Synergistic Effect of Combined tDCS/CIMT in Children with Hemiparesis

Regulatory Sponsor:

Bernadette Gillick
Medical School- PM&R
420 Delaware Street SE, MMC 388
Minneapolis, MN 55455
612.626.3121
612.625.4274
gillick@umn.edu

Funding Sponsor:

CTSI K01 Grant
University of Minnesota
Clinical and Translational Science Institute
717 Delaware St SE, Minneapolis, MN 55414
612.625.2874

Cerebral Palsy International Research Foundation (CPIRF)
186 Princeton Hightstown Road; Building 4, 2nd Floor
Princeton Junction, NJ 08550
609-452-1200

Foundation for Physical Therapy
Magistro Family Foundation Research Grant
1111 North Fairfax Street
Alexandria, Virginia 22314-1488

Study Product:

Transcranial Direct Current Stimulation
Transcranial Magnetic Stimulation
Stereotactic Neuronavigation

Version History

Version #	Approval Date	Significant Changes from Previous Version
Version 1	9/11/14	Original Protocol Version
Version 2	1/6/15	Addition of Typically Developing Subjects
Version 3	3/13/15	Addition of Pregnancy Test/MRI at Follow-up
Version 4	10/22/15	Addition of ECG and Cuff Vitals Monitoring
Version 5	3/6/2017	Addition of bimanual therapy and alteration in tDCS dosage
Version 6	4/13/17	Consent form for Eligibility Screening and Dosage
Version 7	5/9/17	Change in MRI pre-testing

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Study Summary

Title	Synergistic Effect of Combined tDCS/CIMT in Pediatric Hemiparesis due to Stroke
Short Title	tDCS/CIMT in Pediatric Stroke
Principal Investigator	Bernadette Gillick, PhD, MSPT, PT
Study Design	Exploratory pre-test post-test follow up
Study Duration	September 2013-December 2017
Study Center(s)	University of Minnesota, Medical School, 420 Delaware Street SE, Minneapolis, MN 55455; Gillette Children's Specialty Healthcare, 200 University Avenue E. St. Paul, MN 55101
Objectives	Evaluate the safety and determine the efficacy of combined tDCS/rehabilitation in children with hemiparesis. Examine the influence of combined tDCS/CIMT on brain excitability and reorganization.
Number of Subjects	30
Main Inclusion / Exclusion Criteria	*Primary inclusion criteria:* Children ages 8-21 years with congenital hemiparesis due to hemispheric stroke or Periventricular leukomalacia; no evidence of seizure activity within the last 2 years. For Bimanual therapy: Children must display a motor evoked potential on the lesioned hemisphere. *Primary exclusion criteria:* Other neurologic disorder unrelated to stroke (disorders of cellular migration and proliferation, acquired traumatic brain injury), Metabolic disorders, neoplasm, epilepsy, expressive aphasia, pregnancy, indwelling metal or incompatible medical devices, skin disease or skin abnormalities and botulinum toxin or phenol intramuscular block within the preceding five months from scheduled tDCS application. For Bimanual therapy: Children who do not display a motor evoked potential on the lesioned hemisphere.
Study Device	Transcranial Direct Current Stimulation (tDCS)
Duration of Device Exposure	Ten 20-minute tDCS sessions over ten days during concurrent rehabilitation sessions.
Reference Therapy	Control transcranial Direct Current Stimulation with built-in placebo feature. For bimanual therapy: Period of time without intervention.
Endpoints	Safety and Efficacy

Statistical Methods	Descriptive analyses of baseline characteristics and outcomes will include means and standard deviations for continuous variables with frequencies and percentages for categorical variables. *Analysis Populations:* There are 3 analysis populations planned. Intent-to-treat (ITT), Per-protocol (PP), and the Safety population. We do not anticipate these groups to differ. *Aim #1:* Safety analyses will use the safety population and be primarily descriptive, reporting the number and percentage of adverse events.
	Aim #2: The primary analysis will use the Intent to Treat population to compare logit-based AHA units between the intervention and control groups adjusting for baseline values of AHA and presence of MEP for precision. Supportive analyses using the PP population will also be conducted. Secondary endpoints of Canadian Occupational Performance Measure (COPM), TOKEN test, Stereognosis and Finger force measurements will be analyzed in a similar fashion. The association of improved logit-based AHA units with DTI derived fractional anisotropy (FA) and MEP will be evaluated across all patients using generalized linear regression. Secondary analyses will evaluate these associations also adjusting for age and sex due to potential confounding influence though may be limited by sample size. *Aim #3:* Associations between changes in cortical excitability and the primary and secondary outcomes will be evaluated across all patients using generalized linear regression as in Aim #2. *Power and Sample Size:* The sample size and power was primarily driven by the primary analysis of Hypothesis #1 of Aim #2. Power calculations for the primary outcome of logit-based AHA units were based on 10 patients in each. Based on previous studies, we will have 81% power to detect a difference of 5 logit-based AHA units at a significance level of 0.05. This study is intended to determine feasibility and explore preliminary efficacy results to inform the design of a future, larger RCT should promising results be found.

List of Abbreviations

AE	Adverse Event
AHA	Assisting Hand Assessment
CDC	Centers for Disease Control
CFR	Code of Federal Regulations
CIMT	Constraint-Induced Movement Therapy
CMRR	Center for Magnetic Resonance Research
COPM	Canadian Occupational Performance Measure
CRF	Case Report Form
CTSI	Clinical and Translational Science Institute
CWH	Children with Hemiparesis
DSMB	Data and Safety Monitoring Board
DSMP	Data and Safety Monitoring Plan
DTI	Diffusion Tensor Imaging
EEG	Electroencephalogram
EMG	Electromyograph
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GMFCS	Gross Motor Function Classification Scale Score
HIPAA	Health Insurance Portability and Accountability Act of 1996
IDE	Investigational Device Exemption
IRB	Institutional Review Board
ITT	Intent-to-treat
MACS	Manual Ability Classification System
MEP	Motor Evoked Potential
MPRAGE	Magnetization Prepared Rapid Acquisition Gradient Echo
MPSOM	Modified Pediatric Stroke Outcome Measure
MRI	Magnetic Resonance Imaging
NIBS	Non-invasive Brain Stimulation
PHI	Protected Health Information
PP	Per-Protocol
RCT	Randomized Controlled Trial
REPA	Report of External Professional Activities
rTMS	Repetitive Transcranial Magnetic Stimulation
SAE	Serious Adverse Event
SNN	Stereotactic Neuronavigation
tDCS	Transcranial Direct Current Stimulation
TMS	Transcranial Magnetic Stimulation
UADE	Unanticipated Adverse Device Effect
UPIRTSO	Unanticipated Problems Involving Risk To Subjects or Others

1 Introduction

This document is a protocol for a human research study. This study will be conducted according to US and International standards of Good Clinical Practice, applicable government regulations and Institutional research policies and procedures.

All individuals responsible for the design and conduct of this study have completed Human Subjects Protection Training and are qualified to be conducting this research prior to the enrollment of any subjects.

2 Background and Rationale

Cerebral palsy affects an estimated 800,000 people in the United States. The lifetime cost of caring for a person with cerebral palsy is approximately $1 million dollars.(CDC, 2013) The neurologic deficits associated with this condition can take a variety of different forms though one of the most common manifestations affects movement on one side of the body (hemiparesis). Hemiparetic cerebral palsy influences motor function in children during development and throughout their lifetime. The deficits one sees are the result both of the congenitally induced brain lesion and the subsequent plasticity that can impair function of the surviving neurons in the damaged brain.

Unfortunately, many current treatments have limited influence on children's neurorecovery. Constraint-induced movement therapy (CIMT) involving constraining the unaffected limb to encourage use of the affected limb has shown promise, yet with new technology revealing the potential to directly influence the brain, there is an urgent need to study the synergy of combined techniques. Another rehabilitation technique is bimanual therapy. Bimanual therapy is a treatment in which the child works on using two hands for everyday tasks.

Non-invasive brain stimulation (NIBS) as a direct neuromodulatory intervention has the potential to act synergistically with CIMT or bimanual therapy to influence neurorecovery.

tDCS is a novel form of painless, noninvasive brain stimulation. In contrast to other forms of NIBS, tDCS has produced no reported seizures, is less than 1/10th the cost, and is more portable, allowing simultaneous use with rehabilitation interventions. Although motor improvements have been found using tDCS in adult hemiparesis, the potential benefits of this technique in children have not been tested.

Combining behavioral therapies, constraint-induced movement therapy (CIMT) or bimanual therapy with a novel form of neuromodulation, transcranial direct current stimulation (tDCS), we will investigate the influence of this intervention on improved motor outcomes in children with cerebral palsy.

Children with hemiparesis often exhibit reorganization of the area of the brain responsible

for movement (specifically the corticospinal tract of the primary motor cortex). Children with hemiparesis may exhibit contralateral reorganization (meaning the lesioned hemisphere influences movement of the contralateral more-affected hand) or ipsilateral reorganization (meaning the non-lesioned hemisphere maintains control of the contralateral more-affected hand). One method to determine reorganization patterns is our existing neuroimaging and Transcranial Magnetic Stimulation (TMS) testing protocols.

Research Question and Hypothesis

The central hypothesis is that combined tDCS/CIMT or combined tDCS/Bimanual Therapy will be safe and result in greater improvement in hand function than CIMT alone in congenital hemiparesis. Secondary analysis will explore for predictive biomarkers based on baseline measures of clinical characteristics and excitability measures, as well as diffusion tensor imaging (DTI). TMS testing for excitability measures will also determine neuroplastic response to the intervention. CIMT Design: Two-group randomized controlled preliminary trial, 20 children ages 8-21 with hemiparesis, one group receiving active tDCS with CIMT (intervention) and one receiving sham tDCS with CIMT (control), for 10 daily sessions. Bimanual Therapy Design: One-group open-label repeated measures preliminary study, 10 children ages 8-21 with hemiparesis with all children receiving the active tDCS with bimanual therapy (intervention) for 10 daily sessions.

Aim 1. Establish the safety profile of combined tDCS/CIMT in congenital hemiparesis.

Our previous pilot revealed safety with no adverse events surrounding a one-time application of tDCS. We will now explore the safety of 10 serial sessions of tDCS combined with CIMT.

Hypothesis 1: No seizure activity or other serious adverse event will occur in either group.

Hypothesis 2: No decline in paretic or nonparetic hand function will occur in either group.

Preliminary results from the 20 children who have participated in our tDCS/CIMT study totaling 260 neuromodulatory sessions has resulted in no serious adverse events. We will now explore the safety of 10 serial sessions of tDCS combined with Bimanual therapy.

Hypothesis 1: No seizure activity or other serious adverse event will occur.

Hypothesis 2: No decline in paretic or non-paretic hand function will occur.

Aim 2. Determine the behavioral efficacy of combined tDCS/CIMT in congenital hemiparesis. We will assess hemiparetic upper extremity behavioral motor function changes and responsiveness to interventions.

Hypothesis 1: The intervention group will show greater improvement in paretic hand function than controls.

Hypothesis 2: The degree of difference in the integrity of the ipsilesional and contralesional corticospinal tracts as characterized by Diffusion Tensor Imaging, and the presence of ipsilesional motor evoked potentials (MEP), will be associated with improved hand function.

For Bimanual Therapy: **Determine the behavioral efficacy of combined tDCS/Bimanual Therapy in congenital hemiparesis.** We will assess hemiparetic upper extremity behavioral motor function changes and responsiveness to interventions.

Hypothesis 1: The intervention group will result in greater improvement in paretic hand function than the non-intervention period.
Hypothesis 2: The degree of difference in the integrity of the ipsilesional and contralesional corticospinal tracts as characterized by Diffusion Tensor Imaging, and the presence of ipsilesional motor evoked potentials (MEP), will be associated with improved hand function.

Aim 3. Determine the influence of combined tDCS/CIMT on cortical excitability in congenital hemiparesis. Cortical excitability will be tested using single-pulse Transcranial Magnetic Stimulation (TMS).

Hypothesis 1: Changes in cortical excitability will be associated with improved behavioral outcomes.
Hypothesis 2: The intervention group will show greater changes, compared to controls, in contralesional primary motor cortex (M1) cortical excitability (i.e. ↑ motor threshold and ↓ motor evoked potential area)
Hypothesis 3: When an ipsilesional MEP is present, the intervention group will show greater ipsilesional M1 cortical excitability changes (↓ motor threshold and ↑ motor evoked potential area) compared to controls.

For Bimanual Therapy: **Determine the influence of combined tDCS/Bimanual Therapy on cortical excitability in congenital hemiparesis.** Cortical excitability will be tested using single-pulse Transcranial Magnetic Stimulation (TMS).

Hypothesis 1: Changes in cortical excitability will be associated with improved behavioral outcomes.
Hypothesis 2: The intervention period will result in changes in the contralesional primary motor cortex (M1) cortical excitability (i.e. ↑ motor threshold and ↓ motor evoked potential area)

Preliminary Data

Combining electrophysiologic and behavioral methods, we have recently found promising results in pediatric hemiparesis using a synergistic intervention of constraint- induced movement therapy (CIMT) and a form of NIBS- repetitive transcranial magnetic stimulation (rTMS).[1] Of paramount importance, the study determined that alternating 5 treatments using 6-Hz primed low-frequency rTMS with 5 treatments of CIMT applied to the non-stroke hemisphere was safe; without serious adverse events. The most common minor adverse events included headache and cast irritation. As to efficacy, our primary outcome variable, the Assisting Hand Assessment (AHA), revealed a significant difference in hand function between the control and treatment groups. ($p=0.007$) Although significance was not achieved for our secondary outcome measures of the Canadian Occupational Performance Measure (COPM), Stereognosis and Finger Extension force there were within-group improvements.

These recent results demonstrate safety and reveal significant improvements in hand function using rTMS combined with CIMT. However, it is currently very difficult to incorporate the use of rTMS at the same time as performing therapy with the affected upper extremity due to machine size and application challenges. tDCS may be more feasible. Applying tDCS/CIMT concurrently could optimize neuroplastic principles of

concurrent firing of neurons and strengthening of neuronal networks. Also, TMS/rTMS can be ten times the current cost of tDCS and thus cost may be prohibitive when using TMS/rTMS. Furthermore, if the application of tDCS reduces the need for additional therapies or concurrent therapies, a cost savings could be realized. Last, albeit rare, use of rTMS has resulted in reports of adverse events such as seizures and syncopal episodes, both in adults and children.[2] In addition to its cost and portability, tDCS resulted in functional improvements in motor function in adults with and without the concurrent use of CIMT. [3] The important rationale for the investigation of tDCS in this population is that the use of non-invasive brain stimulation could translate into clinical applications, thus improving the quality of life for children with hemiparesis.

After the rTMS study, we completed a tDCS pilot safety study of a one-time application in pediatric hemiparesis.[4] Analysis of 11 subjects, children with congenital hemiparesis, revealed no serious adverse events including seizure. We included a physician evaluation using a modified Pediatric Stroke Outcome measure, and cognitive and behavioral testing with no significant differences from baseline or between groups in level of function. This study established the feasibility and safety of this application.

Bimanual therapy allows for a child to practice tasks with two-hands allowing for motor learning of both hands and mimicking the natural environment. Bimanual therapy is a common therapy approach in the clinical setting. Review of goal setting data suggests that the majority of children with hemiparesis identify and prioritize bimanual tasks as goals (e.g. tying their shoes, putting books in a backpack). Evidence suggests that children with congenital hemiparesis benefit equally from CIMT or two handed, or bimanual, therapy.[5,6]

Device Description

Non-Invasive brain stimulation has been recently investigated for benefits in recovery of motor function in adults[7] and more recently in children[1,8] One form, Transcranial Magnetic Stimulation (TMS), can be used in specific protocols either to test cortical excitability or as an intervention to attempt to influence cortical excitability. In this study we are using TMS only as a test to assess cortical excitability in the area of the brain known as the motor cortex or M1. Recent evidence suggests that 1.0mA and 2.0mA is well-tolerated and results in motor learning both for children with typical development[9] and 1.0 mA in children with hemiparesis.[10] Safety of tDCS is further confirmed in a recent evidence based update with no reports of major adverse events following tDCS.[11] Transcranial Direct Current Stimulation (tDCS) will be used as an intervention, applying stimulation continuously over a period of 20 minutes.

Testing for Cortical Excitability: Transcranial Magnetic Stimulation (TMS): We will use a Magstim Rapid2 TMS stimulator with a flat 70 mm figure-of-eight coil. TMS is a non-invasive method for assessing the excitability of the brain. The TMS stimulator is a non-significant risk device. The technique involves placing a special electrode on the head. The electrode we will use is a flat figure-of-eight coil with a 70-mm diameter for each loop of the figure-of-eight. The center of the coil is hand held on the scalp over the desired region to be stimulated. An electrical current is pulsed through the electrode,

which creates a magnetic field. This magnetic field, in turn, creates an electric field in the surrounding area, including inside the skull, which induces an ionic current to flow on the surface of the brain. Depending on the parameters of the stimulation and the excitability of the underlying cortex, the stimulation may or may not depolarize the nerve membrane to threshold. If it does depolarize, an action potential is generated and conducted to spinal motor neurons, which, depending on their own excitability, may transmit an action potential to muscle. Ultimately, the response is recorded as a motor evoked potential (MEP) with EMG electrodes located over the target muscle.

Intervention: Transcranial Direct Current Stimulation (tDCS): Soterix Medical 1x1 stimulator. This device is intended for the noninvasive stimulation of the cortex via transcranial current stimulation (TCS). The device is capable of direct current stimulation and has a built-in sham condition setting. This sham stimulation feature allows for consistent application of the sham setting with ramp-up, extinguish and ramp-down modulation. As an added measure of safety, we will be using the LTE device which provides built-in adaptation to resistance and current. This device is for investigational research only in the United States. An instructional video from the Harvard Berenson-Allen Center for Noninvasive Brain Stimulation describes the use of Soterix tDCS in detail. http://www.jove.com/video/2744/electrode-positioning-and-montage-in-transcranial-direct-current-stimulation

All investigational devices used in this study will have the following label statement: CAUTION – Investigational Device. Limited by Federal law to investigational use.

Stereotactic Neuronavigation: In order to verify our exact location over the motor cortex we will be using a computerized method of location called Stereotactic Neuronavigation (SNN). (Brainsight Stereotactic Neuronavigation, Rogue Research, Montreal, Canada) Through the use of a locator situated atop the TMS device and a comparative subject-specific MRI image on a computer screen which shows the locator position, we will be able to specify the TMS hotspot location and placement of the tDCS electrodes.

3 Study Objectives

Primary Objective

Determine the safety of contralesional cathodal transcranial Direct Current Stimulation combined with Constraint-Induced Movement Therapy in children with hemiparesis.

For Bimanual Therapy: Determine the safety of contralesional cathodal transcranial Direct Current Stimulation combined with Bimanual Therapy in children with hemiparesis.

Secondary Objectives

Assess behavioral status after combined transcranial Direct Current Stimulation/Constraint-Induced Movement in children with hemiparesis.

For Bimanual Therapy: Assess behavioral status after combined transcranial Direct Current Stimulation/Bimanual Therapy in children with hemiparesis.

4 Study Design

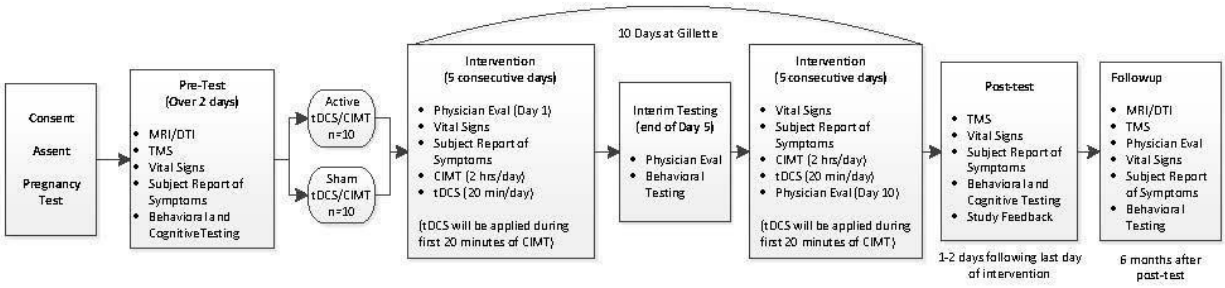

Figure 1a-tDCS/CIMT

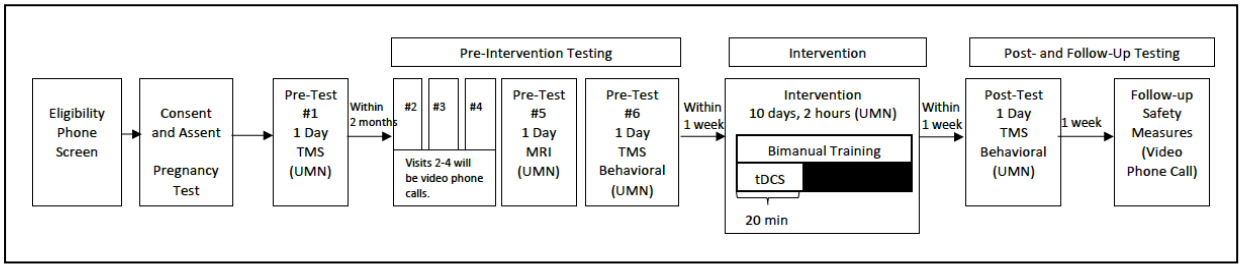

Figure 1b-tDCS/Bimanual Therapy

Overview of Study Design

The study will use a randomized, sham-controlled, blinded, repeated-measures design. (Figure 1a above) Twenty total children with congenital hemiparesis and unilateral infarct as confirmed by MRI will be randomized into one of two groups: active tDCS with CIMT (intervention) or sham tDCS with CIMT (control). Randomization will be 1:1 between intervention and control groups stratified on the presence of an ipsilesional MEP and using randomly permuted blocks of size 2 and 4. The children will receive 10 weekday sessions of daily tDCS and CIMT at Gillette Children's Specialty Healthcare – St. Paul, MN. The study will be conducted biannually in a camp-style format, anticipating 3-5 children participating in each camp. This format is constructed thusly due to the extensive personnel and resources required to safely and effectively run this trial. This study intends to determine feasibility and explore preliminary efficacy results to inform the design of a future, larger RCT, should promising results be found.

For Bimanual Therapy: This group will be studied with a repeated-measures design (Figure 1b above). Ten total children with congenital hemiparesis and unilateral infarct as confirmed by MRI will receive (active tDCS with bimanual therapy). The children will receive 10 weekday sessions of daily tDCS and bimanual at UMN Center for Neurobehavioral Development. The study will be conducted in a camp-style format, anticipating 3-5 children participating in each camp. This format is constructed thusly due to the extensive personnel and resources required to safely and

effectively run this study. This study intends to determine feasibility and explore preliminary efficacy results to inform the design of a future, larger RCT, should promising results be found.

Anticipated Duration of the Clinical Investigation

The anticipated duration of study is as follows: Submission of all indicated applications is presumed to occur over a 4-month period of time, with the potential for revisions within this timeframe. Recruitment of children will be based over a 1 year period of time, running the camps during optimal time off from school, holidays and vacations when children are most readily available. Recruitment accrual rates will vary greatly due to the variation in a child's school and after school activities.

For Bimanual Therapy: The anticipated duration of study is as follows: Submission of all indicated applications is presumed to occur over a 2-month period of time, with the potential for revisions within this timeframe. Recruitment of children will be based over a 6-month period of time, running the camps during optimal time off from school, holidays and vacations when children are most readily available. Recruitment accrual rates will vary greatly due to the variation in a child's school and after school activities.

If the trial ends prior to the study completion, all scheduled subjects will be notified and study visits will be terminated. The CTSI will be notified and all future reserved dates for use of the CTSI will be canceled. All research investigators on the study will be notified. The CTSI funding agency will also be notified.

Action—tDCS/CIMT	**Anticipated Duration**
Award Notice	Start date 9/1/13
Confirm protocol and consent/assent with Gillette Team, Establish full Gillette UMN Team	6 months
Scientific Merit CMRR//IRB/CTSI Applications, Reviews and Approvals	6 months
Recruit Subjects/Study Enrollment and Intervention	18 months
Database Queries and Data Cleaning	1 month
Database Lock and Analysis	1 month
Final Reports and Manuscript Preparation	1 month

Action—tDCS/Bimanual Therapy	**Anticipated Duration**
Award Notice	Start date 9/1/13
Confirm protocol and consent/assent with Gillette Team,	6 months
Scientific Merit CMRR//IRB/CTSI Applications, Reviews and Approvals	4 months

Recruit Subjects/Study Enrollment and Intervention	6 months
Database Queries and Data Cleaning	1 month
Database Lock and Analysis	1 month
Final Reports and Manuscript Preparation	1 month

Primary Clinical Endpoint

The following measures will be used to create a safety profile:

- Demographics
- Manual Ability Classification System Score
- TMS motor threshold
- Vital Signs
- Electromyograph (EMG) Activity of Ipsilateral and Contralateral Musculature,
- Subject Report of Symptoms
- Ipsilateral Hand Function
- Physician Evaluation
    - Specific to Bimanual Therapy: Physician involvement will remain as reviewer of medical records for inclusion/exclusion, Medical Director, Medical Monitor. No physician evaluation will be conducted.

We will use counts and percentages of adverse events to establish the data for this endpoint.

Study Population

Sample Size: 20 children with hemiparesis and unilateral infarct as confirmed by MRI.
Sample Size (Bimanual): 10 children with hemiparesis and unilateral infarct as confirmed by MRI.

35 children will be enrolled and 20 final subjects will meet all criteria and be able to proceed with the study. The sample size of n=20 was based on practical and clinical considerations. Information gleaned from this initial study will be used for development of intervention studies with the results dictating the defined direction of optimal usage of tDCS.

For Bimanual Therapy: An additional 20 children will be enrolled and 10 final participants will meet all criteria and be able to proceed with the study. The sample size of n=10 was based on practical and clinical considerations. Information gleaned from this initial study will be used for development of intervention studies with the results dictating the defined direction of optimal usage of tDCS.

Subject Recruitment: The recruitment subject pool for children with hemiparesis will include children who participated in previous studies, children from an IRB-approved database of families that have expressed interest in Dr. Gillick's research, as well as children from the clinical practices of this study's Medical Director, Dr. Tim Feyma, and Co-investigator, Dr. Marcie Ward. Upon IRB approval, we will further recruit through advertising on the Gillick Pediatric Neuromodulation Research Lab website (z.umn.edu/gillicklab), recruitment newsletters, emails, letters to colleagues, various media outlets as applicable, ResearchMatch.org and on the Children's Hemiplegic and

Stroke Association website (http://www.chasa.org/). Typically developing children needed for a mock walk-through of the logistics of the study will be recruited from the database of children who participated in a previous study and have requested to be notified of other research participation opportunities. Recruitment of typically developing children will also include reaching out to families who have expressed interest in Dr. Gillick's research in response to community presentations and her involvement in community service activities (i.e., elementary school science fair judge).

Subject Screening: In addition to the phone screen, the physician medical records screen, and the on-site screen, all female subjects will need to take a urine pregnancy test. If the test is positive the subject will be excluded from the study as the safety of use of tDCS and TMS during pregnancy has not been established. If the pregnancy test is negative, the subject can proceed into the treatment component of the study.

Prior and Concomitant Therapy

- Permitted- Behavioral therapies including occupational, physical or speech therapies will be allowed.
- Not permitted- Implantable ongoing therapies such as intrathecal baclofen pumps.

Inclusion Criteria

Subjects will be eligible to participate in the study if the following conditions exist:

1. Hemispheric Stroke or Periventricular Leukomalacia confirmed by most recent MRI or CT radiologic report with resultant congenital hemiparesis
2. ≥ 10 degrees of active motion at the metacarpophalangeal joint
3. Receptive language function to follow two-step commands as evidenced by performance on TOKEN test of intelligence
4. No evidence of seizure activity within the last 2 years
5. Presence of a motor evoked potential from at least the contralesional hemisphere if not both hemispheres
6. Ages 8-21 years
7. Able to give informed assent along with the informed consent of the legal guardian
8. Children who have had surgeries, which may influence motor function e.g.- tendon transfer, will be included, yet surgical history will be documented and included in any publication within a participant characteristics table.
9. For Bimanual Therapy: Children who display a motor-evoked potential from the lesioned-hemisphere as elicited by TMS single pulse testing.

Exclusion Criteria

Subjects will be excluded from participation in the study if any of the following conditions exist:

1. Metabolic Disorders
2. Neoplasm
3. Epilepsy
4. Disorders of Cellular Migration and Proliferation
5. Acquired Traumatic Brain Injury
6. Pregnancy

7. Indwelling metal or incompatible medical devices
8. Evidence of skin disease or skin abnormalities
9. Botulinum toxin or Phenol block within [six-months] preceding the study. Children who are within the 5th month following botulinum toxin injections who desire to participate in the study, will be reviewed individually by the PI and Medical Director of the study. A determination of inclusion will be based on the child's typical period of efficacy of injections.
10. For Bimanual Therapy: Children who do not display a motor-evoked potential from the lesioned-hemisphere as elicited by TMS single pulse testing.

Exit/Discontinuation Criteria
Subjects will exit the study if any of the following conditions exist:

1. Subject voluntarily withdraws from the study.
2. Subject death.
3. Subject acquires any of the listed exclusion criteria.
4. Subject completes the protocol.
5. Subject is non-compliant with the protocol.
6. Subject's well-being, in the opinion of the Investigator, would be compromised by study continuation.
7. Subject experiences a serious adverse event or seizure.
8. Medical monitor and/or IRB recommendation

5 Study Procedures

Eligibility Screening Consent
To determine eligibility for participation, caregivers will be asked screening information using the Medical History Survey (version 3.6.17). Prior to the collection of screening information that is identifiable, an Eligibility Screening consent form will be offered to caregivers by email, fax, mail, or waived. If a caregiver chooses to waive the consent for the eligibility screening, we will proceed with the eligibility screening at the time of the caregiver's study inquiry. The waiving of the eligibility screening consent will be documented.

To further protect identifiable information, if the caregiver reports their child is not within the age range of 8-21 years old and does not have a diagnosis of congenital hemiparesis (meaning the stroke occurred within the first year of life), the caregiver will be informed their child does not meet the study enrollment criteria and no further screening questions will be asked of the caregiver.

Informed Consent
For subjects ages 8-17, each legal guardian and subject for this study will be provided a consent and assent form describing this study and the opportunity to discuss the study with the study personnel. (Subjects ages 18-21 will be provided a non-minor consent form only). Information will be provided for an informed decision about their participation in this study. The consent, assent, and Addendum to Assent for Female Minors forms will be submitted with the protocol for review and approval by the IRB. The formal consent/assent of a subject, using the IRB-approved consent/assent form,

must be obtained before that subject undergoes any study procedure. This consent form must be signed by the legal guardian(s) and the assent/addendum assent form(s) must be signed by the subject along with the signature on both forms of the investigator-designated research professional obtaining the consent/assent. The IRB-approved form must be kept on-site and by the sponsor-investigator.

Assent must be obtained from all minor subjects deemed capable by the IRB (between 8 and 17 years old, inclusive) in addition to the Informed Consent of the legal guardian in accordance with Federal Regulations and/or the qualifying Institutional Review Board (IRB).

tDCS/CIMT Randomization Scheme

Each child will be randomized to either the real or sham tDCS arm of the study. The randomization will be done by sealed envelopes constructed by the study biostatistician using a random number generator. The study coordinator will assign envelopes, in numerical order, to the subjects upon their enrollment. The envelopes will in turn be shared by the study coordinator and the research personnel involved in the intervention component of the study.

tDCS/CIMT Blinding

The investigator who performs the testing, and the physician who does the evaluations will be blinded to the treatment arm as well as the child/caregiver/family. The following procedure will be employed:

1. The study coordinator and biostatistician will meet and a sealed envelope will be given to the study coordinator.
2. The study coordinator will share the group assignment with theprincipal investigator in a secure private room, in the absence of the physician, research tester, subject legal guardian and subject. The Medical Monitor to the study will have access to the group assignment.
3. Interventionist will, during the intervention, switch the setting on the tDCS device to the designated placebo setting, hidden from view of the subject. Blinding is applied through the designation of the setting on the tDCS machine of sham or real tDCS. For the first 30-seconds of either setting, a gradual "ramp-up" sensation of the stimulation occurs. This is built into the machine for both settings. However, for the sham stimulation, the sensation then abates, and not until the end of the 20-minute session does the subject receiving the 30-seconds of "ramp-down" sham once again experience the sensation. The sensation then occurs and "ramps-down" the amperage until the machine turns off.
4. Information on subject group assignment will be logged and stored in a designated locked cabinet at the study coordinators office.

tDCS/Bimanual Therapy:

As this is an open-label design, all children will complete multiple baseline assessments to serve as their comparison period without intervention. All children will then participate in the real tDCS/Bimanual Therapy intervention. Children, caregivers, and investigators will not be blinded to intervention. Study collaborators assisting with the scoring of assessments will be blinded to the child's progress during the intervention phase.

Laboratory Testing Procedures

Specimen Preparation: For females, urine samples will be obtained on site at the CTSI with use of private bathrooms. The subject and legal guardian will be instructed on how to obtain the urine specimen by the study PI. The urine sample will then be obtained in a screw-top urine cup and handed to the PI who will be wearing latex gloves.

Specimen Handling and Storage: Immediate assessment of pregnancy status will occur as the PI, in the assignment laboratory specimen assessment room, will utilize the allotted amount of sample required for adequate assessment. Once the testing has occurred, the sample will be flushed in a designated CTSI urinal or disposal sink. No storage of urine material will occur. If pregnancy test is positive, the child will be excluded from the study, and a recommendation to follow-up with their primary care physician will be enacted.

No shipment of specimens will occur in this study.

Clinical Procedures

Phone Screen: All interested subjects are screened by phone for a review of inclusion and exclusion criteria, to obtain general health history of potential subject, and to give opportunity for family to ask questions and have those questions answered.

Study Visit

HIPAA consent is obtained in order to perform a medical record review. Information for all subjects will be collected and managed in accordance with HIPAA policies. This review is completed by the study physicians for review of inclusion/exclusion by history and MRI/CT radiographic reports of the brain. Eligibility will be verified by the principal investigator after this review. Eligibility is then discussed with the legal guardian and a formal schedule is established. The family will be sent a detailed itinerary outlining their visit. Families interested in future study participation will be provided with the "HIPAA For Future Study" form. Informed consent/assent will be completed on the day of enrollment.

tDCS/CIMT:

ASSESSMENTSANDMEASUREMENTS	**Pre-Test**	**InterimTest**	**Post-Test**	**Follow-up**
MRI/DTI	x			X
TMS	x		x	x
Vital Signs	x		x	x
Subject Report of Symptoms	x	x	x	x
Physician Evaluation - MPSOM	x	x	x	X
Behavioral and Cognitive Testing to include: TOKEN, goal review, , AHA,	x		x	x
Behavioral Testing: Hand Dynamometer	X	X	X	X
Behavioral Testing: Participation of activities	X			X
Classification Systems: MACS/GMFCS	X			
tDCS Survey			x	
Study Feedback				x

tDCS/CIMT Pre-Test

Location: Center for Magnetic Resonance Research (CMRR)
Time: 1 hour

- Consent/Assent will be obtained and a pregnancy test for female subjects will be administered.
- Subjects will be scanned on a Siemens 3T system. The scan protocol will include both a T1-weighted structural Magnetization Prepared Rapid Acquisition Gradient Echo (MPRAGE) scan and Diffusion Tensor Imaging (DTI).

Location: Clinical and Translational Science Institute (CTSI)
Time: 2 hours

- Cardiovascular Measurements: Subjects will be instrumented with a 3 or 12-Lead ECG for measurement of heart rate and a non-invasive blood pressure measuring device that will be placed on a finger of their hand. (AD Instruments, Colorado Springs, CO). Subject Report of Symptoms survey will be completed.
- The testing researcher will perform an assessment of cortical excitability using Transcranial Magnetic Stimulation. The subject will be comfortably seated in a reclining chair. Surface EMG electrodes will be attached over the extensor digitorum muscle serving the nonparetic hand, which will record the MEPs resulting from the magnetic stimulation to the contralesional M1. Next, the threshold for TMS activation of the target muscle will be determined. Subjects will wear a tight-fitting Lycra (Invista, Inc., Wilmington, DE) swim cap to allow measurement and drawing of the region where the optimal scalp position ("hotspot") should be located. We will use a 70-mm figure-eight TMS coil connected to a Magstim 200 machine. The coil will be handheld on the swim cap over the approximate hotspot area tangential to the scalp and oriented with the handle pointing posterolaterally at a 45° angle to the sagittal line. It will be moved systematically to find the true location of the hotspot. Single-pulse magnetic stimuli will be delivered manually at approximately 0.1 Hz starting at an intensity of 60% of the stimulator maximum. This level will be adjusted systematically until the resting motor threshold is found, defined as the minimum intensity required to elicit MEPs >50 μV peak-to-peak in at least 5 of 10 trials with the target muscle at rest.
- The testing researcher will perform an assessment of cognitive and behavioral function using: a TOKEN test of intelligence, Assisting Hand Assessment, a measure of the child's goals, ,Hand Dynamometry, the Gross Motor Function Classification Scale Score (GMFCS), the Manual Ability Classification System (MACS), and a measure of the child's general activity level.

Location: Gillette Children's Specialty Healthcare

Time: 15 minutes

- The physician will assess the subject with the Modified Pediatric Stroke Outcome Measure (MPSOM).

Intervention

Location: Gillette Children's Specialty Healthcare – St. Paul, MN
Time: 2 hours/day for 10 (business) days with interim testing after Day 5

- Subject will be randomized into active vs. sham group
- Before the tDCS session, skin under the electrode region will be assessed for lesions and evidence of skin disease or abnormalities which could cause potential irritation. tDCS is not administered if there is any skin damage, rash or other skin lesion under the electrode sites.
- Skin is lightly cleaned with an alcohol swab, taking care NOT to abrade the skin in any manner. Move hair away as best as possible from the site of stimulation in order to increase conductance.
- Sanitized and disinfected rubber electrodes with clean, single-use sponges dampened with normal saline are placed over the stimulation sites and held against the head with wide rubber bands which cover the entire surface of the electrodes. Care is taken to ensure contact with the skin is firm and even over the entire surface of the electrode.
- The static impedance measurement is checked- stimulation does not proceed unless levels are within limits recommended by the tDCS device manufacturer.
- **Active tDCS with CIMT group (intervention)** Stimulation is commenced and subjects are advised to report immediately if the stimulation feels painful, or anything other than low-level itchy or tingling sensations, common yet consistently reported at any time during the period of stimulation. tDCS continues with a weak electrical current of 0.7 mA applied across the scalp for 20 minutes in a single experimental session.
- After the first 2 minutes, the subject is questioned about pain at the electrode sites. If the stimulation is painful, a small amount of additional saline (approximately 4 mL) is added to the sponge, taking care to avoid wetting adjacent hair and thereby increasing the electrode area, and the tightness and placement of the band are checked. If pain persists, the stimulation is stopped and the electrode sites are checked. This procedure is repeated twice (every 5 minutes during tDCS) with a small amount of saline solution being routinely applied at these times.
- During this 20 minute tDCS session and then continuing for the next 1 hour and 40 minutes, the child will be involved CIMT for the paretic hand and arm using a mitt. The mitt will therefore be applied for the 2-hour total period which incorporates this 20 minute tDCS session. The CIMT will be administered to the child on an individual basis for these 2 hours each CIMT day by a CIMT-trained and licensed therapist. Individualized activities will be created by the supervising treatment therapist investigator for shaping and repetition activities. Additionally, children will continue to use their paretic limb during functional activities at home and during a daily parent-supervised and documented home program.
- **Sham tDCS with CIMT group (control)**. These children will receive 10 daily sessions of both CIMT and sham tDCS. Children will receive the same procedures as the active tDCS with CIMT group (intervention), yet the device will be set to an integrated placebo setting which extinguishes the current after a 30 second to 1 minute ramp-up phase and gradually reintroduces the ramp-down at the end of the 20 minute session.
- At the end of stimulation, the electrode site is checked for redness or skin damage. The rubber electrodes and headbands are cleaned with a disinfectant solution.
- Vital signs measurements and Subject Report of Symptoms will be conducted before and after each daily session.
- Interim testing at Day 5 will consist of vital signs, physician assessment, cognitive and behavioral testing as well as subject report of symptoms.

Post-Test

Location: Clinical and Translational Science Institute (CTSI)
Time: 2hours

- Post-testing will occur 1 day following the 10-day intervention and, with the exception of an MRI, the same procedures will be followed as the pre-testing session, In addition the subject will be asked to complete a tDCS Feedback Survey

Follow-Up

Follow-Up will occur 6 months after the intervention, and participants and their families will be reimbursed for travel and housing for this return testing session.

Location: Center for Magnetic Resonance Research (CMRR)
Time: 1 hour

- A pregnancy test for female subjects will be administered.
- Subjects will be scanned on a Siemens 3T system. The scan protocol will include both a T1-weighted structural Magnetization Prepared Rapid Acquisition Gradient Echo (MPRAGE) scan and Diffusion Tensor Imaging (DTI).

Location: Clinical and Translational Science Institute (CTSI)
Time: 2 hours

- Includes TMS testing, behavioral and cognitive measures defined in pre- and post-tests, vital signs measurements, and Subject Report of Symptoms, report of activities performed since post-test and a Family Feedback Survey.

tDCS/Bimanual Therapy:

ASSESSMENTSANDMEASUREMENTS	**PreTest #1**	**Pre-tests # 2-4**	**Pre-Test # 5-6**	**InterimTest**	**Post-Test**	**Follow-up**
MRI/DTI			x			
TMS	X		x		x	
Vital Signs	X		x		x	
Participant Report of Symptoms	X		x	x	x	x
Behavioral to include: goal review, Box and Blocks	X	X	x		x	x
Behavioral Testing: Hand Dynamometer, AHA	X		X	X	X	
Classification Systems: MACS	X		X			
tDCS Survey					x	
Study Feedback						x

Pre-Testing Session # 1:

Location: Center for Translational Science Institute

Time: 2-3 hours

- Consent/Assent will be obtained and a pregnancy test for female subjects will be administered.
- Cardiovascular Measurements: Subjects will be instrumented with a 3 or 12-Lead ECG for measurement of heart rate and a non-invasive blood pressure

measuring device that will be placed on a finger of their hand. (AD Instruments, Colorado Springs, CO). Subject Report of Symptoms survey will be completed.

- The testing researcher will perform an assessment of cortical excitability using Transcranial Magnetic Stimulation. The subject will be comfortably seated in a reclining chair. Surface EMG electrodes will be attached over the first dorsal interosseous muscle serving the nonparetic hand, which will record the MEPs resulting from the magnetic stimulation to the contralesional M1. Next, the threshold for TMS activation of the target muscle will be determined. Subjects will wear a tracker made of light weight plastic to allow for co-registration of the MRI images to the child's head dimensions with the use of stereotactic neuronavigation. We will use a 70-mm figure-eight TMS coil connected to a Magstim 200 machine. The coil will be handheld over the approximate hotspot area tangential to the scalp and oriented with the handle pointing posterolaterally at a 45° angle to the sagittal line. It will be moved systematically to find the true location of the hotspot. Single- pulse magnetic stimuli will be delivered manually at approximately 0.1 Hz starting at an intensity of 60% of the stimulator maximum. This level will be adjusted systematically until the resting motor threshold is found, defined as the minimum intensity required to elicit MEPs >50 μV peak-to-peak in at least 5 of 10 trials with the target muscle at rest.
- The testing researcher will perform an assessment of cognitive and behavioral function using: Assisting Hand Assessment, a measure of the child's goals, Hand Dynamometry, the Manual Ability Classification System (MACS), and a measure of the child's general activity level.

Pre-Testing Sessions # 2-4:

Location: Video phone calls

Time: 30 minutes

- The testing researcher will perform testing with the Box and Blocks test (wherein the child moves as many 1" wooden blocks within 1 minute) and child/caregiver questionnaires. For these pre-tests, we will mail you the supplies.

Testing Session #5:

Location: Center for Magnetic Resonance Research (CMRR)

Time: 2 hours

- Subjects will be scanned on a Siemens 3T system. The scan protocol will include both a T1-weighted structural Magnetization Prepared Rapid Acquisition Gradient Echo (MPRAGE) scan and Diffusion Tensor Imaging (DTI).
- For children who have previously participated in our studies that included a MRI from the CMRR in the past 2.5 years, the MRI will not be repeated.

Testing Session #6:

Location: Clinical and Translational Science Institute (CTSI)
Time: 2 hours

- Cardiovascular Measurements: Subjects will be instrumented with a 3 or 12-

Lead ECG for measurement of heart rate and a non-invasive blood pressure measuring device that will be placed on a finger of their hand. (AD Instruments, Colorado Springs, CO). Subject Report of Symptoms survey will be completed.

- The testing researcher will perform an assessment of cortical excitability using Transcranial Magnetic Stimulation. The subject will be comfortably seated in a reclining chair. Surface EMG electrodes will be attached over the first dorsal interosseous muscle serving the nonparetic hand, which will record the MEPs resulting from the magnetic stimulation to the contralesional M1. Next, the threshold for TMS activation of the target muscle will be determined. Subjects will wear a tracker made of light weight plastic to allow for co-registration of the MRI images to the child's head dimensions with the use of stereotactic neuronavigation. We will use a 70-mm figure-eight TMS coil connected to a Magstim 200 machine. The coil will be handheld over the approximate hotspot area tangential to the scalp and oriented with the handle pointing posterolaterally at a 45° angle to the sagittal line. It will be moved systematically to find the true location of the hotspot. Single- pulse magnetic stimuli will be delivered manually at approximately 0.1 Hz starting at an intensity of 60% of the stimulator maximum. This level will be adjusted systematically until the resting motor threshold is found, defined as the minimum intensity required to elicit MEPs >50 μV peak-to-peak in at least 5 of 10 trials with the target muscle at rest.
- The testing researcher will perform an assessment of cognitive and behavioral function using: Assisting Hand Assessment, a measure of the child's goals, Hand Dynamometry, the Manual Ability Classification System (MACS), and a measure of the child's general activity level.

Intervention

Location: University of Minnesota—Center for Neurobehavioral Development (CNBD)
Time: 2 hours/day for 10 (business) days with interim testing after Day 5

- Before the tDCS session, skin under the electrode region will be assessed for lesions and evidence of skin disease or abnormalities which could cause potential irritation. tDCS is not administered if there is any skin damage, rash or other skin lesion under the electrode sites.
- Skin is lightly cleaned with an alcohol swab, taking care NOT to abrade the skin in any manner. Move hair away as best as possible from the site of stimulation in order to increase conductance.
- Sanitized and disinfected rubber electrodes with clean, single-use sponges dampened with normal saline are placed over the stimulation sites and held against the head with wide rubber bands which cover the entire surface of the electrodes. Care is taken to ensure contact with the skin is firm and even over the entire surface of the electrode.
- The static impedance measurement is checked- stimulation does not proceed unless levels are within limits recommended by the tDCS device manufacturer.
- **Active tDCS with bimanual therapy group (intervention):** Stimulation is commenced and subjects are advised to report immediately if the stimulation feels painful, or anything other than low-level itchy or tingling sensations, common yet consistently reported at any time during the period of stimulation. tDCS continues with a weak electrical current of up to 2.0 mA applied across the scalp for 20 minutes in a single experimental session.

- After the first 2 minutes, the subject is questioned about pain at the electrode sites. If the stimulation is painful, a small amount of additional saline (approximately 4 mL) is added to the sponge, taking care to avoid wetting adjacent hair and thereby increasing the electrode area, and the tightness and placement of the band are checked. If pain persists, the stimulation is stopped and the electrode sites are checked. This procedure is repeated twice (every 5 minutes during tDCS) with a small amount of saline solution being routinely applied at these times.
- During this 20 minute tDCS session and then continuing for the next 1 hour and 40 minutes, the child will be involved bimanual therapy. The bimanual therapy will be administered to the child on an individual basis for these 2 hours each by an interventionist. Individualized activities will be created by the supervising treatment therapist investigator for shaping and repetition activities. Additionally, children will continue to use their paretic limb during functional activities at home and during a daily parent-supervised and documented home program.
- At the end of stimulation, the electrode site is checked for redness or skin damage. The rubber electrodes and headbands are cleaned with a disinfectant solution.
- Vital signs measurements and Subject Report of Symptoms will be conducted before and after each daily session.
- Interim testing at Day 5 will consist of vital signs, cognitive and behavioral testing as well as participant report of symptoms.

Post-Test

Location: Clinical and Translational Science Institute (CTSI)
Time: 2hours

- Post-testing will occur 1 day following the 10-day intervention and, with the exception of an MRI, the same procedures will be followed as the pre-testing session, In addition the participant will be asked to complete a tDCS Feedback Survey

Follow-Up

Location: Video conference call

Time: 20 minutes

- Follow-Up will occur 1 week after the intervention. Includes a portion of the behavioral and cognitive measures defined in pre- and post- tests, and Subject Report of Symptoms, report of activities performed since post-test and a Family Feedback Survey.

Study Protocol Compliance

A home program will be issued by the treatment therapist investigator with journaling of activities performed. This journal will be reviewed daily.

If the subject or legal guardian displays an inability to complete the study due to non-compliance or incomplete involvement in the study, the subject will be withdrawn from the study and no further data will be obtained.

Deviations from the Clinical Protocol

When a deviation from the protocol is necessary for an individual subject, the investigator must complete a description of the deviation from the protocol and justification on the Protocol Deviation Form and inform the IRB of the protocol deviation through formal documentation.

Subject Withdrawal

How to Withdraw Subjects: Subjects may discontinue participation at any time, for any reason. Any subject observed to have unacceptable responses to research procedures, or to be unable to safely or comfortably tolerate participation will be withdrawn.

Subjects withdrawn from study will not be replaced, and the details surrounding the circumstances of the reason for withdrawing the subject from the study will be reported with no identifiers included.

Data Collection and Follow Up for Withdrawn Subjects: If a subject and legal guardian are not compliant with establishing and meeting for the components of the study, the legal guardian will be contacted up to 2 times by phone in succession and by 1 letter thereafter. If no return contact is established, the subject will be withdrawn from the study and any data collected will be analyzed.

6 Data Analysis

Subject Population(s) for Analysis

Any subject who is observed in the study will have their data analyzed per the actual treatment received for evaluating safety.

Statistical Methods

Descriptive analyses of baseline characteristics and outcomes will include means and standard deviations for continuous variables with frequencies and percentages for categorical variables. *Analysis Populations:* There are 3 analysis populations planned. Intent-to-treat (ITT) will include any subject randomized according to their treatment assignment. Per-protocol (PP) will include randomized subjects without major protocol violations and who were compliant (at least 80% of planned sessions with their treatment assignment. A detailed list of the major protocol violations warranting exclusion from the PP analysis will be determined prior to trial commencement. The Safety population will include all subjects who receive treatment, according to treatment received. We do not anticipate these groups to differ.

Aim #1: Safety analyses will use the safety population and be primarily descriptive, reporting the number and percentage of adverse events, in particular, any instances of seizure or other serious adverse event. Instances of decline in paretic or nonparetic hand function as measured by the (Assisting Hand Assessment) AHA scaled score will also be evaluated.

For tDCS/Bimanual Therapy: The same analyses will be conducted as the tDCS/CIMT study outlined in Aim #1.

Aim #2: The primary analysis will use the ITT population to compare logit-based AHA

units between the intervention and control group adjusting for baseline values of AHA and presence of MEP for precision. Confidence intervals and P-values will be based on the t-distribution with corresponding degrees of freedom. P-values < 0.05 will be considered significant. Supportive analyses using the PP population will also be conducted. Secondary endpoints of Canadian Occupational Performance Measure (COPM), TOKEN test, Stereognosis and Finger force measurements will be analyzed in a similar fashion, adjusted for baseline values and presence of MEP with supportive analyses using the PP population. The association of improved logit-based AHA units with DTI derived fractional anisotropy (FA) and MEP will be evaluated across all patients using generalized linear regression and the t-distribution with corresponding degrees of freedom for inference. Secondary analyses will evaluate these associations also adjusting for age and sex due to potential confounding influence though may be limited by sample size. Additional analyses for the comparisons mentioned above will consider non-parametric tests or transformations of variables in the event distributional assumptions do not hold.

For tDCS/Bimanual Therapy: The primary analysis will compare logit-based AHA units pre and post intervention. Confidence intervals and P-values will be based on the t-distribution with corresponding degrees of freedom. P-values < 0.05 will be considered significant. Supportive analyses using the PP population will also be conducted. Secondary endpoints of Canadian Occupational Performance Measure (COPM), caregiver questionnaires will be analyzed in a similar fashion, adjusted for baseline values. Secondary analyses will evaluate these associations also adjusting for age and sex due to potential confounding influence though may be limited by sample size. Additional analyses for the comparisons mentioned above will consider non-parametric tests or transformations of variables in the event distributional assumptions do not hold.

Power and Sample Size: The sample size and power was primarily driven by the primary analysis of Hypothesis #1 of Aim #2. Power calculations for the primary outcome of logit-based AHA units were based on 10 patients in each group with variability estimates from the rTMS/CIMT study mentioned in the preliminary studies section suggesting a standard deviation of approximately 16. The correlation between pre- and post-treatment AHA scores in the rTMS/CIMT study was 0.97. Based on these estimates, we will have 81% power to detect a difference of 5 logit-based AHA units. This study is intended to determine feasibility and explore preliminary efficacy results to inform the design of a future, larger RCT should promising results be found.

Aim #3: Associations between changes in cortical excitability and the primary and secondary outcomes will be evaluated across all patients using generalized linear regression as in Aim #2. The change in contralesional M1 cortical excitability will be compared between intervention and control groups, adjusting for baseline values, using the ITT population. This comparison will be repeated within the subgroup of patients with an ipsilesional MEP. Similar to other aims, confidence intervals and P-values will be based on the t-distribution with corresponding degrees of freedom and supportive analyses using the PP population will also be conducted. Additional analyses for the comparisons mentioned above will consider non-parametric tests or transformations of variables in the event distributional assumptions do not hold.

7 Safety and Adverse Events

Definitions

Adverse Event (AE): An adverse event (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Intercurrent illnesses or injuries will be regarded as adverse events. Abnormal results of laboratory or diagnostic procedures are considered to be adverse events if the abnormality:

- Results in study withdrawal
- Is associated with a serious adverse event
- Is associated with clinical signs or symptoms
- Leads to additional treatment or to further diagnostic tests
- Is considered by the Investigator to be of clinical significance.

Serious Adverse Event (SAE): A serious adverse event (SAE) is any adverse event that is:

- Fatal
- Life-threatening
- Requires or prolongs a hospital stay
- Results in persistent or significant disability or incapacity
- A congenital anomaly or birth defect

Important medical events are events that may not be immediately life-threatening, but are clearly of major clinical significance and may be SAEs. They may jeopardize the subject, and may require intervention to prevent one or the other serious outcomes noted above.

Hospitalization: Hospitalization shall include any initial admission (even if less than 24 hours) to a healthcare facility as a result of a precipitating clinical adverse effect; to include transfer within the hospital to an intensive care unit. Hospitalization or prolongation of hospitalization in the absence of a precipitating, clinical adverse effect (e.g., for a preexisting condition not associated with a new adverse effect or with a worsening of the preexisting condition; admission for a protocol-specified procedure) is not, in itself, a serious adverse effect.

Unanticipated Adverse Device Effect (UADE): An unanticipated adverse device effect is any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan, or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

Unanticipated Problems Involving Risk To Subjects or Others (UPIRTSO): An adverse event that in the opinion of the Principal Investigator is unexpected, related to the device, and serious.

Safety Monitoring Plan

All research procedures will be performed by qualified personnel who have completed required training, including human subjects training. Dr. Bernadette Gillick has been investigating NIBS since 2007 with PhD training in TMS and Neuroimaging.

Additionally, she has been trained by the Harvard Berenson Center for Non-Invasive Brain Stimulation 2012 and NYC Neuromodulation Conference 2013 on the use and application of tDCS, and by Brainsight Stereotactic Neuronavigation President Roch Comeau in 2013.

TMS cortical excitability testing will occur at the CTSI in the designated TMS room with the trained nursing/medical personnel on site, and the hospital emergency response team immediately available.

tDCS/CIMT application will occur at Gillette Children's Specialty Healthcare in St. Paul, Minnesota. Gillette specializes in diagnosing and treating neurological conditions as well as other complex medical conditions. Gillette encompasses a comprehensive team of specialists that provide medical, surgical rehabilitation and assistive technology services. They partner with Regions hospital in the operation of a pediatric intensive care unit.

For tDCS/Bimanual Therapy: tDCS application and intervention will occur at UMN Center for Neurobehavioral Development in Minneapolis, Minnesota. We will have an on-call, physician during the intervention hours.

All personnel will comply with all related regulations and laws, included, but not limited to 45CFR parts 60 and 64, and HIPAA Privacy Regulations. Study data and information will be kept confidential and managed in accordance with requirements of HIPAA. All data will be stored in locked offices and not released without subject permission.

Subjects will be rigorously screened against inclusion/exclusion criteria to ensure that their participation is safe. This screening begins at the initial discussion in the phone screen, continues with review of the medical records by the physicians on the study and is again repeated in-person with an on-site screening tool.

AEs and SAEs will be assessed and followed throughout the study. Vital sign monitoring will occur before and after TMS and tDCS applications. Active adverse events collection through the Subject Report of Symptoms questionnaire will be employed before and after tDCS application

Subjects will have contact information to enable them to contact study personnel easily and quickly.

Anticipated Risks / Risk Mitigation- We anticipate minor adverse events as listed below in this table. For a serious adverse event such as seizure, please refer to the study stopping rules as listed in next section.

Study Procedure	*Anticipated Risks*	*Risk Mitigation*
tDCS	Burn- Electrolysis	Ensure proper electrode contact with skin
tDCS	Stimulation in subjects with reduced sensation	Assess sensation, avoid placing electrodes over areas of decreased sensation
tDCS	Stimulation over broken skin, reduced resistance	Assess skin integrity, avoid placement of electrodes over recent shaving, skin defects

tDCS	Stimulation over conductive implants	Screen appropriately for exclusion criteria of implants
tDCS	Stimulation over a tumor which may alter metabolic activity	Screen appropriately for exclusion criteria of neoplasm.
tDCS	Threshold altering pharmacologic agent	Screen appropriately for exclusion criteria of centrally acting agent.
tDCS	Itching, Tingling, Burning Sensation in the area of the electrodes	Ensure proper contact of surface electrodes with skin. Maintain current dosage within low-range of researched dosages. Ensure that electrode sponges are properly sanitized and that saline solution is appropriately employed.
tDCS	Headache	Ensure that headband securing electrodes is in proper placement, yet not to the level of impingement of scalp area. Maintain current dosage within low range of delivery.
tDCS	Pain- Neck, Scalp	Ensure that electrodes are in proper contact with skin and adjust head position as needed for comfort.
tDCS	Skin Redness	Ensure proper electrode position and proper level of moisture to even stimulation across the electrode
tDCS	Fatigue, Sleepiness	Screen for continuous effect at follow-up visit.
tDCS	Concentration or Mood Changes	Evaluate cognitive status through physician examination and psychometric testing at three timepoints.
TMS	Stimulation over a tumor which may alter metabolic activity	Screen appropriately for exclusion criteria of neoplasm.
TMS	Threshold altering pharmacologic agent	Physician review of each medical record for determination of appropriateness for study inclusion.
TMS	Headache	Ensure that headband securing electrodes is in proper placement, yet not to the level of impingement of scalp area. Maintain current dosage within low range of delivery.
TMS	Fatigue, Sleepiness	Screen for continuous effect throughout observation.
TMS	Temporary mild hearing loss due to noise level of equipment	Ear plugs will be inserted before commencement of TMS testing.

CIMT	Sling/Mitt Irritation	Screen continuously during application and modify sling/mitt position to ensure comfortable fit.
MRI	Potential dislodging of indwelling metals and disruption of medical devices.	Prior to participation screen for existence of indwelling metal/medical devices. Exclude, or, if metal/medical devices are compatible, obtain verification from appropriate physician.
MRI	Metal projectiles inadvertently presented during MRI	Conduct on-site screen and removal of potential projectiles (coins, keys, etc)
MRI	Unknown effects of MRI on the unborn fetus	Administer pregnancy test on all female subjects. Exclude if test is positive.
MRI	Temporary mild hearing loss due to noise level of equipment	Subjects will wear earplugs and headphones during MRI to protect against excessive noise.
MRI	Strong claustrophobia	Claustrophobia will be screened in advance of participation
MRI	Transient dizziness upon removal from the magnet	Subject will be instructed to sit up slowly and remain seated for several minutes before standing. Subject will not be dismissed until dizziness subsides.

Medical Monitoring for Participant Safety

The Principal Investigator will oversee the safety of the study, including careful assessment and appropriate reporting of adverse events. Medical monitoring will include a regular assessment of the number and type of serious adverse events.

The Medical Monitor for the study is:

Linda E. Krach, MD
Vice President of Medical Operations
Courage Kenny Rehabilitation Institute
800 East 28th Street
Mail Route 12101
Minneapolis, MN 55407
612-863-7150

Study Stopping Rules

Both Individual and Entire Study stopping rules are described below:

Death. Study stopped for both individual and entire study. A full investigation of event will be explored by entire study team. The medical monitor will review all details. Report of event will be distributed to all governing and monitoring committees.

Seizure: Individual- Immediate suspension of tDCS application for this particular child and initiation and follow-through of safe and effective seizure management. Refer to

comprehensive seizure management outline. Provide physician letter to subject which describes the research-related adverse event with physician interpretation.

Study Medical Director Evaluation. Recommend further evaluation to the child and legal guardian by pediatric neurologist if not the pediatrician routinely involved in the child's care.

An identification of causality and re-evaluation of treatment design will occur by study researchers, including consultants, medical monitor and physicians in order to proceed. All procedures will be assessed for strict adherence to all intervention steps listed in the protocol. If deviation is found, error will be corrected. Proceed with study.

Entire Study- If another subject incurs a seizure proceed with steps for Individual Stopping Rules as noted above. Study will be suspended at this point and a thorough review by research team, medical monitor and consultants will occur in order to assess the need for amendment of the protocol or full stop/termination of study for future safety concerns.

Anticipated Adverse Events

Subjects will be children who sustained a congenital stroke before, during or one-year after birth. In addition to cited research procedure risk, they will be at risk for complications, morbidities and mortalities associated with pediatric strokes.

Adverse Event Reporting

All Adverse Events occurring during the study period must be recorded. The clinical course of each event will be followed until resolution, stabilization, or until it has been determined that study treatment or participation is not the cause.

The Sponsor-Investigator will promptly review documented adverse effects and abnormal test findings to determine

1) if the abnormal test finding should be classified as an adverse effect;
2) if there is a reasonable possibility that the adverse effect was caused by the investigational device or, if applicable, other study treatment or diagnostic product(s); and
3) if the adverse effect meets the criteria for a serious adverse effect.

If the Sponsor-Investigator's final determination of causality is "unknown and of questionable relationship to the investigational device or, if applicable, other study treatment or diagnostic product(s)", the adverse effect will be classified as *associated with the use of the investigational device or study treatment or diagnostic drug product(s)* for reporting purposes. If the investigator-sponsor's final determination of causality is "unknown but not related to the investigational device or, if applicable, other study treatment or diagnostic product(s)", this determination and the rationale for the determination will be documented in the respective subject's case history.

Adverse Events

All observed or volunteered adverse effects and abnormal test findings, if applicable, or suspected causal relationship to the investigational device or, if applicable, other study

treatment or diagnostic product(s) will be recorded in the subjects' case histories. For all adverse effects, sufficient information will be pursued and/or obtained so as to permit

1) an adequate determination of the outcome of the effect (i.e., whether the effect should be classified as a serious adverse effect) and;
2) an assessment of the casual relationship between the adverse effect and the investigational device or, if applicable, the other study treatment or diagnostic product(s).

Adverse effects or abnormal test findings felt to be associated with the investigational device or, if applicable, other study treatment or diagnostic product(s) will be followed until the effect (or its sequelae) or the abnormal test finding resolves or stabilizes at a level acceptable to the Sponsor-Investigator.

Adverse Events that do not qualify as Serious Adverse Events or as Unanticipated Adverse Device Effects will be reported the IRB with the continuing review progress report.

Serious Adverse Events
Unexpected serious adverse events that are at least possibly related will be reported to the IRB within 10 days of learning of the event.

Unanticipated Adverse Device Effects (UADE)
Investigators are required to submit a report of a UADE to the reviewing IRB as soon as possible, but in no event later than 10 working days after the Investigator first learns of the event.

If the Adverse Event is Serious, Unanticipated, Device Related, and determined by the Sponsor-Investigator to present an unreasonable risk to subjects, the Sponsor must terminate the study within 5 working days of that determination.

Unanticipated Problems Involving Risk To Subjects or Others (UPIRTSO)
Investigators are required to submit a report of UPIRTSO events to the IRB within 10 working days of first learning of the event.

Data Safety Monitoring Board
No DSMB will be incorporated in this study as a medical monitor is in place.

8 Data Handling and Record Keeping

Confidentiality
Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information

- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

Source Documents

Source Data are the clinical findings and observations, laboratory and test data, and other information contained in *Source Documents*. *Source Documents* are the original records (and certified copies of original records); including, but not limited to, hospital medical records, physician or office charts, physician or nursing notes, subject diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, x-rays, etc. When applicable, information recorded on the CRF shall match the *Source Data* recorded on the *Source Documents*.

Case Report Forms

The study case report form (CRF) is the primary data collection instrument for the study. All data requested on the CRF must be recorded. All missing data must be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, write "N/D". If the item is not applicable to the individual case, write "N/A". All entries should be printed legibly in black ink. If any entry error has been made, to correct such an error, draw a single straight line through the incorrect entry and enter the correct data above it. All such changes must be initialed and dated. DO NOT ERASE OR WHITE OUT ERRORS. For clarification of illegible or uncertain entries, print the clarification above the item, then initial and date it.

A Case Report Form will be completed for each subject enrolled into the study. The investigator-sponsor will review, approve and sign/date each completed CRF; the investigator-sponsor's signature serving as attestation of the investigator-sponsor's responsibility for ensuring that all clinical and laboratory data entered on the CRF are complete, accurate and authentic.

1) Eligibility Phone Screen
2) HIPAA Form
3) Demographic Medical History Form including MRI Report
4) Individual Data Collection Forms
5) Exit Forms

Data for this study will be entered by the research investigators and study coordinator immediately into the CRF. The data will then be entered within the next week into a REDCap database , which uses a MySQL database via a secure web interface with data checks used during data entry to ensure data quality. REDCap includes a complete suite of features to support HIPAA compliance, including a full audit trail, user-based privileges, and integration with the institutional LDAP server. The MySQL database and the web server will both be housed on secure servers operated by the University of

Minnesota Academic Health Center's Information Systems group (AHC-IS). The servers are in a physically secure location on campus and are backed up nightly, with the backups stored in accordance with the AHC-IS retention schedule of daily, weekly, and monthly tapes retained for 1 month, 3 months, and 6 months, respectively. Weekly backup tapes are stored offsite. The AHC-IS servers provide a stable, secure, well-maintained, and high-capacity data storage environment, and both REDCap and MySQL are widely-used, powerful, reliable, well-supported systems. Access to the study's data in REDCap will be restricted to the members of the study team by username and password.

Records Retention
All records will be kept in the study coordinator's office in a locked file cabinet. The CRF's will be kept with the study coordinator until the study is completed. Thereafter the PI will maintain all records for 6 years.

9 Study Monitoring, Auditing, and Inspecting

This study will be monitored according to IRB/CTSI/GCP guidelines. The Investigator will allocate adequate time for such monitoring activities. The Investigator will also ensure that the monitor or other compliance or quality assurance reviewer is given access to all study-related documents and study related facilities (e.g. pharmacy, diagnostic laboratory, etc.), and has adequate space to conduct the monitoring visit.

Study Monitoring Plan
The study uses a non-significant risk device. Therefore, independent monitoring of the clinical study for clinical protocol and abbreviated IDE application compliance will be conducted periodically (i.e., at a minimum of annually) by qualified staff of the University of Minnesota's Clinical and Translational Science Institute (CTSI).

Quality Assurance Procedures
Data will be reviewed for completeness and accuracy at the end of the trial by verifying missing data is indeed missing from the paper form and outliers are true values prior to beginning the study analysis.

Auditing and Inspection
The investigator will permit study-related monitoring, audits, and inspections by the IRB, the sponsor, government regulatory bodies, and University compliance and quality assurance groups of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable University compliance and quality assurance offices.

10 Ethical Considerations
This study is to be conducted according to US and international standards of Good

Clinical Practice, applicable government regulations and Institutional research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted independent Institutional Review Board (IRB), in agreement with local legal prescriptions, for formal approval of the study conduct. The decision of the IRB concerning the conduct of the study will be made in writing to the investigator and a copy of this decision will be provided to the sponsor before commencement of this study.

11 Study Finances

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- Cerebral Palsy International Research Foundation (CPIRF)
- Foundation for Physical Therapy Magistro Family Foundation Research Grant

Conflicts of Interest

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must refer to the Regents Policies on Individual Conflict of Interest Policy or Institutional Conflict of Interest Policy. These policies require University Faculty and staff to report external professional activities and business and significant financial interests related to his or her University activities by submitting a REPA (Report of External Professional Activities) at least once per year. Faculty and staff should also file a REPA when substantial changes in business or financial interests occur, when an activity that presents a potential conflict of interest is anticipated, or when submitting an application for research support or technology transfer, submitting research protocols to the IRB, or receiving financial contributions. All University of Minnesota investigators will follow the University conflict of interest policy.

12 Publications Plan

Neither the complete nor any part of the results of the study carried out under this protocol, nor any of the information provided by the sponsor for the purposes of performing the study, will be published or passed on to any third party without the consent of the study sponsor. Any investigator involved with this study is obligated to provide the sponsor with complete test results and all data derived from the study.

13 List of Reference Documents

Below is a list of documents used in the conduct of this study. Copies of these documents can be found in the study's regulatory binder:

1. Phone Screen
2. Manual Ability Classification System form
3. Physician Medical Records Screening Form
4. On-Site Screening Form
5. Consent Form
6. Assent Form
7. Addendum to Assent for Female Minors
8. Subject Report of Symptoms Questionnaire
9. Comprehensive seizure management outline
10. Complete seizure observation documentation form
11. Physician seizure note

14 References

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