*[USE THIS BIOMEDICAL PROTOCOL TEMPLATE IF YOUR PROJECT INVOLVES **ANY** PHYSICAL CONTACT OR MEDICAL INTERVENTIONS WITH PARTICIPANTS]*

INSTRUCTIONS:

- *Use this template to prepare a document with the information from the following sections.*
- *Depending on the nature of what you are doing, some sections may not be applicable to your research.* ***Do not delete any sections, questions, or help text and mark "N/A" if sections do not apply***
- *When you write a protocol, keep an electronic copy. You will need to modify this copy when making changes.*

PROTOCOL TITLE:

Include the full protocol title.
Measuring Brain Activity of School Age Children.

PRINCIPAL INVESTIGATOR:

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UH FACULTY ADVISOR:

If the principal investigator's primary role at UH is resident, fellow or student, identify a faculty advisor. **N/A**

Name
Primary Department
Telephone Number
Email Address

OTHER DEPARTMENTS INVOLVED IN THIS STUDY (IF APPLICABLE):

Case Western Reserve University School of Nursing
Case Western Reserve University School of Medicine
Department of Radiology, Case School of Medicine

VERSION NUMBER:

Include the version number of this protocol if assigned by an outside entity.
N/A

DATE:

Include the date of submission or revision.
03/13/2021

Objectives

1. *Describe the purpose, specific aims, or objectives.*
2. *State the hypotheses to be tested.*

Purpose: Our goal is to characterize structure and function of dopaminergic pathways and the cortical regions innervated by those pathways in post-hypoxic former preterm children. We hypothesize that dopaminergic projections, originating in the substantia nigra pars compacta (SNpc) and ventral tegmental area (VTA), projecting primarily to the striatum and prefrontal cortex (PFC) to modulate motor control and cognitive function, will be structurally and functionally impaired. Our primary study cohort is comprised of former preterm children born in 2004-2010 with birth gestational age between 22-28 weeks in whom we have characterized their postnatal hypoxic exposure continuously during their first eight weeks of life. To meet recruitment targets, we may additionally recruit additional former preterm children born between the ages of 9 and 17 years old at consent, with birth gestational age between 22-30 weeks and birth weight appropriate for gestational age (AGA). For comparison, we plan to also recruit healthy control children based on eligibility criteria (between the ages of 9 and 17 years at time of consent; without diagnosis of autism, epilepsy, metallic implants, dental braces, or those who have been treated for a concussion), and who are within the age range of the eligible former preterm children at the time of consent.

Specific Aim 1: We will quantify and compare the structural integrity of dopaminergic circuits originating in the substantia nigra pars compacta (SNpc) and ventral tegmental area (VTA) that project to striatum, prefrontal cortex, and nucleus accumbens, in post-hypoxic former preterm children versus healthy control children born at term within the age range of the eligible former preterm children.
Specific Aim 2: We will quantify and compare functional activity during tasks that engage executive function within cortical brain regions of post-hypoxic former preterm children versus healthy control children born at term within the age range of the eligible former preterm children at the time of consent. Our emphasis will be upon the prefrontal cortex which receives projections from the SNpc and VTA.

Hypothesis 1: Post-hypoxic former preterm children will manifest significantly reduced white matter density within dopaminergic circuits originating from the SNpc and VTA when compared to healthy controls.
Hypothesis 2: Post-hypoxic former preterm children will exhibit reduced activity within cortical networks innervated by the SNpc and VTA when compared to healthy controls.

Background

1. *Describe the relevant prior experience and gaps in current knowledge describing how it will add to existing knowledge.*
2. *Describe any relevant preliminary data.*
   Please add relevant references at the end of the protocol, not at the end of this section.

Hypoxic insults occurring during the perinatal period remain the leading cause of permanent brain impairment.[1] Apparent cognitive and motor dysfunction, such as that

seen in cerebral palsy, will occur in 4-10% of those post-hypoxic newborns.[2,3] Subtle impairment, such as that seen in disorders of minimal brain dysfunction will occur in > 3 million post-hypoxic newborns.[4,5] Collectively, hypoxia-induced morbidity and mortality afflicts 3% of all newborns, worldwide, and leads to substantial personal and socioeconomic burden.[6]

Specific neuropathology, elicited by subtle hypoxic insults that lead to cognitive dysfunction, is not well described in humans. Over 84% of preterm infants experience apnea of prematurity with accompanying intermittent hypoxia.[7,8] Neuropathology, cognitive impairments, and motor impairments induced by *severe* hypoxic insults are well described[9] and frequently lead to a clinical diagnosis of cerebral palsy.[6,10] Cognitive and motor deficits are also associated with *mild to moderate* hypoxic insults,[11] but the specific neuropathology is poorly defined. Mild to moderate hypoxic insults resulting from apnea of prematurity do not elicit the overt neuropathology observed following severe hypoxic events. As such, standard neuroimaging and diagnostic techniques,[12] with the exception of positron emission tomography requiring infusion of radioactive ligands,[13] have failed to identify major changes in brain structure or function. Nonetheless, disorders of minimal brain dysfunction and cognitive impairments do exist.[14-16]

To better characterize the behavioral and neurochemical morbidity induced by mild hypoxic insults, we developed a rodent model emulating this clinical scenario. Our rodent model recapitulates many cognitive and behavioral dysfunctions observed in preterm infants including impaired working memory, hypersomnolence, locomotor hyperactivity, and increased responsivity to novelty.[17-19] Analyses of post-hypoxic rodent brains has revealed reduced levels of extracellular dopamine and increased protein expression of dopamine D1 receptors and vesicular monoamine transporter (VMAT2) within the caudate putamen nucleus.[17,18] These findings suggest functional and structural deficits within dopaminergic circuits comprising mesotelencephalic pathways.

Our goal is to characterize structure and function of dopaminergic pathways and the cortical regions innervated by those pathways in post-hypoxic former preterm children. This project's scientific premise and specific aims are supported by findings from our rodent model and represent the next logical step of our research.

Inclusion and Exclusion Criteria

1. *Describe how individuals will be screened for eligibility.*
   For Study Group Children: Birth gestational age between 22-30 weeks and birth weight appropriate for gestational age (AGA). Healthy control children: Birth gestational age ≥ 38 weeks gestation and birth weight appropriate for term gestation within the age range of the eligible former preterm children at the time of consent.

   Our primary study group will first be recruited from a cohort of children, born between 23-28 weeks gestation, with available oxygen saturation level data recorded continuously from the first day of life to 8 weeks postnatal age. Eligible and interested former preterm

children will be identified by site principal investigator Deanne Wilson-Costello, MD and co-investigator Juliann Di Fiore. These children are prematurely born survivors from Rainbow Babies & Children's Neonatal Intensive Care Unit, and have been followed since birth. Children in this cohort have already participated in research, and remain willing to participate in future projects. Eligibility from this group includes children born in 2004-2012, male or female, and able to provide assent. Exclusion criteria includes history of epilepsy, autism, or mental or physical impairment preventing valid administration of cognitive testing measures. Other exclusions include children who have contraindications to MRI such as cardiac pacemakers, intracranial aneurysm clips, metallic implants or external clips within 10 mm of the head; implanted metallic devices such as pumps or previously implanted neurostimulation devices; cochlear implants, defibrillators, pacing wires, body piercings that cannot be removed; metal filings such as shrapnel; dental braces; tattoos on the head and neck, or medical conditions contraindicated for MRI safety. Additionally, we will exclude children with a history of claustrophobia or who are currently pregnant or planning pregnancy. Dr. Wilson-Costello and/or Juliann Di Fiore will provide our research team with names/contact information of interested individuals. We will contact those individuals by telephone to describe the study and conduct a prescreening.

If recruitment targets for study group children cannot be achieved, we will engage the assistance of Dr. Wilson-Costello to recruit additional former preterm children between the ages of 9-17 with birth gestational age between 22-30 weeks and birth weight appropriate for gestational age (AGA). We will also expand recruitment with study notices in print and digital newsletters, community bulletin boards, flyers, and targeted emails using the TriNetX database.

We will approach a subset of 5 children if they are willing to be re-studied (i.e. volunteer a second time for the same study) to enable the team to establish reproducibility of study measures.

PRESCREENING

The purpose of the prescreening telephone call will be to further explain the study to the parents, confirm their interest in taking part, and determine their child's eligibility. We will introduce ourselves as research scientists from Rainbow Babies and Children's Hospital, University Hospitals Cleveland Medical Center and Case Western Reserve University conducting a research study comparing the brains of children born at full term, with brains of children born prematurely. We will tell them we are looking at how certain parts of the brain look and how they work. We will tell the interested individual that we plan to take pictures of the brain using an MRI scanner. We will also record EEG, which measures brain waves, by having the child wear a stretchy cap on their head with gel placed into little holes in the cap. These same tests are often done in medical practice. During the MRI scan, we will ask the child to do a memory test. We will also ask children to play a timed board game during the EEG recording. While the child is being tested, we will ask parents to fill out questionnaires about the child's health, behavior, and sleep.

We will describe that an MRI involves using a strong magnet and radio waves to produce a picture of body parts. EEG involves recording electrical activity of the brain from the scalp. This research project will involve taking pictures of a person's head combined with patterns of brain activity recorded on the surface of their head. This will help us gain a better understanding of the human brain. We will tell the parents/children that we expect to enroll at least 20 children for this study who were born prematurely and 10 children who were born at or near their due date. We will emphasize that participation in this study is voluntary.

If they continue to express interest in study participation, we will determine if they meet study inclusion criteria (e.g. we will ask them if the child is between 9 and 17 years old; how close to the due date the child was born; if the child would be able to play a board game and push a button during a memory game). Then we will determine if they have any exclusionary criteria including a history of epilepsy, autism, or previous history of concussion requiring medical treatment. We will also assess for any contraindications to MRI scans. We will ask them if they have a cardiac pacemaker, intracranial aneurysm clips; intravascular shunt; dental devices such as braces or dentures; metallic implants or external clips within 10 mm of the head; implanted metallic devices such as pumps or previously implanted neurostimulation devices; cochlear implants, defibrillators, pacing wires, body piercings that cannot be removed; metal filings such as shrapnel; tattoos on the head and neck; or a history of claustrophobia, or a current pregnancy (if female).

If they meet inclusion criteria and do not possess any exclusionary criteria, one of the certified research team members will schedule an appointment with the child/parent to obtain written informed assent and consent.

2. *Describe the criteria that define who will be **included** in your final study sample.*

	Inclusion
1.	For Study Group Children: Birth gestational age between 22-30 weeks and birth weight appropriate for gestational age (AGA).
2.	For Healthy Control Children: Birth gestational age ≥ 38 weeks gestation and birth weight appropriate for term gestation within the age range of the eligible former preterm children.
3.	Ability of the child to provide assent, with the parent/legal guardian able to provide written informed consent for study procedures.
4.	Sensory and motor capability to complete study tasks (i.e. Grooved Pegboard test; verbal n-back memory test).

3. *Describe the criteria that define who will be **excluded** in your final study sample.*

	Exclusion
1.	Mental Development index < 80 at 2-year follow-up for preterm cohort.
2.	Past history of concussion requiring medical treatment to avoid confounding of MRI

	data.
3.	Current history of epilepsy to avoid confounding of EEG data.
4.	Current diagnosis of autism.
5.	Child who suffers from claustrophobia (per parent report).
6.	Child unable to participate in neuroimaging due to claustrophobia or medical contraindication to MRI including any implanted medical device, dental braces, surgical clips for aneurysms in the head, heart valve prostheses, electrodes or other metallic objects; pregnancy
7.	Healthy control children who were treated in the Neonatal ICU during the newborn period for breathing difficulties.
8.	Healthy control children who were hospitalized for breathing problems in the first 3 months of infancy.
9.	If the child is suffering from an acute illness, he or she will be temporarily deferred.

Number of Research Participants

1. *Indicate the target number of research participants to be accrued locally.*
   Our goal is to obtain 30 complete data sets (preferably Study group = 20; Healthy control = 10). Due to movement artifact in the MRI, some scan data may not be usable so we may need to enroll up to 35 participants. We may also conduct repeat studies on a subset of up to 5 children (~15%) to establish reproducibility of collected data. Only subjects who checked "yes I agree to be contacted..." on their first signed parent consent form will be approached by phone to ascertain interest in participating in the study a second time. Participants studied twice will be re-consented for the second data collection session.
2. *If this is a multi-site study, indicate the total number of research participants to be accrued across all sites.*
   N/A

Vulnerable Populations

1. *Indicate specifically if you will include each of the following special populations by checking the appropriate box:*
   - ☐ **Adults unable to consent**
   - ☒ **Minors (infants, children, teenagers)**
     - ☐ Wards of the state
     - ☐ Foster Children
   - ☐ **Pregnant Women**
   - ☐ **Neonates**
   - ☐ **Neonates of Uncertain Viability**
   - ☒ **Employees of CWRU or UHHS**
   - ☐ **Prisoners**
   - ☐ **Illiterate Individuals**
   - ☒ **Non-English Speaking**
   - ☐ **University Students**

2. *If the research involves individuals that are included in a vulnerable population, describe the additional safeguards included to protect the rights and welfare of the individuals for each population indicated.*

   We intend to recruit pediatric patients ages 9-17 who qualify as a vulnerable population because they are minors. These children will have a separate pediatric assent form along with a parental consent form. We will make sure all the child's questions are answered regarding the study. We will take the necessary time to explain all procedures and explain things in a more basic language to the children participating in this study, appropriate to their level.

   It is possible that children/parents in the former preterm study cohort may not be fluent in the English language. Eligible study participants (children or their parent) who are not fluent in English will not be excluded. We will submit a translated version of the informed consent form to the IRB for approval prior to use. Only a UH-based certified professional translator who is fluent in both English and the child's/parent's language will conduct the informed consent. Other study related documents and procedures that need to be completed by the child or parent will be translated into the participant's native language.

   We may encounter candidate study recruits whose parents are coincidentally employees of either Case Western Reserve University or University Hospitals. Although meeting criteria as a "vulnerable population" our recruitment procedures are not specifically targeting employees or students of University Hospitals/Case Western Reserve University. Nonetheless, all research participants, including potential employees/students of UH/CWRU, will have their records and study findings stored in de-identified formats and all efforts are made to maintain study participant anonymity.

3. *If excluding pregnant women, illiterate or non-English speaking individuals, provide a scientific rationale for the exclusion. Inconvenience or cost is not an acceptable rationale.*

   Child participants may not be pregnant because they will receive an MRI scan as part of participation and the effect of MRI on pregnancy and a fetus is not known. Pregnancy in the female parent of the child is permissible.

Recruitment Methods

1. *Describe the source of the research participants.*

   Many subjects will come from the practice of a study investigator (i.e. Dr. Wilson-Costello) and may be referred or recruited from other physicians' practices. Subject recruitment will also occur by advertisement or flyers, particularly for recruitment of healthy control participants.

2. *Describe the methods that will be used to identify potential research participants.*

   The proposed study will involve participation of male and female children to achieve a total number of 30 complete data sets. All children to be studied will range in age between 9-17 years during the funding period. Study participants will include survivors of preterm birth, with birth gestations of 22-30 weeks and birth weights appropriate for gestational age.

   We intend to focus our recruitment on 20 children who were born preterm with birth gestational ages between 22-30 weeks, are survivors from Rainbow Babies & Children's Neonatal Intensive Care Unit, and have been followed since birth. The children invited for participation will be part of the maintained cohort for whom continuous oxygen saturation data were collected in their first 8 weeks of postnatal life. Co-Investigator Juliann Di Fiore maintains this research cohort. In the event that we cannot enroll 20 children who have continuous oxygen saturation data from their neonatal hospital stay, Dr. Wilson-Costello will assist us to identify other preterm survivors who are similar to the study group population but may be between 9 and 17 years old and/or have birth gestations up to 30 weeks. We will also recruit for other preterm survivors via study flyers and advertisements.

   In addition to children recruited from the existing preterm cohort, we aim to study 10 children who were born at term, and were within the range of normal birth weights. Healthy control participants will be recruited using various strategies: (1) study flyers given to the parents of the prematurely born cohort children to pass along to parents of other children with ages similar to their own child. Interested parents will be asked to contact us if they wish to learn more about the study. This approach is currently and successfully used by our Co-Investigator Dr. Taylor in his research (Heverly-Fitt et al., 2014);(2) the study flyers will be given to the parents of the prematurely born cohort children to pass along to parents of other children with ages similar to their own child; (3) study flyers will be posted in Primary Care Pediatric Clinics; (4) Study flyers will be distributed by professional colleagues/pediatric physicians to potential candidate children/families meeting study inclusion criteria; and (5) Study flyers will be posted in libraries, coffee shops, community/recreational centers, and local government and/or nonprofit organizations that provide services or are in communications with families. Study flyers will instruct interested parents of eligible children to contact us if they would be interested in learning more about the study.

   Social media recruitment and virtual recruitment:

   Facebook: We will digitally post study flyers on Facebook and post to community groups created to share knowledge within the Northeast Ohio area, groups specifically geared toward parents (with and without former pre-term children), with appropriate permission from the group's administrator and/or organization. We will also allow individuals to 'share' our study flyer on their personal pages. Individuals will be allowed to comment

on posts but study investigators will direct individuals to the contact information posted on the study flyer for more information.

NextDoor: NextDoor is a platform to communicate information throughout the community. Investigators will post the study flyer on the app/website, which provides contact information if families are interested in participating. Individuals will be allowed to comment on posts but study investigators will direct individuals to the contact information posted on the study flyer for more information.

Twitter: Study investigators will post their flyer on Twitter accounts operated by investigators and CWRU-owned and operated accounts. Individual Twitter users will be able to retweet and reply to investigators. Investigators and account owners will respond by directing families to our contact information on the flyer.

ResearchMatch.org: The study will be posted on ResearchMatch.org so that families searching for research studies can view our study title and contact information. Recruitment language to be used on ResearchMarch.org: Dr. Michael Decker and Dr. Elizabeth Damato at CWRU, and Deanne Wilson-Costello at Rainbow Babies and Children's Hospital are looking for families to participate in a study on brain development. The study involves one 3-hour visit to the CWRU/University Hospitals campus where a research team will measure brain activity. First, children will lie quietly for about 30 minutes in the MRI scanner while playing a visual task-response game. After the MRI scan, brain activity will again be measured with EEG. This involves having the child wear a stretchy cap while playing the visual task response game and completing a pegboard puzzle. Parents will complete questionnaires about the child's health history, behavior, and sleep. Both parents and children will be compensated for their time. The investigators are especially seeking children who were born prematurely (gestation 22-30 weeks) and also children who were born full term (gestation 38-41 weeks). Children with epilepsy, autism, medical implants, dental braces, or those who have been treated for concussion are not eligible. Please call 216-368-2597 for more information.

The CWRU Daily: We plan to advertise our study on the CWRU Daily. The submission to the Case Daily is attached to this modification. Interested families are instructed to contact the study investigators.

TriNetX: Research personnel will work the with TriNetX personnel to identify families who meet eligibility requirements. Researchers will then use the approved email template to contact families as well as phone scripts for communication. We will call families a total of 3 times and leave a voicemail if they do not pick up our phone call. The original application to IRB requested a HIPAA waiver authorization and we will continue to utilize this authorization to work with the TriNetX team.

Heverly-Fitt, S., Wimsatt, M.A., Menzer, M.M., Rubin, K.H., Dennis, M., Taylor, H.G., Stancin, T., Gerhardt, C.A., Vannatta, K., Bigler, E.D., & Yeates, K.O. (2014).

Friendship quality and psychosocial outcomes among children with traumatic brain injury. *Journal of the International Neuropsychological Society, 20*(7), 684–693. doi:10.1017/S1355617714000393

3. *Justify the feasibility of recruiting the required number of suitable research participants within the agreed recruitment period. For example, how many potential research participants do you have access to?*

   Inclusion of the 20 children for the study cohort will be based upon the age range represented within the total cohort maintained by Co-Investigators Di Fiore and Wilson-Costello. There are currently 42 children in the cohort available for recruitment.

4. *Describe when, where, and how potential research participants will be recruited.*

   Co-Investigator Julie Di Fiore and site principal investigator Dr. Wilson-Costello will identify former preterm children who meet study criteria. Dr. Wilson-Costello will contact the parent and determine if they are interested in learning more about the study. With parent permission, Investigators Dr. Damato, Dr. Decker or one of the study research assistants trained for consenting will contact the parent to further explain the study using the IRB-approved pre-screening script. If the parent/child remains interested after hearing of the study, Dr. Damato, Dr. Decker or one of the study research assistants trained for consenting will obtain informed consent.

   Interested healthy control participants who respond to a study flyer will contact the investigators. We will further explain the study using the IRB-approved pre-screening script.

5. *Describe materials that will be used to recruit research participants.*

   The flyer will indicate that we are conducting a study on brain activity in school age children and that we wish to enroll a broad representation of children. Parents would then be asked to contact us if they would be interested in taking part in the study. This strategy would allow us access to a large pool of potential controls who meet eligibility requirements. Using an IRB-approved telephone script, our research staff will then contact the parents of the child. The purpose of the telephone call will be to further explain the study to the parents, confirm their interest in taking part, and determine their child's eligibility. We are prepared to discuss any aspect of a child's participation at greater length, including research participant rights. Telephone numbers of the study PIs are provided to those asking for more or different information.

   The term-born healthy control participants are selected based on eligibility criteria (between 9 and 17 years old; without diagnosis of autism, epilepsy, metallic implants, dental braces, or those who've been treated for a concussion) and approximately matched to study children based on age. All healthy control candidate participants will have been of normal birth weight (> 2500 grams) and with gestational age > 37 weeks.

Additionally, we will exclude children from the healthy control group if they were treated in the neonatal ICU during their birth hospitalization for breathing problems or were hospitalized for breathing problems in the first 3 months of infancy. Children in special education programs will not be excluded as controls. Both groups of children are expected to be in generally good physical health, although we anticipate that the group of preterm-born children may have more chronic conditions (e.g. asthma) and more health-related functional limitations than the term group.

Setting

1. *Describe the sites or locations where your research team will conduct the research.*
2. *Identify where your research team will identify and recruit potential research participants.*
3. *Identify the physical location where research procedures will be performed.*

The research team will conduct the research from affiliated Case Western Reserve University departments of study investigators Dr. Damato-FPB Nursing; Dr. Decker-Physiology & Biophysics-Case SOM. Both have private offices where research materials can be kept in a locked cabinet behind locked doors. Identification and recruitment of potential research participants will take place in University Hospitals/Rainbow Babies & Children's Hospitals, primarily in the Preterm Follow-Up clinic, and by telephone follow-up to interested research participants. Consented study participants (child and parent) will be asked to come to the Case Western Reserve University Magnetic Resonance (MR) Facility located within University Hospitals on 11100 Euclid Ave, Cleveland OH 44106 at a scheduled date/time to participate in the research study.

Consent Process

Indicate whether you will be obtaining consent:

☒ Yes ☐ No

If yes describe:

- *Where the consent process will take place*
- *Any waiting period available between informing the prospective subject and obtaining the consent*
- *Any process to ensure ongoing consent*
- *The role of the individuals listed in the application as being involved in the consent process*
- *The time that will be devoted to the consent discussion*
- *Steps that will be taken to minimize the possibility of coercion or undue influence*
- *Steps that will be taken to ensure the research participants' understanding*

Following a telephone pre-screening process, the consent form will be presented privately in person or by telephone to the child and parent, based on parent's preference. One of the study investigators (Dr. Damato or Dr. Decker) or one of the research staff certified to

obtain consent will be present during the presentation of the informed consent, the signing of the consent, and initiation of the research study. Study personnel will present the benefits, risks and alternatives to study participation. Subjects will be given a copy of the assent and consent forms explaining the procedure. The child/parent will be given adequate time to read the information and ask questions before they sign and date the form. A delay of at least 2 days will be allowed between the telephone screening process and the scheduled date to obtain written consent. The certified staff will allow adequate time for the child/parent to make an informed decision and to minimize the possibility of coercion or undue influence. Throughout the telephone pre-screening process and written informed consent process, we will repeatedly inform the parent/child that study participation is voluntary and confirm their interest in participating. The research team member obtaining consent will ask the parent/child to describe the study procedure in their own words to ensure understanding of the protocol. Prior to the scheduled MRI study date, one of the principal investigators or certified staff will contact the parent by phone to confirm continued consent for study participation. Copies of the assent and consent forms will be given to the person signing the document. The language used by those obtaining consent will be in English for those children/parents who are fluent in English; documents will be translated into the appropriate language for any interested families and a certified person proficient in the specific language will be used to translate during the consent process and protocol. We will use the child assent/parent consent form submitted with this application and the UH MRI safety screening form, which has also been submitted.

In rare instances, a parent may be unable to attend a consent visit or study visit (due to illness, location, etc.). Because of this, we will allow parents to sign consent forms while a study team member explains the consent process via phone. Our language to the parent is identified in a document called, "R21 Parental consent via telephone." The parent will understand that they are giving permission for their child to be accompanied by a parent proxy with whom they have trusted to leave their child (prior to our study team's involvement). In this instance, child assent will still happen in person and we will instruct the parent to ask the child the parent's first and last name to confirm identity. Prior to consent, the study team will also ask the parent to provide us with the first and last name of the caregiver who is accompanying the child to the study visit. During consent and study day, we will ask caregiver to provide identification that bears the same name.

Waiver or Alteration of Consent Process or Documentation (consent will not be obtained, written consent will not be documented)

Indicate which part of the consent process you are requesting be waived or altered:

- ☐ I will obtain consent, but not participant's signature
- ☒ I will obtain consent, but request a waiver for pre-screening purposes
- ☐ I will obtain consent, but request a waiver of some of the elements of consent (e.g. use of deception)
- ☐ I will not obtain consent, and I am requesting a full waiver of consent

1. *Give the rationale for the request of a waiver or alteration of the consent process or documentation.*
2. *If you will obtain consent, but not document consent in writing (e.g. over the phone, verbally, electronic survey, etc.), please describe and provide a rationale.*
   Describe how you will be documenting that a research participant has consented

   Be sure to upload a consent script or information sheet with your study protocol

   We are requesting a waiver of HIPAA authorization for the pre-screening process over the telephone. The waiver also includes pre-screening for eligible former preterm infants by accessing their information in the database maintained by Co-Investigator Di Fiore and site investigator Dr. Wilson-Costello and obtaining their contact information to further describe the study and recruit participation.

   The telephone pre-screening process requires that we access subject phone numbers and other potentially identifying information (e.g. names, knowledge of gestational birth history) in order to determine study eligibility. The waiver of signed consent will allow us to accurately identify those persons who are study eligible. For interested parents whose child has exclusionary criteria, the informed consent document would be the only document linking the interested parent/child with the study. All study eligibility data will be destroyed for any parent/child found not meeting study eligibility criteria. Study eligible parents who express an interest in participation will be asked to sign a written informed consent document and their child will sign a child assent document.

   Using telephone pre-screening, we need to determine study eligibility of study cohort children, identified by Co-Investigator Di Fiore and site investigator Dr. Wilson-Costello, who agree to learn more about the study. We will also need to determine study eligibility of healthy cohort children who contact us in response to study flyers. If interest is affirmed after learning more about the study and the child meets study eligibility criteria, we will meet with the parent/child and obtain written parent consent and written child assent for participation.

   This project will involve two groups: study participants and healthy controls. For both groups, we will speak to the parent first before approaching a child about the study.

   Study participants will primarily be selected from a cohort of families who have expressed interest in research study participation. Parents of children maintained in the cohort will be first identified by Co-Investigator Di Fiore and then contacted by Dr. Wilson-Costello by telephone and/or via postal mail and given an opportunity to indicate their willingness to be contacted to discuss possible participation in a research study. Using our HIPAA-compliant and IRB-approved pre-screening telephone script, our research staff will contact those parents who assented to be contacted for research, and identify children who meet major study eligibility

criteria. Eligible families that express an interest in participation will be invited to participate. We are prepared to discuss any aspect of a child's participation at greater length, including research participant rights. Telephone numbers of the study PIs are provided to those asking for more or different information.

Healthy control children will be selected from those responding to study flyers. The flyer will indicate that we are conducting a study on brain activity in school age children and that we wish to enroll a broad representation of children. Potentially eligible children/parents would then be asked to contact us if they would be interested in taking part in the study. The purpose of the telephone call will be to further explain the study to the parents, confirm their interest in taking part, and determine their child's eligibility. We are prepared to discuss any aspect of a child's participation at greater length, including research participant rights. Telephone numbers of the study PIs are provided to those asking for more or different information.

Participants approached for re-study will have indicated their willingness to be contacted for future studies on the initial signed parent consent form. Only parents who indicated on their first signed consent form will be approached by telephone. A separate telephone screening script for re-study participants is included in this addendum submission.

Only trained research personnel who have completed necessary certification for human subjects research will directly interact with children and parents involved in this study. Only parents who provide consent to be contacted for potential research participation are contacted by our research personnel. Following the telephone pre-screening process, the consent form will be presented in person or by telephone to the child/parent. Written child assent and written informed consent from the parent is obtained. One of the key study investigators or one of the listed research team members who can obtain consent on this protocol will always be present during the signing of the consent and the initiation of the research study. We will present the benefits, risks and alternatives to study participation. Children/families will be given a copy of the consent form explaining the procedure. The child/family will be given adequate time to read the information and ask questions before they sign and date the assent/consent forms. We will allow adequate time for the child/family to make an informed decision and to minimize the possibility of coercion or undue influence. A copy will be given to the child/parent signing the documents. We will also provide every consented child/parent with a copy of the study flyer as an easy-to-read information sheet about the study. The language of the informed consent is written at an 8th grade reading level and the language of the child assent is written at a 4th grade reading level. We will seek translation to another language as needed for eligible children/parents in the cohort study sample and in the healthy control sample. The top portion of the submitted MRI screening form documents the steps of our informed consent process.

Our consent forms explain the nature of all procedures using lay terminology, and we stress that participation is voluntary. Our research assistants and Co-PIs are available to answer questions. One of the study investigators (Dr. Damato or Dr. Decker) is also available to answer questions about the study at other times. All activities are compliant with local IRB and HIPAA guidelines, such as destroying all pre-screening forms and obtaining verbal permission, as appropriate, for phone interviews. At the beginning of the study, and then periodically, any IRB, HIPAA or privacy requirements that may be in effect at that time also will be checked to assure that study procedures are compliant with current rules. With permission from the parent, the health care provider for consented eligible children are contacted to identify/clarify any exclusionary criteria.

Additional Considerations for Consent Process with Adults

Non English Speakers

- *If research participants who do not speak English will be enrolled, describe the process to ensure that the oral and written information provided to those research participants will be in that language during initial consent as well as throughout the study. Indicate the language that will be used by those obtaining consent.*
- *List the language(s) other than English that will be included.*

Eligible study participants (children or their parent) who are not fluent in English will not be excluded. We will submit a translated version of the informed consent form to the IRB for approval prior to use. Only a UH-based certified professional translator who is fluent in both English and the child's/parent's language will conduct the informed consent. Other study related documents and procedures that need to be completed by the child or parent will be translated into the participant's native language. We will include any languages for which a UH-based certified professional translator is available.

Adults Unable to Consent

- *Describe the process to determine whether an individual is capable of consent.*
- *List the individuals from whom permission will be obtained in order of priority (e.g. durable power of attorney for health care, court appointed guardian for health care decisions, spouse, and adult child).*
    - *For research conducted outside of the state, provide information that describes which individuals are authorized under applicable law to consent on behalf of a prospective subject to their participation in the procedure(s) involved in the research.*
- *Describe the process for assent of the research participants. Indicate whether:*
    - *Which subjects that are unable to consent will be required to give assent? If not all, explain why.*
    - *Describe whether assent of the research participants will be documented and the process to document assent.*

N/A

Research Participants Who Are Not Yet Adults (infants, children, teenagers)

1. *Will parental permission be obtained from:*
   - ☒ *One parent even if the other parent is alive, known, competent, reasonably available, and shares legal responsibility for the care and custody of the child or*
   - ☐ *Both parents unless one parent is deceased, unknown, incompetent, or not reasonably available, or when only one parent has legal responsibility for the care and custody of the child*
   - ☐ *Waiver of parental permission*
2. *Describe whether permission will be obtained from individuals other than parents, and if so, who will be allowed to provide permission. Describe the process used to determine these individuals' authority to consent to each child's participation in research.*
3. *Indicate whether assent will be obtained from all, some, or none of the children. If assent will be obtained from some children, indicate which children will be required to assent.*
4. *When assent of children is obtained describe how it will be documented.*

Written child assent and parent consent (from one parent) will be obtained for all participants in this study. Permission will only be obtained from parents. The consent form will be presented in person or by telephone to the child/parent. Child participants will range in age from 9-17 years old; thus all child participants will sign a written assent form to document their willingness to participate in the study. Based on parent preference, consent forms may be mailed in advance to the parent prior to a mutually scheduled telephone call to conduct the consent process. The parent will sign the paper consent form(s) and return the signed documents to the investigative team in a provided stamped return envelope.

Sharing of Results with Research Participants

Describe whether results (study results or individual subject results such as results of investigational diagnostic tests, genetic tests, or incidental findings) will be shared with the research participants or others (e.g. the subject's primary care physicians) and if so, describe how the results will be shared.

☐ Results will not be shared with research participants

Research scans are not designed with the validity and vigor required for identification of any potential incidental findings. It is standard practice at other institutes, as well in all other ongoing studies within the Case Center for Imaging Research at UHCMC, that the IRB protocols and consent forms state that "no diagnostic review will be conducted." However, it is possible that abnormalities may be noted. Less than 3% of research MRI scans performed on healthy children will show clinically significant abnormalities (Gur et al., 2013). Abnormal waveforms on the EEG may be detected in approximately 2-3% of healthy children without neurological symptoms (Grant et al., 2016). If incidental health issues are noted, Dr. Wilson-Costello will discuss this with the parent and advise them to

seek further evaluation from the child's healthcare provider. Otherwise, research subjects will not be given the results of the tests.

Grant AC, Chau L, Arya K, Schneider, M. Prevalence of epileptiform discharges in healthy 11- and 12-year-old children. *Epilepsy & Behavior* 2016; 62:53-56.

Gur RE, Kaltman D, Melhem ER, Ruparel K, Prabhakaran K, Riley M, Yodh E, Hakonarson H, Satterthwaite T, Gur RC. Incidental findings in youths volunteering for brain MRI research. *Am J Neuroradiol* 2013; 10.3174/ajnr.A3525.

Study Design, Procedures and Timeline

1. *Describe and explain the study design.*
2. *Provide a description of all study-related **research procedures** being performed including procedures being performed to monitor research participants for safety or minimize risks.*
3. *Describe:*
   - ☐ *Procedures performed to lessen the probability or magnitude of risks*
   - ☐ *List all drugs and devices used in the research and the purpose of their use and their regulatory approval status (more detailed information is requested in the section on Drugs and Devices at the end of this document.)*
   - ☐ *The source records, including medical or educational records, which will be used to collect data about subjects*
4. *Describe when research procedures will take place and the duration of an individual subject's participation in the study. Use of the descriptive table listing the study procedures that indicates the visit/week of the interventions below is encouraged.*

	Pre-Screening	Visit 1	Visit 2	Visit 3	Six week Follow up
Estimated time requirement					
Data Collection	X				
Study Procedure 1		X	X	X	
Study Procedure 2		X		X	
Study Procedure 3		X		X	
Phone Call Questionnaire					x

DESIGN & DESCRIPTION: The investigators will conduct an observational study comparing two groups of children to determine whether differences in birth events and oxygen levels during the newborn period lead to structural and functional impairment within the brain's dopaminergic pathways and the cortical regions innervated by those pathways. The dopaminergic system is involved in modulating motor control and cognitive function.

Our goal is to characterize **structure** and **function** of dopaminergic pathways and the cortical regions innervated by those pathways in post-hypoxic former preterm children. We will accomplish this through the use of neuroimaging analysis techniques, such as

diffusion tensor imaging with subtraction analyses and fMRI coupled with high-density electroencephalographic (EEG). We hypothesize that dopaminergic projections, originating in the substantia nigra pars compacta (SNpc) and ventral tegmental area (VTA), projecting primarily to the striatum and prefrontal cortex (PFC) to modulate motor control and cognitive function, will be structurally and functionally impaired. The primary sample for our proposed study is derived from a cohort of preterm infants admitted to Rainbow Babies & Children's Hospital between 2004 and 2009 at a gestational age of 23 to 28 weeks. The purpose for developing the original cohort was to establish the effects of maintaining oxygen saturation levels between 85%-95% to decrease the development of retinopathy of prematurity. Oxygen saturation levels and desaturation events were recorded continuously from the first day of life to 8 weeks' postnatal age. If recruitment targets for study group children cannot be achieved, we will engage the assistance of Co-Investigator Dr. Wilson-Costello to recruit additional former preterm children currently 9 to 17 years old with birth gestational age between 23-30 weeks and birth weight appropriate for gestational age (AGA for comparison, we plan to recruit healthy control children within the age range of the eligible former preterm children. Our findings will provide new insight into the neural basis of cognitive dysfunction reported in many former preterm children who experienced mild to moderate hypoxic insults.

APPROACH: Eligible and interested former preterm children will be identified by Deanne Wilson-Costello, MD and Juliann Di Fiore. These children are prematurely born survivors from Rainbow Babies & Children's Neonatal Intensive Care Unit, and have been followed since birth. Children in this cohort have already participated in research, and remain willing to participate in future projects. Dr. Wilson-Costello and/or Juliann Di Fiore will provide our research team with names/contact information of interested individuals. We will contact those individuals by telephone to describe the study and conduct a prescreening.

Healthy control children will respond to study flyers. The study flyers will be (1) given to the parents of the prematurely born cohort children to pass along to parents of other children with ages similar to their own child; (2) posted in the Rainbow Primary Care Pediatric Clinics; (3) distributed by professional colleagues/pediatric physicians to potential candidate children/families meeting study inclusion criteria. Study flyers will instruct interested parents of eligible children to contact us if they would be interested in learning more about the study; and (4) posted in libraries, coffee shops, and community/recreational centers.

Following a telephone pre-screening process, the consent form will be presented in person to the child and parent. The principal investigator or one of the listed staff will be present during the presentation of the informed consent, the signing of the consent, and initiation of the research study. We will use the child assent/parent consent form submitted with this application and the UH MRI safety screening form, which has also been submitted.

In rare instances that parents or legal guardians cannot be present at the consent process or study visit, parents/legal guardians can be consented via telephone. Parents will also provide permission to the study team to allow the study team to contact the child first via phone to assess willingness to participate and subsequently provide permission, for their child to be assented in person (as usual) and come to the study visit with a trusted parent proxy. This will happen before child assent visit. At the day of the consent, we will ask child to bring a student ID or report card to verify their own identity.

No study procedures will take place before we receive the signed consent form from the parent.

If children come to either the consent process visit or the study visit (with their parent proxy who has been verbally approved by parent/guardian) and declines participation, the study team will cease all study related activities. We will then call the parent/guardian to inform them of the circumstances.

The study team will confirm with parent/guardian before the consent phone call that child is under the supervision of a caregiver and ask for caregiver's full name. The study team will verify the caregiver's identity using state-issued ID or credit card bearing the same name given by parent at consent. During the study visit, the study personnel will have the caregiver present a photo ID before beginning any study-related procedures.

Compensation is given to the parent or parent proxy who completes the necessary questionnaires about child behavior or sleep. We will inform the parent that this is our process in these rare and special circumstances.

Consented study participants (child and one parent) will be asked to come to the Case Western Reserve University Magnetic Resonance (MR) Facility located within University Hospitals on 11100 Euclid Ave, Cleveland OH 44106 at a scheduled date/time. A research staff member will contact participants by phone 1 and 3 days prior to the scheduled data collection visits to complete a COVID-19 screening form (see COVID-19 screening form).

The child should have washed their hair on the day of the study visit and not used any hair oils, conditioners, or hair products after shampoo. Data collection will involve 1 visit lasting approximately 2-3 hours in length. Participants who volunteer for re-study will have a second data collection visit lasting approximately 2-3 hours in length.

Dr. Damato, Dr. Decker or a member of the research team will review the procedures to participants and confirm that written informed consent has been obtained. A research team member will assess the participant's temperature using a no-touch infrared thermometer at the start of the study visit. We will supply clean disposable facemasks to participants for use during the study. Research staff will wear facemasks at all times during the study visit. Prior to the neuroimaging session, a magnetic resonance imaging

(MRI) screening will be repeated to ensure study eligibility for MR scanning and that it is safe for the child to take part in the study.

A qualified physician or nurse practitioner will perform a focused neurological history and physical examination. All females will be asked to provide a urine specimen for pregnancy testing. If pregnancy test is positive, the child will be removed from the study due to exclusionary criteria.

The child will be acclimated to the MRI/mock scanner and then be instructed on the verbal n-back memory task that will be administered during a portion of the MRI scan and during the EEG recording.

Once positioned on the MRI scan table, an MRI scan is performed. We will provide earplugs or headphones that the child will be required to wear. A structural scan, DTI, and fMRI will be performed (total acquisition scan time = 30 minutes). During the fMRI, the child will perform the n-back memory task by pressing a button in response to alphabet letters presented on a screen in the scanner.

While the MRI scan acquisition is occurring, one parent will complete questionnaire items regarding their child's typical behavior (estimated time 25-30 minutes).

Following the MRI scan, a stretchy cap with holes in it will be placed over the top of the child's head. Some gel will be put through the holes and some wires will be attached to the cap that will record brain activity across the scalp. Placement of the cap takes approximately 40 minutes including proper programming of the HD-EEG equipment.

We will obtain 15 minutes of baseline EEG recording. During the baseline EEG recording, Dr. Damato, Dr. Decker or a member of the team will administer a neurobehavioral assessment, which will include the Grooved Pegboard test, where the child is timed while placing pegs into a board. Following completion of the EEG recording, child is assisted to remove gel from scalp and hair.

Study incentive is provided for study completion ($50 gift card to child plus $50 gift card to parent or caregiver present).

NOTE: A positive pregnancy test in girls under the age of 13 will be reported to the parent and to the child as well as to the Cuyahoga County Department of Children and Family Services (216-696-KIDS) as required by law. If the child is age 14 or older, we will report a positive pregnancy test to the child and will tell the parent about the pregnancy test results only if the parent asks for that information. We will also notify University Hospitals Social Work (216-844-8965) about any positive pregnancy tests so they can provide support to the child. If we become aware of abuse or neglect of a child in this study, we will notify the appropriate county social services agency as required by law (216-696-KIDS).

Procedure	Responsible Party
Confirmation of signed informed child assent / parent consent & repeat MRI safety screen	Dr. Damato or member of research team approved to obtain consent
Confirm that child has washed hair that day and not used any hair products after the shampoo	Research assistant
Perform brief neurologic history and physical exam	Nurse Practitioner (Dr. Damato) or Physician (Dr. Wilson-Costello)
Acclimate child to MRI / mock scanner	Research assistant
Instruct child on verbal n-back memory task (5 minutes)	Research assistant
Transfer child to MRI scanning room	Dr. Flask or MR technician
MRI scan (structural, DTI, fMRI) performed. n-back memory test is administered during fMRI scan (30 minutes)	Dr. Flask or MR technician
While child is in the MRI scanner, parent completes Child Behavior Checklist, Vanderbilt Assessment Scale, and Child Sleep Assessment (25-30 minutes).	Research assistant
Following MRI scan, apply HD-EEG head cap on child's scalp, apply EEG gel, and program EEG acquisition software, check impedances (40 minutes)	Research assistant
Obtain 15 minutes of baseline EEG recording	Research assistant
While EEG is being recorded, administer grooved pegboard task and n-back memory test (5 minutes)	Research assistant
Following completion of EEG data collection, child is assisted to remove gel from scalp and hair	Research assistant
Study incentive payment is provided	Research technician/Dr. Damato/Dr. Decker

Radiation and Radioactive Substances

1. Does the research involve the use of radiation or radioactive substances?
   ☐ Yes ☒ No – leave rest of the section blank

If yes, answer the following questions.
Please note that you must receive Radiation Safety Committee (RSC) prior to IRB submission.

2. Is the radiation use only for the purposes of the research study (e.g. over and above standard of care)
   ☐ Yes ☐ No

3. Does the protocol use radionuclides?
   ☐ Yes ☐ No

4. Provide justification for the additional risk associated with the research radiation use.

ClinicalTrials.gov Information

Has this study been registered on ClinicalTrials.gov?

☒ Yes. Provide the following:

i. The ClinicalTrials.gov identifier: NCT03407729
ii. Investigator/sponsor responsible for registering: Michael J. Decker, PhD

☐ No. Explain if there are plans to register or why registration is not required (i.e., the study is not NIH funded, registration is in process, or does not meet the definition of a clinical trial)

List of Data to be Collected

1. *Indicate what identifiers you will collect*

☒ Name
☒ Address
☒ Dates related to an individual *(e.g., Date of admission, birth, surgery, etc.)*
☒ Telephone number
☐ Fax number
☒ Email address
☐ Social security number
☐ Medical record number
☐ Health plan beneficiary number
☐ Account number
☐ Certificate/license number
☐ Any vehicle or other device serial
☐ Device identifiers or serial numbers
☐ Web URL
☐ Internet protocol (IP) address
☐ Finger or voice prints
☐ Photographic images
☐ Other: Any characteristic that would uniquely identify the individual

2. *List all other data to be collected for the research study (e.g. laboratory values, physician notes, length of stay, etc.).*

- Magnetic Resonance Imaging, specifically T1 structural scan, Diffusion Tensor Imaging (DTI), and functional Magnetic Resonance Imaging-Blood Oxygen Level Dependent (fMRI-BOLD)
- High density electroencephalography (HD-EEG)

- Neurobehavioral Assessments of child: Verbal n-back; Grooved Pegboard task Parent report of child behavior (parent-report): Child Behavior Checklist, Vanderbilt Assessment Test, Child's Sleep Habits Questionnaire (for children ages 9-12), Pediatric Sleep Questionnaire (for children ages 9-17).
- Urine collection (to determine pregnancy exclusion for female child participants)

Data Analysis Plan

1. *Describe the data analysis plan, including any statistical procedures. Provide a power analysis if applicable.*
2. *If applicable, describe the primary and secondary study endpoints including safety endpoints.*

Our intent in this exploratory cross-sectional two-arm pilot study is to develop sufficient Scientific Rigor to support a future study appropriately powered to account for our proposed primary outcome measures and co-variates. Our sample will include 20 prematurely born children who experienced hypoxic insults during postnatal life. To allow comparison to "normative" expectations, we will compare these 20 former preterm children with 10 healthy term-born controls without exposure to hypoxia and of similar age, sex, race distribution as the preterm group. Data from these 30 children will be used to develop appropriate sample sizes, using actual rather than predictive data, for future studies characterizing neural structure and function following postnatal hypoxic insults.

Specific structural and functional characteristics used in our analyses will include

- apparent diffusion coefficients and fractional anisotropy generated from DTI data
- fMRI-BOLD, measured during the pediatric verbal n-back, and HD-EEG sLORETA
- neurobehavioral assessment results (grooved pegboard test, verbal n-back, Child Behavior Checklist, Vanderbilt Assessment test, Child's Sleep Habits Questionnaire, Pediatric Sleep Questionnaire)

Covariates include 1) age, 2) sex, 3) race, 4) preterm vs. term birth, and 5) frequency of hypoxic insults (< 5000 versus ≥ 5000) during the first 8 weeks of life within the preterm group. The continuous outcome measure variables will be summarized using descriptive statistics (mean, standard deviation, median, interquartile range). Frequency analyses and stem-n-leaf graphs will characterize data distributions. Skewed continuous variables will be transformed to satisfy normality assumptions of hypothesis testing. Outcome measures for the two groups will be compared graphically using box plots. We will perform hypothesis tests for equality of data distribution for the two groups using t-tests or Wilcoxon sign rank test, as appropriate, with a significance level of 10%.

As we are interested in the differences of above mentioned outcome measures in two groups, we will focus on effect size estimation for the differences of our measures. To detect significant effect size, we will perform regression analysis on the outcomes of interest with the primary covariate of interest being group membership (preterm vs. term birth). In the regression analyses, we will control only for significant confounding effects of age, sex, race, and frequency of hypoxic insults. Using regression analyses, we will determine point

estimates, regression coefficients (beta), as well as 90% confidence interval of betas. The confidence intervals will be main estimated effect size or the differences in outcomes in two groups due to preterm and term birth.

Confidentiality of Specimens and Banking

☒ I am not storing specimens in this research project – *please leave the rest of this section blank*

Describe:

- ☐ *The source of the specimens*
- ☐ *Where the specimens will be stored*
- ☐ *How long the specimens will be stored*
- ☐ *How the specimens will be labeled*
- ☐ *How the specimens will be accessed*
- ☐ *Who will have access to the specimens*
- ☐ *When and how will the specimens be destroyed*
- ☐ *How will the specimens be transported (Please note if transporting specimens, a Material Transfer Agreement (MTA) is required).*

Describe:

☐ *The procedures to release specimens including:*

i. *The process to request a release*
ii. *Approvals required for a release*
iii. *Who can obtain specimens*
iv. *The data to be provided with specimens, including if the data will be identifiable to others*

☐ *For genomic data, please include an attestation of no master list and no attempt will be made to re-identify the specimens.*

Are you storing the specimen for future use for other research projects?

- ☐ Yes
- ☐ No

Confidentiality of Data

1. To maintain the confidentiality of the data:
   - ☒ I will use a unique study identifier (not derived from the participants personal identifiers) to code individuals' data and I will store this ID log separate from study data.
   - ☐ Other (please explain)

2. How are you storing your electronic data?
   - ☒ UH Redcap
   - ☐ CWRU Redcap

☐ Secure Research Environment (SRE)
☐ CWRU Box
☐ OnCore
☒ UH Secure Network Drive
☐ CWRU Secure Network Drive
☐ Other - List storage method and provide justification:

3. ☒ I acknowledge that paper research data and documents will be stored in a double-locked secure environment in the following location:
Location: PI Michael Decker's laboratory office; CWRU School of Medicine

4. If sharing data, describe:
   - *The exact data elements that will be shared*
   - *How data will be sent*

(Please note if sharing data, a Data Use Agreement (DUA) is required.
N/A

HIPAA Authorization

If you are going to be accessing PHI (Protected Health Information), indicate how HIPAA authorization will be obtained (check all that apply):

☒ HIPAA authorization is in the consent form
☒ Requesting a full or partial waiver of HIPAA for prescreening
☐ Requesting a full or partial waiver of HIPAA

1. *Describe why the study cannot be completed without the specified identifiable information.*
2. *If the identifiable information will be used or disclosed by anyone other than the research team, please state who those individuals/entities are and provide justification for the disclosure.*
3. *Describe how long identifiers will be kept for in relation to study length and data collection and analysis.*

The purpose of requesting identifiable information is to reduce research participant burden. We intend to first speak to potential research candidates by phone, at which time we will describe the study and establish their interest in participating. During the call, we will also establish the presence of inclusion criteria and any overt exclusionary criteria that may exist, before inviting the study candidate to meet in person with us to provide informed consent and obtain signatures. We appreciate that these steps increase the workload of the investigative team. However, they will reduce research participant burden by identifying non-eligible study participants before they take the time to meet with us in person for further evaluation of inclusion and exclusion criteria. We will destroy all pre-screening documents and records as soon as the child is determined either (1) study-ineligible or (2) parent has signed a written consent form and the child has signed a written assent form to participate or (3) child and/or

parent has opted to not participate in the study. No persons outside the research team will have access to identifiable information. Research data will be stored by the PI for 5 years after closure of the study.

☒ I assure that protected health information collected for purposes of this research study will not be reused or disclosed to any other person or entity, except as required by law, for authorized oversight of the research study, or for other research for which the use of disclosure of protected health information for which an authorization or opportunity to agree or object is not required by 45 CFR 164.512

Risks to Research Participants

1. *List the reasonably foreseeable risks such as breach of confidentiality, discomforts, hazards, or inconveniences to the research participants related to their participation in the research. Include a description of the probability, magnitude, duration, and reversibility of the risks. Include the physical psychological, social, legal, and economic risks.*
2. *If applicable, indicate which experimental procedures may have risks to the research participants that are currently unforeseeable.*
3. *If applicable, indicate which procedures may have risks to an embryo or fetus should the research participant or their partner be or become pregnant.*
4. *If applicable, describe the risks to others who are not research participants.*
5. *Describe the availability of medical or psychological resources that research participants might need.*

Potential Breach of Confidentiality: Accessing of PHI involves the risk of potential breach of confidentiality. Participant's names will not be used in any written or oral report of the study. A number will be used to identify all information supplied. Participant identity will be known only to the study staff.

Potential Time Burden: Participation may require the children to miss school and their parents to miss work, although we will preferentially schedule evening and weekend appointments. We will also schedule data collection during school holidays and summer vacation whenever possible.

Telephone screening/In-person interviews of child/parents: The procedures used in evaluating children and families for the study are similar to those used in clinical follow-up of children. There may be some minimal risks associated with initial telephone screening. There are also minimal risks that the children or their caregivers will become anxious about the testing, or will experience some distress in being questioned about their personal lives.

Neurobehavioral Assessments: Risks related to the neurobehavioral assessments, i.e. the pediatric verbal n-back, grooved pegboard task, parent-reported behavioral questionnaires, are minimal. These may include frustration with remembering the appearance of letters on a screen or the time burden of completing the tasks.

Electroencephalography (EEG): This non-invasive procedure is associated with minimal risk, or at the most, minor risk. Those include skin sensitivity to the gel or to the adhesive tape which is sometimes used to secure a recording electrode or wire.

Neuroimaging (MRI)

Collision Hazard: The subject's participation in this study involves minimal risk. Because the MRI machine exposes the body to a very strong magnetic force, loose magnetic or metallic objects can fly into the magnet with great force if brought into the environment of the MRI scanner. The participant is asked to remove the following before entering the magnet room: hearing aids, beeper, cell phone, keys, eyeglasses, hair pins, barrettes, jewelry, body piercing jewelry, watch, safety pins, paperclips, money clip, credit cards, bank cards, magnetic strip cards, coins, pens, pocket knife, nail clipper, steel-toed boots/shoes, hair bands, eye shadow, and tools. We have established a security zone to prevent objects containing iron from coming into proximity of the magnet. To prevent the likelihood of wearable metallic substances in the scanning room, we will routinely ask subjects to change into a hospital gown or other suitable garment. Some persons should not participate in an MRI study and we will exclude these persons: people with metallic implants such as aneurysm clips or some types of prostheses (fake body parts), or with electronic implants such as cardiac pacemakers, intravascular shunts, stents, or filters; hearing aids, dental devices such as braces or dentures.

Claustrophobia: The confining conditions of the MRI scanner can precipitate claustrophobia (feelings of being “closed in”) in some people. The radiology suite offers facilities that promote comfort and reduce anxiety. The mock scanner can assist in acclimating the child to the MR scanning procedure. If a child has feelings of claustrophobia during the study, the study will be terminated.

Hearing: The MRI scanner produces tapping sounds during operation which may reach objectionable levels. To minimize any discomfort, subjects are provided with disposable earplugs or headphones. Children may discontinue their participation if the noise of the MRI scanner becomes too loud to tolerate.

Radio Wave Exposure: There have been no ill effects reported from exposure to the magnetism or radio waves used for these studies, however that it is possible that harmful effects could be recognized in the future. The child will be able to communicate with the scanner staff using an intercom and/or signaling device. The staff will try to help the subject feel as comfortable as possible in the scanner. The subject can ask to stop the scan and be removed from the scanner at any time by using the intercom or signaling device.

Health/Sexual Activity: The effect of MRI on pregnancy and a fetus is not known. For that reason, if a female child is pregnant, or is planning to become pregnant, the child may not participate in this study. We will perform a urine pregnancy test on pubertal females and if the result is positive, we will inform the parent of the result and the child will be removed from study participation. We will also notify University Hospitals Social Work. The Cuyahoga County

Department of Children and Family Services will be notified of positive pregnancy test results for females under the age of 14 as required by law.

Provisions to Protect the Privacy Interests of Research Participants

Describe the steps that will be taken to protect research participants' privacy interests. (consider issues such as physical space, proximity to other, and participant preferences)

Subjects and their parent/ guardian will be given adequate time and space to sit down and comfortably and privately review the consent forms and screening forms. Consent forms presented in person will be reviewed and signed in a private room; data collection (grooved pegboard task, completion of questionnaires by parents) will be occur in a private room. Based on parent preference, consent forms may be mailed in advance to the parent prior to a mutually scheduled telephone call to conduct the consent process. The parent will sign the paper consent form(s) and return the signed documents to the investigative team in a provided stamped return envelope.

Subjects are provided with individual lockers in the MR scanning facility for storing their personal belongings during the scan. Subjects may use a locked room for changing their clothes and cleaning the gel off the scalp after the EEG. The scanner suite is secure and populated by the members of the research team and clinical staff only.

Paper documents that can identify subjects will be kept in a locked cabinet in the faculty office of Dr. Michael Decker, Robbins Building, office E510. Only the Research Principal Investigators Drs. Elizabeth Damato and Michael Decker and the site principal investigator Dr. Wilson-Costello will have access to the locked file cabinet. Subject privacy during study procedures will be ensured by anonymizing the data through the use of a unique identifier number. These data will be stored on the UH REDCap system to ensure that the data is maintained behind institutional firewalls with access available only to Elizabeth Damato, Michael Decker, Deanne Wilson-Costello, and their certified staff associated with the study.

Raw imaging data will be stored on the UH data only storage system using a unique identifier number. Imaging data using the unique identifier, as well as HD-EEG data, will be stored on REDCap, or a UH-approved encrypted flash drive, to be processed using specialized software with access available only to the primary investigator and certified staff. Results will be reported in an aggregate fashion with no individual identifying demographic information available.

Dr. Elizabeth Damato will be responsible for providing and documenting appropriate user access to the study database in REDCap and will prevent potential security concerns such as unauthorized access to data or malicious intent to destroy data and systems. Dr. Decker and Dr. Damato will oversee data audit software (REDCap) that is used to document user access, document data modification and backups. Dr. Decker and Dr. Damato will provide appropriate investigative team members with user accounts to enter data. Subject information and results will be stored by study ID numbers. REDCap software will be

used to de-identify PHI in the database. The paper data linking sheet holding identifiable information will be stored in the locked cabinet in faculty office of Dr. Michael Decker, Robbins Building, office E510. The linking sheet will be destroyed at the end of the study. Signed paper consent forms will be stored separately from the linking sheet in a different locked cabinet in Dr. Decker's office. Only Dr. Damato, Dr. Decker and Dr. Wilson-Costello will have access to the locked cabinets. The data linking sheet is attached to this submission.

Potential Benefit to Research Participants

1. *Describe the potential benefits that individual research participants may experience from taking part in the research. Include the probability, magnitude, and duration of the potential benefits. Indicate if there is no direct benefit.*
2. *If no direct benefit, state the potential benefit to society or others. Do not list compensation.*

There is no direct benefit to the child by their participation in this research study. Information derived from this study may enable us to determine the underlying neuropathology causing the cognitive dysfunction that can occur following mild-moderate intermittent hypoxic insults in the postnatal period.

Withdrawal of Research Participants

1. *Describe the anticipated circumstances under which research participants will be withdrawn from the research without their consent.*
2. *Describe the procedures that will be followed when research participants withdraw or are withdrawn from the research, including partial withdrawal from procedures with continued data collection.*

A child participant would be removed from this study by the investigators if they cannot cooperate with study procedures or if previously undetected exclusionary criteria become evident during the data collection. These circumstances may include, but may not be limited to: (1) children who cannot cooperate with study procedures such as the ability to perform neurobehavioral tests; (2) if their hairstyle does not permit adequate EEG signal conduction (e.g. dreadlocks are a known problem); (3) if they meet exclusionary criteria such as claustrophobic behavior during the MRI scan or a positive pregnancy test. Data collection will occur in one visit; thus partial withdrawal with continued data collection does not apply to this protocol.

A subject's participation in this research study is voluntary. Refusing to participate, withdrawing or being withdrawn by study staff will not alter their usual health care or involve any penalty or loss of benefits to which they are otherwise entitled. The images collected are for research purposes only and do not form part of the subject's routine health care or offer interventions. The images are not a benefit of being in this research study. In the event new information becomes available that may affect the risks or benefits associated with this study or a subject's willingness to participate in it, they will be notified so that they can decide whether or not to continue participating.

Alternatives to Participation

1. *Please list other available clinical treatments.*
2. *Please state if a subject could continue on standard of care therapy and what that might include.*
3. *If not a clinical trial you may state that the alternative is not to participate. If there is a viable alternative you must list it in the consent.*

This is an observational study and clinical treatment is not provided. This study is being performed for research purposes only. The alternative to the study is simply not to participate.

Costs to Research Participants

☒ There are no costs to research participants or their insurance companies – *please leave the rest of this section blank*

1. *If applicable, describe what costs the research participants will be responsible for because of participation in the research including but not limited to: transportation to study visits, parking for study visits, costs of procedures, lost, broken or stolen devices, costs of drugs or therapy, etc.*
2. *You must clearly state if insurance will be charged and who will be responsible if insurance does not pay.*
3. *List what research procedures and research interventions will be covered by this study.*

Research Participant Compensation

☐ There is no compensation for research participants – *please leave rest of this section blank*

1. *Describe the schedule, payment method and payment total of any incentives or compensation that research participants will receive for participation in the research (e.g., gift cards or cash with amounts, t-shirts, devices, bags, swag, etc.)*
2. *Describe the schedule, payment method and payment total of any reimbursements that research participants will receive for participation in research (e.g., parking, mileage, meals, etc.)*

As a token of appreciation of the time and effort made by the parent and child to participate in this study, we will compensate each child who completes the protocol with a $50 Amazon gift card. Each parent whose child completes the protocol and completes the parent questionnaires will also be compensated with a $50 gift card [note: only one parent per participating child is eligible]. In special circumstances that require a parent proxy to come with the child to the study visit, the study team, parent, and caregiver will make a decision as to who can best respond to the questionnaires about the child's activities and behaviors. The parent or the caregiver who completes the questionnaire will be compensated $50. The total compensation for the child/parent unit is $100 value. If two children participate from the same family (e.g. one healthy child and one former preterm child OR two healthy OR two former preterm children), they will be eligible for $100 for each participating child/parent

unit. If a child/parent completes the protocol a second time, the child will receive a $50 Amazon gift card and the parent will receive a $50 gift card for completing the re-study.

The $50 parent/caregiver incentive is also meant to cover expenses of parking during the time of data collection. Both the child and the parent/caregiver will receive their incentives on the day of the data collection visit.

Compensation for Research Related Injury

Describe who will pay for the costs of medical treatment and/or compensation in the event of a research related injury:

- ☐ Funding agency is providing some/all payment for injury
- ☒ Funding agency is providing no payment for injury
- ☐ Not applicable

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

1. *Describe the Data and Safety Monitoring Plan for the proposed study. Describe how often the data will be monitored for completeness, accuracy and adherence to the protocol.*
2. *Is there a formal Data and Safety Monitoring Board/Committee? If yes, provide information about the DSMB/C including the contact information of the committee member(s) (as applicable); whether it is independent from the study sponsor; how often it meets; the type of data that will be used; written reports, etc.*

Given the minimal risk of the procedures involved in the study the likelihood of adverse events is very low. Overall risk to participants should be similar to that of a clinical MRI scan. Collection of EEG data is non-invasive. The unblinded study coordinator will monitor records and debrief data collection personnel each week to detect adverse events. Data will be reviewed and monitored to ensure that its accuracy, completeness, and collection is in compliance with the protocol. All adverse events will be classified by severity and will be reported to the IRB in accordance with the rules regulating each severity class (expected vs. unexpected; serious vs. other; related vs. unrelated). With consultation of the physician involved in the project (Dr. Wilson-Costello), criteria for urgent medical referrals will also be established. Per NIH policy, we have developed a detailed Data and Safety Monitoring Plan, which has been approved by NINR/NIH. The approved 7-page document is attached. A DSMB has been assembled with 4 members outside the study team in addition to 3 members of the study team (Dr. Decker, Dr. Damato, and biostatistician Dr. Sattar). Data and procedures will be monitored weekly by the study team to ensure compliance with the protocol and integrity of the data. Quarterly written reports to outside DSMB members summarizing study progress and adverse events will be provided by Drs. Decker and Damato. The DSMB will be included in all formal procedures that report adverse events to the oversight University Hospital IRB and identify any need for premature termination of the protocol.

DSMB members will include (1) Carolyn Landis, PhD: Licensed Clinical Psychologist & Professor of Pediatrics, Division of Developmental/Behavioral Pediatrics & Psychology, Rainbow Babies & Children's Hospital, Carolyn.Landis@uhhospitals.org. Dr. Landis will serve as DSMB chairperson; (2) Asim Shahid, MD: Assistant Professor of Pediatric Neurology/Staff Pediatric Epileptologist, Rainbow Babies & Children's Hospital, Asim.Shahid@uhhospitals.org; (3) Richard J. Martin, MD: Director, Neonatal Research Programs, UH Cleveland Medical Center, Professor of Pediatrics, CWRU School of Medicine, Richard.Martin@uhhospitals.org: (4) Ian Vannix, Lead Teaching Assistant, CWRU School of Medicine, Department of Physiology & Biophysics, isv@case.edu. Mr. Vannix will serve as the DSMB Executive Secretary. Dr. Wilson-Costello, UH-based site PI, will be invited to attend any meetings and be provided with interim written DSMB report updates.

Drugs or Devices

☒ There are no drugs or devices being utilized in this research project – *please leave rest of this section blank*

1. *If the research involves drugs or device(s), describe your plans to store, handle, and administer those drugs or device(s) so that they will be used only on research participants and be used only by authorized investigators.*
2. *How will the drug(s) be dispensed (i.e., indicate the pharmacy that will be used)?*
3. *If the drug is investigational (has an IND) or the device has an IDE or a claim of abbreviated IDE (non-significant risk device), identify the holder of the IND/IDE/Abbreviated IDE*

Additional Information

If you have any additional information regarding your study not covered in the template, please include it here.

Community-Based Participatory Research

☒ This is not a community-based participatory research project – *please leave rest of this section blank*

If applicable, describe the involvement of the community in the design and conduct of the research.
Note: Community based research is research that is conducted as an equal partnership between academic investigators and members of a community. In Community Based Participatory Research (CBPR) protects, the community participates fully in all aspects of the research process.

International information

☒ This is not an international study – *please leave rest of the section blank*

☐ We will be conducting this research at the following international sites:
1.

☐ We are recruiting participants outside of the US from the following locations:
1.

☐ We are sending data outside of the US to the following locations:
1.

☐ We are receiving data from outside of the US from the following locations:
1.

MULTI-SITE RESEARCH (when UH or CWRU is the IRB of Record)

Does this project have multiple sites?

☐ **Yes**

☒ **No**

Non-Local Site Information for Multi-Site Studies

*If this is a multi-site study where you are the **lead investigator,** list the following information for each relying site:*

1. Name of site:
2. PI of relying site:
3. Name of IRB contact:
4. Phone number of IRB contact:
5. Email address of IRB contact:

Non-Local Recruitment Methods for Multi-Site Studies

*If this is a multi-site study and research participants will be recruited by methods **not under the control of the local site** (e.g. call centers, national advertisements) describe those methods. Local recruitment methods are described above.*

1. *Describe when, where, and how potential research participants will be recruited.*
2. *Describe the methods that will be used to identify potential research participants.*
3. *Describe the materials that will be used to recruit research participants.*

Multi-Site Research Communication Plan (when you are the lead investigator)

*If this is a multi-site study where you are the **lead investigator**, describe the processes to ensure communication among sites including:*

- *All sites will have the most current version of the protocol, consent document, and HIPAA authorization*
- *All required approvals (initial, continuing review and modifications) have been obtained at each site (including approval by the site's IRB of record)*
- *All modifications have been communicated to sites, and approved (including approval of the site's IRB of record) before the modification is implemented*

- *All engaged participating sites will safeguard data, including secure transmission of data, as required by local information security policies*
- *All local site investigators conduct the study in accordance with applicable federal regulations and local laws*
- *All non-compliance with the study protocol or applicable requirements will be reported in accordance with local policy*

*If this is a multi-site study where you are the **lead investigator,** describe the method for communicating to engaged participant sites:*

- *Problems*
- *Interim results*
- *The closure of the study*

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Please reference the Investigator Manual for local institutional requirements.