Study Protocol: Multimodal Longitudinal Assessment of Infant Brain Organization and Recovery in Perinatal Brain Injury

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Purpose: Perinatal brain injury is a primary cause of cerebral palsy, a condition resulting in lifelong motor impairment. Infancy is an important period of motor system development, including development of the corticospinal tract (CST), the primary pathway for cortical movement control. The interaction between perinatal stroke recovery, CST organization, and resultant motor outcome in infants is not well understood.

Methods: Here, we present a protocol for multimodal longitudinal assessment of brain development and motor function following perinatal brain injury using transcranial magnetic stimulation and magnetic resonance imaging to noninvasively measure CST functional and structural integrity across multiple time points in infants 3 to 24 months of age. We will further assess the association between cortical excitability, integrity, and motor function.

Discussion: This protocol will identify bioindicators of motor outcome and neuroplasticity and subsequently inform early detection, diagnosis, and intervention strategies for infants with perinatal stroke, brain bleeds, and related diagnoses.

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Key words: cerebral palsy, infant, magnetic resonance imaging, movement assessment, perinatal stroke, transcranial magnetic stimulation

INTRODUCTION

Perinatal stroke and other forms of perinatal brain injury have potentially disabling consequences.[1] For example, 50% to 75% of infants with perinatal stroke occurring due to ischemic or hemorrhagic events, from early gestation through the first month after birth, will develop lifelong motor impairment and 10% to 60% will also have cognitive deficits.[2,3] These impairments lead to challenges in the school and home environments, with a decreased likelihood of eventual employment and independence and increased caregiver burden.[4,5] In addition, perinatal brain injury is one of the primary causes of cerebral palsy (CP),[6] a permanent neurological condition affecting motor function, with individual lifetime costs of care exceeding US $1 million.[7]

The first 2 years of life constitute a critical period of brain development. Axonal projections undergo significant myelination,[8] and although synaptic connections decrease in number, the remaining connections increase in strength.[9] These years feature heightened neuroplasticity, in which exogenous factors, such as nutrition and the environment, can impact brain function and affect subsequent behavior.[10-12] Therefore, this period offers a "window of opportunity" for understanding and influencing the complex development of brain connectivity or "circuitry" and motor function in infants after perinatal brain injury. One key example of brain organization that impacts long-term motor function is the formation of corticospinal tracts (CSTs), the primary descending motor pathways controlling voluntary movement, which rapidly develop during infancy.[13] In brain development for a typical infant, the initial bilateral organization of the CST develops into a predominately crossed CST organization. However, after an early injury such as perinatal stroke, ipsilateral projections from the less affected hemisphere may be strengthened while contralateral projections from the more affected hemisphere may weaken.[14-16] This

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postinjury corticomotor organization may be the cornerstone of maladaptive plasticity mechanisms, contributing to long-term impairments.[14,17,18] CST organization is an important bioindicator[19] of functional change and development and should be considered when assessing the relationships between neural organization and motor function, as well as when designing interventions targeted to improve limb use.

Many rehabilitation approaches for older children with CP have been investigated, including intensive training of the upper extremities to drive activity in corticomotor circuits,[20-23] based on theories of motor learning and use-dependent plasticity.[24] Further research is needed to optimize these approaches for infant populations. There is now consensus that, due to brain plasticity and rapid development, providing early intervention may result in optimal recovery and lower care costs.[25-31] Although historically the diagnosis of CP has not occurred up until approximately 2 years of age,[32] diagnosis can now often be established within 6 months of age integrating specialized assessments of infant movement and neuroimaging. While earlier diagnosis allows for access to intervention during this period of heightened neuroplasticity,[6] at present the diagnosis timeline remains inconsistent, with understanding of brain development after perinatal brain injury remaining limited. Improvements in classification of the type and/or topography of CP are also necessary to determine the most appropriate intervention.[6] We anticipate yet greater response to intervention once current treatments are tailored to the individual's unique pattern of brain organization and development. Little is known about the interaction between recovery after perinatal brain injury, normative programmed cortical development, and resultant motor outcome, creating a gap, which leads us to ask the following: (1) What are the adaptive and maladaptive neuroplastic changes in the motor system that occur during infancy? and (2) How do these changes relate to motor outcomes? In this study, we propose to use noninvasive brain stimulation, neuroimaging, and behavioral assessments to analyze associations between brain development and potential diagnosis of CP. This protocol will lay a foundation for identifying individual patterns of early brain organization, allowing for future design of tailored rehabilitation interventions, delivered during an optimal time frame.

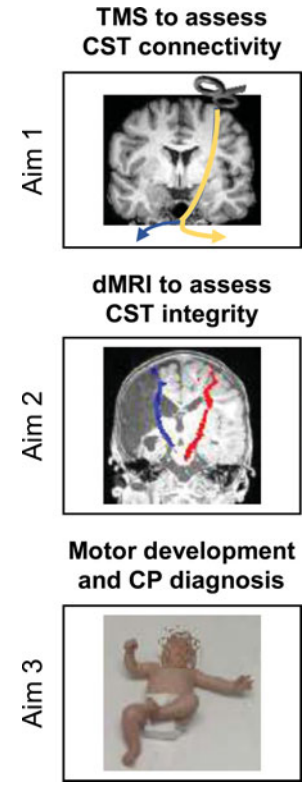

Fig. 1. Summary of experimental design and assessments. Aim 1, integrates TMS to assess CST connectivity. Aim 2 integrates dMRI to assess CST integrity. Aim 3 evaluates motor development in relationship to CP diagnosis. TMS indicates transcranial magnetic stimulation; CST, corticospinal tract; dMRI, diffusion MRI; CP, cerebral palsy. This figure is available in color online (www.pedpt.com).

OBJECTIVES

The overall objective of the proposed study is to perform a multimodal longitudinal assessment of infant brain development and motor function following perinatal brain injury that will lead to the identification of bioindicators for adaptive and maladaptive brain development, guiding future investigations of treatments and their mechanisms. We will use magnetic resonance imaging (MRI) and single pulses of transcranial magnetic stimulation (TMS) to assess functional and structural integrity, excitability, and connectivity of the CSTs and examine the association with motor outcomes via standardized assessment (Figure 1). In addition, we will examine biological response to TMS, including vital signs and infant stress response. The primary aims and hypotheses to be tested are detailed in Table 1. The study implementing this protocol is currently funded by the National Institutes of Health/National Institute of Child Health and Human Development and the National Institute of

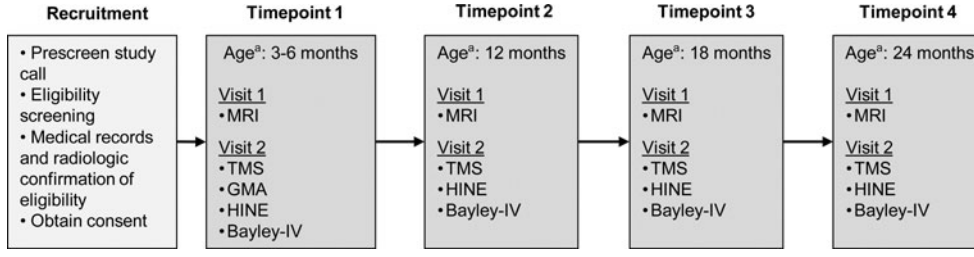

Fig. 2. Study design and assessment schedule. MRI indicates magnetic resonance imaging; GMA, General Movements Assessment; HINE, Hammersmith Infant Neurological Examination; TMS, transcranial magnetic stimulation; Bayley-IV, Bayley Scales of Infant and Toddler Development IV. [a]Age corrected for prematurity.

TABLE 1
Study Aims and Hypotheses

Aim	Hypothesis
1. Map the presence and excitability of corticospinal pathways	1. The proportion of infants with a contralateral MEP from the affected/more affected hemisphere will increase over time from baseline 2. Among infants with an MEP present in either hemisphere at baseline, the difference in resting motor threshold between hemispheres will increase over time due to the slower development of CST on the affected/more affected side
2. Map the structural integrity and connectivity of corticospinal pathways	1. Structural integrity, as estimated by dMRI tractography, will be lower in the affected/more affected CST than in the unaffected/less affected CST 2. The CST will continue to develop over time; however, the mean change in structural integrity of the affected/more affected CST will be smaller than the unaffected/less affected CST
3. Compare motor outcomes from clinical behavioral assessments against CST excitability and integrity	1. Atypical motor function will be associated with lower CST excitability in the affected/more affected hemisphere 2. Atypical motor function will be associated with lower structural integrity of the affected/more affected CST

Abbreviations: CST, corticospinal tract; dMRI, diffusion MRI; MEP, motor evoked potential.

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METHODS

Participants

Enrollment and Recruitment. After initial identification and eligibility screening, 50 infants, 3 to 6 months' corrected age, will be enrolled in this study for longitudinal assessment at 4 time points until 24 months of age. Physicians and clinicians within regional hospitals and neonatal intensive care units will assist to identify potential participants and approach families with information about the study. We conservatively estimate that 1 in 60 infants admitted to participating recruitment sites will meet the eligibility criteria, making 50 infants eligible per year. From our infant pilot study and established community recruitment contacts, we predict another 3 eligible infants per year (53 per year total). With an approximate 50% enrollment rate, we will recruit and enroll 26 infants per year on average over the 2.5 years of enrollment, resulting in a total of 65 infants. Conservatively estimating, based on our pilot, an attrition of 6 infants per year during the 2.5-year recruitment time frame (15 total), this strategy will allow us to recruit and evaluate 50 infants at each time point in this longitudinal study as determined by the power analysis described in the "Data Analysis" section. The study protocol has been approved by the local Institutional Review Board and received a nonsignificant risk determination by the US Food and Drug Administration.

Participant Eligibility Criteria. Determination of eligibility will follow 3 steps. First, the study team will complete a predefined initial screening. Second, the screening results and relevant medical records will be sent to the study's Medical Director. Third, based on the provided information, the Medical Director will make the final decision for participation eligibility. The Medical Director Determination of Eligibility form is presented in the Supplementary Materials (available at: http://links.lww.com/PPT/A368).

Inclusion Criteria. Infants born preterm and term will be included if they have radiologically confirmed periventricular leukomalacia or acute unilateral or bilateral brain lesions, including neonatal hemorrhagic or thrombotic stroke, involving the motor cortex and/or subcortical structures.

Exclusion Criteria. Infants with any of the following will be excluded: (1) metabolic disorders; (2) chromosomal abnormalities or congenital syndromes; (3) neoplasm; (4) uncontrolled seizures or active seizure disorder on medications; (5) disorders of cellular migration and proliferation; (6) acquired traumatic brain injury; (7) surgical procedures that may constrain current spontaneous movements; or (8) other neurological disorders unrelated to perinatal stroke. At the time of each assessment, infants will also be excluded if any of the following apply: (1) mechanical ventilation; (2) indwelling metal or incompatible medical devices; (3) uncontrolled seizures or active seizure disorder on medications; or (4) ongoing apneic episodes and/or syncope.

Study Design

This is a prospective longitudinal study with assessments at 4 time points in early development, corrected for gestational age: (1) between the ages of 3 and 6 months; (2) at 12 months; (3) at 18 months; and (4) at 24 months. Each time point will include 2 visits: MRI during visit 1 and TMS and motor behavior assessments during visit 2 (Figure 2).

Assessments and Data Acquisition

MRI Assessment.

Procedure. Scanning sessions will be scheduled around the child's sleep schedule and at the convenience of the caregivers. Before the start of the scan, infants will be swaddled and rocked to sleep by the caregiver in the darkened scanner room or a separate room. Once asleep, infants will be positioned on a memory foam mattress secured to the scanner table. To protect the developing auditory system, we take special care to attenuate sound levels for a reduction of approximately 45 to 55 dB[33,34] by (1) lining the bore of the scanner with sound-attenuating foam, (2) placing moldable silicone earplugs in the ears after the infant

falls asleep, and (3) fitting the infant with custom headphones. A study team member will remain with the infant throughout the scanning session to monitor responses and ensure the infant remains asleep, while one caregiver will also be allowed to stay in the scanner room during the session.

Scanning Modalities and Protocol. Infants will be scanned on a 3-Tesla Discovery MR750 MRI scanner (GE Healthcare, Waukesha, Wisconsin). The imaging protocol includes structural, diffusion, and multicomponent relaxometry imaging. Each sequence will take approximately 5 to 10 minutes, and the total scan time will last approximately 1 hour.

Structural Imaging. T1-weighted imaging will be obtained using a custom MPnRAGE sequence, a self-navigated imaging method that provides high-resolution, motion-corrected, T1-weighted images and T1 relaxometry maps.[35,36] The T1-weighted scan will be used in the analysis pipeline to confirm lesion location and guide TMS neuronavigation. High-resolution T2-weighted images will additionally be acquired using GE's 3-dimensional CUBE sequence.

Diffusion-Weighted Imaging. A multiple *b*-value diffusion MRI data set 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 to correct for susceptibility distortions.[37] Multiband imaging (factor = 3) will be used to shorten the acquisition time.

mcDESPOT Imaging. mcDESPOT imaging acquires rapid and time-efficient SPGR (SPoiled Gradient-Recalled) and bSSFP (balanced Steady-State Free Precession) image data across multiple flip angles.[38,39] The number and size of the flip angles will be optimized for age range of infants based on prior literature.[40] mcDESPOT imaging will be used to compute T1 and T2 relaxometry indices, as well as the myelin water fraction, a neuroimaging measure sensitive to myelin content.[38]

TMS Assessment. TMS will be used to assess cortical excitability and circuitry (not as a neuromodulation intervention) during the second visit. Single-pulse TMS (Magstim 200^2; Magstim, Spring Gardens, Whitland, United Kingdom) will be used to measure the resting motor threshold (RMT) and motor evoked potential (MEP) amplitude from the M1 region of both hemispheres under the guidance of a frameless stereotactic neuronavigation system (Brainsight; Rogue Research, Montreal, Quebec, Canada).[41,42]

Each infant's T1-weighted MRI (obtained within 7 days) will be projected onto the neuronavigation system to assist with localization of the motor cortex.[16] Infants will be comfortably positioned on a caregiver's lap. Single-pulse TMS will be delivered with a hand-held figure-of-eight surface coil (Magstim D70^2). Coil placement will be guided in real time by the stereotactic neuronavigation system to ensure accuracy of both location and coil orientation, to achieve optimal coil placement tangential to the scalp at a 45° angle to the nasal-inion line, perpendicular to the central sulcus. This orientation ensures a posterior-anterior current direction optimal for stimulation of the motor cortex.[43] Electromyography (EMG) signals will be recorded using surface gel-based EMG electrodes attached over upper-limb muscles (biceps and wrist flexor) bilaterally, based on a preliminary EMG assessment of the feasibility of facilitating isometric contraction on infants developing typically.

Determination of Motor Threshold. Our primary outcome measure is the presence or absence of MEPs from stimulation of each hemisphere, along with associated MEP amplitudes, latencies, and RMTs. Based on previous pediatric TMS protocols and a safety and feasibility infant pilot study,[44-46] we will deliver single-pulse stimuli at 50% maximum stimulator output (MSO) over the region of presumed primary motor cortex (M1) corresponding to upper extremity movement. Single pulses of TMS will be delivered with no less than 10 seconds of interstimulus interval. This level will be adjusted systematically (ie, in 10% increments) until the RMT is found, defined as the minimum intensity required to elicit MEPs of 50 μV or more peak-to-peak amplitude in at least 3 of 5 trials. If an MEP is found, we will investigate a more precise estimate of the RMT by lowering stimulation by increments of 5% MSO until no MEP is detected. If no MEP is found at 100% MSO and the participant is tolerating the procedure well based on safety assessments, we will continue delivering pulses at 100% MSO, up to 100 pulses in 1.0-cm increments in circumlocution around the initial M1 target to determine the motor hot spot (ie, the brain region at which the RMT is lowest). If no MEP is found there or in adjacent motor cortex cortical regions, a lack of MEP in that hemisphere will be recorded. We will then proceed with evaluation of the other hemisphere as previously up to 100 pulses per hemisphere. No greater than 200 total pulses will be delivered in the TMS session for each participant.

The participant's status will be assessed prior to, during (at 5-minute epochs), and after stimulation using a previously published "Participant Safety Monitoring Form."[47] Comments and assessments from the caregivers present for the session will be integrated at each time point. If at any point during the session the participant displays an increase in irritability/anxiety, we will pause the TMS assessment and attempt to calm the participant. If the participant is able to calm, we will consult with the caregiver and confirm willingness to continue with assessment before proceeding. If the participant continues to display signs of irritability and anxiety, or based on determination from the caregiver and/or the investigator team, the session will be discontinued.

The active TMS session as described earlier will last a total of 10 to 30 minutes. The total time in this session is anticipated to be 1.0 to 2.0 hours including preparation and assessments. All MEP data will be collected using the Brainsight EMG system (Brainsight; Rogue Research).

TMS Safety. In this protocol, TMS will be used as single-pulse assessment only. The use of single-pulse TMS has long been established as an effective method to probe motor pathways and cortical representation in varied research and clinical applications.[43,48-51] The most serious risk of TMS, when used repetitively as an intervention, is seizure, with minor adverse events reported including dizziness, fatigue, and hearing changes.[52] To the best of our knowledge and review, across a growing number of studies in children younger than 2 years, no serious adverse events (ie, seizure) have been

TABLE 2
Studies Performing TMS Assessment With Children Younger Than 2 Years

Authors	Year	Number of Children <2 y	Diagnosis	Adverse Events and Tolerability
Koh and Eyre[53]	1988	18	Developing typically	Well tolerated; no adverse events
Eyre et al[54]	1991	Unknown	Developing typically	None reported
Müller et al[55]	1991	13 children <3 y	Developing typically	None reported
Müller et al[56]	1992	Unknown	Hemiparesis of varied etiologies	None reported
Nezu et al[57]	1997	6 children <3 y	Developing typically	None reported
Tamer et al[58]	1997	Unknown	Developing typically and malnourished	None reported
Eyre et al[59]	2000	223	Born preterm or term	None reported
Fietzek et al[60]	2000	Unknown	Developing typically	None reported
Eyre et al[15]	2001	18	Developing typically	None reported
Collado-Corona et al[61]	2001	4	Varied	No effect of TMS on auditory function
Dachy and Dan[62]	2002	2	Spasticity	None reported
Geerdink et al[63]	2006	13	Spina bifida	All infants tolerated magnetic stimulation without discomfort
Eyre et al[64]	2007	71	Developing typically; acute brain lesions	None reported
Dabydeen et al[65]	2008	16	Neonatal encephalopathy or white matter disease with prematurity	None reported
Santiago-Rodríguez et al[66]	2009	30	Developing typically; periventricular leukomalacia	None reported
Koudijs et al[67]	2010	6	Intractable epilepsy	No adverse events occurred in children <3 y; tolerated TMS without discomfort
Yang et al[32]	2013	5	Hemiparetic cerebral palsy	Well tolerated; no adverse events reported during the study or at final follow-up
Narayana et al[50]	2015	4	Variable developmental delays	No adverse events, no seizures
Narayana et al[68]	2017	1	Seizure disorder	No TMS-induced seizures occurred
Nemanich et al[47]	2019	6	Perinatal intracranial hemorrhage/stroke	No serious adverse events during TMS sessions or within 24-h follow-up
Kowalski et al[46]	2019	10	Perinatal intracranial hemorrhage/stroke	No serious adverse events during TMS sessions or within 24-h follow-up

Abbreviation: TMS, transcranial magnetic stimulation.

reported following single-pulse TMS (Table 2). We have established and published protocols to safely administer and monitor single-pulse TMS during the proposed experiments.[18]

Motor Behavior Assessments.

General Movements Assessment. Each General Movements Assessment (GMA) will be captured via a 3- to 5-minute recorded video. Infants will be supported in supine position while awake and calm, without the use of a pacifier. Infants will wear a diaper or onesie to allow clear observation of spontaneous movements of neck, trunk, and extremities. Two raters (one of whom will be blinded to diagnosis and neuroimaging) will independently assess and score all GMA videos. A preliminary assessment of interrater reliability between the 2 raters will be conducted by review of GMA videos that were collected separately for training purposes. Once data collection commences, final rating will be determined by consensus, or if consensus cannot be reached, a third rater who is blinded to the initial ratings will serve as a "tiebreaker."

Bayley Scales of Infant Development IV. The primary behavioral assessment is the Bayley Scales of Infant Development IV (BSID IV), administered and scored by a physical therapist to evaluate developmental outcomes between 1 and 42 months of age.[69] The BSID IV contains 3 assessment scales: a motor scale composed of fine and gross motor subscales, a cognitive scale, and a language scale composed of receptive and expressive subscales. Based on the former edition, BSID III, the interrater reliability of the 3 assessment subscales is good to excellent ($r = 0.99$),[70] ICC = 0.76-0.99,[71] ICC = 0.86-0.98.[72] The BSID IV assessments will be video-recorded and a separate trained rater, who will be blinded to diagnosis and neuroimaging, will score the assessments from the video recording to assess reliability. If the 2 scores vary by more than 1 standard deviation (SD) on any subscale, the video will be reviewed and consensus will be reached by the 2 raters. If consensus cannot be reached, a third rater who is blinded to the initial ratings will serve as a "tiebreaker."

Hammersmith Infant Neurological Examination. A trained pediatric physical therapist will administer and score the Hammersmith Infant Neurological Examination (HINE). The HINE consists of 26 items and assesses primitive reflexes, muscle tone, posture, and movement patterns.[73] Each item is scored on a scale of 0 to 3, and the total of all items provides a global score with a range of 0 to 78, with 78 being the optimal score, reflecting highest motor function. HINE scores

will be compared with established cutoffs indicating high risk for CP diagnosis.[73] The HINE will also be video-recorded and a separate trained rater, who will be blinded to diagnosis and neuroimaging, will score the assessments from the video recording. Reliability on the HINE will be defined as having a 7.5-point difference or less in total score (>0.90 reliability) and coding of typical or atypical based on cutoff score. If there is a greater than 7.5-point difference, then the 2 raters will come to a consensus on the score or a third rater will be used as a "tiebreaking" rater. Prior to data collection, reliability on the HINE will be established between raters using 10 previously recorded cases.

Medical Monitoring and Follow-up. An independent physician medical monitor will assess the overall status of each participant. In addition to already described monitoring during the TMS session, we will continue to monitor safety and infant status via phone call to the caregiver within 24 hours after completion of a study visit and monthly throughout the 24 months of participation. After study completion, we will document the long-term status of the participant with a 1-year follow-up phone call. The study team will remain accessible by phone at any time throughout this period.

Data Analysis

Descriptive features will be summarized using means and SDs for continuous variables and counts and percentages for categorical variables. All longitudinal analyses will use generalized estimating equations with a banded working correlation structure to account for correlation among multiple measurements from the same participant and robust variance estimation for confidence intervals and *P* values.

MRI.

Processing. Structural MRI data will be assessed quantitatively and visually for motion artifacts. Images will be aligned to age-specific atlases[74,75] to ensure consistent orientation for subsequent viewing and region-of-interest (ROI) identification.

The pair of diffusion scans will be processed using the *topup* from the FMRIB Software Library (FSL) to correct for susceptibility distortions.[76] Further dMRI processing will include the following: removal of Rician noise,[77] removal of Gibbs ringing artifact,[78] and correction for eddy currents and motion using FSL's EDDY tool[79] with outlier replacement[80] enabled. FSL's EDDY tool with the outlier detection and replacement option will be used to identify individual images for removal due to severe artifacts. Diffusion tensors will then be calculated from preprocessed dMRI data using Diffusion Imaging in Python software (DIPY).[81] Diffusion tensor imaging is a widely used mathematical model for dMRI data, from which parameters such as fractional anisotropy (FA) can be derived (higher FA indicates greater white matter organization). Previous studies show that measuring FA of the CST offers additional benefit over conventional neuroimaging in classifying[82] and predicting[83,84] future motor outcomes in infants with perinatal brain injury.

Probabilistic white matter tractography of the CST will be performed using MRtrix3.[85] Two seed ROIs (brainstem and precentral gyrus) will be used to guide tractography and confine tracking to the CST. Masking will be applied to eliminate tractography into nonphysical regions. The tract volume will be determined from the tract mask, and the masked probability distribution will be used to compute the weighted mean FA per CST.

Statistical and Power Analyses. Evaluation of FA between hemispheres within an individual will use a paired *t* test. In addition, exploratory analyses using natural cubic splines along with higher-order terms to allow flexibility in the functional form of longitudinal trajectories and associations will be conducted. Graphical analysis accompanied by loess smoothed curves will support this effort. Stratified analyses will be used to explore results by relevant biological variables including sex, lesion size, and term or preterm birth. Regression-based imputation techniques will be considered for missing data issues (eg, multiple imputation). All tests will use type I error of 0.05. Using a conservative correlation of 0.5 for between-hemisphere measurements within an infant and SD of 0.03 based on Navarra et al.[86] A sample size of 50 will provide 80% power to detect a difference in FA of 0.010. In the longitudinal evaluation, based on variability referenced earlier, and an average correlation between measurements within an individual of 0.5 over follow-up time points, we will have 80% power to detect a slope of differences of 0.0015 per year between hemispheres and 0.015 between lesion side and control slopes per year.

TMS.

Processing. EMG data will be processed using a custom MATLAB program to determine whether an MEP was evoked in each TMS trial according the following criteria: a peak-to-peak amplitude of at least 50 μV, greater than 120% of the SD of the prestimulus EMG amplitude, and the area under the curve of the MEP greater than the prestimulus area under the curve (calculated as the 10-ms period from −13 to −3 ms).[46,87] MEP presence will be determined for each hemisphere, where the presence of an MEP is indicated by at least 3 TMS trials eliciting an MEP (ie, an RMT can be determined).

Statistical and Power Analyses. The proportion of infants with a contralateral MEP over time will be evaluated using logistic regression with a term for time, to summarize the trend in odds of MEP presence over time. The baseline proportion based on preliminary data is anticipated to be approximately 60%. As such, with a sample size of 50 infants, each evaluated at all 4 assessments, and an average correlation between measurements within an individual of 0.5, we will have 80% power to detect an increase in odds of MEP of approximately 2.0 per year. Among those with an MEP at baseline, the trend in difference in thresholds between hemispheres within an individual over time will be evaluated with linear regression to summarize the average change in the difference over time.

DISCUSSION

Crucial relationships between perinatal brain injury, maladaptive as well as adaptive development, and motor outcome have not yet been fully explored. By integrating state-of-the-art multimodal, comprehensive neurological and developmental assessment tools, we propose to elucidate the relationship between neurophysiological and neuroanatomical biomarkers and resultant motor function across a unique period of

recovery and development after perinatal brain injury/bleed. The importance of these findings lies in their potential to assist early detection of maladaptive development and resultant CP diagnosis and early individualized interventions to maximize outcomes for a lifetime.

CONCLUSION

This study protocol has been developed to investigate the relationship between cortical excitability/circuitry and motor function. Our findings will establish a foundation for future studies to investigate cortical excitability in expanded sensorimotor regions as predictors of mobility and gait outcomes in CP. This study will also inform the safety construct for future randomized, controlled, clinical neuromodulatory intervention trials as an adjuvant approach to optimizing early interventions. Finally, this work may inform future trials in related childhood-onset diagnoses (eg, epilepsy, autism spectrum disorder), interventions (eg, stem cell therapies), and assessments.

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