Protocol Title	Effects of single-session transcranial direct current stimulation in children with cerebral palsy
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REVISION HISTORY

Revision #	Version Date	Summary of Changes	Consent Change?

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ABBREVIATIONS/DEFINITIONS

AE	Adverse Event
AHA	Assisting Hand Assessment
ANOVA	Analysis of Variance
ANCOVA	Analysis of Covariance
BOLD	Blood Oxygen-Dependent Level
CIMT	Constraint-induced Movement Therapy
CMRR	Center for Magnetic Resonance Research
CNBD	Center for Neurobehavioral Development
CRF	Case Report Form
CTD	Children with Typical Development
CTSI	Clinical and Translational Science Institute
EMG	Electromyography
FLASH	Fast Low Angle Shot
GMFCS	Gross Motor Function Classification Scale Score
IHI	Interhemispheric Inhibition
iSP	Ipsilateral Silent Period
JTTHF	Jebsen Taylor Test of Hand Function
M1	Primary Motor Cortex
MP-RAGE	Magnetization Prepared Rapid Acquisition Gradient Echo
MACS	Manual Abilities Classification Scale
MB	Multi-band
MEP	Motor Evoked Potential
MRI	Magnetic Resonance Imaging
MT	Motor Threshold
NNL	Non-invasive Neuromoduluation Laboratory
SO	Supraorbital Prominence
NIBS	Non-invasive Brain Stimulation
PP	Paired-pulse
SAE	Serious Adverse Event
SimNIBS	Simulation of Non-invasive Brain Stimulation
rTMS	Repetitive Transcranial Magnetic Stimulation
tDCS	Transcranial Direct Current Stimulation
TMS	Transcranial Magnetic Stimulation
TR	Time to Recovery
UCP	Unilateral Cerebral Palsy

1.0 Objectives

1.1 Purpose: To characterize motor cortex neurophysiology and to understand how one form of non-invasive brain stimulation (NIBS) called transcranial direct current stimulation (tDCS) changes brain excitability and behavior in children diagnosed with cerebral palsy, as compared to children with typical development (CTD).

Aim 1: Using transcranial magnetic stimulation (TMS), characterize brain excitability, specifically interhemispheric inhibition, in children with CP and CTD.

Aim 2: Evaluate the immediate effect of tDCS on brain excitability and motor performance in children with UCP and CTD.

Aim 3: Compare the responses to tDCS in each with individual estimated electric field intensity from computational modeling.

2.0 Background

2.1 Significance of Research Question/Purpose: Hemiparesis, or weakness on one side of the body, is common following stroke early in life. The broader clinical diagnosis for this type of childhood movement impairment is unilateral cerebral palsy (UCP). Cerebral palsy effects about 3 out of every 1000 live births in the Unites States[1], and produces lifelong motor, sensory, and cognitive disability.

Neurorehabilitation has primarily focused on intensive motor training to encourage use of the affected extremities in an effort to produce use-dependent neuroplasticity in the brain. Such interventions are effective, but require a burdensome amount of time, 60-90 hours per week, for both the child and therapist. Furthermore, some children do not respond at all to such training.

Neuromodulation is a relatively new field that aims to influence the brain's neuronal activity through direct application of magnetic (TMS) or electric (tDCS) energy. It is thought the combination of neuromodulation and motor training may reduce the dosage of training needed, and would promote recovery to a greater extent for more individuals. Indeed, previous work in adult stroke demonstrate a benefit of combining repetitive TMS (rTMS) and tDCS with motor training, compared to training alone.[2, 3] These types of synergistic interventions are just beginning to be used in children with UCP, with some preliminary data showing potential benefit.

One of the many questions surrounding neuromodulatory interventions like tDCS is how to reliably predict changes in neuronal activity. The currently hypothesized effects of tDCS are polarity-specific: anodal tDCS depolarizes membranes resulting in increased in neuronal excitability; cathodal tDCS hyperpolarizes tDCS resulting in decreased neuronal excitability. Furthermore, these effects scale with the intensity of stimulation: the larger

the direct current delivered, the greater the change in excitability. This framework has been used to guide almost all studies using tDCS to produce a change in brain function and resulting behavior.

More recently, the field is beginning to appreciate that this framework may be overly simplistic. For example, when a cognitive task is performed concurrently with tDCS, there are reported non-linear effects related to current intensity and direction of change in excitability.[4] Such work has a significant impact on the use of tDCS in rehabilitation, which advocates for the pairing of stimulation with on-going activity.

One common approach to using tDCS in individuals with stroke is to target the non-lesioned hemisphere. Following stroke, there is an imbalance of communication between brain hemispheres. This communication, known as interhemispheric inhibition (IHI), is a normal control process whereby the activated motor cortex sends an inhibitory command to the opposite motor cortex to momentarily interrupt its activity, allowing for the execution of controlled unilateral movements. IHI is exaggerated in the non-lesioned hemisphere after stroke, resulting in increased inhibition on the lesioned hemisphere.[5, 6] Applying inhibitory current to the non-lesioned hemisphere may *disinhibit* this side and allow for recovery in the lesioned hemisphere.

IHI is mediated through fibers passing through the corpus callosum and can be examined non-invasively using TMS. First and foremost, IHI has been shown to exist in children and young adults[7, 8], indicating that this mechanism is not exclusively a feature of the developed adult nervous system. The effect of NIBS to modulated IHI has been demonstrated in adults with stroke, but less clearly in children. One reason for this is a lack of data characterizing IHI in children after perinatal brain injury. It is feasible, through ongoing adaptive and maladaptive neuroplasticity, that IHI is weakly present (or not at all) in these children as compared to adults. As studies continue to focus on NIBS interventions targeting the non-lesioned hemisphere, a more comprehensive understanding of the motor control mechanisms present in children with UCP is needed to guide these interventions. Therefore, one objective of this study is to characterize IHI of both brain hemispheres in children with UCP.

At the moment, it is unclear what the acute effects of a single session tDCS are, when paired with motor training, on brain excitability or motor performance in children with and without UCP. This leads us to designing the proposed study, which will offer insight into the mechanisms of tDCS and lead the field toward a better understanding of how tDCS be implemented in a neurorehabilitation setting for both children and potentially adults.

2.2 Preliminary Data: Data from our previous study using TMS demonstrates the potential effect of cathodal tDCS to decrease cortical excitability. In a subset of 10 children, five of who received real stimulation and five received sham stimulation, we observed a decrease in motor evoked potential (MEP) amplitude following the two-week intervention period (Figure 1). These results indicate a potential neurophysiologic effect on the non-lesioned hemisphere using a small dose (0.7 mA) of tDCS. No effects on the excitability of the lesioned hemisphere were noted.

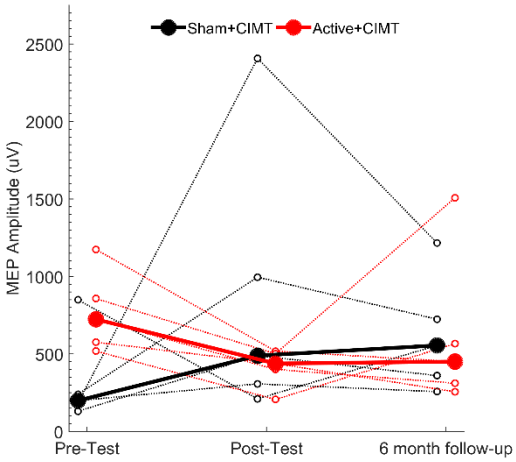

Figure 1. Change in brain excitability following tDCS. Children receiving cathodal tDCS (red line) showed a decrease in excitability compared to those in the sham group (black line).

2.3 Existing Literature*:* In one study of children with UCP, Kirton et al. used repetitive TMS to down-regulate the non-lesioned hemisphere, thereby decreasing IHI, in an effort to improve function of the more-affected upper limb.[9] They found increases in grip strength in a small sample after the real intervention compared to a sham intervention. The same group also explored IHI in CTD, showing that IHI decreased with age and was correlated with unimanual performance.

The proposed study will, at the moment, be the first to offer comprehensive data specifically on interhemispheric inhibitory control mechanisms in children with UCP. We predict that children with intact functional connections from the lesioned hemisphere will show IHI, while those with only connections from the non-lesioned hemisphere will not.

The neurophysiologic effects of tDCS have not been widely reported in children with UCP. One study showed an increase in lesioned hemisphere excitability following anodal tDCS following 10 sessions of combined motor training and tDCS.[10]

The proposed study is novel in that we will measure physiologic responses *immediately* following stimulation to capture the acute effect of the intervention and to potentially target its neural mechanisms. Immediate effects of tDCS are thoroughly described in healthy adult populations[4, 11] but are less described in people with neurologic conditions. Furthermore, comparing physiologic and behavioral responses with computational modeling of electric fields produced by tDCS is a novel approach toward predicting responsiveness to brain stimulation interventions. The results from this study will help guide future usage of combined tDCS and motor training interventions in larger clinical trials.

3.0 Study Endpoints/Events/Outcomes

3.1 Primary Endpoint/Event/Outcome: The primary outcome is magnitude of brain excitability as measured by motor evoked potentials from TMS. The primary behavioral outcome is time to complete a novel movement task.

3.2 Secondary Endpoint(s)/Event(s)/Outcome(s): The secondary neurophysiological outcomes are interhemispheric inhibition as measured by ipsilateral silent period (iSP) and paired pulse (PP) TMS (see *5.2* Study Procedures). The secondary behavioral outcomes are the Box and Blocks Test and Grip Strength. Safety and tolerability of the study, as measured through our participant-report of symptoms questionnaires, are also secondary outcomes.

4.0 Study Intervention(s)/Investigational Agent(s)

4.1 Description: Non-invasive brain stimulation has been recently investigated for benefits in recovery of motor function in adults[2] and more recently in children.[12, 13] 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[14] and 1.0 mA in children with hemiparesis.[15] Safety of tDCS is further demonstrated in a recent evidence based update with no reports of major adverse events following tDCS.[16] Transcranial Direct Current Stimulation (tDCS) will be used as an intervention, applying stimulation continuously over a period of 20 minutes.

Testing cortical excitability: Transcranial Magnetic Stimulation (TMS): We will use a Magstim Rapid[2] TMS stimulator (Magstim Corp, Dyfed, UK) 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.

We will use 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 MEP with electromyography (EMG) electrodes located over the target muscle.

Intervention: Transcranial Direct Current Stimulation (tDCS): One of two potential tDCS devices will be used. The first is a Soterix Medical 1x1 stimulator (Soterix Medical, New York, NY). This device is intended for the noninvasive stimulation of the cortex via transcranial current stimulation. The device is capable of direct current stimulation up to 1.5 mA 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 Limited Total Energy (LTE) device which provides built-in adaptation to resistance and current. These devices are 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.

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 magnetic resonance imaging (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.

Three-tesla (3T) Magnets for MRI will be used through the Center for Magnetic Resonance Research (CMRR). These devices pose a non-significant risk and have a claim of an abbreviated IDE.

4.2 Drug/Device Handling: All tDCS stimulators, electrodes, and related supplies will be stored in a locked closet inside the Gillick laboratory space, which requires keypad access. For each study, the research team will transport the device to the testing facility (Neuromodulation Lab, 717 Delaware Bldg.) for the day. The devices will be returned to the Gillick lab at the end of data collection.

IND/IDE:

Device	**510(k) Number(s)**	**Applicant**
TMS	K060847, K143531	Magstim Corp US, LLC Woburn, MA

tDCS	K170291	Soterix Medical Inc., New York, NY

5.0 Procedures Involved

5.1 Study Design: This is a randomized, sham-controlled, double-blinded study. The intervention consists of a single, 20 minute session of tDCS paired with motor training (see Figure 2). Participants will be randomized to either real or sham tDCS. The participants and the members of the research team involved in assessments and testing will be blinded to intervention group (real or sham tDCS), but the other research staff/PI/Co-Is will be unblinded.

5.2 Study Procedures:

Pre-study

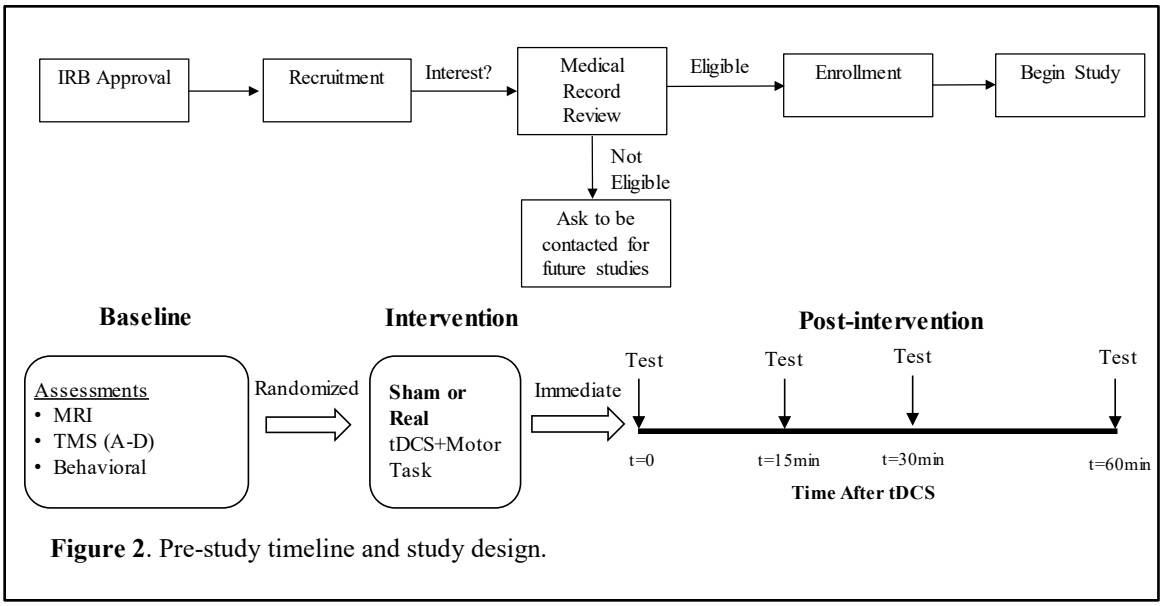

Figure 2. Pre-study timeline and study design.

Participant Screening and Enrollment

Participants will be initially screened for inclusion and exclusion criteria during a phone interview (Appendix A). Initial consent will be obtained over the phone to allow the caregiver to disclose protected health information (PHI) about his/her child. If the family is interested following this phone screen, we will obtain HIPAA consent to perform a medical record review (Appendix B and C). A review is then completed by the study medical director for review of inclusion/exclusion by history and MRI/CT radiographic reports of the brain (Appendix D). 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. A pre-study letter will then be sent (Appendix E). Informed consent/assent will be completed before on the day of the MRI acquisition.

The research team will utilize the CMRR Center's screening tools and adhere to the screening SOP during enrollment of all research participants in this protocol. The CMRR Center's screening tools and SOP are IRB approved under the CMRR Center Grant (HSC# 1406M51205) and information regarding screening procedures is publically available on the CMRR website.

Randomization

Participants will be randomly assigned to receive real or sham tDCS. Children with presence of a lesioned hemisphere MEP response may receive 1) ipsilesional anodal; 2) contralesional cathodal tDCS or 3) sham tDCS. Children without a lesioned hemisphere MEP may receive 1) contralesional anodal or 2) sham tDCS. Participants and their families will be blinded to group assignment. Participants will be unblinded after completing the study.

Magnetic Resonance Imaging (MRI) Acquisition

Location: Center for Magnetic Resonance Research (CMRR)

Time: 1 hour (including preparatory time)

MRIs will be performed at the CMRR on the University of Minnesota campus. We will obtain a structural image of brain anatomy to be used for stereotactic neuronavigation and individual brain modeling described below (Pre-Test Assessment: TMS and Computational Modeling).

Children and their caregivers will be screened using pre-approved CMRR safety screening forms. Children will change into scrubs and be given a "tour" of the scanning facility room. In our experience, this can alleviate anxiety related to MRI scanning in children. Caregivers will be allowed to watch through the control room window.

When ready, children will lie on the scanner bed comfortably with cushioning, pillows, etc. A movie of their choice will be projected behind them to watch during the scan. Scanning will consist of a localizer sequence (< 1min), and a T1-weighted magnetization prepared rapid acquisition gradient echo (MP-RAGE) sequence (spatial resolution 1 mm isotropic, < 6min), T2-weighted fast low-angle shot (FLASH) sequence (spatial resolution 0.7x0.7x4.0 mm, < 6min), a pair of diffusion scans (spatial resolution 1.5 mm^3), a task fMRI blood oxygen-dependent level (BOLD) scan and a resting-state fMRI BOLD scan (spatial resolution 2mm^3, TR = 0.8s, MB = 8). If image quality is not deemed acceptable, we will repeat the T1-sequence as needed. Children will be able to talk to the scan operator at any time.

Day of Study

Location: Non-invasive Neuromodulation Lab—Clinical and Translational Science Institute (CTSI) or Pediatric Brain Stimulation Lab—Center for Neurobehavioral Development (CNBD)

Time: 3 hours

Pre-Test Assessment: TMS

All procedures will be performed on the non-lesioned, then lesioned hemisphere unless noted otherwise.

A. Motor threshold (MT): To find the motor threshold, we will begin testing at the estimated location of the hand region of motor cortex as identified on the reconstructed brain image in the stereotactic neuronavigation system. We will test at 50% MSO. The motor threshold, is defined as the lowest stimulator output that produces MEPs of at least 50 μV on 50% (i.e. 5 of 10) trials. The location associated with the motor threshold is denoted as the motor hotspot. We will test up 100% MSO if tolerated by the participant to determine a motor threshold.

B. MEP Amplitude: Twenty pulses will be delivered at the motor hotspot using a testing intensity equivalent to 120% of the MT.

C. Cortical Silent Periods: Twenty pulses will be delivered at the motor hotspot using a testing intensity equivalent to 120% of the MT with the target hand muscle activated.

D. Paired-Pulse Assessment: Using two TMS coils, a conditioning stimulus will be delivered to one hemisphere at an intensity equivalent to 100% MT. Simultaneously, a test stimulus will be delivered to the opposite hemisphere at an intensity equivalent to 120% RMT. A total of 20 pairs of stimuli will be used (10 with interstimulus interval = 10 ms, ten with interstimulus interval = 0 ms), delivered in a pseudorandom order.

Pre-Test Assessment: Behavioral

We will use the Gross Motor Function Classification Scale Score (GMFCS), and the Manual Ability Classification System (MACS) as clinical characterization of each participant. Members of the research team will assess hand function using the following measures: Assisting Hand Assessment (AHA), Box and Blocks Test, Grip Strength Dynamometry, and Jebsen Taylor Test of Hand Function (JTTHF). A novel motor performance task will also be employed to assess motor performance and potential effects of tDCS on motor learning.

Intervention

The intervention will last a total of 30 minutes, including preparatory time. Before stimulation, the area of skin underneath the electrode will be inspected for abrasions/lesions and then cleaned with an alcohol swab. We will use an M1-SO electrode montage, where one tDCS electrode is placed on the motor hotspot (M1) as determined by TMS testing, and the other electrode is placed on the supraorbital prominence (SO) of the opposite side. Sanitized rubber electrodes housed in single-use, sterile 3 cm x 5 cm sponges moistened with saline will be placed on the stimulation sites and held in place by elastic bands. To ensure adequate electrical conductance, care is taken to maintain firm contact of the sponge to the scalp. The static

impedance measurement is checked and stimulation does not proceed unless levels are within limits recommended by the tDCS device manufacturer.

Children in the sham group will receive the same procedures as the active tDCS group, yet the device will be set to an integrated sham 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.

After the first 2 minutes of stimulation, the participant is questioned about pain at the electrode sites. If the stimulation is painful, a small amount of additional saline (2-4 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 intensity is decreased, and symptoms re-assessed. If pain still persists, stimulation is stopped and the electrode sites are checked. This procedure is repeated twice (every 5 minutes during tDCS) with saline solution (2-4 mL) added as needed.

Participants will receive a total of 20 minutes of active or sham tDCS. During stimulation, participants will practice the novel reaching task described above at a comfortable pace. No conversations between participant and researchers or caregivers will be allowed, except those that pertain to safety.

Post-intervention Assessments

Immediately following the intervention, TMS and Behavioral assessments will be performed at 0, 15, 30, and 60 minutes following the intervention (see Figure 2).

Other Procedures

Computational Modeling

Computational modeling of electric fields produced by tDCS will be performed using SimNIBS (Simulation of Non-invasive Brain Stimulation). Using T1-anatomical images, individual skull and brain anatomy will be reconstructed, and electric fields computed using a finite element method. The primary outcome is the estimated peak electric field strength for the M1-SO montage.

Safety Monitoring

We will use questionnaires (Appendix F) to document symptoms associated with non-invasive brain stimulation before and after the intervention and testing session. This tool asks participants about the presence and severity of symptoms such as tingling, itchiness, and headache. We will also measure heart rate and blood pressure before and after the procedures.

Follow-Up: A member of the research team will contact each participant and their caregivers within one week of completing the study to check for any adverse events. There is no long-term follow-up data collection planned.

5.3 Study Duration: Each participant will complete the study in either one day (MRI and intervention, four hours total) or on two separate days (one hour MRI, and three hours intervention). If done on two days, the MRI and intervention will be separated by no longer than a two week (14 day) period.

We expect to enroll all participants, both CTD and children with UCP, in a 24-month time period after the approval of the study.

All study procedures and data analysis will be completed within 36 months from the approval of the study.

5.4 Individually Identifiable Health Information: Protected Health Information will be obtained from participants in this study. A HIPAA authorization release form will be signed by the participant (if older than 18) or the parent/legal guardian of the participant (if younger than 18) to allow the researchers to use this information for research purposes.

5.5 Use of Radiation: N/A

5.6 Use of Center for Magnetic Resonance Research*:* This research will involve the Center for Magnetic Resonance Research (CMRR) facilities. See attached Pre-IRB approval from the CMRR.

6.0 Data and Specimen Banking

6.1 Storage and Access: Urine specimens will be obtained for pregnancy testing (Icon 25HCG One-Step, Beckman Coulter, Brea, CA) of all pubescent females and immediately used for assessment of pregnancy status. Specimens are discarded at the CTSI through specimen procedures.

6.2 Data: No data elements will be collected and banked

6.3 Release/Sharing: The results of pregnancy tests, if positive, will not be shared with the participant or his/her caregiver. Instead, they will be informed that they no longer meet the inclusion/exclusion criteria to continue in the study.

7.0 Sharing of Results with Participants

7.1 This study is not designed to produce a direct benefit to the participant. We will not share specific individual results with participants and families. At the time of publication of any manuscripts associated with this study, we will send a lay summary and a copy of the article to each participant and their family.

8.0 Study Population

8.1 Inclusion Criteria: Participants with UCP must have a clinical diagnosis of cerebral palsy with confirmed radiologic evidence of hemispheric stroke or periventricular leukomalacia.

All participants (UCP and CTD) will be eligible if they meet all of the following criteria:

1. Aged between 7 years 0 days and 21 years, 355 days (see *10.2 Vulnerable Populations)*

2. Able to give informed assent (if under 18 years of age)

3. Able to follow 2-step commands

4. Presence of an MEP in the less affected (UCP) or non-dominant (CTD) hand when stimulating the non-lesioned hemisphere

8.2 Exclusion Criteria: Participants will be excluded if they meet any of the following criteria:

1. Evidence of a seizure within the past two years
2. Other neurological or metabolic conditions/diagnoses
3. Treatment with injectable agents (e.g. Botox) for spasticity management
4. Is pregnant (females only)
5. Presence of indwelling metal in the head (e.g. aneurysm clip) or medical device. Dental braces are allowable if approved by the CMRR safety monitor and PI.

8.3 Screening: Participants 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 record by the PI and Medical Director, and is again repeated in-person by reviewing the medical record (Appendix D). All pubescent (verification of menstrual cycle from caregiver/parent) female participants will need to take a urine pregnancy test. If the test is positive, the participant will be excluded from the study as the safety of use of tDCS and TMS during pregnancy has not been established.

The research team will utilize the CMRR Center's screening tools and adhere to the screening SOP during enrollment of all research participants in this protocol. The CMRR Center's screening tools and SOP are IRB approved under the CMRR Center Grant (HSC# 1406M51205) and information regarding screening procedures is publically available on the CMRR website.

9.0 Vulnerable Populations

9.1 Vulnerable Populations:

☒ Children

☐ Pregnant women/Fetuses/Neonates
☐ Prisoners

- ☐ Adults lacking capacity to consent and/or adults with diminished capacity to consent, including, but not limited to, those with acute medical conditions, psychiatric disorders, neurologic disorders, developmental disorders, and behavioral disorders
- ☐ Approached for participation in research during a stressful situation such as emergency room setting, childbirth (labor), etc.
- ☐ Disadvantaged in the distribution of social goods and services such as income, housing, or healthcare
- ☐ Serious health condition for which there are no satisfactory standard treatments
- ☐ Fear of negative consequences for not participating in the research (e.g. institutionalization, deportation, disclosure of stigmatizing behavior)
- ☐ Any other circumstance/dynamic that could increase vulnerability to coercion or exploitation that might influence consent to research or decision to continue in research
- ☐ Undervalued or disenfranchised social group
- ☐ Members of the military
- ☒ Non-English speakers
- ☐ Those unable to read (illiterate)
- ☐ Employees of the researcher
- ☐ Students of the researcher
- ☐ None of the above

9.2 Additional Safeguards: We are studying children and young adults aged 7-21 with a specific diagnosis of cerebral palsy. As we are a pediatric laboratory with experienced pediatric researchers, clinicians and trainees, comprehensive efforts have been made to ensure that our procedures are developmentally appropriate to both child and family. Recruitment materials, study information, and conversations are tailored to a pediatric population. Participant-specific study materials are provided before participation in interventions and testing sessions, and age-appropriate adaptations for each procedure/test are used. Our team has created videos that help explain the research and procedures to families. These videos can be viewed at any time before enrolling or participating in the study. (Gillick Lab Video; TMS Video). We also have a network of past participant families who have offered to share their experiences in our research studies with potential participants.

For MRI testing, we introduce children to the MRI environment with a mock scanner, consisting of a "tunnel" in which children can lie. This provides an indication of the dimensions of the actual scanner. We will provide audio files of scanner sounds to familiarize children with MRI sounds. During the actual scan, children can watch a movie or listen to music. Although the caregivers will have the ability to see their child in the scanner from the control room, if necessary, a caregiver may stay with the

child in the scanner room (assuming the caregiver meets all MRI safety criteria). Children and families will be given the opportunity to tour the TMS testing intervention rooms to ask questions about the equipment and technology.

During the intervention and testing session, behavioral and environmental strategies will be implemented for all children to optimize tolerance and completion of each session. These may include but are not limited to: predictable routines, visual timer, distraction techniques, child-friendly descriptive language, and positioning.

Our team is trained to be attentive to the child's mood and comfort, which are important factors when asking children to engage in long testing sessions. Throughout their participation, the research team will continually check in with the participants for real-time verbal feedback on their experience. We recognize the value and importance of feedback from children and families about their experience during the study, and have developed surveys to collect this type of information (Appendix G). We will continue to adapt study procedures based upon this feedback. We will provide drinks and snacks throughout the child's participation in the study and provide breaks as necessary.

For non-English speaking participants, we will work with the IRB and other community groups to provide all information in the participant's native language.

10.0 Local Number of Participants

10.1 Local Number of Participants to be Consented: Based on recruitment in previous studies in this population performed by our lab, we expect that about 75% of our sample of children with UCP will reside in the state of Minnesota. The remaining 4 participants will be recruited from the greater Midwestern and Western regions. We expect to enroll all CTD from the greater Twin Cities Metropolitan area. The maximum number of enrolled participants is 40 children with UCP and 10 CTD.

11.0 Local Recruitment Methods

11.1 Recruitment Process: Recruitment will take place immediately after approval and continue, at the latest, through the 24th month of the study. We expect most participants will be recruited from the state of Minnesota. Based on our previous recruitment data, approximately 25% will reside in other states.

We will use established databases from our previous work, totaling nearly 400 children with UCP who, barring changes in medical status, meet the proposed study criteria. In addition, we will recruit using the following sources/methods: other existing databases, newspaper advertisements, television/radio programs, webpages (the Children's Hemiplegia and Stroke Association (chasa.org), HemiKids website (http://www.hemikids.org/),

ResearchMatch.com), social media, and clinician contact postings We have experienced exceptional participation (increase in overall enrollment in our studies from 9% to 14% over the last 5 years), retention (100% in 3 studies of 50 total children), and adherence (99.8%) in our trials of over 539 total visits.

Source of Participants: With IRB approval, we will screen children for research recruitment through physician-based referrals. This has been our most effective recruitment tool to date (>57% of referrals) and will allow expansion of our current database. Additional sources are the local, state, and national communities that respond to advertisements and postings on websites described in Section 12.1

11.2 Identification of Potential Participants: All interested caregivers/participants will be screened on the telephone by the study coordinator or an authorized member of the research team to determine if the child meets the inclusion/exclusion criteria using IRB-approved pre-screening forms (Appendix A). Following telephone screen, we will send the caregiver/participant a medical record release form that grants release of their child's medical records to further determine eligibility (Appendix B and C). When we receive this signed form, we will submit it to the appropriate hospital/clinic. The medical director will review the medical records for appropriate inclusion.

11.3 Recruitment Materials: We will use emails (Appendix H) and printed flyers (Appendix I) to advertise this study.

11.4 Payment: Participants will be paid $50 in the form of a debit card after completing the study. The Greenphire ClinCard will be used for payments. Payment will be made using a pre-paid debit card called Greenphire ClinCard. It works like a bank debit card. We will give you a debit card and each time you receive a payment for participation in this study, the money will be added to the card after each completed visit.

You may use this card at any store that accepts MasterCard or you can use a bank machine to remove cash. However, there may be fees drawn against the balance of the card for cash withdrawals (ATM use) and inactivity (no use for 3 months). We will give you the ClinCard Frequently Asked Questions information sheet that answers common questions about the debit card. You will also receive letters with additional information on how you can use this card and who to call if you have any questions. Be sure to read these letters, including the cardholder agreement, for details about fees.

The debit card system is administered by an outside company. The company, Greenphire, will be given your name. They will use this information only as part of the payment system. Your information will not be used for any other purposes and will not be given or sold to any other company. Greenphire will not receive any information about your health status or the study in which you are participating.

Any demographic information collected and provided to Greenphire is stored in a secure fashion and will be kept confidential, except as required by law.

Payment you receive as compensation for participation in research is considered taxable income. If payment to an individual exceeds $600 in any one calendar year, the University of Minnesota is required to report this information to the Internal Revenue Service (IRS). Research payments to study participants exceeding $600.00 during any calendar year will result in a FORM 1099 (Miscellaneous Income) being issued to you and a copy sent to the IRS.

At the end of the study, you will be provided with information regarding how your hand movements changed before and after the intervention. This information is not intended to have clinical significance.

12.0 Withdrawal of Participants

12.1 Withdrawal Circumstances: Participants will be withdrawn from the study under any of the following scenarios:

Death: Study stopped for both individual and entire trial. Full investigation of event explored by entire study team. Medical monitor to review all details. Report of event will be distributed to all governing and monitoring committees.

Seizure—Individual: If at any time during the study procedures a participant experiences a seizure, testing will be immediately suspended for that individual and the study team will follow seizure management guidelines. Refer to comprehensive seizure management outline (Appendix J) and the complete seizure observation documentation form (Appendix K). A letter from the Study Physician will be sent to the participant. (Appendix L). The medical director will recommend further evaluation of the child by pediatric neurologist or pediatrician routinely involved in the child's care.

An identification of causality and re-evaluation of treatment design will be performed 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, the error will be corrected.

Seizure—Multiple: If more than one individual experiences a seizure during the participation in the study, the entire study will be stopped and a thorough review performed by the research team and medical monitor. If a change in protocol is deemed necessary for the safety of participants, an amendment will be submitted to the IRB.

12.2 Withdrawal Procedures: If a participant voluntarily withdraws, we will ask the participant if we can continue to use information collected from any data collected up until that point. They will have the option to re-enroll at a later time if desired.

12.3 Termination Procedures: If a participant is removed from the study by one of the investigators, any data collected up until the point of termination will be used after termination.

13.0 Risks to Participants

All research procedures will be performed by experienced personnel who have completed required training, including human participants, HIPAA, and CMRR training.

13.1 Foreseeable Risks: The tables below outline the anticipated risks associated with tDCS, TMS, and MRI, our plan to mitigate each risk, and the probability of each risk (Improbable--No reported cases, unlikely (few reported cases), likely (many reported cases). Most risks are reversible with proper medical care/treatment, however there is less information on this aspect of risk mitigation.

Risks Associated with Transcranial Direct Current Stimulation (tDCS)		
Anticipated Risks	**Risk Mitigation**	**Probability of Risk**
Burn- Electrolysis	Ensure proper electrode contact with skin	Unlikely
Stimulation in participants with reduced sensation	Assess sensation, avoid placing electrodes over areas of decreased sensation	Unlikely
Stimulation over broken skin, reduced resistance	Assess skin integrity, avoid placement of electrodes over recent shaving, skin defects	Unlikely
Stimulation over conductive implants	Screen appropriately for exclusion criteria of implants	Improbable
Stimulation over a tumor which may alter metabolic activity	Screen appropriately for exclusion criteria of neoplasm.	Improbable
Threshold altering pharmacologic agent	Physician review of each medical record for determination of appropriateness for study inclusion.	Improbable/Unknown
Itching, Tingling, Burning Sensation	Ensure proper contact of surface electrodes with skin. Maintain	Likely

in the area of the electrodes	current dosage within low-range of researched dosages. Ensure that electrode sponges are properly sanitized and that saline solution is appropriately employed.	
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.	Likely
Pain- Neck, Scalp	Ensure that electrodes are in proper contact with skin and adjust head position as needed for comfort.	Unlikely
Skin Redness	Ensure proper electrode position and proper level of moisture to even stimulation across the electrode	Likely
Fatigue, Sleepiness	Screen for continuous effect at follow-up visit.	Unlikely
Concentration or Mood Changes	Evaluate cognitive status through physician examination and psychometric testing at three time points.	Unlikely

Risks Associated with Transcranial Magnetic Stimulation (TMS)		
Anticipated Risks	**Risk Mitigation**	**Probability of Risk**
Stimulation over a tumor which may alter metabolic activity	Screen appropriately for exclusion criteria of neoplasm.	Improbable
Threshold altering pharmacologic agent	Physician review of each medical record for determination of appropriateness for study inclusion.	Improbable
Headache	Screen for continuous effect throughout session through	Likely

	planned and spontaneous inquiry as well as invitation to report discomfort at any time.	
Fatigue, Sleepiness	Screen for continuous effect throughout session through planned and spontaneous inquiry as well as invitation to report discomfort at any time.	Likely
Temporary mild hearing loss due to noise level of equipment	Ear plugs will be inserted before commencement of TMS application.	Unlikely

We will use IRB-approved screening forms provided by the CMRR to screen both participants and caregivers accompanying participants. This screening will occur immediately prior to scanning.

Risks Associated with Magnetic Resonance Imaging (MRI)		
Anticipated Risks	**Risk Mitigation**	**Probability of Risk**
Claustrophobia	Screening for history of fear of small spaces, introduction of MRI environment before scanning	Likely
Metal projectiles	Thorough participant and caregiver screening before scan, high-quality safety practices of research team	Unlikely
Interruption of implanted medical devices or dislodging of indwelling metal	Review of medical records, thorough participant and caregiver screening before scan	Improbable
Other physiologic responses (nausea, headache, muscle stiffness)	Emphasize hydration and ensuring rest before scanning	Unlikely
Effects on unborn fetus	Pregnancy screening of females	Improbable
Dizziness following scan (orthostatic response to lying down)	Moving from a supine to sitting position after completion for 1-2 minutes, accompanying child out of the scanner room	Likely
Temporary mild	Use of foam ear plugs to	Unlikely

hearing loss due to scanner noise	reduce noise intensity before scanning	

13.2 Reproduction Risks: Both TMS and MRI have unknown risk on the fetus. Therefore, any pregnant women will not be allowed to participate.

13.3 Risks to Others: For parents/guardians accompanying participants in the CMRR, they are subject to some of the risks associated with MRI scanning. Therefore, all individuals accompanying the participant will be screened using CMRR screening tools.

14.0 Potential Benefits to Participants

14.1 Potential Benefits: There may be a short-term benefit in movement function from a single-session of tDCS, as described in other studies.[17, 18] However, this benefit is not expected in our participants with UCP, nor is the objective of the study to improve movement function or control.

There is no direct benefit to CTD from participation in this study. We do not expect a single-session of tDCS to significantly alter movement function in these children, however improvements in motor learning have been demonstrated in CTD following tDCS.[14] The safety of tDCS has been clearly demonstrated in children ages 7-21 in our previous work[19] (and Gillick et al. In Review) and other systematic reviews.[16, 20, 21] Therefore, we justify using CTD in our study as a scientifically-sound comparison group.

15.0 Data Management

15.1 Data Analysis Plan: Baseline and demographic information will be summarized by descriptive statistics for continuous variables, and the number and percentage of participants in each category for categorical variables. The primary analysis will compare changes in behavioral and neurophysiologic measures between the two intervention groups (real and sham tDCS). When possible, we will use repeated measures ANOVA to account for differences between groups. If measures are non-normally distributed, we will use Wilcoxon signed-ranks tests. We will use correlation analysis to compare modeled peak electric field strength with changes in behavioral and neurophysiologic outcomes.

Summary of power analysis with alpha of 0.0125 and N per group of 8

	MEP		
Correlation	Δ	SD	Power
0.3	0.75	0.5	0.71
0.4	0.75	0.5	0.75
0.5	0.75	0.5	0.81
0.6	0.75	0.5	0.87
0.7	0.75	0.5	0.94

15.2 Power Analysis: With the data and literature available, we completed power calculations for the primary neurophysiological outcome, MEP, and the behavioral clinical outcome, the Assisting Hand Assessment (AHA) scaled score (Table 2). These were based on the difference between the pre- and post-test measurements

adjusting for baseline values, similar to ANCOVA analyses, for added precision. These calculations used the sample size formula for normally distributed statistics with a Bonferroni corrected type I error level of 0.0125 for the four potential primary comparisons between the: 1) Anodal Ipsilesional tDCS group versus $Sham_c$ tDCS, 2) Cathodal Contralesional tDCS versus $Sham_c$ tDCS, 3) Anodal Ipsilesional tDCS group versus Cathodal Contralesional tDCS, and 4) Anodal Contralesional tDCS versus $Sham_i$ tDCS to maintain an overall type I error level of 0.05. Power was computed for 8 participants per treatment group across a range of possible values for the correlation between pre- and post-treatment measurements. These were computed for a change in the MEP of 0.75 mV. The mean change and standard deviation of the MEP in the study population was based on the tDCS/CIMT study. The correlation between pre- and post-treatment MEP in the tDCS/CIMT study was approximately 0.5. Based on these estimates, we will have 81% power to detect a change in the MEP of 0.75 mV, which translates into a large effect size (Cohen's d = 1.5).

15.3 Statistical Analysis: Descriptive analyses of baseline characteristics and outcomes will include means and standard deviations for continuous variables and frequencies for categorical variables. Compliance and tolerance of the intervention will also be evaluated. Safety analyses will be primarily descriptive reporting the number and percentage of any adverse events and will be evaluated and monitored throughout the trial.

This analysis will be conducted based on the intent-to-treat principle to compare the mean neurophysiologic change measured using the MEP from pre- to post- intervention between each tDCS stimulation dose group and sham tDCS adjusted for baseline neurophysiologic measures. Confidence intervals and p-values will be based on robust variance estimation. Statistical significance will be considered as $p<0.0125$. Supportive analyses may be conducted with consideration of adjustment for residual imbalances between treatment groups after randomization (e.g., gender). The primary analysis will evaluate the change between pre- and post- measurements. A secondary analysis will evaluate the change between pre- and 30 minutes post.

15.4 Data Integrity: See section *18.1*

16.0 Confidentiality

16.1 Data security: 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.

As disclosure of PHI is an aspect of participation in this study, there is a potential risk of unauthorized disclosure of PHI. To prevent this risk, we collect and store all PHI in a locked filing cabinet located in our keypad-controlled laboratory. Electronic PHI will be stored on HIPAA-compliant RedCap repositories. Pictures and other collected PHI will be stored on the University of Minnesota Box account, which is approved for the storage of PHI. No copies of the consent will be associated with the participant's medical or employment record.

17.0 Provisions to Monitor the Data to Ensure the Safety of Participants

17.1 Data Integrity Monitoring.

There will not be a designated data integrity monitor associated with this study. Instead, the PI will work with the study coordinator to ensure all data is collected, recorded, and maintained properly, and that regulatory and compliance procedures are followed accordingly.

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 participant enrolled into the clinical study. The investigator will review, approve and sign/date each completed CRF. The investigator's signature serves as attestation that all clinical and laboratory data entered on the CRF are complete, accurate and authentic.

The CRF shall contain at a minimum the following components:

1) Eligibility documentation, Phone Screen Form
2) HIPAA Form
3) Demographic Medical History Form
4) Individual Data Collection Forms
5) Exit and Survey Forms

Record Handling: Data for this study will be entered by the research investigators and study coordinator immediately into the case report form (CRF) for each participant. The data will then be entered into aa 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.

Record Keeping: All records and CRFs will be kept in the study coordinator's locked file cabinet in her office until completion of the study. Thereafter the PI will maintain all records for 6 years.

17.2 Data Safety Monitoring.

Adverse Event

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

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 participant, and may require intervention to prevent one or the other serious outcomes noted above.

Individual and Entire Study Stopping Rules

a. Death. Study stopped for both individual and entire trial. Full investigation of event explored by entire study team. The PI and Medical Director will review all details. An event report will be distributed to all governing and monitoring committees.
b. Transient Functional Decline in Motor and/or Cognitive ability.
    i. Entire Trial: After the first half of participants are enrolled, the PI will perform an interim safety analysis to determine if the intervention is causing harm. The primary outcome will be performance on the reaching task. We will also consider reports of any adverse events during the study or that occur after participation during a follow-up phone call with the family/participant. If the difference between sham and real tDCS groups exceeds 2 standard deviations in favor of sham tDCS, the study will be stopped at this interim for review by the PI and medical director. If they deem that the protocol has indications for change due to the differences between means, the study will be reviewed by the investigative team and will be changed and submitted for re-approval by the IRB before recommencing the study.

c. Seizure
    i. Individual: Removal of child from the study and from any remaining study procedures. Initiation and follow-through of safe and effective

seizure management. Refer to comprehensive seizure management outline (Appendix J) and the complete seizure observation documentation form (Appendix K). Provide Physician letter to participant. (Appendix L).
Study Medical Director Evaluation. Recommend further evaluation to the child and legal guardian for evaluation by pediatric neurologist if not the pediatrician routinely involved in the child's care.

If participant and caregiver are willing, we will assess post-seizure status and potential change of status.

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.

ii. Entire Study: If another participant incurs a seizure, proceed with steps for Individual Stopping Rules for Seizure (18.2.c.i). Study will be suspended at this point and thorough review by research team, medical director 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.

1. All research procedures will be performed by qualified personnel who have completed required training, including human subjects training. Clinical procedures will be conducted only by personnel who are qualified by training and licensure to perform the procedures.

2. 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 (CRF) will be stored in locked offices and not released without participant permission.

3. Participants 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 record by the PI and Medical Director and Pediatric Neurologist on the study and is again repeated in-person by reviewing the screening documentation.

4. AEs and SAEs will be assessed and followed throughout the study using tools developed by our laboratory (Appendix F). Vital sign monitoring will occur before and after the information.

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

18.0 Provisions to Protect the Privacy Interests of Participants

18.1 Protecting Privacy: Information about study participants 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 participant authorization informing the participant of the following:

- What protected health information (PHI) will be collected from participants in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research participant to revoke their authorization for use of their PHI.

In the event that a participant revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of participant authorization. For participants 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 participant is alive) at the end of their scheduled study period.

For participants under the age of 18: All consent/assent procedures will be done with at least one parent/legal guardian present. During all study procedures, participants will be accompanied by at least one parent/legal guardian, or an authorized proxy of the parent/legal guardian (e.g. grandparent), which we will refer to as the caregiver. We encourage the caregiver to remain with the child participant for the duration of the study. At minimum, the caregiver must be in the same building where the study is being conducted.

We will provide ample time to answer questions before enrolling in our study. We also will provide resources (Gillick Lab and TMS) that describe our study procedures to prepare children and families for their experience. Our experience working with children and their families has made us aware of the importance of gathering feedback, listening to parent's questions/concerns, and adapting our procedures to best meet these needs.

18.2 Access to Participants: Participants will be given a HIPAA Authorization form authorizes the research team to collect PHI once enrolled in the study. This form is optional and enrollment is not contingent on this form being completed. We do not anticipate collecting additional medical information after enrollment in the study.

19.0 Compensation for Research-Related Injury

19.1 Compensation for Research-Related Injury: There is no compensation for any research-related injury. Any injury that does occur will be billed to the participant's health insurance.

19.2 Contract Language: N/A

20.0 Consent Process

20.1 Consent Process:

Consenting will take place immediately prior to beginning the study procedures. Parents/participants will have the opportunity to review the consent form beforehand. Consent may also take place over video (e.g. FaceTime or Skype) before participating in the study. Both parents and child will be present on screen. Written documentation of video-based consent processes will be included in the CRF.

The formal consent/assent of a participant, using the IRB-approved consent/assent form, must be obtained before that participant undergoes any study procedure. This consent form must be signed by both legal guardians and the assent form must be signed by the pediatric participant. The authorized member of the research team who obtained consent/assents will sign both the forms. The forms will be kept in each participant's CRF.

20.2 Waiver or Alteration of Consent Process: N/A

20.3 Non-English Speaking Participants:

For non-English speaking participants and families interested in participating, we will use an interpreter to orally provide information about the study. For the consent process, the written consent document will be read by an interpreter to the participant/family in their native language. A translated short form will also be provided in their native language.

We will use an interpreter to accompany the participant/family during the study procedures to help with communication.

20.4 Participants Who Are Not Yet Adults (infants, children, teenagers under 18 years of age):

Assent will be obtained using the Assent Script (Appendix M) from all child participants deemed capable by the IRB (older than 7 but younger than 18 years of age) in addition to the Informed Consent of the legal guardian in accordance with Federal Regulations and/or the qualifying Institutional Review Board (IRB). A copy of the Assent form (Appendix N) signed by the child and the authorized research team member obtaining assent will be kept in the participant's CRF.

Both parents/legal guardians will sign a written consent form (Appendix O) describing this study and be provided sufficient information for an informed

decision about the participation of their child in this study. The signature of a single parent/legal guardian will be permissible in the following situations:

- The second parent/legal guardian is deemed legally incompetent
- The second parent/legal guardian does not have legal custody of the child

In these cases, documentation will be provided with the consent form.

21.0 Setting

21.1 Research Sites: Potential participant will be recruited from the following sources:

- Gillick lab databases (previous and interested families)
- Newspaper and radio/television advertisements
- CHASA (Children's Hemiplegic and Stroke Association) website
- ClinicalTrials.gov website
- Hemikids website
- ResearchMatch website
- Social media
- Clinician referrals

Research procedures will take place at the following centers/buildings on the University of Minnesota Twin Cities campus: Center for Magnetic Resonance Imaging (CMRR), the Clinical and Translational Science Institute (CTSI), and the Center for Neurobehavioral Development (CNBD).

22.0 Multi-Site Research

N/A

23.0 Resources Available

23.1 Resources Available:

Recruitment Resources

We are confident in our ability to recruit the intended sample from this study. Our current database contains over 400 families and we regularly receive inquiries into our current studies. In our most recent study, which completed two years ahead of schedule, we enrolled 20 out of 141 interested families.

Therefore, we intend to complete this research, once we obtain approval, in two years.

Facilities

The Clinical and Translational Science Institute (CTSI) at the UMN offers comprehensive research support for clinical investigators, from concept through publication. The mission of CTSI is to accelerate discoveries that will impact human health at the level of individuals and populations.

The Non-invasive Neuromodulation Laboratory (NNL) is within the CTSI facility and houses our equipment and supplies. The NNL is supported by MnDRIVE (Minnesota's Discovery, Research and InnoVation Economy) program which is a landmark partnership between the university and the state of Minnesota. The program of Brain Conditions includes non-invasive neuromodulation and supports a Non-invasive Neuromodulation Laboratory specifically for helping faculty members and staff conduct their neuromodulation related experiments. The NNL has a space of 500 square feet for experiments and consenting paperwork. Parking is free and easily accessible for participants. With equipment and facilities, the NNL is able to conduct all of the non-invasive TMS excitability assessment and neuromodulation paradigms including cortical excitability assessment (TMS using EMG and stereotactic neuronavigation equipment and supplies), neuromodulation interventions (tDCS), sensory function evaluation and customized protocol training. The CTSI/NNL is located one block from the University of Minnesota Medical Center, which offers emergency medical services in the event of an injury or serious adverse event during the study.

The Center for Magnetic Resonance Research (CMRR) is a world-renowned, interdisciplinary research facility providing state-of-the-art instrumentation, interdisciplinary research expertise, and infrastructure to carry out biomedical research utilizing the unique capabilities provided by high field MRI. The central aim of the research conducted in CMRR is to non-invasively obtain functional, physiological, and biochemical information in intact biological systems, and use this capability to probe biological processes in health and disease. The Center is housed in a freestanding ~34,000 square foot facility and is equipped with multiple high-field magnets with field strengths ranging from 3 to 10.5 Tesla for humans and up to 16.4 for animals. Three private rooms for participant screening and consultation are also available. Parking is free and easily accessible for participants. The CMRR is conveniently located on campus and available for testing 24 hours a day, 7 days a week.

Located one floor above the CTSI, the Center for Neurobehavioral Development (CNBD 9000 sq. ft.) is an inter-disciplinary setting for psychological, developmental, and cognitive neuroscientists to conduct studies. Its mission is to engage in basic and clinical research addressing the underlying mechanisms of typical and atypical neurobehavioral development. Currently,

the CNBD supports over 35 studies investigating children's cognitive and neurobehavioral functioning. The CNBD provides a family-friendly research environment, with free and easily accessible parking, sibling care, a caregiver waiting room and child playroom available to families in testing. The PI is a faculty member of the CNBD.

Study personnel training

All research team members will be trained in the Good Clinical Practice of conducting research, including HIPAA and Responsible Conduct of Research training. In addition, all members will be have completed CMRR safety training and lab-specific protocol training as related to TMS and tDCS procedures. For each study procedure, there will be present a minimum of two research team members.

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