Remotely Monitored Transcranial Direct Current Stimulation in Children With Cerebral Palsy

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Remotely Monitored Transcranial Direct Current Stimulation in Children with Cerebral Palsy

Protocol Number: 2021-0691

Principal Investigator: Bernadette Gillick

IDE Sponsor: [Bernadette Gillick]

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Protocol Version History

Protocol Version	Version Date	Summary of Revisions Made	Rationale
1.0	08/30/2021	Initial version	
2.0	07/18/2022	- Add safety monitor team member to be on site to monitor safety - Change the Soterix Medical 1x1 tDCS mini-CT stimulator to the Soterix 1x1 LTE tDCS stimulator. - Add recruitment methods: self-identify and flyers - Study Coordinator changed - Remove Preparation	-Increases the safety for the participants within the study -The Soterix LTE tDCS device has been safely and feasibly used over the last decade with IRB approvals and FDA IDE exemptions

		- Add references - Device will not be mailed to home	-Preparation referred only to the mini-CT stimulator device and not the LTE device - Safety monitor will bring device and take after each session
3.0	9/15/22	- Change inclusion criteria to specify hemiparetic CP with history of perinatal brain bleed/stroke - Add the possibility to use mock device in training - Editorial changes	- The study was intended to specifically include children with CP as a potential future target for interventions - The goal of the study to justify feasibility of teleneuromodulation is enhanced by giving participants as much independent training as possible - Clarity
4.0	10/18/22	-Addition of vital measurements pre/post stimulation sessions 2-5 -Box and blocks test and adverse event survey will now also be during session 2 as it is during 3-5 -Addition of new recruitment strategies -clarification of intellectual disability population - removal of device log which is not needed - clarification of screening procedures and inclusion of more parental demographic information -potential for more than one study monitor in the home	-Increase safety of participant by monitoring vitals throughout and motor function and adverse events even during sham stimulation -Other changes were to clarify procedures already approved - added additional recruitment measures to ensure we could enroll enough participants in the short timeframe we have - ensuring safety for the study monitors
5.0	12/14/22	- Adding MRI screening visit - Adding AE surveys to Session Day 1 - Adding a therapy questionnaire	- Adding AE surveys to Day 1 will give us good baseline information for whether just wearing the device without stimulation affects the subject - Previously we have discussed acquiring information but did not have a formal survey for assessing this information
6.0		Expanding age range to 21 years	
7.0	3/23/23	Allow participation from participants 18-21 who have a legally authorized representative and lack the capacity to consent to study participation	

8.0	5/4/23	-Changing funding source -Adding an optional 6 month follow up study	Allows us to follow up on the health and motor function of individuals who participated in receiving tDCS stimulation in this study

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1.0 STATEMENT OF COMPLIANCE

I confirm that I have read this protocol. I will comply with the IRB-approved protocol, and applicable regulations, guidelines, laws, and institutional policies.

I agree to ensure that all study team members involved in the conduct of this study are informed about their obligations in meeting the above commitment.

Name	Signature	Date
_____ Principal investigator	_____	_____
_____ Sponsor	_____	_____

2.0 LIST OF ABBREVIATIONS

AE	Adverse Event
CFR	Code of Federal Regulations
CP	Cerebral Palsy
C-PROGRESS	Center for Pediatric Rehabilitation: Growing Research, Education, and Sharing Science
CTMS	Clinical Trial Management Software
DHHS	Department of Health and Human Services
DSMC	Data & Safety Monitoring Committee
DSMP	Data & Safety Monitoring Plan
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
IDE	Investigational Device Exemption
ICTR	Institute for Clinical and Translational Research
IND	Investigational New Drug Application
IRB	Institutional Review Board
MRI	Magnetic Resonance Imaging
NIH	National Institutes of Health
OHRP	Office for Human Research Protections
OnCore	Online Collaborative Research Environment
PI	Principal Investigator
REDCap	Research Electronic Data Capture
SAE	Serious Adverse Event
SMC	Safety Monitoring Committee
SMP	Study Monitoring Plan
tDCS	Transcranial Direct Current Stimulation
UP	Unanticipated Problem
UP	Unanticipated Problem

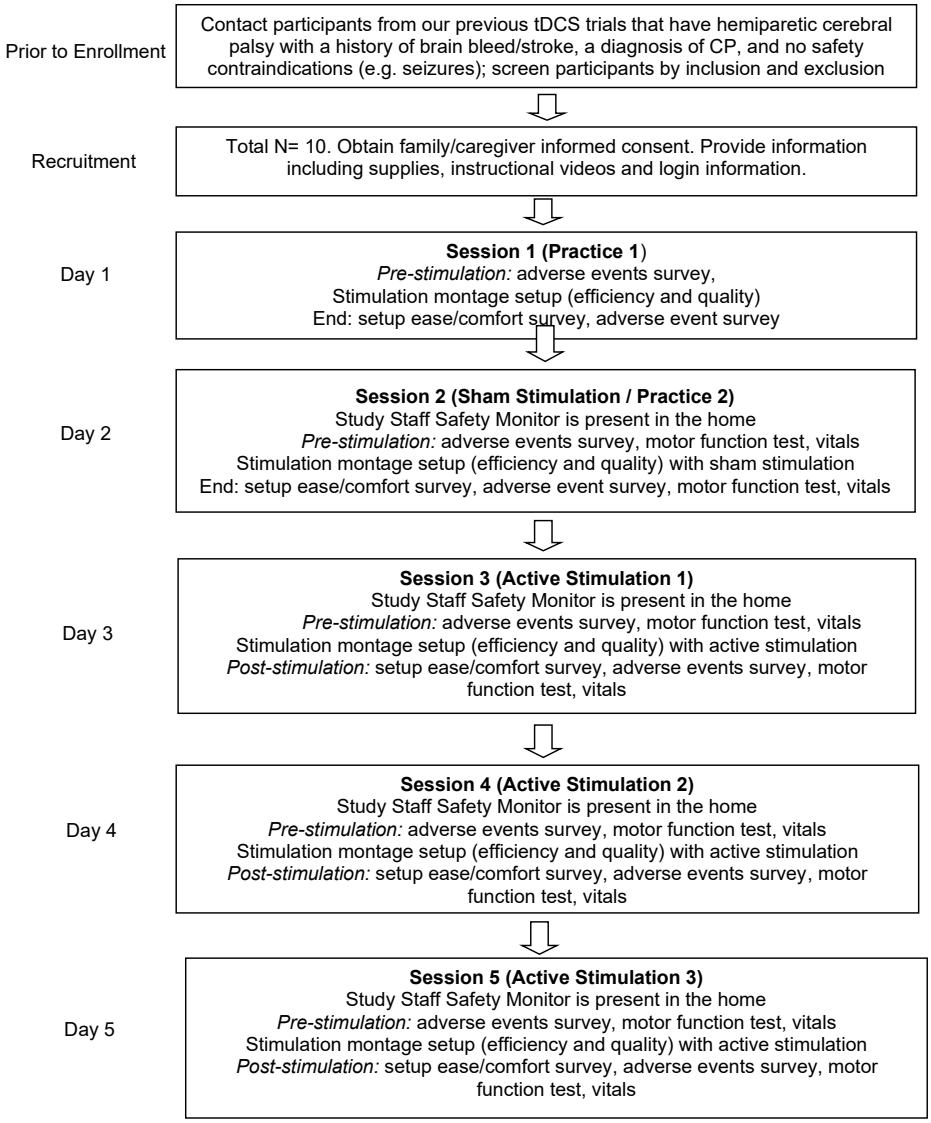
3.0 STUDY SUMMARY

3.1 Synopsis

Full Title	**Remotely Monitored Transcranial Direct Current Stimulation in Children with Cerebral Palsy**
Short Title	Pediatric Brain and Movement
Protocol Number	[HS IRB]
ClinicalTrials.gov Identifier & Summary	This study is being performed to determine the safety, tolerability and feasibility of remotely monitored transcranial direct current stimulation for children with cerebral palsy.
Number of Site(s)	This study is being done at one site: The University of Wisconsin Madison.
Main Inclusion Criteria	• Children with hemiparetic cerebral palsy with a radiologically confirmed perinatal brain bleed/stroke • Ability to follow 2-step commands • Aged between 8 years 0 days and 21 years.
Main Exclusion Criteria	• Inaccessibility to internet and a working computer/laptop/device • Neoplasm • Presence of metal implants • Epilepsy • History of seizure within 2 years preceding the study
Objective(s)	Primary Objective • To assess safety and tolerability of remotely monitored tDCS using our safety survey and optional 6-month/12-month follow up Secondary Objectives • To evaluate the quality, ease and comfort of in-home device set-up. • To evaluate the quality of tDCS stimulation.
Endpoints	Primary Endpoint Adverse events survey (pre, during, and post stimulation on sessions 1-5) and Box and Blocks test (pre and post stimulation sessions 2-5) will assess possible adverse effects. Secondary Endpoints • Setup speed • SMARTscan™ electrode contact quality
Study Design	This is an exploratory pilot open label trial that will assess the safety and feasibility of active tDCS in the home setting under caregiver and remote investigator supervision and direction, with a study safety monitor in the home on days when there is an active device present. An optional 6 month/12-month follow up session will be completed to to assess Box and Blocks scores and medical status since r participation in the primary study.

IND or IDE Number	Abbreviated IDE requirements apply for Non-Significant Risk Device
Study Intervention	Participants will receive 20 minutes of 1.5 mA transcranial direct current stimulation (tDCS) for three consecutive days.
Total Number of Subjects	A total of 10 subjects will be recruited.
Study Population	Male and females aged 8 to 21 with established diagnosis of hemiparetic cerebral palsy with a history of perinatal stroke/brain bleed who are US residents.
Statistical Methodology	Adverse event reporting frequency (% of total participants enrolled) and tolerability will be compared to pediatric tDCS studies performed within the laboratory setting and administered by trained research personnel. This data is publicly available in the form of published trials from our group and other groups. For participants in the 6-month/12-month follow-up, we will monitor for any change in motor function by comparing box and blocks scores from the primary study and 6-month/12-month study follow up visits. We will also assess current medical status by pursuing updated medical records.
Estimated Subject Duration	The duration of the study for each subject is approximately 5 days.
Estimated Enrollment Period & Study Duration	Study enrollment and follow-up will occur over 10 months with the total expected duration of the trial to be 12 months.

3.2 Schematic of Study Design



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6 month//12-month follow up	**Optional 6 month/12-month Follow up** Informed Assent and Consent obtained Medical Records Obtained In home remote Box and Blocks motor assessment GMFCS, Pediatric Cognition, Current Therapy, tDCS tolerance, and tDCS Subject Report of Symptoms surveys

4.0 KEY ROLES

The following is a list of all key personnel and roles:

Principal Investigator	Bernadette T. Gillick, PhD, MSPT, PT Associate Professor, Departments of Pediatrics University of Wisconsin-Madison Waisman Center 1500 Highland Ave Madison, WI 53705 Phone Number:608-262-7457 bgillick@wisc.edu
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5.0 INTRODUCTION

5.1 Cerebral Palsy and Motor Rehabilitation

An estimated 3.6 per 1,000 births in the United States are affected by stroke or brain bleeds which can lead to Cerebral Palsy (CP), a developmental disorder associated with motor impairment[1,2]. While, the majority of rehabilitation approaches focus on behavioral repetition to improve gait and upper extremity function, these therapies can require extensive practice times and extent of recovery is variable. Thus, there is a need for novel strategies which can optimize the speed and consistently of rehabilitation outcomes for this population [3,4]. Brain development during childhood is characterized by heighted neuroplastic potential[5] stressing the importance for intervention methods that harness neuroplasticity. Accordingly, several therapies (e.g., intensive training of the upper extremities) are theoretically based in mechanisms of motor learning and use-dependent plasticity[6].

5.2 Investigational Procedure

Non-invasive brain stimulation (NIBS), specifically transcranial direct current stimulation (tDCS), provides an approach for modulation of neuroplasticity that is safe, inexpensive, and portable. Furthermore, rehabilitation approaches combined with tDCS have shown promise to improve motor function recovery and quality of life after stroke in adults[7]. Integrating the application of NIBS may allow for enhanced rehabilitation during the enhanced neuroplastic period of childhood and NIBS has demonstrated promising outcomes in increasing the rate and extent of recovery[8]. The Pediatric Neuromodulation Laboratory has pioneered the development of combined pediatric rehabilitation interventions and tDCS to improve motor function[9–11]. Our studies have shown that in children with CP the use of tDCS is safe, feasible, and successful at modifying motor performance when in combination with other physical therapy interventions. tDCS is not currently available to subjects without taking part in the study. In this study, we plan to have a trained study team member instruct administration of tDCS in the remote setting during a synchronous zoom call with another trained study team member at the site of stimulation to monitor safety during sessions with the active device. To ensure the device is safely used in the home setting, and only during designated times, the safety monitor will bring the active device to each stimulation session and remove the device from the home after the session is finished.

5.3 Rationale

Several studies have demonstrated improved effects of rehabilitation interventions when they are combined with tDCS[12]. However, traveling to the laboratory or clinic may increase the difficulty and burden on families to complete an intervention with multiple sessions. This highlights the opportunity for remotely supervised at-home interventions. In adults, telerehabilitation, including integration of tDCS in the at-home environment, has offered the opportunity to improve access, lower the cost, and improve compliance with such treatments that require repetitive practice[13,14]. However, there is further need to explore the feasibility and tolerability in pilot studies for pediatric application, and to expand the investigation in larger randomized controlled clinical trials to assess reproducibility and efficacy[15].

To advance the reach of teleneuromodulation in pediatric rehabilitation it is crucial to extend the safety and accessibility of this affordable intervention. However, prior to the COVID-19 pandemic, there were no studies remotely performing tDCS for *pediatric* populations. During the pandemic Stay-at-Home mandate, we completed a novel feasibility investigation of performing remote *mock* tDCS in children by working with a child-caregiver pair. We found that remote *mock* tDCS is feasible in the home-setting without compromising the efficiency, quality, and comfort of administration. Children and their caregivers were able

to follow remote instructions without compromising the quality of placement and comfort while wearing the tDCS device[16].

With this proposal, we aim to follow-up and build upon our study that demonstrated mock tDCS setup feasibility, to assess ease of use and tolerability of at-home *active* tDCS in children with CP due to perinatal stroke. Together with gathered feedback about the experiences of children and caregivers during the procedure, knowledge gained will allow us to design a larger scale effectiveness study of a combined teleneuromodulation and rehabilitation intervention for recovery of motor deficits by targeting neuroplasticity and motor skills in pediatrics. Effective remote neuromodulation therapy can provide access to in-person rehabilitation and aid in accommodating mobility and financial challenges. This intervention has the potential to improve motor rehabilitation outcomes and can offer telehealth access, which may reduce treatment cost and improve outcomes when there is limited access to clinic or hospital facilities. Ultimately, this will contribute to a wider reach in improving quality of life across the lifespan in individuals with CP.

6.0 STUDY OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
To assess safety and tolerability of remotely monitored tDCS using our safety survey.	-Reporting of adverse events/discomfort -Optional 6 month/12-month follow up
Secondary	
To evaluate speed of device setup.	Time to complete montage setup
To assess the quality of stimulation.	SMARTscan™ electrode contact quality
Correlative/exploratory	
To assess interest and engagement in future teleneuromodulation rehabilitation interventions	Follow-up feedback Box and Blocks test assesses hand function pre-stimulation and post-stimulation sessions 3-5.

6.1 Aims

Aim 1. Determine the safety and tolerability of 20 minutes of at-home active tDCS with remote instruction.
Hypothesis 1: Children will tolerate the stimulation well with no serious adverse effects.
Hypothesis 2: The repeated and guided sessions will result in increased comfort and confidence reported by the caregivers and children in performing tDCS at home.

Aim 2. Determine the feasibility of remotely instructed teleneuromodulation with active tDCS.
Hypothesis 1: Based on our preliminary feasibility study, we expect caregivers and children to correctly and reliably setup a stimulation montage with children after following remote instructions over two practice sessions.
Hypothesis 2: Participants will be able to initiate and successfully complete active tDCS over repeated sessions, with increasing quality of stimulation delivery.

Exploratory Aim 3 - Integrate feedback from the child and caregivers to assess their interest or commitment to engaging in future at-home tDCS interventions towards the construct of an advanced clinical trial.
Hypothesis 1: The majority of families will express interest in future participation.

7.0 STUDY DESIGN

7.1 General Design

Exploratory single site open label unblinded trials will assess the feasibility of active tDCS in the home setting under caregiver, remote investigator supervision and direction, and in-home safety monitoring. The study population will consist of 10 children and adults between ages 8 – 21 years and 365 days that have hemiparetic cerebral palsy with a history of a perinatal brain bleed or stroke. Medical records will be obtained for confirmation of hemiparetic cerebral palsy with a perinatal brain bleed or stroke. Medical records for current medical status will be gathered and reviewed by our medical director Dr. Chris Ikonomidou to confirm diagnosis and that the participant meets the study criteria. The study will occur over five consecutive days with 20 minutes of active 1.5 mA tDCS stimulation on days 3-5. We will conduct optional 6 month/12-month follow up sessions where we will reassess Box and Blocks performance , responses to surveys, and review medical records. Participants can be involved in the "6-month/12-month follow up" +/- 1 month (5-7 months after participation in primary study for 6-month visit, 11-13 months after participation in primary study for 12-month visit).

Pre	Experiments	Session 1 P1	Session 2 Sham	Session 3 A1	Session 4 A3	Session 5 A4	Post
supplies videos login info	**Beginning**	AE survey	AE survey Vitals motor function test	AE survey Vitals motor function test	AE survey Vitals motor function test	AE survey Vitals motor function test	exit survey
	Setup	Efficiency (speed) Quality (errors)	Efficiency (speed) Quality (errors)	Efficiency (speed) Quality (errors)	Efficiency (speed) Quality (errors)	Efficiency (speed) Quality (errors)	
	Stimulation	AE survey	AE survey	AE survey	AE survey	AE survey	6 month/12-month follow up
			Stim quality SMARTscan™	Stim quality SMARTscan™	Stim quality SMARTscan™	Stim quality SMARTscan™	
	End	setup ease/comfort survey AE survey	setup ease/comfort survey AE survey Vitals	setup ease/comfort survey AE survey Vitals	setup ease/comfort survey AE survey Vitals	setup ease/comfort survey AE survey Vitals	
			motor function test	motor function test	motor function test	motor function test	

Figure 1. Study design and assessments.

7.2 End of Study Definition

A participant is considered to have completed the primary study if they have completed all phases of the study including return of equipment to study team and the 1 week follow-up to assess the family's overall experience. Additionally, participants will be given the option to participate in 6-month/12-month follow-up. After these sessions are completed and the medical records are obtained, a participant is considered to have completed the follow-up study visits.

8.0 SUBJECT SELECTION

8.1 Inclusion & Exclusion Criteria

Inclusion Criteria
1. Aged between 8 years 0 days and 21 years 365 days

2. Children who have hemiparetic cerebral palsy with a history of perinatal brain bleed/stroke
3. Receptive language function to follow two-step commands
4. Able to give informed assent along with the informed consent of the legal guardian. If the participant is 18-21 (with the capacity to consent), they must be able to give informed consent.
5. Intentional about representing the sub-population of children with CP who experience intellectual disability (at least 2/10 participants with mild intellectual disabilities will be recruited)
6. ≥ 10 degrees of active motion at the metacarpophalangeal joint
7. 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.

Exclusion Criteria
1. Inaccessibility to internet and a working computer/laptop/device.
2. Implants
3. Neoplasm
4. Metabolic Disorders
5. Epilepsy
6. Seizure within two years preceding the study
7. Acquired Traumatic Brain Injury
8. Pregnancy
9. Indwelling metal or incompatible medical devices
10. Evidence of skin disease or skin abnormalities
11. Botulinum toxin or Phenol block within [six-months] preceding the study
12. Disorder of Cellular Migration and Proliferation

8.1.1 Inclusion/Exclusion Criteria for Optional 6 Month/12-month Follow-up

To be eligible for the optional 6-month/12-month follow-up, participants must have previously participated in the primary study and have access to a reliable internet connection and a functioning computer, laptop, or mobile device. Apart from these requirements, there are no other exclusion criteria.

8.2 Vulnerable Populations

Vulnerable populations excluded from participation in the study
1. Pregnant women/fetuses/neonates for the primary study. If participants become pregnant after participating in primary study, they may participate in the 6- and 12-month follow up sessions..
2. Non-English speakers.

3. Those unable to read (illiterate).
4. Employees of the researcher.
5. Students of the researcher.
6. Individual or group that is approached for participation in research during a stressful situation such as emergency room setting, childbirth (labor), etc.
7. Individual or group with a serious health condition for which there are no satisfactory standard treatments.
8. Individual or group with a fear of negative consequences for not participating in research (e.g. institutionalization, deportation, disclosure of stigmatizing behavior).
9. Any other circumstance/dynamic that could increase vulnerability to coercion or exploitation that might influence consent to research or decision to continue in research.

This study will enroll children because the research is critical to advance the care and rehabilitation of children with CP and presents minimal risk to the children. From enrollment in past studies, we have found children with a CP diagnosis may be receiving physical or occupational therapy. If a child is receiving any concurrent therapies, all of the therapies will be documented. Data collected will inform future larger clinical trial evaluating the efficacy of at-home combined tDCS and rehabilitation in CP. Integrating tDCS as an adjuvant modality to telerehabilitation has the potential to enhance the efficacy of telerehabilitation therapies and offers a novel approach for remote intervention access, particularly relevant to reduce treatment cost and burden in case of limited access to clinic or hospital facilities. To further minimize risks to children, a trained study team member will supervise for safety concerns during all tDCS sessions in person and permission will also be obtained from a parent/guardian. If the participant is 18-21 years of age and has the capacity to give consent (adult child), permission will be obtained from the participant and the parent as participation is required from both parent and child.

When in contact with potential participants between the ages of 18-21, we will determine if they have the capacity to consent (10.3.3 Adults Unable to Consent).

We will NOT enroll participants whose capacity to consent may fluctuate throughout their involvement in the study. Using videoconferencing, a lab member will instruct the participants on how to perform tDCS stimulation. This will include 1 day of practice with inactive tDCS, 1 day of sham stimulation, and 3 days of active tDCS.

We are studying children and young adults aged 8-21 who have hemiparetic cerebral palsy with a history of perinatal brain bleed/stroke. The knowledge to be gained from this study will be beneficial in developing protocols for continuing pediatric rehabilitation therapy during mandated Stay-At-Home directives and other access restrictions (e.g., rural communities). We anticipate minor adverse events as listed in the adverse events section below. During the testing session, behavioral and environmental strategies will be shared, as needed, with the parent/caregiver for all children to optimize tolerance and completion of each session. These may include but are not limited to predictable routines, a visual timer, distraction techniques and child-friendly descriptive language. 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 participant and family. Recruitment materials, study information, and conversations are tailored to a pediatric population. Participant-specific study materials are provided before participation in testing sessions, and age-appropriate adaptations for each procedure/test are used. Our team has created videos that help explain the research and videos specific to the procedures of this study will be shared with families.

8.3 Lifestyle Considerations

Not applicable

8.4 Subject Identification

8.4.1 Self-Identification

Since study subjects will need to be in an age range between 8 years to 21 years potential subjects will not be able to self-identify. However, parents/legal guardians of children that meet inclusion criteria could 'self-identify' due to their parental role. Participants who are between 18-21 years of age can self-identity as long as they have consent capacity. Parents/legal guardians, and participants 18-21 with consent capacity can respond to Institutional Review Board (IRB)-approved recruitment efforts, such as web postings, posters/flyers, radio or TV ads, newspaper ads, mass mailings, email blasts, etc. IRB-approved screening scripts, eligibility questionnaires, and email response templates will be utilized when communicating with parents/legal guardians of potentially eligible subjects who respond to these recruitment methods. Information collected from the parents/legal guardians of potential subject is to be limited to protect the potential subject's privacy, and information collected from potential subjects who fail pre-screening will be destroyed. Indirect recruitment materials and response communications will not contain subject health information.

8.4.2 Pediatric Neuromodulation Laboratory Database

We will use our own database from participants who have previously participated in our studies and have signed consent to be contacted for this study.

8.5 Subject Recruitment

A total of 10 subjects will be recruited. Several recruitment strategies are as detailed below. The phone screening script will be used in response to calls or emails from potential subjects.

Based on recruitment in previous studies in this population performed by our lab, we expect that about 75% of our sample of children will reside within the state where the laboratory exists, i.e., Wisconsin. The remaining participants will be recruited from the greater Midwestern and Western regions. We have experienced exceptional participation (increase in overall enrollment from initial inquiries 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. 7 participants from the pilot study in our lab expressed interest for future studies and agreed to be re-contacted for participation. Recruitment will take place immediately after IRB approval and continue for 12 months. The baseline diagnosis for children who have hemiparetic cerebral palsy with stroke/brain bleeds has been established and documented through previous involvement in our studies; however, we will gather medical records for current medical status to confirm there are no changes in medical status.

8.5.1 Email

Children who have hemiparetic cerebral palsy with a history of perinatal brain bleed or stroke will be recruited from our database of previous participants. We will contact the list of previous participants in our laboratory studies who have agreed to be re-contacted and expressed interest in participation in future studies. We will recruit participants through email and establish a time to screen via telephone.

8.5.2 Self-Identify

Self-identify: Parents/legal guardians of children who meet inclusion criteria could self-identify in response to IRB-approved recruitment materials, such as web posters/flyers, social media posts, emails, mailings, etc. Anyone who sees information about this study may pass the information onto potentially eligible families, who may choose to contact the study team. Relevant local and national groups will be provided with IRB-approved recruitment materials and language to be posted on their

websites and social media platforms. Participants 18-21 with capacity to consent are able to self-identify in response to any IRB approved recruitment materials.

8.5.3 Flyers

Flyers announcing that volunteers are needed for the study will be posted or sent out to various specialty clinics or schools serving our population of interest. Several key details of the study will be included in the flyer (key eligibility criteria, number and length of visits. location of study site, type of remuneration) along with a call back number for people to call in case they are interested.

8.5.4 Health Records

We will work with UW ICTR's Clinical Research Data Service (CRDS) to identify eligible patients at within UW Health.

Additionally, study team with electronic medical record access may search patient lists made available to them as part of their research access to identify potential subjects at recruiting sites for study eligibility evaluation. The research team will conduct further prescreening of individual records to identify potential participants.

8.5.5 Mailing Opt-Out Letters

Study team with research access to the electronic medical record system will use appropriate ICD codes to identify potential participants. Families at UWHealth will be mailed the opt-out letter. This letter informs families that a study team member will be calling within two weeks to discuss the study and inquire about the family's interest. Upon receipt of the letter, the family may choose to email the study team to express interest in the study or opt-out of contact.

8.5.6 Calling

Within 2 weeks of mailing the opt-out letter, a study team member will reach out to the potential participant family. Up to three call attempts will be made by the study team. If call goes to voicemail, the approved voicemail phone script will be used.

8.5.7 Waisman Registry

We will work with the Intellectual & Developmental Disabilities Research Registry at the Waisman Center. The individuals enrolled in this registry may be contacted to potentially participate in this study. The research team will set up a time to screen the participants if they are interested in participating in this study.

8.5.8 Clinical Practice

Hospital/clinic care providers at institutions serving our target population may identify potential participants during routine clinical care based on inclusion/exclusion criteria. They may provide IRB-approved recruitment materials to patient families and invite them to contact the study team if they are interested in learning more.

8.6 Remuneration and Retention Strategies

Based on our previous experience in pediatric non-invasive stimulation and infant stroke studies, we will utilize the following retention tools:

- Once eligibility has been confirmed, we will contact the parents/legal guardians or adult child participant and their parent to schedule a conversation in-person or a video chat to answer any additional questions and to introduce our team and put a face with a name.
- Throughout the five consecutive days of the study, we will check in with the parents/legal guardians or adult child participant to answer questions and provide any pertinent information.
- We will contact the parents/legal guardians or adult child participant via phone one week before their visits to answer any questions/concerns.
- We have a dedicated laboratory study phone number which we share with parents/legal guardians/adult child participants, and to which we attend regularly.

- We will invite parents/legal guardians/adult child participants to be on our mailing list to receive biannual Pediatric Neuromodulation Lab newsletters for updates.
- A consistent point of contact will be maintained with parents/legal guardians/adult child participants, from recruitment to study completion, to establish rapport and build a positive relationship between the family and research team.
- A thank-you letter with a summary of participation will be sent to parents/legal guardians/adult child participants after completion of all sessions. Upon completion of the 5 sessions, each family will receive $100 for participation. If the study is stopped due to an adverse event or because the participant wants to stop for any reason, they will receive compensation at a prorated rate based upon the number of sessions completed. Participants will receive $50 for each additional optional follow-up visit they complete. This will total to an additional $100 for completing both the 6-month and 12-month follow-up visits.

8.7 Early Termination and Withdrawal

Families are free to withdraw from participation in the study at any time upon request.

The Principal Investigator (PI) may discontinue or withdraw a subject from the study for the following reasons at his/her discretion:

- Legal guardian/parent of the child voluntarily withdraw from the study
- Participant death
- Pregnancy
- Subject non-compliance with study requirements (e.g., study intervention non-compliance)
- If any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the subject
- If the subject is no longer an appropriate candidate for participation
- There is evidence of progressive disease or unacceptable toxicity
- Subject unable to complete the 5 sessions within two weeks

Participants withdrawn from study will be replaced, and the details surrounding the circumstances for withdrawing the participant from the study will be reported, with no identifiers included. Data collected up to the point of withdrawal will be kept and used for analysis. Participants who withdraw from the study will be given the opportunity to be involved in the 6-month/12-month follow up study visits.

If the study ends prior to the study completion, all scheduled participants and families will be notified, and study sessions will be terminated. All research investigators on the study will be notified. The funding agency will also be notified.

9.0 STUDY INTERVENTION

9.1 Study Intervention Description

The device used for this intervention will be the Soterix 1x1 Limited Total Energy tDCS Stimulator Model 1401.

With IRB approvals and FDA IDE exemptions, we have safely and feasibly used the Soterix LTE tDCS model over the last decade. Previous IRB approval has been obtained using an FDA IDE exemption with NSR status (see FDA letter/Wasserman). The Soterix LTE tDCS model will be used to deliver low-intensity tDCS in the home setting, to children with CP assisted by the parent/legal guardian and monitored by the safety monitor team member – henceforth referred together as the ‘participant team’ - and with synchronous remote instruction by the investigative team. The procedure will target the primary motor

cortex (M1) using a bilateral M1 electrode montage. The M1 is a cortical area of interest for interventions aimed at improving motor skills in our participant population who have hemiparetic cerebral palsy with perinatal stroke and brain bleed, and as is conventional using this montage, we will place the anode over the lesioned or more-involved hemisphere. We intend to deliver tDCS in three active sessions, at a current intensity of 1.5 mA (based on child tolerance) and 20 min duration in each of the three active stimulation sessions.

9.1.1 Source

Soterix Medical will distribute LTE Transcranial Direct Current Stimulator to the study site. The contents of the shipment will then be reviewed and verified against the packing slip and will be documented as instructed at the initiation visit.

Soterix Medical Inc.
Aspen Corporate Park,
1480 US Highway 9 North, 204, Woodbridge, NJ 07095
Email: *contact@soterixmedical.com* Phone: +1 888 990 8327
Fax: 212-315-3232

The study team will be responsible for procuring the LTE tDCS stimulator.

9.1.2 Packaging and Labeling

Device installation and maintenance will follow manufacturers' instructions for approved use. The device will be delivered by the safety monitor study team member to the participant.

9.1.3 Storage and Stability

Investigational product must be stored in a secure area accessible only to authorized trial personnel. When not out at participants' homes, the device will be installed and housed in the Pediatric Neuromodulation Laboratory, in a dedicated and locked research space, accessible only by/with authorized study team personnel. The Pediatric Neuromodulation Laboratory is located within the Waisman Center, and the facility meets all the requirements needed for appropriate installation, functioning, and storage of the device following manufacturer's instructions. The device must be stored away from fluids and heat sources. The storage temperature of the device must be between 50°F - 80°F with a maximum humidity of 70%. The temperature must be monitored and documented on the appropriate form for the entire time that the investigational product is at the trial site. If the storage temperature deviates from the permitted range, the investigational product must not be administered, and the site investigator or responsible person should contact Soterix Medical for further instructions. The device will also follow these precautions and warnings:

- *The Soterix Medical LTE tDCS Stimulator must be stored away from fluids and heat sources.*
- *To clean the Soterix Medical LTE tDCS Stimulator, use a dry cloth to wipe dust from the external surface when necessary. Do not spray liquid cleaners directly on the Soterix Medical LTE tDCSStimulator, as this will void your warranty.*
- *Do not disinfect the Soterix Medical LTE tDCS Stimulator*
- *Do not immerse the Soterix Medical LTE tDCS Stimulator in water or any other fluids.*
- *The Soterix Medical LTE tDCS Stimulator should not be used in a moist environment or if any parts of the stimulator are damp or wet.*
- *Do not drop the device.*
- *The Soterix Medical LTE tDCS Stimulator should not be used if there are any signs of external damage.*
- *Carefully inspect the device on arrival and prior to each use.*

- *If any controls or displays are not working as indicated in the manual. Immediately return the device to Soterix Medical Inc. for repair.*
- *Storage and operation temperature must be between 50° F and 110° F*

At the start of each experimental session, the investigative team will carefully inspect the device, together with the participant team, via video conference.

9.1.4 Accountability

The study coordinator will maintain records of product delivery, site inventory, and product return. The safety monitor will be responsible for bringing the device to the participants home for every session and taking it after completing the session.

In the event of a quality issue, the site should quarantine the investigational product and contact Soterix Medical for further instructions.

9.1.5 Dosing and Administration

tDCS stimulation will be delivered at 1.5mA for 20 minutes while the caregiver and study team members evaluate the participant for any potential adverse event. Refer to the adverse events section below for more information. If it is uncomfortable to go to the full intensity, we will adapt and modify the stimulation to 1.0 mA by adjusting the device's dial in person by the caregiver or safety monitor as directed by the study coordinator.

9.2 Study Procedural Intervention(s) Description

9.2.1 Administration of Procedural Intervention

Active tDCS stimulation will be delivered to the participants during sessions 3-5 of the study after participants have been evaluated and cleared for quality set-up of the tDCS montage. A trained study team member will interact virtually with the caregiver to activate the tDCS stimulation device while a safety monitor team member will be located in person to supervise any safety concerns.

9.3 Method for Assigning to Treatment Groups

This is an open label study; there are no blinding procedures.

9.4 Study Intervention Compliance

Protocol compliance will be assessed directly by trained lab members. The lab team will witness and monitor the activation of the LTE device by the trained caregiver. The caregiver administering stimulation must be the individual who was successfully trained during the practice sessions. The safety supervision lab member will assess any safety concerns throughout the process at the site of the stimulation.

9.5 Concomitant Therapy

9.5.1 Permitted Concomitant Therapy

Concomitant therapies and medication are permitted and will be documented during the screening visit. This is not expected to affect the primary or secondary outcome measures of the study.

9.5.2 Prohibited Concomitant Therapy

Concomitant participation in another neuromodulation study is prohibited considering concurrent neuromodulation may directly affect the endpoints of the study. Additionally, participants who received Botulinum toxin or phenol block within the last six months preceding the study are prohibited from participating. However, after completion of the tDCS stimulation sessions, participants will be eligible to

participate in the optional 6 month/12-month visits as long as they have participated in the study before and have access to working internet and computer/laptop/device.

10.0 STUDY VISITS AND PROCEDURES

10.1 Study Calendar

The procedures performed at each study visit are listed in the table below.

Procedure	Screening	Session 1	Session 2	Active stimulation Session 3-5	1 week post day 5 completion
Informed Consent	x				
Review Eligibility Criteria	x				
Obtain Medical History	x				
Vitals Measured			x	x	
Stimulation montage setup		x	x	x	
Setup ease/comfort survey		x	x	x	
Safety Monitor Present In-home (active device use)			x	x	
Motor Behavior Assessment[1] pre, post stimulation			x	x	
Adverse Events Survey pre, during, post stimulation		x	x	x	
Device stimulation administration			Sham	Active	
Follow-up					x

Procedure	Optional 6-month/12-month follow up
Informed Consent/Assent	X
Obtain Medical History	X
Motor Behavior Assessment[1]	X
Surveys[2]	X

[1] Box and Blocks Test
2 Gross Motor Function Classification System, Pediatric Cognition Survey, Current Therapy survey, Demographic Survey, tDCS Tolerance Survey, tDCS Subject Report of Symptoms Questionnaire

10.2 Overview of Study Procedures

Individuals who respond as being interested in the study will scheduled for a phone or video call to discuss study procedure. At this point we will evaluate whether the family has appropriate computer/ internet access. If the family (e.g. parent/caregiver and child) are interested in participating, we will proceed to performing consent/assent via phone call or video conference. As we will request for photos/video of electrode placement, a photo/video authorization form will also be required. We will request for permission to record the videoconference call via the consent form. Following these enrollment procedures, the parent/legal guardian – henceforth referred to as 'caregiver' throughout the protocol- will be asked to participate in a pre-visit which may occur in the same visit as the enrollment. If the participant is an adult with consent capacity (between the ages of 18-21) both the adult and the parent of that adult will be involved in the call. During the pre-visit, an address for the safety monitor study team member, and videoconferencing times will be scheduled for completion of the five-day study. There are two types of sessions that will occur throughout the study (practice and active stimulation). A trained study team member will be present via videoconference with the caregiver/child during the entirety of the sessions. A study team member will be on-site, in-home during active device use to solely ensure safety of the participant. Unless indicated for safety, the safety monitor will not provide guidance in setting up the device or delivering tDCS to the participant. The protocol for survey's, questionnaires, and assessments are detailed below.

10.2.1 Transcranial Direct Current Stimulation

Montage Set-up Protocol

The Soterix Medical bilateral M1 tDCS montage set-up protocol will be completed during all five sessions of the study. Participants will be sent instructional videos on how to perform the following procedures via REDCap. They will be asked to view these videos prior to the videoconferencing call on practice session 1. Participants will receive a mock device that does not have the ability to stimulate to allow them to practice setup with the instructional videos.

For all sessions: the lab team will press the "now" button on the survey to begin recording the time duration to place the tDCS headgear on the head appropriately. Parent Participants will be instructed to:

1) Connect the provided cables to the device using the banana plugs on the back of the device
2) Place the tDCS headgear on the child's head with the arrow aligned with the nose and upload an image of the step
3) Mark locations below the red and black markers with the provided pen/pencil
4) Use the provided alcohol pads to clean the skin at the marked locations and identify any redness, cuts, pimples, etc.
5) Insert the connector cord pin securely into the opening of the receptacle on the rubber insert
6) Snap on the two tDCS sponge pads saturated in saline to the red and black markers and upload an image.
   Both the caregiver and the laboratory team will record the time these steps were completed.

Non-active Mock Device

Practice Day 1: Now, participants will be asked to leave the tDCS setup in place for 20 minutes. Caregivers will observe the child during this time to see if the electrode sponges move or if the child adjusts the headgear. After the 20 minutes, the caregiver will be instructed to mark the new location of the arrow and measure the distance the arrow may have moved during the 20 minutes. An adverse event survey will be conducted prior to the session, at the 10-minute mark, and post stimulation

Active Device – At least one safety monitor study team member is present in the home of the participant team

Sham Day 2: The study team staff will evaluate the tDCS montage set-up for successful set-up. If set-up is completed correctly, the caregiver will activate the tDCS device for a sham stimulation. Participants will receive 30 seconds current ramp-up to 1.5mA immediately followed by ramp-down back to 0. They will continue to wear the headgear with no stimulation until the end of the 20-minute session when the current will once again receive ramp up to 1.5mA immediately followed by 30 second ramp-down. This will allow the child to potentially experience the mild skin tingling in order to adjust and prepare for the active sessions. The level of stimulation will be adjusted if necessary. An adverse event survey will be conducted prior to the session, at the 10-minute mark, and post stimulation. Vitals (blood pressure, respiration rate, and heart rate) will also be taken before and after stimulation. The participant will be given the option to use an iPad to watch videos during the 20-minute session.

Active Days 3-5: Same as Day 2, except participants will receive 20 minutes of tDCS stimulation. Caregivers and the investigative team will observe the child during this time to see if the electrode sponges move or if the child adjusts the headgear. After the 20 minutes, the caregiver will be instructed to mark the new location of the arrow and measure the distance the arrow may have moved during the 20 minutes of stimulation. If the child were to experience a mild adverse event, the caregiver and study team staff will opt to stop the active stimulation, assess the event, discuss with the study Medical Monitor and reassess. If deemed appropriate by the Medical Monitor the laboratory investigative team would discuss the plan to move forward with the Participant Team and make adjustments to stimulation intensity for future sessions for comfort.

10.2.2 Setup ease/comfort survey

This survey will be completed at the end of all five sessions. The survey will evaluate the participant's overall experience of the session by addressing the following topics:

- Caregiver: - How difficult were the tDCS setup instructions to understand?
- Caregiver: - How could instructions be improved in the future?
- Child - How comfortable was wearing the tDCS cap and sponges?
- Child – How could we make wearing the cap more comfortable?
- Any general comments

10.2.3 Vitals

Blood pressure, heart rate, and respiration rate will be taken pre and post stimulation on days 2-5 to ensure participant safety and monitor any changes in vitals. The safety monitor will take all vital measurements. These will be recorded on REDCap.

10.2.4 Motor assessments – Box and Blocks Test

Hand motor function will be assessed as a control measure before and after stimulation on days 2-5 with the Box and Blocks test. Instructions to this task will be read directly to the participant during the videoconferencing call. The testing researcher will guide testing with the Box and Blocks test (wherein the child moves as many 1" wooden blocks within 1 minute). There will be 1 trial period and 4 subsequent tests of the dominant and non-dominant hand (2 tests per hand).

10.2.5 Adverse events survey

Tolerance and report of any symptoms will be formally assessed using tDCS-specific participant safety questionnaires. This includes common mild effects like skin tingling and itching, as well as others such

as headache, anxiety and mood changes, or any other events. This survey is filled out before, during at the 10-minute mark, and after tDCS stimulation sessions 1-5.

10.2.6 1-week Follow-up

We will ask the participants an open-ended question to check-in, assess the family's experience with the overall procedure and potential interest in future studies. This will be called the tDCS tolerance survey. This will occur via telephone one week after completion of the session.

10.2.7 Optional 6-month/12-month Follow-up

10.2.7.1 Medical Records

To conduct a medical record review and assess medical status and the potential for new onset seizures since participation in the primary study, we will obtain a consent for a standardized medical record release under the Health Insurance Portability and Accountability Act (HIPAA), provided the previous HIPAA consent for medical record release has not expired. Our goal is to collect medical records that reflect the participant's current medical status. We will obtain participant's most updated medical records to review their current health status and review any changes since participation in the primary study. We are more specifically looking for any key factors relevant to our study inclusion/exclusion criteria such as new onset of seizures, development of epilepsy, changes in motor function, and development of long-lasting symptoms potentially relating to tDCS.

We are also collecting information regarding the pregnancy status of participants as it is crucial for our research and subsequent follow-up visits. Understanding the pregnancy status is important due to the wide-ranging effects that pregnancy can have on the physiological and anatomical systems, including its impact on motor function. By identifying if participants are pregnant, we can accurately analyze and interpret their medical status since participation in the primary study. This knowledge will enable us to account for any potential influences that pregnancy may have on the outcomes and ensure that our analysis is comprehensive and accurate.

10.2.7.2 Motor Assessments – Box and Blocks Test

At the 6-month/12-month timepoint, we will administer the Box and Blocks test. We will send the necessary supplies to the participant and provide them with instructions over videoconference call. Participants will return Box and Blocks in the same packaging with a return label. The test will consist of one trial period followed by four tests, with two tests for each hand (dominant and non-dominant).

10.2.7.3 Survey(s)

At the 6-month/12-month timepoint, we will send the Gross Motor Function Classification System survey, Pediatric Cognition Survey, Current Therapy Survey, Demographics Survey, tDCS tolerance survey, all which were completed in the primary study, to the participant over REDCap. We will also include a tDCS Subject Report of Symptoms Questionnaire which will be a guided interview of questions investigating potential adverse events that may have occurred since participation in the primary study.

Commented [JF1]: I searched for the word "records" throughout the protocol and found that previous descriptions indicate that medical records will be reviewed only to confirm eligibility. Please revise 10.2.7.1 to describe more specifically what information will be collected during follow up to assess current medical status. This would also be a good place to provide the rationale for identifying pregnancy status.

Commented [PC2R1]: This has been included, thank you

10.3 Screening and Enrollment

The Screening and Enrollment visits and procedures are described in detail below.

10.3.1 Pre-screening

When caregiver(s) of potential subjects or adult potential participants contact the study team, a study team member will review a brief description of the study's purpose and participation requirements with them. This must also include a statement that participation is voluntary. The screener will ask the callers if they have questions and whether they are interested in participating. This portion must be completed with the participant and the parent if the participant is above the age of 18 years old with consent capacity. If the potential participant is between 18-21 and does not have the capacity to consent, the screening call must be completed by the guardian.. If the participant is below the age of 18, they do not need to be a part of this screening call.

If the caregiver and\or adult participant expresses interest, the study team will ask to collect the demographic information listed below.

Demographics
The demographics section will include background information of the caregiver/child including:

- Age of child
- Child's full name
- Sex of child
- Child's date of birth
- Child's race and ethnicity
- Legal guardian's full name
- Preferred phone number
- Home address
- Previous participation in a brain stimulation study (TMS or tDCS)
- Relationship of child and caregiver
- Caregivers highest education (high school, bachelors, etc.)

We will potentially collect more demographic information if the participant enrolls into the study. We will once again ask to collect demographic information if participations are willing to participate in the optional 6 month/12-month follow up sessions.The consenting parent/guardian will be asked if they would be willing to fill out demographic survey using a secure REDCap link. Demographic information collected from the consenting parent/guardian may be used in analysis and reporting. We will request:

- Age
- Zip code
- Race and ethnicity
- Educational level
- Employment status
- Total annual gross income of house hold
- Number of people supported by this income
-

After the team member collects the first half of the demographic information, they will do an initial screen for inclusions/exclusion criteria and any tDCS contraindications. This call is estimated to take 20 minutes.

After all questions have been answered and if no exclusion criteria are found during the prescreening call, the study team member will ask if the caregiver\legal guardian and\or adult child participant are interested in proceeding to the next step for further screening for inclusion/exclusion criteria. A Health Insurance Portability and Accountability Act (HIPAA) consent for a standardized medical record release is obtained in order to perform a medical record review. We will gather a medical record with current medical status to confirm inclusions and exclusion criteria are met. 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. The medical director will confirm participant eligibility in the study.

If a participant is excluded or declines participation, parents/guardians and\or adult child participant will be asked if they would like to have their contact information retained for future studies and/or to receive biannual lab newsletters. If yes, contact information will be kept separately from screening data. The parent/guardian and\or adult child participant will be notified of the information to be kept, including child name, child date of birth, child diagnosis, parent name, and parent contact information (phone number, email address and/or address).

Ineligible screening data will be stored until the close of enrollment to prevent re-contacting parents\legal guardians and\or adult child participants after screening. Once enrollment is completed, identifiers will be destroyed. De-identified screening information will be used to describe and analyze the recruitment process. The data will be stored securely in our HIPAA-compliant database to prevent unauthorized use of the information. This database will be accessible to a select number of study team members.

10.3.2 Informed Consent and Assent

All study team staff are trained to guide participants through the consent/assent process.

Preliminarily eligible subjects will be contacted via phone and/or email for informed consent and assent. The informed consent process will be conducted following all federal and institutional regulations relating to informed consent. Informed consent will be obtained prior to conducting any study-related activities. After families respond to the email recruitment script and express interest in participating in our study, we will send the consent form via email for them to review and follow up with a phone call. During the phone call, trained study personnel will explain the study and complete pre-screening. Participants, under the age of 18 and 18-21 without the capacity to consent will then be asked if they would like to discuss the assent form at this time and be invited to a video session or schedule a separate session. The Teach Back practice will be used to obtain informed consent/assent and confirm their understanding. Participants are welcome to complete the consent/assent at the time of review with trained study personnel or take their time to think about participation before completing the form. This consent form must be signed by one parent/legal guardian. We will require only one parental/legal guardian signature for consent due to the minimal risk of this study. If the participant is between 18-21 and does not have the capacity to consent, an LAR will sign the consent form. Assent will be obtained from all participants who lack the capacity to consent (8-17 year-olds and adults 18-21 lacking consent capacity). The study procedures will be explained to the participant in an understandable way and the participant's assent will then be requested. Only participants who can provide affirmative agreement that they wish to participate will be included. The consent form has a signature block to document the participant's assent. If the child is over 18 years old and has the capacity to give consent, they must sign the consent form themselves in addition to their parent as they both are involved in the study as an adult child/parent dyad. Neither children nor adults will be required to provide justification if they do not wish to participate. This will facilitate refusal to participate due to reasons that the child does not wish to disclose (e.g. possible pregnancy) Abbreviated IDE requirements apply for Non-Significant Risk Device. Individuals who are 18-21 that lack the capacity to consent will not be able to participate in the optional MRI study.

10.3.3 Adults with Impaired Decision-Making Capacity

Before enrolling potential participants aged between 18-21, we will evaluate whether they have the ability to provide informed consent. To assess their capacity to consent, we will utilize the teach-back method to ensure they understand the research's purpose, potential risks, absence of direct benefit,

and voluntary nature of participation. If the evaluation confirms their consent capacity, they will be asked to provide consent to participate in the study, unless guardianship requires the guardian's consent. We will adhere to HRP-013 and consult the Office of Legal Affairs to determine the appropriate Legal Authorized Representative (LAR) for individuals deemed to lack consent capacity, as well as any legal queries regarding consent. We will obtain assent from all participants who lack the capacity to consent, and we will describe the study processes in simple language using the teach-back method. Only those participants who give affirmative agreement to participate will be included in the study.
Video sessions will be conducted via HIPAA-compliant WebEx version, secure Zoom, or Microsoft Teams available to UW researchers. In case of remote consent, a 21 Code of Federal Regulations (CFR) Part 11 compliant version of DocuSign, provided by UW, will be used. The authorized member of the research team who obtained consent/assents will sign the form. Printed signed forms will be kept in a locked cabinet in the lab's office, which is only accessible to certain study team members.

Following enrollment, the research team will consistently communicate with the parent/child team during study interactions to confirm their understanding and comfort with the procedures. Specific questions asked by the parent/legal guardian or child will be documented to assist us with determining how best to support their understanding.

10.3.4 Enrollment

A research subject will be defined as "enrolled" in the study when they meet the following criteria:

- The subject has been consented and assented by study staff.
- The subject and study staff have completed all screening documentation.
- The PI has verified that the subject meets all of the inclusion criteria.
- The PI has verified that subject meets none of the exclusion criteria.

10.3.5 Screen Failure and Re-enrollment

A screen failure will occur if, after review of the medical records, the caregiver/child do not fit the criteria to participate. In that case, enrollment will not take place and the study team will discuss the findings with the family/caregivers. No re-enrollment will be considered due to age range and inclusion criteria.

10.3.6 Optional MRI Screening

If subjects meet all other enrollment criteria and confirm interest in being a part of the study, but their medical records do not include radiological confirmation of brain breed or stroke, we will offer them an MRI screening visit. This MRI will be paid for by research funds and will be consented separately as an optional screening visit. Separate consent is preferable, given that the findings of the MRI will determine if subjects can enroll in the main study. The consent/assent process follow the procedure detailed on 10.3.2.

The potential participant will be provided with a link to a walk though guide of how an MRI is completed at the Waisman Center: (*https://pnl.waisman.wisc.edu/tests-and-interventions/*), or (*https://www.youtube.com/watch?v=jFxO_XGp3UM&t=2s*). The potential participant will also be provided with a link to listen to what an MRI scan may sound like, such as: (*https://www.youtube.com/watch?v=S4DHUim_Lc8*). In addition, if the subject is particularly anxious, s/he will be offered an additional mock scan. At the Waisman Center, the mock scanning room has been designed to very closely enact a neuroimaging procedure with the exception that the scanning apparatus is not capable of generating a magnetic field. Importantly, it also allows for a practice session prior to data collection. The participants will hear an audio file that replicates the scanner noise that occurs during the real scanning session. Study personnel will support and coach subjects if they have any difficulties accommodating to the scanner environment. During this mock practice session the

importance of keeping the head still during the scan is emphasized, and participants have a chance to practice this. These methods have been standard child MRI scans and work well with children.

After completion of an MRI safety screening form, participants will receive an MRI scan at the Waisman Center for Brain Imaging (1500 Highland Ave.; Madison, WI 53705) or at WISPIC (6001 Research Park Blvd.; Madison, WI 53719. The parent/legal guardian may be permited to be in the scanning control room during the session, after completing a safety screening, in accordance with facility policy.

Scanning Protocol: The MRI will be done using a 3 Tesla Discovery MR750 MRI scanner (GE Healthcare, Waukesha, WI). Our imaging protocol includes structural imaging and diffusion MRI. The exact scan length and parameters of each scan type (T1, T2, DWI) will be set for this study in coordination with the Waisman Brain Imaging Core staff and the UW radiology team to optimize the quality of data for purposes of determining study eligibility. All of the imaging methods have been previously implemented at UW-Madison. Each sequence will take approximately 5-10 minutes and the total scan time will be approximately 60 minutes.

- Structural Imaging
  - T1-weighted: Anatomical T1-weighted imaging will be obtained using techniques the custom MPnRAGE sequence[25,26], which inherently removes the intensity variations from inhomogeneities in the coil sensitivities and motion artifacts. This technique has been widely utilized across imaging studies at the Waisman Center, including infant and pediatric populations. The T1-weighted scan will be used in the analysis pipeline to confirm lesion location.
  - T2-weighted: T2-weighted images will be acquired using GE's 3-dimensional CUBE sequence, allowing for high resolution T2-weighted images.
- Diffusion Weighted Imaging: DWI uses extra gradients applied after excitation and before data sampling to encode information amount small displacements of water. The strength, direction, and timing of the gradients (called b-value) determine sensitivity of diffusion. A multiple b-value dataset will be acquired, with the number and strength of the b-values and gradient directions optimized for the age range of infants studied. Diffusion imaging data will be acquired with reverse phase encoding schemes in order to correct for susceptibility distortions. Multiband imaging (factor=3) will be used to make the acquisition faster.

A neuroradioligist will review the scan and produce a radiological report to be reviewed by the study medical director who will ultimately determine eligibility. At the request of the subject and caregiver, the medical director will meet also with the subject and their parent to discuss the results of the radiological report within 30 days if the recommendation of the radiologist is to further investigate the unusual results of the images with the participant's own physician. Study teams will not inform subjects of their eligibility until after the results have been communicated by the medical director to the subject and their caregiver or they have declined this discussion.

- "Souvenir" Radiology Images: If an MRI scan was completed with an participant, per IRB policy a three-view research radiology souvenir will be offered for families. The images will be labelled as "Research images, not for diagnostic use". Images will be emailed in an encrypted document to the parent/caregiver after the neuroradiologist review. Families can choose not to receive these images. Images will be sent to the parent/legal guardian in a password protected document through encrypted email or mail, as preferred by the parent/legal guardian.

10.3.7 Optional 6 month/12-month follow up

Participants who completed any number of sessions during the primary study a

10.4 Unanticipated Problems

An unanticipated problem (UP), as defined by the Department of Health and Human Services (DHHS) Office for Human Research Protection (OHRP), is any incident, experience, or outcome that meets all of the following criteria:

- The incidence, experience, or outcome is unexpected given the research procedures described in protocol-related documents (e.g., the study protocol, the informed consent documents) and the characteristics of the subject population being studied. An event may be considered unexpected if it exceeds the nature, severity, or frequency described in the study-related documents, Investigator's Drug Brochure, product labeling, or package insert.
- The incidence, experience, or outcome is related or probably related to participation in the research study. "Probably related" means the incidence, experience, or outcome is more likely than not to be caused by the research study procedures.
- The occurrence of the incidence, experience, or outcome suggests that the research places subjects or others at a greater risk of harm (physical, psychological, economic, or social) than was previously known or recognized.

The investigator will report UPs to the reviewing IRB and to the PI. The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number;
- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;
- A description of any changes to the protocol, informed consent documents, or other corrective actions that have been taken or are proposed in response to the UP.

10.5 Unanticipated Adverse Device Effect

An unanticipated adverse device effect means 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 application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

An investigator shall submit to the sponsor and to the reviewing Institutional Review Board (IRB) a report of any unanticipated adverse device effect occurring during an investigation as soon as possible, but in no event later than 10 working days after the investigator first learns of the effect.

10.6 Protocol Deviations

Refer to section 11.5.
Any planned protocol deviations will be submitted to the sponsor, the FDA and the IRB before implementation when applicable. If an unplanned deviation occurs in case of emergency to protect the life or physical well-being of the participant, it will be reported no later than 5 working days.

10.7 Incidental Findings

N/A

10.8 Safety Oversight

The full details of the planned study monitoring are included in the Data Safety and Monitoring Plan (DSMP).

The PI will oversee the safety of the entire study, including careful assessment and appropriate reporting of all AEs and SAEs. A trained study team member will be present during stimulation to monitor the safety of the participant. The parent/legal guardian or adult participant and study team will report any adverse events, which arise after any session of tDCS or behavioral assessment, to the investigator and the investigator will convey the concerns to the Medical Monitor immediately upon receipt of this information to determine the optimal recommendation for care. The Medical Monitor will review each case after independent analysis of vital signs/symptoms and the occurrence of any minor or SAE. Incorporation of this Medical Monitor review will occur in addition to the safety and risk mitigation plans that we have established during each active session with the child and family. The Medical Monitor will review these reports and determine continuation of study based on comparative analysis of study stopping rules.

The Medical Monitor for this study is:
Melissa Villegas, MD
Assistant Professor (CHS), Department of Pediatrics
1500 Highland Avenue
Madison, WI 53705
608-263-8663

Dr. Villegas holds board certifications in General Pediatrics, Physical Medicine and Rehabilitation, and Pediatric Rehabilitation Medicine. Dr. Villegas will utilize this background and her experience evaluating patients with cerebral palsy as the Waisman Center Cerebral Palsy Clinic Director to fulfill the role of Medical Monitor.

10.9 Study Monitoring

We have contracted with the UW Institute for Clinical and Translational Research (ICTR) Study Monitoring Service (SMS) for the proposed study to provide ongoing monitoring services to conduct and follow-up of monitoring visits throughout the life cycle of the study. The purpose of the SMS Program is to provide independent, ongoing monitoring to support compliance with good clinical practice (GCP) guidelines, federal, state and institutional regulations, policies, and guidance. The primary role of the SMS is to validate the integrity of the data collected and to assess compliance with the IRB approved protocol and applicable regulatory requirements, while ensuring the rights, safety and welfare of subject are protected.

For this study, SMS personnel will conduct a Site Initiation Visit (SIV) and ongoing Interim Monitoring Visits (IMVs), either on-site, remotely, centrally or a combination thereof, throughout the duration of the study. During IMVs, the monitors will review study materials, including but not limited to: regulatory files, consent forms, and drug accountability logs. SMS will review FDA communications to ensure compliance with applicable FDA IDE ~~IND~~ regulations, guidelines, and institutional policies. SMS personnel will conduct a Close-Out Visit (COV) upon completion of the study at the study site.

Monitoring will consist of all (100%) consent and screening documents for each enrolled subjects along with all (100%) study-related records for a minimum of 20% of subjects enrolled. SMS personnel could increase the percentage of study or subject records to be reviewed if warranted by the ongoing monitoring findings, resulting in a partial or full review of up to 100% of the study-related subject records. In addition, the SMS staff will verify adherence to protocol eligibility criteria, verify documentation for the accountability and administration of the study product, verify documentation of study procedures, and verify that FDA required SAE reports were appropriately submitted.

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

Pregnancy: If at any time during the study, the participant states that they are pregnant, the participation will not be allowed to continue within the primary study. They will be allowed to participate in the 6 and 12-month follow up visits as described in 14.6 Reporting of Pregnancy.

Transient Decline in Motor Function (Individual). Immediate suspension of TMS intervention for the particular participant and initiation of assessment of the change. A written report with detailed documentation of decline in function will be submitted to the Medical Monitor. The participant's pediatrician and neurologist will also be contacted. Follow-up testing will then occur one week after suspension of the study to track progress and change in status with physicians contacted with results directly thereafter.

Transient Decline in Motor Function (Entire Trial). If any participant shows a decrease in function following any component of the proposed study (tDCS or behavioral assessment), the study will be stopped at that time for review by the Medical Monitor. If the Medical Monitor deems that the change in function does not indicate need for termination of the study, the study will recommence. If the Medical Monitor deems that the protocol has indications for change, the study will be reviewed by the investigative team, including consultants and will be changed and submitted for re-approval by the IRB before recommencing the 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.

Study Medical Director Evaluation. Recommend further evaluation to the participant and legal guardian by a neurologist if not the pediatrician\physician routinely involved in the participant'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.

10.11 Economic Burden to Subjects

Subjects will not have to pay for study procedures (tDCS equipment). The subject will not be billed by the healthcare system or their health insurance company for any costs related to a study procedure.

Subjects will be responsible for any costs related to follow-up as directed by their healthcare team, such as clinic visits, including all out-of-pocket costs.

10.12 Facilities and Locations

All recruitment and study procedures will be performed at a single site: The University of Wisconsin-Madison. All interventions will occur in the participants home during a videoconferencing session with

trained study team members giving instructions. A study team member will also be on site of active device use to monitor safety. Unless indicated for safety, the safety monitor will not provide guidance in setting up the device or delivering tDCS to the participant.

10.13 Feasibility of Recruiting the Required Number of Subjects

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. We will be in contact with 15 participants who have received tDCS in our previous studies (67% of these subjects are needed for our project enrollment of 10). 7 participants from the pilot study in our lab expressed interest for future studies and agreed to be re-contacted for participation (70% of our projected subject enrollment of 10). Recruitment will take place immediately after IRB approval and continue for 12 months.

10.14 Principal Investigator Considerations

10.14.1 Time Devoted to Conducting the Research

The Principal Investigator has 2% time effort devoted to this study, recognized by the Department of Pediatrics.

10.14.2 Process for Informing Study Teams

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.

Staff will participate in initial training, follow-up training, and ongoing monitoring and supervision, to ensure understanding of ethical issues involved in this research that includes, but is not limited to, courses offered by UW-Madison's Human Research Protection Program, and a training on HIPAA and measures to protect confidentiality.

All study personnel involved in tDCS stimulation will receive formal training including but not limited to review of critical safety literature and device manuals, hands-on procedural training by PI's, and mentoring by trained graduate students or post-doctoral fellows within the lab familiar with study techniques. All study personnel involved in the use and application of tDCS will demonstrate competence prior to use with study participants. All study personnel involved in neuromodulation will be supervised by the site PIs.

As a lab team, every lab member will be trained by Dr. Gillick on how to conduct a remote tDCS session. We will walk through each component of the session (surveys, Box and Blocks test, tDCS stimulation, etc.) as a team from start to finish. Each team member will perform two mock sessions: one with another team member and one with a community partner. The safety monitor will be trained to be able to prevent, assess, and monitor safety during each session.

Dr. Lench, a postdoctoral researcher, will be acting as a consultant at the Medical University of South Carolina. He will not be interacting directly with participants during videoconferences, analyzing identifiable data, conducting experiments, participant recruitment, or consent. He will only assist with data analysis and manuscript preparation with access to no identifiable data. All experiments will be performed remotely, therefore no participants will be recruited through, or experiments conducted in other physical location, such as MUSC. The communication plan between the UW research team and MUSC team is detailed in HRP-830 -WORKSHEET -Communication and Responsibilities (uploaded separately). This communication plan will ensure MUSC will have the most current version of the

protocol, consent document, and HIPAA authorization throughout the study. Dr. Lench will request a determination from MUSC IRB that they do not consider him engaged in the research. The PI will ensure via regular project meetings that all required approvals will be obtained at each site (including approval by the site's IRB of record) and all modifications will be communicated to MUSC and Dr. Lench and approved (including approval by the site's IRB of record) before the modification is implemented. No identifiable data will be shared outside of UW servers. All local site researchers will conduct the study in accordance with applicable federal regulations and local laws.

10.15 Availability of Medical or Psychological Resources

All participants will have virtual availability to the medical monitor as needed. In the case of an adverse event, a response protocol has been developed to include a call to 9-1-1 as needed.

11.0 REFERENCES

1. O'Shea M. Diagnosis, Treatment, and Prevention of Cerebral Palsy in Near- Term/Term Infants. Clin Obs Gynecol. 2008;51(4):816–28.
2. Yeargin-Allsopp M, Van Braun KN, Doernberg NS, Benedict RE, Kirby RS, Durkin MS. Prevalence of cerebral palsy in 8-year-old children in three areas of the united states in 2002: A multisite collaboration. Pediatrics. 2008;121(3):547–54.
3. Morgan C, Darrah J, Gordon AM, Harbourne R, Spittle A, Johnson R, et al. Effectiveness of motor interventions in infants with cerebral palsy: a systematic review. Dev Med Child Neurol. 2016;58(9):900–9.
4. Moreau NG, Bodkin AW, Bjornson K, Hobbs A, Soileau M, Lahasky K. Effectiveness of rehabilitation interventions to improve gait speed in children with cerebral palsy: Systematic review and Meta-Analysis. Phys Ther. 2016;96(12):1938–54.
5. Ballantyne AO, Spilkin AM, Hesselink J, Trauner DA. Plasticity in the developing brain: Intellectual, language and academic functions in children with ischaemic perinatal stroke. Brain. 2008;131(11):2975–85.
6. Chen CY, Georgieff M, Elison J, Chen M, Stinear J, Mueller B, et al. Understanding brain reorganization in infants with perinatal stroke through neuroexcitability and neuroimaging. Pediatr Phys Ther. 2017;29(2):173–8.
7. Feng W, Kautz SA, Schlaug G, Meinzer C, George MS, Chhatbar PY. Transcranial Direct Current Stimulation for Poststroke Motor Recovery: Challenges and Opportunities. PM R. 2018;10(9):S157–64.
8. Saleem GT, Crasta JE, Slomine BS, Cantarero GL, Suskauer SJ. Transcranial Direct Current Stimulation in Pediatric Motor Disorders: A Systematic Review and Meta-analysis. Arch Phys Med Rehabil [Internet]. 2019;100(4):724–38. Available from: https://doi.org/10.1016/j.apmr.2018.10.011
9. Gillick B, Rich T, Nemanich S, Chen CY, Menk J, Mueller B, et al. Transcranial direct current stimulation and constraint-induced therapy in cerebral palsy: A randomized, blinded, sham-controlled clinical trial. Eur J Paediatr Neurol [Internet]. 2018;22(3):358–68. Available from: https://doi.org/10.1016/j.ejpn.2018.02.001
10. Nemanich ST, Rich TL, Chen CY, Menk J, Rudser K, Chen M, et al. Influence of combined transcranial direct current stimulation and motor training on corticospinal excitability in children with unilateral cerebral palsy. Front Hum Neurosci. 2019;13(April):1–12.
11. Nemanich ST, Rich TL, Gordon AM, Friel KM, Gillick BT. Bimanual Skill Learning after Transcranial Direct Current Stimulation in Children with Unilateral Cerebral Palsy: A Brief Report. Dev Neurorehabil [Internet]. 2019;22(7):504–8. Available from:

https://doi.org/10.1080/17518423.2019.1600065
12. Charvet LE, Kasschau M, Datta A, Knotkova H, Stevens MC, Alonzo A, et al. Remotely-supervised transcranial direct current stimulation (tDCS) for clinical trials: Guidelines for technology and protocols. Front Syst Neurosci. 2015;9(MAR):1–13.
13. Charvet LE, Shaw MT, Bikson M, Woods AJ, Knotkova H. Supervised transcranial direct current stimulation (tDCS) at home: A guide for clinical research and practice. Brain Stimul [Internet]. 2020;13(3):686–93. Available from: https://doi.org/10.1016/j.brs.2020.02.011
14. Gough N, Brkan L, Subramaniam P, Chiuccariello L, De Petrillo A, Mulsant BH, et al. Feasibility of remotely supervised transcranial direct current stimulation and cognitive remediation: A systematic review. PLoS One [Internet]. 2020;15(2):1–27. Available from: http://dx.doi.org/10.1371/journal.pone.0223029
15. Palm U, Kumpf U, Behler N, Wulf L, Kirsch B, Wörsching J, et al. Home Use, Remotely Supervised, and Remotely Controlled Transcranial Direct Current Stimulation: A Systematic Review of the Available Evidence. Neuromodulation. 2018;21(4):323–33.
16. Lench DH, Simpson E, Sutter EN, Gillick BT. Feasibility of remote transcranial direct current stimulation for pediatric cerebral palsy during the COVID-19 pandemic. Brain Stimul [Internet]. 2020;13(6):1803–4. Available from: https://doi.org/10.1016/j.brs.2020.10.010
17. Brunoni AR, Amadera J, Berbel B, Volz MS, Rizzerio BG, Fregni F. A systematic review on reporting and assessment of adverse effects associated with transcranial direct current stimulation. Int J Neuropsychopharmacol. 2011;14(8):1133–45.
18. Van De Winckel A, Carey JR, Bisson TA, Hauschildt EC, Streib CD, Durfee WK. Home-based transcranial direct current stimulation plus tracking training therapy in people with stroke: An open-label feasibility study 11 Medical and Health Sciences 1117 Public Health and Health Services. J Neuroeng Rehabil. 2018;15(1):1–10.
19. [National Research Council. The Prevention and Treatment of Missing Data in Clinical Trials. Washington, DC: National Academies Press, 2010.
20. Little RJ, D'Agostino R, Cohen ML, Dickersin K, Emerson SS, Farrar JT, Frangakis C, Hogan JW, Molenberghs G, Murphy SA, Neaton JD, Rotnitzky A, Scharfstein D, Shih WJ, Siegel JP, Stern H. The prevention and treatment of missing data in clinical trials. N Engl J Med. 2012 Oct 4;367(14):1355-60.]
21. Rich T**, Nemanich ST, Chen M, Friel KM, Feyma T, Krach LE, Nawshin T**, Meekins G, Gillick BT. "Transcranial direct current stimulation (tDCS) paired with occupation-centered bimanual training in children with unilateral cerebral palsy: A preliminary study
22. Groth S, Rich T*, Kubat K*, Martin J*, Miller T*, Morse S*, Myhrman K*, Tobias A*, Gillick BT, “Localizing the primary motor cortex as a target for transcranial direct current stimulation (tDCS): A comparison of the 10-20 Electroencephalogram (EEG) System and Transcranial Magnetic Stimulation (TMS) methods: Study in Progress.”
23. Nemanich S*, Rich T*, Chen CY*, Lixandrao M*, Meekins G, Feyma T, Ward M, Krach LE, Gillick BT . “Changes in Hand Function and Motor Cortex Excitability Following tDCS and CIMT Therapy in Children with Unilateral Cerebral Palsy with Different Patters of Corticospinal Organization.”
24. Nemanich ST*, Sutter E*, Kowalski J*, Nawshin T*, Francis S*, Gillick BT. Targeted applications of tDCS based on corticospinal connectivity patterns in children with hemiparesis: study protocol and preliminary results
25. Kecskemeti S, Samsonov A, Hurley SA, Dean DC, Field A, Alexander AL. MPnRAGE: A technique to simultaneously acquire hundreds of differently contrasted MPRAGE images with applications to quantitative T1 mapping. *Magn Reson Med*. 2016;75(3):1040-1053. doi:10.1002/mrm.25674
26. Kecskemeti S, Samsonov A, Velikina J, et al. Robust Motion Correction Strategy for Structural MRI in Unsedated Children Demonstrated with Three-dimensional Radial MPnRAGE. *Radiology*. 2018;289(2):509-516. doi:10.1148/radiol.2018180180