the motor map of the affected UE showing greater improvements than children receiving other tDCS conditions immediately after treatment and maintained at the 6 month followup.

We will assess changes in motor cortex excitability measures using TMS associated with HABIT+tDCS.

Transcranial Magnetic Stimulation

TMS will be conducted at Burke Neurological Institute for all participants making the process as child friendly as possible.[35]

Resting motor threshold (rMT): Resting MT is a measure of excitability of the motor cortex. The rMT is the minimum stimulator output required to evoke an MEP over 50μV in the FDI muscle in 6 of 10 trials while children have relaxed their arms.[57]

Active motor threshold (aMT): Active MT is a measure of excitability of the motor cortex. The aMT is the minimum stimulator output required to evoke an FDI MEP over 50μV in 6 of 10 trials during low-level squeeze of the tips of the thumb and index finger.[57]

Recruitment curve (RC): RCs quantify changes in MEP over different stimulus intensities. Ten TMS pulses will be delivered at <0.1 Hz at each of the following stimulation levels: 90%, 110%, 120%, 130%, and 150% rMT. RCs will be done at hotspots for each FDI. Stimuli will be delivered in an order unpredictable to subjects. RCs will be performed up to 150% rMT or maximum stimulator output, whichever is lower.

Motor evoked potential (MEP) amplitude: MEP is a measure of the strength of motor response to TMS. EMG will be exported to MATLAB for filtering and processing. The MEP for each muscle at each stimulation site will be defined as the peak-to-peak amplitude of the EMG response. Trials will be excluded if the child was not relaxed before the TMS pulse. MEPs will be averaged for stimuli delivered at the same site.

Bilateral TMS mapping of motor cortex: Muscle activity will be recorded using surface EMG electrodes. A multi-channel recording system (NeuroConn, Germany) will be used to simultaneously record EMG activity bilaterally in the first dorsal interosseous (FDI), wrist flexor and extensor muscles. The TMS device will trigger the recording system such that EMG activity is recorded at 4000 Hz 400ms before and 400ms after each TMS pulse is delivered. The position of each stimulation point over the scalp will be recorded in 3D and overlaid on the child's MRI using neuronavigation software (Brainsight Frameless, Rogue Research, Montreal, Canada).

Stimulation will begin in a medial portion of the affected motor cortex (M1). The coil will be progressed laterally until a motor evoked potential (MEP) for the affected FDI is obtained. If an MEP is found, a rectangular grid of 1cm-spaced sites will be generated in Brainsight, centered around the point of strongest activation of the affected FDI ("hotspot"). This site will be marked for subsequent use of the tDCS. The coil will be moved along the grid M1 until responses are no longer found for any recorded muscles. Both hemispheres will be mapped.

Area of motor map: If the average MEP is greater than 50 μV for a muscle at one site, that site will be categorized as controlling that muscle. The total number of sites will constitute the area of digit and wrist maps for each hand. This measure serves as the primary measure of motor cortical physiology.

Expected Outcome: We predict that changes in motor map size and cortical excitability will be largest when tDCS is targeted to the cortex controlling movement of the affected hand. We further expect to have determined that changes will be larger in response to HABIT+ targeted tDCS compared to HABIT+ untargeted tDCS and HABIT+ sham tDCS.

Magnetic Resonance Imaging

Each child will undergo a structural MR scan and diffusion tensor imaging scan without sedation on a Siemens MRI tDCS Study Protocol at the Citigroup Biomedical Imaging Center, at Weill Cornell Medicine, New York, NY, USA. The structural MRI will be used to co-register TMS stimulation targets with specific brain landmarks for TMS neuronavigation. For TMS localization, there is normal variability in brain topography relative to scalp landmarks. For structural scans, 165-slice images will be taken at a resolution of 256 x 256 px. The structural MRI will also be

used to identify the lesion type and extent. The DTI scan will be performed during the same session using a 65-direction protocol, 75 slices per direction at a resolution of 112 x 112 px each.

Classification of CP etiology: Each child's medical history (in particular the neurological report) will be used to determine their diagnosis, and this will be confirmed by the child's physical or occupational therapist and during the screening process.

Diffusion tensor tractography: DT images will be imported into DTI Studio software (V3, Johns Hopkins U., Baltimore, MD) for processing and analyses. Image series for each participant will be screened for movement artifact, and slices showing artifact will be removed. Since we will obtain images using 65 gradients and will perform duplicate scans, up to 30% of slices can be removed without compromising feasibility of tract reconstruction. After screening for movement artifact, color maps of fractional anisotropy will be constructed, showing the integrity of different neural pathways. To visualize fiber streams, seeds will be placed in the internal capsule and cerebral peduncle.

Statistical Analysis Plans

The accuracy of all data will be verified by two researchers. For both aims a statistician blinded to treatment group will use a group x test session ANOVA with repeated measures on test session and Tukey posthoc tests corrected for multiple comparisons to examine differences among groups on each primary and secondary measure of hand function. The interaction will determine differential group effects, whereas a lack of an interaction will indicate statistically similar outcomes irrespective of treatment group. If data are missing we will use a mixed linear model analysis. We will also add in (stepwise) covariates including gender, age, side of impairment, lesion type, lesion size, CST connectivity, CST fractional anisotropy and number of

streamlines (determined by DTI), and baseline hand function. If the data are not normally distributed we will use nonparametric statistics.

Procedure for Handling Missing Data: Intention-to-treat analysis will be used. To account for children who miss assessments, we will analyze data using a mixed linear model regression, which accounts for unequal time points among individuals. Mixed linear models on test sessions will be performed for all clinical outcomes with time as a fixed factorial factor to see improvements over time. Mixed linear models allow the estimation of interindividual variability and intraindividual patterns of change over time, while accounting for missing data.

Data Management

All data will be stored for 3 years after study completion. Data analysis will be conducted in collaboration with a statistician. Data will be stored on an online, HIPAA-compliant database (REDCap). All study-related electronic files will be accessible only by key personnel, and all computers will be password protected. All subjects will be given a unique identifier at the time of enrollment that will be used for all study-related documentation. Paper case report forms and study files will be kept in the study coordinator's locked cabinet in a secure office.

Resource sharing plan

We have made a commitment to publish, in a timely manner, all the relevant scientific information that they will derive during this project. Unpublished information could be made available to interested parties via a request to the Principal Investigator. Anonymized data will

be made available via the Data and Specimen Hub (DASH) at the Eunice Kennedy Shriver National Institute of Child Health and Development.

Ethics and dissemination

The study has been approved by the BRANY Institutional Review Board (IRB# 18-10-285-512) and is registered with Clinicaltrials.gov (NCT03402854). The study will be conducted according to the principles of the Declaration of Helsinki. Safety will be monitored by an independent Data Safety Monitoring Board (DSMB) which will meet twice per year to monitor progress and safety. Subjects will be discontinued in the case of an adverse event. Important protocol modifications will be reported to the IRB, DSMB and clinicaltrials.gov. The results of this RCT will be published in open access, peer-reviewed scientific journals and presented at national and international meetings. We will leverage our patient and family relationships to maximize dissemination. The study results will be shared with the academic and stakeholder community, including dissemination of training tools through patient associations and patient/family advocacy groups. Participants will receive a plain language report at the end of the study.

Acknowledgments

We thank the children and families who participated in the pilot study and the volunteers who worked with the participants. We thank Bernadette Gillick for assistance with tDCS application in children with USCP and Talita Campos, Grace-Anne Herard, Lindsey Soles, Orit Herzberg-Keller, Ellen Osei, Genni Hester, and Amanda Sarafian for clinical evaluations.

Contributors: AMG and KMF are the study Principal Investigators, conceptualized the study concept and study design, and are responsible for the conduct and reporting of the work. CLF and MTR assisted with collection and analysis of pilot data. KC was responsible for ethics applications and reporting and summarizing preliminary data. MB analyzed pilot AHA videos and supervised interventions. KMF and AMG will take the lead roles on preparation for

publication of the clinical outcomes. AMG and KMF drafted the final version of this manuscript. All authors have contributed to the writing and critical review of the manuscript and have approved the final version.

Funding: This work is supported by the National Institutes of Health (2R01 HD076436-06) to KMF and AMG. MTR was supported by a Postdoctoral training award from Fonds de Recherche en Santé du Québec. CLF was supported by NIH/NCATS Grant #TL1-TR-002386. The funders have no role in the study.

Competing interests: None declared.

Patient and public involvement: Patients were involved in the design, conduct, reporting, and dissemination plans of this research.

Patient consent for publication: Not required.

Figure Legends

Fig. 1. Corticospinal tract (CST) connectivity patterns and tDCS montages.. Top row – CST connectivity is maintained from lesioned hemisphere to affected hand. Targeted tDCS – anode placed over motor map of affected UE in affected hemisphere. Untargeted tDCS – cathode placed over less-affected hemisphere. Bottom row – CST connectivity is lost from lesioned hemisphere, and shifted to the ipsilateral hemisphere Targeted tDCS – anode placed over motor map of affected UE in less-affected hemisphere. Untargeted tDCS – cathode placed over less-affected hemisphere. For all tDCS montage, the second electrode will be placed on the forehead contralateral to the first electrode.

Fig. 2. Experimental design.

Fig. 3 Assessments.

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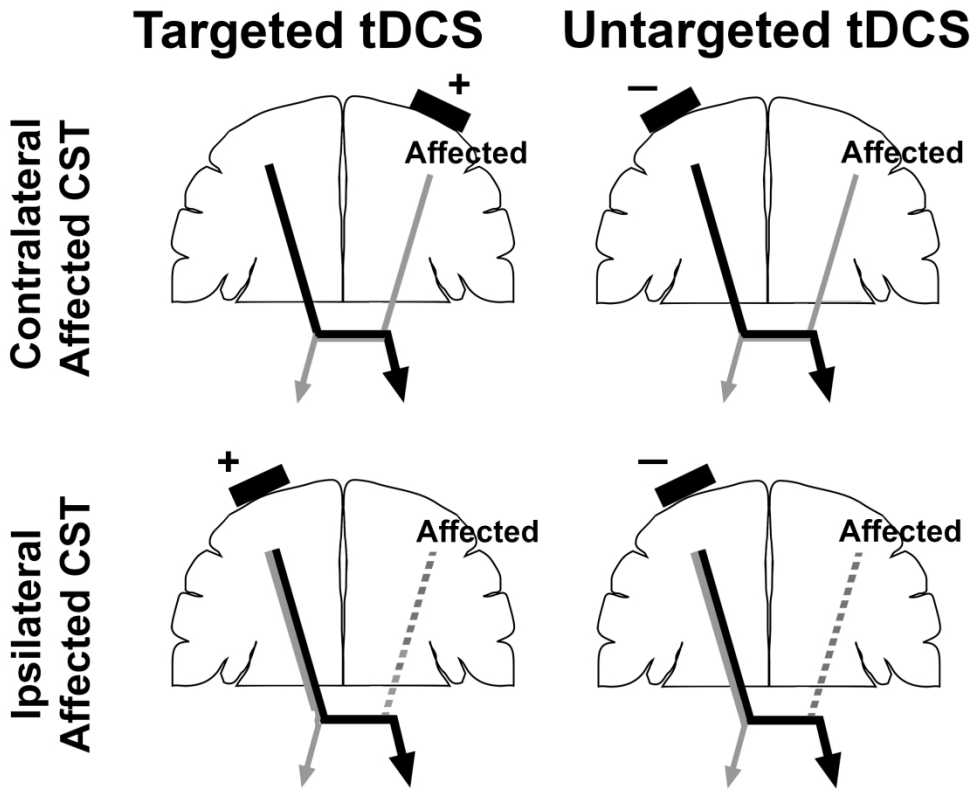

Fig. 1. Corticospinal tract (CST) connectivity patterns and tDCS montages.. Top row – CST connectivity is maintained from lesioned hemisphere to affected hand. Targeted tDCS – anode placed over motor map of affected UE in affected hemisphere. Untargeted tDCS – cathode placed over less-affected hemisphere. Bottom row – CST connectivity is lost from lesioned hemisphere, and shifted to the ipsilateral hemisphere Targeted tDCS – anode placed over motor map of affected UE in less-affected hemisphere. Untargeted tDCS – cathode placed over less-affected hemisphere. For all tDCS montage, the second electrode will be placed on the forehead contralateral to the first electrode.

860x714mm (72 x 72 DPI)

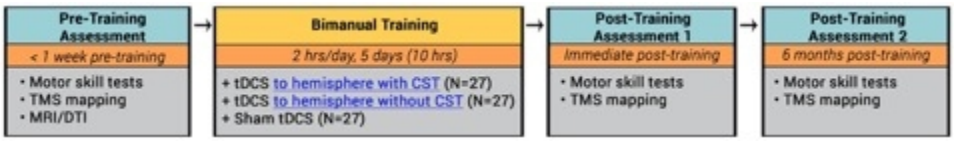

Fig. 2. Experimental design.

168x24mm (72 x 72 DPI)

Assessment	Measurement	Outcome Measure	Test Duration	Equipment
Primary Measures:				
Transcranial Magnetic Stimulation	CST laterality	Which hemisphere evokes movement of the affected hand when TMS is applied	90 minutes	TMS device, Neuroconn system, EMG electrodes
Box and Blocks Test	Unimanual movement speed	# of 2.5cm³ blocks moved from one box, over a barrier, into adjacent box in 1 min	30 minutes	BBT test kit – box, blocks, blindfold, nitrile gloves
Assisting Hand Assessment	Bimanual UE use	Effectiveness with which child uses affected UE in bimanual activities (AHA Units)	20 minutes	AHA test kit – board game, toys
Secondary Measures:				
Structural MRI, Diffusion Tensor Imaging	CST laterality	Which hemisphere shows visualization of the affected CST	1 hour	MRI scanner, DTI Studio software
Cooper Stereognosis	Ability to identify objects using only touch	# of objects identified correctly (out of 16), time taken to identify each object	20 minutes	16 standardized objects & shapes for child to identify
ABILHAND-Kids	UE impairments in children	Parent/caregiver report of child's ability to perform 21 specific motor tasks	5 minutes	Questionnaire form (parent/caregiver)
Canadian Occupational Performance Measure	Assess outcome relating to goals for self-care	Parent/caregiver report of child's performance of up to 5 parent- or child-selected self-care goals, as well as satisfaction	5 minutes	Questionnaire form (parent/caregiver)
Participation and Environment Measure-Children and Youth	Assess participation in the home, school and community settings	Parent/caregiver report of child's participation in 3 settings, alongside environmental factors (20 questions)	5 minutes	Questionnaire form (parent/caregiver)
Dimensions of Mastery Questionnaire	Assess child's mastery-related behaviors	Parent/caregiver report of child's levels of mastery motivation (41 questions)	5 minutes	Questionnaire form (parent/caregiver)

Fig. 3 Assessments

Post Brain Stim Symptoms Checklist

Study ID _____

Date of Brain Stimulation: _____

Which Type of Brain Stim?
☐ TMS
☐ tDCS

Post TMS1 Blood pressure: _____

Post TMS1 Heart rate: _____

Post TMS1: Is the participant currently experiencing...?

	None	Mild	Moderate	Severe
Headache	○	○	○	○
Neck pain	○	○	○	○
Scalp pain	○	○	○	○
Itchy scalp	○	○	○	○
Tingling on scalp	○	○	○	○
Hearing difficulties	○	○	○	○
Skin irritation	○	○	○	○
Body ache	○	○	○	○
Unusual mood	○	○	○	○

Post tDCS

Post tDCS blood pressure: _____

Post tDCS heart rate: _____

Post tDCS: Is the participant currently experiencing...?

	None	Mild	Moderate	Severe
Headache	○	○	○	○
Neck pain	○	○	○	○
Scalp pain	○	○	○	○
Itchy scalp	○	○	○	○
Tingling on scalp	○	○	○	○

Hearing difficulties	○	○	○	○
Skin irritation	○	○	○	○
Body ache	○	○	○	○
Unusual mood	○	○	○	○

Post TMS2: Is the participant currently experiencing...?

	None	Mild	Moderate	Severe
Headache	○	○	○	○
Neck pain	○	○	○	○
Scalp pain	○	○	○	○
Itchy scalp	○	○	○	○
Tingling on scalp	○	○	○	○
Hearing difficulties	○	○	○	○
Skin irritation	○	○	○	○
Body ache	○	○	○	○
Unusual mood	○	○	○	○

Notes

Notes about any present symptoms

_____

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description
Administrative information		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym. TITLE PAGE
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry. P18, L11
	2b	All items from the World Health Organization Trial Registration Data Set. THROUGHOUT
Protocol version	3	Date and version identifier. N/A
Funding	4	Sources and types of financial, material, and other support. P19, L13
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors. TITLE PAGE, P19, L5
	5b	Name and contact information for the trial sponsor. P19, L13
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities. P19, L13
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee). P19, L5
Introduction		
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention. P3, L11-24
	6b	Explanation for choice of comparators. P3, L15
Objectives	7	Specific objectives or hypotheses. P3, L20 – P4, L5

Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory). P4, L12-17

Methods: Participants, interventions, and outcomes

Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained. P8, L14
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists). TABLE 1, P10, L1-11
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered. P8, L7 – P11, L18
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease). P18-L12
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests). P10, L5-11
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial. P8, L14
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended. P11. L19- P13, L21
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure). P11, L24
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations. P7, L14
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size. P4, L19

Methods: Assignment of interventions (for controlled trials)

Allocation:

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions. P7, L22
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned. P7, L22
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions. P7, L22
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how. P8, L1
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial. N/A
Methods: Data collection, management, and analysis		
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol. P17, L1-24
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols. P7, L14
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol. P17, L1-24
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol. P17, L1
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses). N/A
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation). P17, L12

Methods: Monitoring

Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed. P18, L12
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial. P18, L12
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct. P11, L17
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor. P18. L12.

Ethics and dissemination

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval. P18, L10
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators). P18, L17
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32). P5, L7
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable. N/A
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial. P17, L18
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site. P19, L16
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators. P17, L18
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation. N/A

Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions. P18, L4-20
	31b	Authorship eligibility guidelines and any intended use of professional writers. P19, L24
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code. P18, L3
Appendices		
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates. SUBMITTED
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable. N/A

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.