Perinatal Stroke: Understanding Brain Reorganization through Infant Neuroimaging and Neuromodulation

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Project Summary

Title	Perinatal Stroke: Understanding Brain Reorganization through Infant Neuroimaging and Neuromodulation
Short Title	Perinatal Stroke: Understanding Brain Reorganization
Principal Investigator	Bernadette Gillick
Study Design	Cross-sectional study
Study Duration	5 years
Study Centers	University of Minnesota, Medical School, 420 Delaware Street SE, Minneapolis, MN 55455
Objectives	Examine the brain reorganization after perinatal stroke and impact on motor behaviors in infants between 3 and 24 months of (corrected) age
Number of Participants	50 with perinatal stroke and 10 past participants will be followed-up remotely
Main Inclusion/Exclusion Criteria	*Primary Inclusion Criteria*: Infants and children (<5 years old) with the diagnosis of perinatal stroke *Primary Exclusion Criteria*: Genetic disorders, metabolic disorders, neoplasm, disorders of cellular migration and proliferation, traumatic brain injury, indwelling, prior surgeries that constraint spontaneous movements, or other neurologic disorders unrelated to stroke including uncontrolled seizures
Study Device	TMS will not be used due to COVID-19 and limitations on in-person study visits.
Duration of Device Exposure	No TMS will be delivered as part of the remote study.
Endpoint	Safety, Cortical Excitability, Sensorimotor development
Statistical Methods	Sample size was based on a combination of enrollment feasibility in the available timeframe and what is appropriate given the preliminary nature of this pilot, safety and feasibility study. Note: No further data will be collected to address Aims 1-5 due to transitioning this study to take place remotely. Aim 1: The cortical map volumes of ipsilesional and contralesional hemispheres will be summarized and compared with a paired t-test Aim2: Differences in CST integrity (fractional anisotropy) between ipsilesional and contralesional hemispheres will similarly be evaluated with a paired t-test. The association of the cortical map volume with fractional anisotropy will be evaluated using generalized

	estimating equations. Transformations and non-identity link functions will be considered in exploratory analyses to evaluate non-linear relationships. Aim3: The association of movement quality with ipsilesional cortical excitability and relative tract integrity between hemispheres will be summarized with odds ratios from logistic regression. Aim 4: Safety outcomes will describe all adverse events, reporting the number and percentage along with seriousness, severity, frequency (within a participant), and relatedness. Aim 5: The association between lesion size and corticomotor excitability will be evaluated using linear regression with robust variance estimation for confidence intervals and P-values to determine if larger lesion size is associated with Corticomotor excitability. Aim 6: Use MRI and computational modeling to estimate individualized electric fields from each infant's neuroanatomy. This will be compared to modeling in 20 typically developing children acquired from the baby connectome project (BCP), and from at least one infant with perinatal stroke. The association between lesion size and peak electrical field will be evaluated using linear regression and robust variance estimation. Aim 7. Determine relationship between presence/absence of an MEP at initial testing and initial motor assessment with development of CP. Aim 8. Describe the developmental trajectory of a case series of infants related to early imaging and neurophysiological assessments and later motor development

List of Abbreviations

AE	Adverse Event
AHC-IS	Academic Health Center's Information Systems
BCP	Baby Connectome Project
BDAC	Biostatistical Design and Analysis
BP	Blood Pressure
CMRR	Center for Magnetic Resonance Research
CNBD	Center for Neurobehavioral Development
CP	Cerebral Palsy
CRF	Case Report Form
CST	Corticospinal Tract
CT	Computer Tomography
CTSI	Clinical and Translational Science Institute
DTI	Diffusion Tensor Imaging
EMG	Electromyography
ERP	Event related potential
FA	Fractional Anisotropy
GMA	General Movements Assessment
HARDI	High Angular Resolution Diffusion Imaging
HCP	Human Connectome Project
HINE	Hammersmith Infant Neuromotor Examination
HR	Heart Rate
IHI	Interhemispheric Inhibition
MEP	Motor Evoked Potential
MRI	Magnetic Resonance Imaging
MT	Motor Threshold
NICU	Neonatal Intensive-care Unit
PEDI-CAT	Pediatric Evaluation of Disability Inventory Computer Adaptive Test
PHI	Protected Health Information
RR	Respiratory Rate
SAE	Severe Adverse Event
SGA	Small for Gestational Age
SNN	Stereotactic Neuronavigation
TMS	Transcranial Magnetic Stimulation
UADE	Unanticipated Adverse Device Effect
UMMCH	University of Minnesota Masonic Children's Hospital
UPIRTSO	Unanticipated Problems Involving Risk to Participants or Others

Background and Significance

Perinatal stroke, which occurs between the 20th week of gestation and 28 days after birth, affects more than 1 in 2,300 live births.[1, 2] Perinatal stroke is the most common cause of hemiparetic cerebral palsy (CP).[3] Children with hemiparetic CP due to perinatal stroke show impaired motor function and sensation on one side of the body and usually their participation in daily activities suffers from this decreased function. In spite of presentation as young as in the neonatal period, and certainly within the first months of life, and even with prompt behavioral therapy, ongoing significant residual sensorimotor impairments are common. Therefore, innovative interventions that take advantage of the early critical window for optimizing outcomes are urgently needed—in infancy. These interventions would then occur during the time when the brain may be more neuroplastic and the development of corticospinal tract (CST) has not yet largely reorganized. Current pediatric studies have employed non-invasive brain stimulation, and most commonly use the single or paired-pulses of Transcranial Magnetic Stimulation (TMS) to evaluate and influence brain plasticity. TMS influences cortical excitability through electromagnetic depolarization of targeted cortical neurons through painless pulses delivered over the scalp. However, these studies have mainly investigated older children with hemiparetic CP.[4-6]

Corticospinal development continues postnatally over the first few years of life and damage to the system before, during, or after birth can have a resultant detriment to function throughout the individual's lifetime.[7, 8] Although initially the CST typically develops bilaterally, the integrity of the ipsilateral projections is compromised and control of the limbs develops predominately from the contralateral hemisphere. This loss in ipsilateral projections is driven by activity-dependent competition that exists between the two hemispheres. As the individual continues in movement and exploration of the environment through bimanual to unimanual activity, the crossed CST integrity continues to be strengthened. Typical interhemispheric inhibition (IHI) is progressively revealed as potent interaction between the motor cortices of the two hemispheres with accompanying corticospinal activation allows unimanual function. If a child incurs perinatal stroke on one side of the brain, the CST displays the potential for plasticity through reorganization of the two hemispheres. The ipsilesional hemisphere may lose the developing crossed-CST integrity and the contralesional hemisphere strengthens its ability to control bilateral movement. This adaptation however can have a negative impact on the quality and timing of hand function.[9, 10]

The reorganization process of cortex and CSTs is believed to start from early infancy. Thus early inhibition of the exaggerated IHI from the contralesional hemisphere may be an efficacious way to both shape the reorganization optimally and improve long-term developmental outcomes in infants with perinatal stroke. In order to understand brain reorganization and plasticity with perinatal stroke, investigation during infancy may allow exploration of the optimal time for intervention. Studies using TMS in infants have been safely performed, garnering information on tract integrity and cortical excitability.[7, 11] To date, however, there is only one infant study using TMS to assess CST integrity with perinatal stroke.[7] Indeed, more studies are needed to confirm and expand the current knowledge. As a unique aspect of investigation, combining Magnetic Resonance Imaging (MRI)/ Diffusion Tensor Imaging (DTI) and TMS, will provide an additional opportunity to assess reorganization of CST integrity and cortical excitability in infants with perinatal stroke. Such information would contribute to the assessment of optimal timing of our interventions to improve motor outcomes.

Identifying the association between laboratory assessment results and developmental outcomes is critical, first to understand the impact of brain injuries and reorganization on neurologic impairments in this infant population, and then to guide the direction of early neuromodulatory and combined behavioral interventions. In clinic, there are many standardized and reliable methods to assess motor outcomes in infants. The General Movement Assessment (GMA) is a quick and non-invasive way to evaluate motor performance in infants, before 20 weeks of age (corrected age for preterm infants), who are at risk for later neurologic impairments, such as those born preterm or with perinatal stroke.[12] GMA has shown high

sensitivity to predict future diagnosis of motor dysfunction, and as a predictor of CP is considered cost-efficient compared to MRI assessment.[13] Thus, the GMA is an ideal tool to evaluate motor outcomes in infants with perinatal stroke. The Hammersmith Infant Neuromotor Examination (HINE) or Bayley may also be used for assessments at 3 and 24 months corrected age. The HINE is a valid and sensitive assessment for early prediction of CP as well as the type or severity of CP.[14] The Pediatric Evaluation of Disability Inventory (PEDI), Gross Motor Function Classification Scale (GMFCS), and Mini-Manual Ability Classification Scale (mini-MACS), included in the remote follow-up portion of the study, will provide an assessment of fine and gross motor ability as well as participation in developmentally-appropriate roles and activities.

In instances of perinatal stroke, understanding not only the changes to the central nervous system but also the associated neurologic impairments during early infancy is a prerequisite before researchers and clinical practitioners can develop and provide timely and efficacious interventions. Therefore, the purpose of this study is to use MRI/DTI, and TMS to comprehensively examine both the CST integrity and cortical excitability in infants following perinatal stroke, and to identify association with sensorimotor outcome as evaluated by behavioral assessment. The remote component of the study will aim to relate neuroimaging and brain stimulation results to motor outcome in early childhood (age 2-5 years). This study will also investigate the relationship between modeled electric field and measured MT across hemispheres. This may help identify anatomical markers that can predict electric field strength and thus could be used for dosing considerations for future neuromodulation interventions. We will also examine critical timing to provide future early neuromodulatory and combined behavioral interventions in infants with perinatal stroke.

Specific Aims/Study Objectives

No further data will be collected to address Aims 1-5 in the remote modification to the study, as TMS and MRI will not be used. However, results obtained for the participants from previous TMS and MRI sessions will be incorporated into the revised aims.

Aim 1: Use TMS to index maladaptive cortical reorganization by assessing the relative excitability of corticospinal projections from each hemisphere to upper extremity musculature.
Hypothesis: The ipsilesional hemisphere will have a smaller "map volume" (lower cortical excitability) than the contralesional hemisphere (larger map volume/higher cortical excitability).

Aim 2: Index maladaptive cortical reorganization by evaluating the organizational integrity of the CSTs bilaterally via fractional anisotropy (FA), a standardized metric derived from DTI
Hypothesis 1: Ipsilesional CST will have a lower value of FA than the contralesional CST.
Hypothesis 2: Smaller cortical excitability volumes will be associated with lower values of FA.

Aim 3: For infants with perinatal stroke, examine the relationship between movement quality derived from the GMA and cortical excitability and with CST integrity.
Hypothesis: Atypical GMA outcome scores will be associated with a lower FA value and lower ipsilesional CST excitability.

Aim 4: Monitor for adverse events during TMS cortical mapping and MRI scanning of infants with perinatal stroke.
Hypothesis: No seizure or other serious adverse event related to TMS or MRI/DTI will occur in this study.

Aim 5: Aim 1: Using TMS, define the relationship between lesion heterogeneity, corticomotor excitability and circuitry.

Hypothesis: We hypothesize that the larger the lesion, the higher the motor threshold and the greater the probability of atypical ipsilateral CST circuitry.

Aim 6: Using MRI and computational modeling, estimate individualized electric fields from each infant's neuroanatomy.
Hypothesis 1: We hypothesize that the larger the lesion and motor threshold, the lower the modeled peak electric field.
Hypothesis 2: We hypothesize that there is an association between the electric field and individual neuroanatomic characteristics.

The following aims are included to transition this study to be completed remotely. These aims will contribute towards determining the relationship between biomarkers obtained via MRI and TMS in early infancy (<1 year) and later motor outcome (age 2-5 years)

Aim 7. Determine relationship between presence/absence of an MEP at initial testing and initial motor assessment with development of CP.

Hypothesis 1: We hypothesize that absence of an MEP from the more affected hemisphere at initial testing will be related to diagnosis of CP at age 2-4 years.

Aim 8. Describe the developmental trajectory of a case series of infants related to early imaging and neurophysiological assessments and later motor development

Hypothesis 1. Infants with greater asymmetries on early imaging and TMS assessments will have greater functional impairment (as assessed with GMFCS, MACS, and PEDI-CAT) at age 2-4 years

***Device Description*:**
Note: All in-person assessments have been deferred due to COVID-19. Transcranial Magnetic Stimulation devices will not be used in this remote study.
Non-Invasive brain stimulation has been recently investigated for benefits in recovery of motor function in adults and more recently in children. 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 primary motor cortex or M1.

Testing for Cortical Excitability (TMS): We will use a Magstim BiStim^2 TMS stimulator with a coil to test the cortical excitability of the brain in infants with perinatal stroke. The center of the coil is hand held on the scalp over the desired region to be stimulated. An electrical current is pulsed through the electrode, which creates a magnetic field. This magnetic field, in turn, creates an electric field in the surrounding area, including inside the skull, which induces an ionic current to flow on the surface of the brain. Depending on the parameters of the stimulation and the excitability of the underlying cortex, the stimulation may or may not depolarize the nerve membrane to threshold. If it does depolarize, an action potential is generated and conducted to spinal motor neurons, which, depending on their own excitability, may transmit an action potential to muscle. Ultimately, the response is recorded as a motor evoked potential (MEP) with electromyography (EMG) electrodes located over the target muscle.

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 participant- specific MRI image on a computer screen which shows the locator position, we will be able to specify the TMS hotspot location.

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

Research Design and Methods

Study Design and procedures overview
Due to COVID-19, concern for the health and safety of participants, and the limited time remaining to complete the research, this study will be conducted remotely via virtual/remote assessments conducted during one ZOOM session with a parent/guardian.

Anticipated Duration of the Clinical Investigation
This study is expected to be completed within a two-year period beginning in August 2019. Submission of all indicated applications is presumed to occur over an initial 6-month period of time, with the potential for revisions within this timeframe. Recruitment of infants will be based over a 18 month period of time. Data analysis and write-up of results will occur during the last six months of this two-year period, as outlined in the table below.

<table>
<tr><th>0-6 months</th><th>6-12 months</th><th>12-18 months</th><th>18-24 months</th></tr>
<tr><td>IRB</td><td colspan="3"></td></tr>
<tr><td></td><td colspan="2">Recruitment/Data Collection</td><td></td></tr>
<tr><td colspan="2"></td><td colspan="2">Data Analysis and Results Write-up</td></tr>
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If the trial ends prior to the study completion, all scheduled participants and families will be notified and study visits will be terminated. The Clinical and Translational Science Institute (CTSI) will be notified and all future reserved dates for use of the CTSI will be canceled. All research investigators on the study will be notified. The CTSI funding agency will also be notified.

Participants
Sample Size: This follow-up study will be offered to all previous participants in the infant pilot study, with the aim of recruiting 10 infants for participation

Inclusion Criteria: Participants will be eligible to participate in the study if the following conditions exist.
1. Birth diagnosis of perinatal stroke by Cranial Ultrasound, Computer Tomography (CT), or MRI.

2. Previous participant in the pilot study: Perinatal Stroke: Understanding Brain Reorganization through Infant Neuroimaging and Neuromodulation (parent/guardian indicated consent to be contacted for future studies)

3.. Age less than or equal to 5 years

Exclusion Criteria:
1. Lack of wireless internet access or computer access to participate in virtual Zoom call.

Exit/Discontinuation Criteria:
1. Legal guardians of the infant voluntarily withdraws from the study
2. Participant death
3. Participant acquires any of the listed exclusion criteria
4. Participant completes the protocol
5. Participant is non-compliant with the protocol
6. IRB recommendation

Participants Recruitment Plan**:** Our primary recruitment method will be contacting families who previously participated in our pilot study in perinatal stroke who indicated on the pilot study signed consent form that they are open to being contacted for future studies. Parents/guardians of infant participants that did not indicate willingness to be contacted for future studies via the signed consent form

will not be contacted. Contacts will be initiated via email or phone via approved email/phone scripts. No new participants (that did not previously participate in the pilot study) will be recruited

Procedures
After a phone screen, the investigator will obtain the authorization forms from the legal guardian of the infant to request medical records from hospitals/clinics. Once we have determined eligibility for study criteria for the infant we will send the consent form via the approved UMN approved template e-consent within REDCap, and study staff will follow-up with a phone call to discuss any questions as needed. If the parent or guardian deems appropriate, this can occur on the same day as the remote Zoom visit. The child participant will not need to be present during the Zoom visit.

No MRI or TMS sessions will occur due to the study being conducted remotely in response to COVID-19.

From the medical record, the research team will extract data regarding the following elements, as applicable:

1. Diagnosis of cerebral palsy
2. Recent movement or developmental assessments
3. Types and amounts of rehabilitation therapies received
4. Speech, cognition, or sensory assessments
5. Surgeries or major procedures
6. Recent imaging
7. Comorbidities

1. Questionnaires – completed over Zoom

Questionnaires will be completed by the investigator in REDCap while on a virtual Zoom call with the parent or legal guardian of the participant. The child participant will not need to be present. In order to facilitate completion and comprehension of all questionnaires, the investigator will read the questions to the parent and enter the parent's responses directly into REDCap. For the PEDI-CAT, the investigator will enter data into the Pearson Q-Global testing system (see below), but will not enter any identifying participant data to ensure anonymity of data entered into this system. The output of the PEDI-CAT will then be entered by the investigator into REDCap. The Zoom call will not be recorded.

GMFCS: The GMFCS (https://canchild.ca/en/resources/42-gross-motor-function-classification-system-expanded-revised-gmfcs-e-r) is a five-level classification system to describe the gross motor function of children with cerebral palsy. Distinctions between levels are based on functional abilities, assistive technology use, and quality of movement. The GMFCS Family and Self Report Questionnaire will be used for a parent/guardian to classify their child's motor abilities. A format of the questionnaire is available for an age group of 2 to <4 years. This assessment takes < 5 minutes to complete.

Mini-MACS: The Mini-MACS (https://www.macs.nu/files/Mini-MACS_English_2016.pdf) is a classification system to describe how children with cerebral palsy aged 1-4 years use their hands in daily activities. Ability is ranked on five levels based on the child's self-initiate activity and their need for assistance/adaptation when handling objects. It will be completed by the researcher by asking the parent/guardian about their child's manual abilities, as indicated by the assessment. This assessment takes < 5 minutes to complete.

PEDI-CAT: The PEDI-CAT will be delivered using Pearson's Q-global testing system (https://www.pearsonassessments.com/store/usassessments/en/Store/Professional-Assessments/Behavior/Pediatric-Evaluation-of-Disability-Inventory-Computer-Adaptive-Test/p/100002037.html) To deliver this assessment, the lab member will have access to the PEDI-CAT software, but will read the questions to the parent/guardian of the child and enter their responses into the

software. This delivery method has been chosen so that contact information of participants is not provided to an outside entity. No participant identifying information will be entered into the Pearson Q-global system. The PEDI-CAT software will elicit a document stating item responses and summary score, which will then be uploaded into REDCap by the study staff.

The PEDI-CAT uses Item Response Theory statistical models to estimate a child's ability from a minimal number of items. There are three functional domains that will be assessed: Daily Activities, Mobility, and Social/Cognitive. The Speedy form of the PEDI-CAT (less than or equal to 15 items per domain) will be used. It takes approximately 12 minutes to complete. The PEDI-CAT provides normative standard scores as age percentiles. It is appropriate for children age 0-21 years. Test-retest reliability is high for the three domains (>0.97) and has been found to have good construct validity and responsiveness to change.[14, 15]

The single virtual visit, including time to complete questionnaires, is estimated to take <1 hour.

Computational Modeling (offline analysis)

Based on MRI data previously collected as part of the pilot study,. we will analyze the hypothetical TMS-induced electric field strength (effective dose) and compare it across hemispheres. We will further test anatomical predictors for the modeled electric field. This will help to identify anatomical markers that can predict the effective TMS dose in pediatric stroke. Success in these efforts would identify anatomical markers that can predict electric field strength and thus could be used in dosing considerations for future neuromodulation interventions.

To obtain greater data accuracy in our MRI processing and computational modeling we will include and use the iBEAT (Infant Brain Extraction and Analysis Toolbox) V2.0 software, as our current image processing software does not accurately correct for characteristics of an infant brain. The software was developed in 2012 by the Developing Brain Computing Lab and the Baby Brain Mapping Lab in the University of North Carolina at Chapel Hill and is used specifically to process and correct structural infant and pediatric brain images, which typically exhibit low contrast.

A one-time use of iBEAT V2.0 software will be used to process 4 de-identified pediatric brain image files from 1 participant that were taken at4 and 24 months (2 images from each time point). The 4 de-identified image files will be uploaded by our study staff from our secure BOX storage into the software program and processed, and those processed images will then be downloaded back into our secure BOX drive and used by our team for more accurate data analysis. This will not compromise any PHI.

iBEATV2.0 software website: https://ibeat.wildapricot.org/

***Family/Infant Withdrawal*:** Families may discontinue participation at any time, for any reason.. The details surrounding the circumstances of the reason for withdrawing the participant from the study will be reported with no identifiers included.

Safety and Adverse Events Monitoring

Due to COVID-19 and the removal of in person assessments using TMS and MRI, risk of adverse events will be decreased.

Adverse Events

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

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

Serious Adverse Event (SAE) 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.

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

Safety Monitoring Plan
All research procedures will be performed by qualified personnel who have completed required training, including human participants training.

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

AEs and SAEs will be assessed and followed throughout the study.

Caregivers of participating infants will have contact information to enable them to easily contact study personnel.

Anticipated Risks/Risk Mitigation:

Study Procedures	**Anticipated Risks**	**Risk Mitigation**

Data collection	Data breach	All participant data will be secured in REDCap database, on Box servers, or in a locked file cabinet (for paper medical records)

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Study Stopping Rules

***Anticipated Adverse Events*:** Participants will be parents/legal guardians of infants who sustained a congenital stroke before, during or shortly after birth. There are no anticipated adverse events for the infants, who will not be present for the study. The only anticipated risk is a risk of data breach.

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

The Sponsor-Investigator will promptly review documented AEs and abnormal test findings to determine
1) if the abnormal test finding should be classified as an AE;
2) if there is a reasonable possibility that the AE was caused by the investigational device or, if applicable, other study treatment or diagnostic product(s); and
3) if the AE meets the criteria for a SAE.

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

Adverse Events
All observed or volunteered AEs and abnormal test findings, if applicable, or suspected causal relationship to the investigational device or, if applicable, other study treatment or diagnostic product(s) will be recorded in the participants' case histories. For all AEs, sufficient information will be pursued and/or obtained so as to permit
1) an adequate determination of the outcome of the effect (i.e., whether the effect should be classified as a serious adverse effect) and;

2) an assessment of the casual relationship between the AE and the investigational device or, if applicable, the other study treatment or diagnostic product(s).

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

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

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

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

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

Statistical Considerations

Sample size was based on a combination of enrollment feasibility in the available timeframe and what is appropriate given the preliminary nature of this pilot, safety and feasibility study.

Aim 1: The cortical map volumes of ipsilesional and contralesional hemispheres will be summarized and compared with a paired t-test

Aim2: Differences in CST integrity (FA) between ipsilesional and contralesional hemispheres will similarly be evaluated with a paired t-test. The association of the cortical map volume with FA will be evaluated using generalized estimating equations (to account for correlation of paired measurements from each participant: volume and FA from each hemisphere). Transformations and non-identity link functions will be considered in exploratory analyses to evaluate non-linear relationships.

Aim3: The association of movement quality (atypical vs. typical movement) with ipsilesional cortical excitability and relative tract integrity between hemispheres (ratio of FA values) will be summarized with odds ratios from logistic regression.

Aim 4: Safety outcomes will describe all adverse events (AEs), reporting the number and percentage along with seriousness, severity, frequency (within a participant), and relatedness. The statistical analyses were planned and will be conducted by Dr. Rudser (collaborator) at the Biostatistical Design and Analysis Center (BDAC).

Aim 5:. The association between lesion size and corticomotor excitability will be evaluated using linear regression with robust variance estimation for confidence intervals and P-values to determine if larger lesion size is associated with corticomotor excitability.

Aim 6: The association between lesion size and peak electrical field will be evaluated using linear regression and robust variance estimation. This will be compared to modeling in 20 typically developing children acquired from the baby connectome project (BCP).

Aim 7. Presence/absence of an MEP at initial testing will be compared with diagnosis of cerebral palsy. based on medical record. This relationship will be compared with a Chi Square test.

Aim 8. The developmental trajectory and assessment scores of a case series of infants will be presented with descriptive statistics.

Data and Record Keeping

All identifiable data are confidential and under protected. Each participant will be assigned a number and all data collected forms will use only the assigned number for identification.. Password will also be used to protect digital data.

All data will be kept for six years after the completion of this study.

Confidentiality
Information about study participants will be kept confidential and managed according to the requirements of the HIPAA of 1996. 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 or legal guardian to revoke their authorization for use of their PHI

In the event that a participant or legal guardian 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 or their legal guardian 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.

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

Data for this study will be entered by the research investigators and study coordinator directly into the electronic REDCap database. Any data collected on other electronic forms (PEDI-CAT) will then be entered within the next week into a REDCap database, which uses a MySQL database via a secure web interface with data checks used during data entry to ensure data quality. REDCap includes a complete suite of features to support HIPAA compliance, including a full audit trail, user-based privileges, and integration with the institutional LDAP server. All electronic documents not stored in REDCap will be stored securely on the Gillick Lab Box account, with access provided only to individuals specified in the study protocol as needed. 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 Retention
The PI will maintain all records for 6 years.

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