TO: INSTITUTIONAL REVIEW BOARD

TITLE OF STUDY: Pediatric Functional Neuroimaging Research Network

I. Abstract

Functional magnetic resonance imaging (fMRI) has emerged as an important non-invasive methodology in 21st century studies of language networks and functional connectivity in the human brain. We have previously assessed a cohort of over 300 normally developing children between the ages of 5-18 to determine the various neural signatures of language development. The purpose of this study is to go a step beyond what we have done before as part of a five-year cross-sectional and longitudinal of language and attention in normally developing children.

The current protocol is designed with the contract parameters in mind with the goal of ascertaining the various functional networks in the brain associated with both language and attention. We hope to successfully scan up to 300 children between the ages of 0-18 over the span of a NICHD contract, using arterial spin labeling (ASL) and blood-oxygen-level dependent (BOLD) fMRI. The differences between our previous study of normal language development and this endeavor include the extension of the range of ages studied, as well as the use of ASL. We hope that the outcome of this project is a more mature version of other studies we have completed in the past.

Specific goals of this project include: scanning this cohort of 0-18 without sedation, using passive listening and attention tasks in those under the age of seven, and adding an active component for older children and adolescents; developing methods and software which can be translated to other centers across the nation and potentially the world; building a secure database with the ability to hold and disperse our anonymized data, as well as to collect data from a variety of other sources; and to integrate data processing across all cites with which we come in contact. In short, the goal of this project is to collect all of the information that we can while carrying out the methods requested by the NICHD

II. Purpose of Study

Pediatric neuroimaging provides opportunities for learning how the brain develops in normal children and in those afflicted with a variety of diseases and behavioral disorders. Magnetic resonance imaging (MRI) provides safe, noninvasive methods for the in vivo characterization of developing brain structure and function. However, many obstacles have impeded pediatric functional neuroimaging research. These difficulties include (1) complications in obtaining data from children given limitations in their ability to comply with procedures, (2) the absence of a gold-standard for fMRI scanning protocols and analytic techniques, (3) the lack of brain perfusion studies with data categorized by age, (4) the lack of an adequate representative database with which to characterize normal brain function, (5) the lack of a standardized approach for investigating brain-behavior relations during typical and atypical development, (6) the lack of adequate image analysis software for characterizing developmental changes in brain function, and (7) limited venues and means for sharing data and image analysis software.

The primary objectives of this project will mirror the requirements of the contract announcement necessities above, and will include development of standardized blood-oxygen-level dependent (BOLD) fMRI and arterial spin labeling (ASL) protocols for use with typically developing children, brain perfusion studies using ASL, and passive fMRI assessment of 300 children between the ages of infancy and 18-years-old. In addition, 60 typically developing children in an age range of 0-3 years and another 45 in the age range of 7-9 years will be assessed longitudinally through integrated fMRI and ASL using activation tasks targeted at the neurocognitive domains of language and attention in the developing brain. Children will not be sedated for scanning in this project but the results of this study will *provide the scientific community with protocols, software, and an initial database of representative fMRI-ASL data* in children ranging in age from 0 to 18 years.

Specific aims of this project:

1. Standardized methods for acquiring resting state ASL brain perfusion and BOLD fMRI data in typically developing children 0-18 years of age.
2. Standardized methods for recruitment and retention of infants and children for functional brain imaging studies, objective quantification of image quality, subject failure rates and rejection of poor quality image data from infants and children.
3. Software for analysis and integration of ASL perfusion and BOLD fMRI data and correlation with neurobehavioral data across ages and developmental levels.
4. Standard brain activation paradigms that are age appropriate for use in children age 7-18 for the study of developmental trends in attention and language.
5. Methods and preliminary data for a longitudinal study of normative brain development using neurobehavioral measures and BOLD fMRI and ASL brain activation paradigms in children age 0-3 and 7-9 years.
6. Quality control and routine quality assurance methods to insure consistent MRI scanner performance and brain imaging data quality across scanners, sites, subjects and longitudinally within subjects scanned at multiple time points.
7. Database structure and web-based interface for archival and retrieval of subject demographic and neurobehavioral data and with pointers to neuroimaging data for each subject.
8. Initial database of resting state ASL perfusion and BOLD fMRI data using the standardized methods developed in (1) above of all qualified children age 0-18.
9. Pipeline architecture for database queries and execution of image analysis algorithms integrating ASL and BOLD fMRI data with neurobehavioral data.
10. Documentation of all methods, software and database structures and function.
11. A manual of standard operating procedures for performing functional neuroimaging studies in children from infancy through adolescence.

At the conclusion of this 5-year contract the methods deployed and documented through this study will be fully tested at the principle site (CCHMC) as well as a secondary site (UCLA), in terms of their standardization, documentation and translatability from one site to another. Data sets from multiple subjects obtained at different times and different sites will be examined in terms of repeatability and the final methods published from this study will be optimized to minimize variability and to detect developmental brain changes in resting and active state brain activity. Failure rates of subjects at different ages will be documented and results from the cross-sectional and longitudinal cohorts tested during the last 3 years of the project will be published in the open scientific literature.

III. Significance of Study in Relation to Human Health

The rationale for this study is that functional neuroimaging with MRI at 3 Tesla has now reached a level of technical maturity sufficient to warrant standardization of methodologies for use of this technology in large-scale, multi-site studies of normative brain development in children. Furthermore, normative reference data documenting age dependent changes in cerebral perfusion and BOLD effect is a fundamental building block for future studies of functional neuropathology in children using functional MR imaging methods because abnormalities in the neural substrates of attention, language, memory and other developing neurocognitive domains can only be fully understood against the backdrop of normal age-dependent trends in these same neural circuits. Consequently, further research regarding brain functional pathology must be set in the context of normal development of the neural circuitry supporting the corresponding neurocognitive domains. For example, the pattern of brain activity supporting sentential language processing in a 7 year old boy may look very different from that of an 18 year old girl, even in absence of language pathology or brain injury.

This work is relevant to development of more complete models of child brain development as well as better models of developmental disease. For example, in children with epilepsy who were candidates for temporal lobectomy we found that the hemispheric dominance for language in these children, determined by fMRI, was more variable than expected from earlier reports in normal adults.[1] Now, with a large normative reference data set, we can unequivocally attribute variability or aberrant patterns of language lateralization in children with epilepsy, brain injury, or other diseases, to the diseases, rather than normal development. A normative reference frame for fMRI is critical to understanding a number of neuroscience questions as well as developmental diseases affecting the brain. The study proposed in this contract will allow us to acquire a normative reference frame for interpretation of fMRI data from children.

Our normative fMRI reference data for child language development is being used in applications in children with epilepsy, traumatic brain injury, stroke, and developmental disorders.[2] We expect that having a normal reference frame available for interpretation of pediatric fMRI data will begin to make this new imaging technology more accessible for clinical research, and ultimately clinical diagnosis and treatment.

IV. Previous Work Done in this Area

Before non-invasive neuroimaging methods were widely available, knowledge about normal brain development was difficult to obtain, as the classical approach, neuroanatomical observation, was limited by the low mortality of normal children.[3,4] Following the introduction of computed tomography (CT) and positron emission tomography (PET) first attempts to describe brain development were made. However, these techniques invariably expose the subject to ionizing radiation, which makes them unsuitable for studying truly normal children due to ethical concerns. It was therefore only after the introduction of magnetic resonance imaging (MRI) that normal brain development could be assessed in a more systematic fashion.[5] MRI gives excellent soft tissue contrast, is repeatable and has become more and more widely available. Consequently, normal brain development has been the focus of a growing number of MRI-studies[6,7], culminating with the recent NIH study of normal child brain development.[6]

More recently, functional brain imaging studies using fMRI have become common in adults and have extended to studies of normal functional brain development in children.[7] The minimal risks associated with MRI scanning make it feasible to use this modality to study normal brain

development in healthy children[8] and to examine children longitudinally[9] using various neurocognitive stimulation paradigms. Although functional MRI is now a powerful tool for imaging of brain functional development in children in various neurocognitive domains, with a few notable exceptions, [2] published studies using fMRI to map normal brain development in children have examined relatively small numbers of children in non-representative age and demographic samples. As stated in the NICHD's Request for Proposals, in … "*a recent review of PubMed articles published in the past five years, 92% of 210 functional neuroimaging articles involving children involved adolescents 18 years or older and 98% involved sample sizes less than 15 per group".* Non-representative samples, small sample sizes, variable magnet field strength and non-standard methodologies utilized in these clinically motivated studies make it impossible to generalize findings. "*Larger-scale studies are needed in order to make more reliable interpretations of pediatric fMRI data."* This proposal outlines an ambitious plan to develop and standardize methods for performing large-scale, multi-center functional MRI studies of child brain development across neurocognitive domains and across the age span from 0 to 18 years.

In addition, in young children, we will evaluate the reliability of [HbO_2] measured by a non-invasive scalp NIRS monitor as a surrogate marker of cortical perfusion. Scalp NIRS monitoring has been studied for use in this setting for over 20 years [50], and the recent availability of commercial NIRS monitors has seen the use of NIRS in cortical tissue oxygenation monitoring intra-operatively and postoperatively. Unfortunately, how the tissue oxygen output from these monitors correlates with cortical perfusion is unclear. NIRS measurements in healthy children will be compared to ASL-fMRI as a first step in establishing guidelines for treating cerebral perfusion derangements in infants in the ICU setting where MRI is unavailable.

Currently the field of neuroimaging research benefits from the widespread availability of modern 3 Tesla clinical MRI systems for brain imaging, multi-channel RF coil technology, algorithms and software for acquisition and analysis of large anatomical and functional brain image data sets, high-quality MRI-compatible audio-visual systems and even MRI compatible EEG and PET systems. Such developments have facilitated the translation of neuroimaging methods from clinical use to basic research in human brain function and more recently to studies of brain development [2,6,10,11]. The proposed study builds on these technical and intellectual achievements as well as the experience of our group performing neuroimaging studies in children since 1994 to develop standardized methods, tools and reference data for the Pediatric Functional Neuroimaging Research Network. Following delivery of the methods outlined below and testing of these methods at a secondary site, the proposed methods for functional neuroimaging research in children will facilitate high-quality neuroimaging research in children at sites around the world.

V. Study Design

1. *Recruitment:*

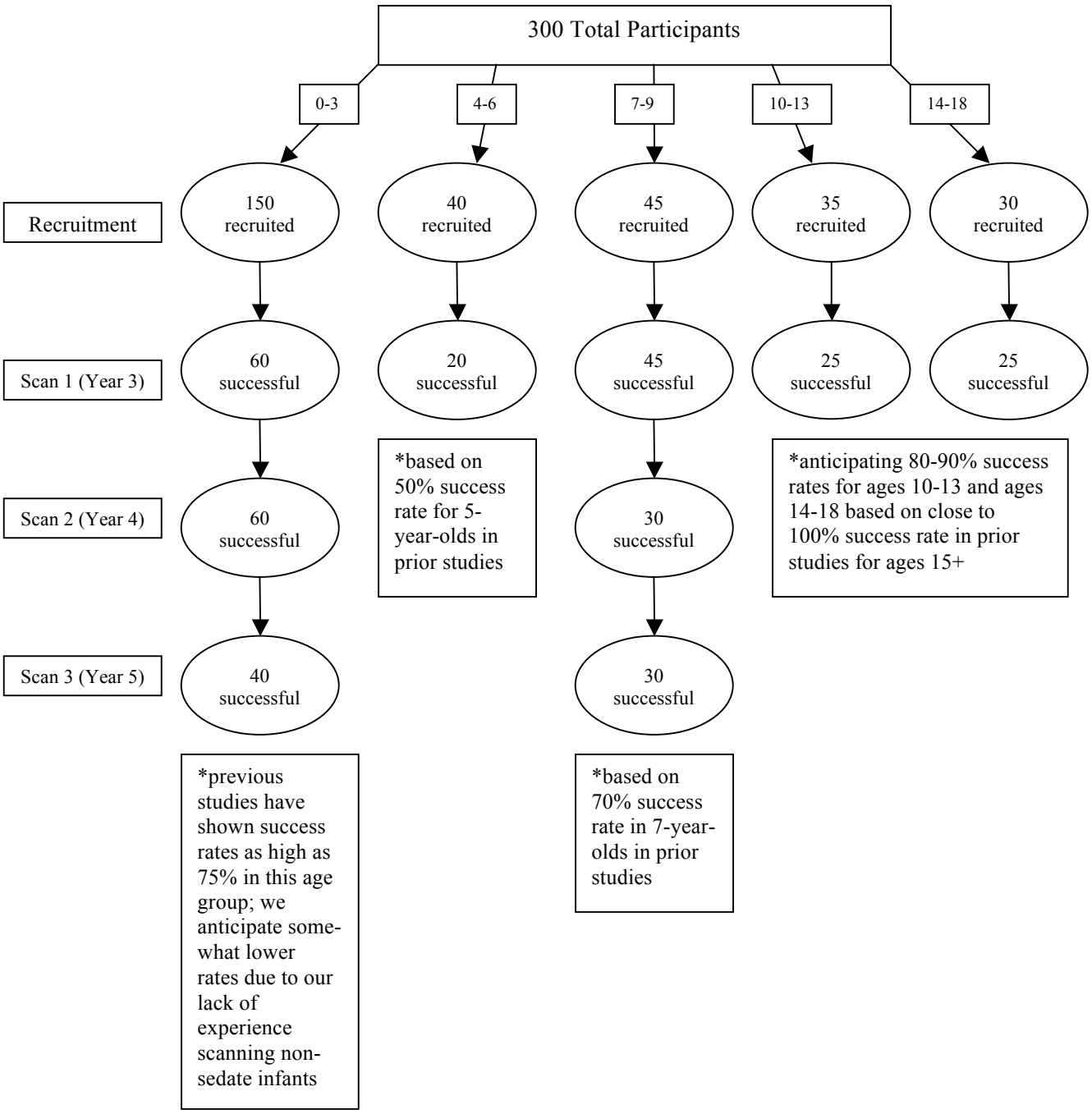
   The contract guidelines state that we must acquire data on at least 50 children between the ages of 0-18. Because we have five age ranges (see table below), we determined that we will need successful scans on 200 participants in total. We propose to recruit a number much greater to account for failure and attrition. We have found that failure and attrition rates are especially high in the 0-3 age range. Therefore, this study is based upon recruitment of n=300 pediatric subjects (approximately 150 girls, 150 boys) spanning an age range from 0-18 years at the Cincinnati site. If a participant fails to successfully complete the study, study staff will recruit an additional participant to replace them. Additionally, a longitudinal cohort of n=45

subjects from the Cincinnati cross-sectional cohort will be included in a longitudinal sub-group of subjects in the age range of 7-9 years; and a longitudinal cohort of n=150 subjects from the cross-sectional cohort in the age range of 0-3 years will be included. These subjects will be scanned and tested 3 times in years 3-5 of the proposed contract period.

Age Range	**0-3**	**4-6**	**7-9**	**10-14**	**15-18**
Number of Participants Recruited	150 (longitudinal group)	40	45 (longitudinal group)	35	30

Two considerations will be made in the recruitment of subjects by age group. First, our experience indicates that the rate of failure of fMRI of language due to motion is greater for boys (22%) than for girls (4%).[12,13] It is therefore likely that we will need to recruit more male subjects than female subjects in order to meet the group size requirements for each age group. This is likely to be more problematic for the youngest age groups. The second consideration is that the youngest children in the study, up to age 6 year olds, may not be able to remain motionless during four fMRI language paradigms and 3D anatomical scan (up to one hour). Therefore, we will only plan to perform resting state ASL and BOLD fMRI in the youngest age brackets; below age 7.

Illustration of recruitment and estimated success rates:



The project coordinator and recruiter will track prospectively the study population based on race and gender to ensure it reflects the intent of the cross-sectional population of the metropolitan community and the study as outlined in the enrollment table. If potential skew or deficiencies in gender or ethnic status of the study population is encountered, outreach programs such as the recruitment from the Primary Care Clinic at CCHMC which serves a more underprivileged and minority population can be undertaken.

In addition to the age group of 0 – 18 described above, another group will be recruited in the age range of 21 and older. This will be a very limited group of no more than 15 people. This group will be used to examine subtle adjustments to MRI methods designed to improve data

quality. These adjustments do not represent any additional risk or discomfort to participants. This group will have different inclusion criteria than the younger population, which is detailed below. Most of these participants will be recruited from Cincinnati Children's Hospital employees. No member of the study staff or employee who is supervised by a member of the study team will be involved in this cohort of participants to avoid any actual or perceived coercion. They will not be offered any compensation for their participation and by virtue of being an employee may already be at the main hospital location and have no need for travel.

Inclusion of Women and Minorities – Both males and females will be actively sought for study inclusion. Therefore, it is anticipated that relatively equal numbers of males and females should be represented in the study cohort. The targeted/planned enrollment table was completed based on this assumption and the Project Coordinator will monitor enrollment on a continuing basis to insure that equal numbers of male and female subjects are enrolled.
Minority subjects will be actively encouraged to enroll in this study and no exclusion will be made on the basis of race or ethnicity. The racial and ethnic composition of the Cincinnati metropolitan area is primarily white and of northern European descent. Less than 20% of the local population is considered minority, with African-Americans making up the majority of the minority population. The Recruiter and Project Coordinator will provide regular recruiting updates to the PI and project leadership team in order to monitor the racial and ethnic distribution of the subjects enrolled in the study to achieve the demographic recruitment goals outlined in the Enrollment Table.

Inclusion of Children – Our study population includes only infants, children and adolescents. Cincinnati Children's Hospital is one of the nation's leading child health care facilities and is at the forefront to provide the most "child-friendly" and "family-centered" environment to practice medicine. All personnel in this study have extensive experience in evaluating, treating, and interacting with children.

a) Inclusion Criteria
   1. Children between the ages of 0 and 18 years.
   2. Body Mass Index within the 5th to the 95th percentile for age and gender.
   3. Negative history for neurologic or psychiatric disease in the infant or pre-schooler.
   4. Negative family history for neurologic or psychiatric disease (in first-degree relatives only) to include genetic disorders.
   5. Assent of children between 5 and 17 and informed consent of 18-year-olds.
   6. Informed consent of parent or guardian of children between 0 and 17 years of age.
   7. Conforms to expected population distribution based on gender, race, and SES.

b) Exclusion Criteria
   1. Standard MRI exclusion criteria
   2. Orthodontic braces or other metallic implants which obscure or interfere with the MRI.
   3. Special education placement of the child based on ability or behavior.
   4. Previous history of head trauma that is not included in the medical record.
   5. Gestational ageless than 37 weeks or greater than 42 weeks.
   6. A birth weight less than the 10th percentile, which corresponds to approximately 6.25lbs for boys and 6.0lbs for girls.
   7. Any chronic illness.

c) Exit Criteria

1. Gross neurologic examination abnormal.
2. Head circumference <5th or >95th percentile.
3. Abnormal MRI findings.

Inclusion criteria for the population of adults 21 and older:

1. Adults at least 21 years of age.
2. Negative history of neurological disease or injury.
3. Consent of participant

Exclusion criteria for the population of adults 21 and older:

1. Standard MRI exclusion criteria
2. Orthodontic braces or other metallic implants which obscure or interfere with the MRI.

Participants will be recruited with the assistance of the clinical trials office at CCHMC. We plan to recruit 35 participants in the age range of 10-13 and 30 participants in the age range of 14-18. Due to the relative difficulty of completing non-sedated MRI scans in infants and young children, we plan to recruit 40 participants in the 4-6 years age group, 45 in the 7-9 years age group, and 150 participants in the 0-3 age range. The desire for successful longitudinal data in as many children as possible is an additional reason to increase recruitment of 7-9 and 0-3 year-olds.

Based on the goal to recruit 300 neurologically normal participants, the Clinical Trials Office (CTO) proposes the following recruitment tactics:

- Database recruitment – use query from CTO database for children and adults 0-18 years old
  - For this age group, the CTO database currently includes 947 children and adults

- Study Flyers – Study flyers will be posted on boards designed for this purpose at Cincinnati Children's-main hospital, outpatient and satellite clinics, and community-based practice referrals-use 19+ study flyer boards. Flyers designed and printed by CTO to include on boards at following locations:
  - 4 flyer boards at main hospital-near cafeteria, Family Resource Center, A Hallway, ED and GCRC
  - 1 flyer board at CCHMC Oak Location-study clinic waiting area
  - 7 flyer boards at CCHMC satellite locations
    - Hopple St. Clinic-low income
    - Northern Ky-mid income
    - Mason-mid to high income
    - Anderson-mid to high income
    - Eastgate-low to mid income
    - Fairfield-low to mid income
    - Liberty (3 boards at this location)-mid to high income
  - 5 community partners (with low income population)
    - Price Hill Health Center
    - Crossroad Health Center-Over-the-Rhine
    - Santa Maria-Price Hill
    - Urban Appalachian Council-Price Hill
    - Norwood Pediatric Clinic
  - 2 Cincinnati School Districts
    - Mt. Healthy
    - Northwest Schools
  - Flyer pads distributed by parent mentors

- Flyer Pad Cost:
    - Designed by CTO

- Study Postings on Internet and intranet – study to be posted on the Cincinnati Children's web site-for external audience and internal site-for employees
- Community events such as family expos, and community health fairs where face to face contact may be made and study materials distributed
- Cincinnati Children's publications including print and electronic newsletters, magazines and other publications (no cost) – Study to be placed on waiting list to be featured in publications such as CCHMC "Young and Healthy", "Research Forward" newsletter, "Round the Center"

2. *Sedation*

No sedation will be required for the MRI scans proposed in this study. Infants and toddlers (age 0-5 years) enrolled in this study will be conditioned to perform the passive MRI scanning procedures during natural sleep. Children age 5 and up will be systematically desensitized to the MRI scan procedures so that they will be able to cooperate with the MRI scanning procedures in a fully alert state.

3. *Randomization:*

There is no randomization in this study.

4. *Study Procedures:*

We will implement standard methods for ASL perfusion mapping and BOLD fMRI across development (from infancy to 18 years), including quality control procedures for longitudinal and/or multi-center studies. We will develop software for analysis of the ASL and BOLD data, and integrate it into the widely-used LONI Pipeline, which enables inclusion and integration of software from different laboratories and environments, for maximum flexibility. The software will also include the capability for state-of-the-art data processing algorithms such as Dynamic Causal Modeling and Granger Causality Analysis to analyze functional and effective connectivity, as well as Hierarchical Multivariate Linear Modeling to analyze longitudinal studies. Routines will also be developed to combine data across multiple sites or across different hardware or software platforms on the same scanner.

In addition, we will acquire passive ASL and BOLD fMRI data from a cohort of 300 normal children from infancy to 18 years of age. We will also acquire longitudinal ASL and BOLD data from tasks encompassing two cognitive domains: language and attention in a cohort of children ages 7-9 years, as well as passive longitudinal data from the 0-3 years cohort; they will be scanned longitudinally over the last three years of the study. A SQL database program will be developed which will enable searching for subgroups of study participants by criteria such as demographic or cognitive variables, and delivering the appropriate datasets and variables to the LONI pipeline for processing and analysis.

fMRI Procedures:

fMRI scans are to be performed in the Imaging Research Center on the 3.0 Tesla Philips scanner. A registered radiological technologist will explain the procedure to the participant, and review the standard checklist of patient questions used for clinical MRI protocols. One of the investigators will explain the informed consent process, answer

any questions that the participant or the parent/guardian may have, and request that the participant and parent/guardian sign the informed consent/assent.

Desensitization to the scanning procedures includes components completed prior to the scan and on the day of the scan. These are somewhat different for young versus older children. For the youngest children, the procedures of Almli and colleagues [14] and those from our own experience with large-scale pediatric studies will be employed. Aimli et al. have reported that these procedures result in successful scans for two thirds of their subjects. We have obtained even better success rates with older children. To begin, parents and children are introduced to the scanner environment so that they will have seen it prior to their child's scan. The scanner environment has been decorated to make it child-friendly. For the youngest children, parents are provided with audio recordings (tape or CD) of scanner noises to play at home (during both sleep and wake periods) to accustom children to the sounds they were hear. Parents may also be provided with ear plugs or headphones resembling the actual MR ear protection ahead of time so that these are familiar to the child prior to scanning. Parents are encouraged to incorporate these into play sessions with their child so that they are introduced within a pleasant context. For children age two and above, the parents will be given a video made specifically to introduce children to the scanning procedures. This video follows a young girl through all the phases of an experiment (behavioral testing and scanning). This includes a demonstration of the girl receiving an MRI scan. Although very young children are not expected to understand the video, it provides a context for the parents to talk with their children about their scan and a prior reference for reassurance for preschool children who may wake up after arriving for their scan.

For infants, scans are scheduled during periods where the child is typically asleep (daytime naps or night). Toddlers and preschoolers will be brought, in pajamas, after their normal evening bedtime. Both parents and children are screened for contraindicated items (metal on clothing, implanted medical devices for parents). Children may be rocked or placed in cribs if they are not already asleep when arrive for their scan. Parents will be encouraged to use bedtime routines (feeding, reading, rocking) to assist their child in falling asleep. If children do not fall asleep within 60 minutes, the scan is typically rescheduled. Scans will be rescheduled up to two times before missing data is allowed for that child (see [9] concerning treatment of missing data in longitudinal imaging studies). Once asleep, young children will be transferred to the scanner bed. Infants will be swaddled during the scan and older children provided with blankets. Children are typically placed on their back, but other sleeping positions can also be accommodated if those are more typical for the child. Positioning may be assisted with rolled towels or styrofoam bead bags (which compress gently around the child as the air is removed from the bag) may be used with infants and preschool children. Earphone placement also assists positioning for toddlers and older children. When appropriate (given MR safety precautions), parents will be provided with hearing protection and invited to remain in the scanner room with their child. They may place a hand on the child's legs to reassure the child of their presence should the child awake during the scan. Parents may also monitor their child and alert the MR technician to signs of wakening or distress in their children. Children are monitored during the scan for overt movement, waking, or signs of distress. If a parent is unable to be in the room with the scanner, another study staff member will serve in this role. Young infants will also be monitored with pulse oximetry. If needed, children can be removed from the scanner within seconds and returned to their parents. Tangible reinforcers (such as stickers, pencils, model cars, etc.) are used to shape the children's compliance and cooperation with the functional tasks and imaging procedures.

For older children, we will use procedures that we have already successfully employed with over 400 children from 5 to 18 years of age [15]. Children and their parents arrived in the clinical area and were met by one of the investigators or the nurse coordinator. They watched an 8-minute video detailing the rationale of the study as well as the behavioral and task requirements while introducing the scanner and the associated computers and equipment. Female participants over the age of nine will be given a verbal pregnancy screening either on the day of desensitization (if this visit is needed) or on the day of the scan. This verbal screening will be conducted in such a way that the study staff does not outright ask the participant if she is pregnant, as this would put us in the position of needing to inform the parents. Instead, we will tell the participant that we will be asking about pregnancy, and inform her that if she feels uncomfortable being asked, it may be best if she refrain from participation.

For the over-21 adult cohort, we will ensure that they are comfortable with the small environment of the MRI scanner, and take steps to continue their comfort level. If someone is uncomfortable with the MRI and no longer wishes to continue, they will be removed immediately with no consequences for their decision.

On the day of each scan, children take a brief tour of the facility, including looking at the magnet, MRI head coil, patient bed, video goggles, and response system. They practice each of the "magnet games," by completing practice items on a personal computer that is next to the magnet console. The child practices each task until it is clear that he or she understands it. At this point, the child enters the magnet room and a systematic, step-by-step approach is used to introduce all of the equipment (headphones, push button response system, etc.) and procedures. In addition to the standard MRI equipment, the IRC uses an MRI-compatible audio-visual system (Resonance Technologies Inc., Van Nuys, California) that allows for presentation of high fidelity auditory and visual stimuli. In addition, popular videotapes are shown via the audio-visual system in order to distract and relax children during the portions of the scanning protocol that do not require their active participation. Typically, the child is provided with the video input as soon as he or she lies down on the scanner bed so that attention is already engaged with the program before entering the magnet. Once the child is acclimated to the scanner and demonstrated no overt signs of distress that would preclude the experiment, the scanning protocol begins. The technician visually monitors the child through the scanner bore and speaks with the child during the scan to let them know when the scanner noise will begin and whether the child can watch their video or must do one of the rehearsed tasks during this portion of the session. If the child produces overt movement, the scan is stopped. If movement was not due to stress, the session is continued with reminders to hold still. Otherwise the session is discontinued immediately.

Either on the day of desensitization or on the day of the first scan before entry into the magnet, each participant will undergo a neurological examination performed by a board certified neurologist, and also a hearing test. The hearing test will be administered by an audiologist and/or by the project coordinator and recruiter once they have received adequate training.

Participants who will be sleeping may have a combined EEG/fMRI on either one or both MRI visits. Directly before scanning, the MRI-compatible EEG electrode cap, provided with the Electrode Arrays system, will be applied to the participant. Electrodes will be secured with conductive paste, a gel like substance. Electrode placement is according to the standard 10/20 system and low electrode impedance will be confirmed (<20 kOhm). The participant will then be escorted into the scanner room and asked to recline in a

supine position on the bed of the scanner. Head padding specifically designed for this EEG-fMRI equipment will be used to decrease discomfort from the electrodes.

Participants ages 7-18 will participate in our active-response brain activation protocols. In our previous experience scanning children, we have found that 7-year-olds and up can successfully complete multiple fMRI tasks without excessive head motion in the scanner. These domains and tasks were chosen because of their track record of use as fMRI protocols as well as their potential for observing developmental changes across the selected age range. Participants in the over-21 population may be asked to participate in this active-response brain activation protocol.

Participants ages 7-9 will be asked to return for two longitudinal series of scans at one-year intervals following their initial scan. We chose to focus on this age range for our longitudinal cohort because this developmental period may reflect continued development in the domains of language (in particular, semantic processing) and attention (specifically, the ability to filter out irrelevant information).

In addition, participants ages 0-3 with successful scans will be asked to return for two longitudinal series of scans at one-year intervals following their initial scan. We chose to focus on this age range for our second longitudinal cohort because it has the ability to capture changes in development during the critical period for language, and also because our previous studies cover the age range of 5-18. Longitudinal data from 0-3 will complete the younger end of the developmental trajectory, contributing a valuable data resource to the field.

fMRI Tasks:

The language and attention tasks will involve the auditory or visual presentation of words, images, or sentences during fMRI scanning. The participant will be required to watch, listen and make judgments in response. Several tasks will be presented to each participant if time allows (i.e., the participant will not be in the scanner for more than 60 minutes in the standard version of the fMRI protocol). The tasks will focus on sentence and word comprehension, verbal memory, speech perception, prosody, and attention and are designed to activate left- lateralized or bilateral language networks.

In order to ensure an adequate fMRI data set, we will be scanning each participant on two occasions. The first scan session will focus mainly on the neuroanatomy and perfusion characteristics of the brain. The second scan session will focus more on functional imaging with a very basic anatomical component for fMRI overlay. In most cases, an individual scan will not exceed one hour, but the time may be extended if a scan needs to be repeated due to motion. No participant will be asked to remain in the MRI scanner when they are no longer comfortable. In addition, participants who are sleeping may have a scan that exceeds one hour to acquire both scanning sessions in one evening. This will only be done with the consent of the parents or legal guardians. In fact, individual scan sessions may be as short as 30 minutes, which can dramatically improve our success rates, especially in the younger cohort. If a participant is unable to make it through the first scan session, he or she will not be invited back for the second session and his or her study participation will be considered complete.

In addition to fMRI, we will be collecting EEG data in order to monitor sleep state. Determination of the level of attention in fMRI studies is of paramount importance. While task performance monitoring can provide indirect information regarding the level of wakefulness, EEG staging is the gold standard and utilization of the available in our center EEG/fMRI methods provides clear advantage over simple performance monitoring, especially in younger subjects where only passive fMRI tasks can be used. We intend on using ten electrodes in order to do this sleep state monitoring, with a board-certified electrophysiologist in attendance either throughout the duration of the study, or until he decides that other members of the study staff are knowledgeable enough to ascertain sleep states from EEG recordings on their own.

Neuropsychological Testing:

Measures of general intelligence and specific neuropsychological domains may be made for each participant in the study in a separate visit after the date of at least the first MRI scanning session, if not both. These measures will be used to characterize the cognitive function of the subject sample as well as to examine associations between functional MRI activation patterns and behavior.

In summary, our test battery will include tests in the following domains for most age groups, though some age groups (mainly the youngest) will not have testing in all domains:

- Intelligence
- Verbal fluency
- Vocabulary
- Verbal memory
- Visual-constructional ability
- Motor function
- Executive function
- Behavior

We anticipate that the neuropsychological test battery will take between 2-3 hours.

Separate EEG testing

A separate visit will examine EEG measures of the same fMRI tasks described above. A separate visit is required because the methods described above are optimized for fMRI and therefore not appropriate for EEG analysis of brain networks related to the task. The EEG recording described above is only used for the assessment of sleep rather than cognitive processes related to the task. In this visit, the EEG in response to the auditory or visual stimuli will be assessed. The sounds presented will be at a comfortable listening level through headphones or speakers. The subject will be asked to make decisions regarding the stimulus via button press, or will watch a movie while the sounds are presented in the background. This single session will last no longer than three hours. This length of time is required to get sufficient quality EEG signals. Unlike the MRI scanner, subjects are seated upright in a reclinable padded chair. They are encouraged to take breaks and walk around.

Near-infrared spectroscopy testing

Participants who are under 4 years old will be asked to participate in a scalp Near-infrared spectroscopy (NIRS) testing. NIRS is a non-invasive and easy to use method that does not require an MRI scanner and associated logistical complexities. Because of this validation of NIRS as a sensitive measure of cortical perfusion will provide new data supporting its clinical use in neonatal and pediatric ICU monitoring. These measures will be correlated with the cerebral blood flow measured by arterial spin labeling made during the MRI.

Prior to entering the MRI scanner, using a gentle tape-like adhesive, an infant FORE-SIGHT probe will be placed on the participant's scalp just behind the left ear, and a Vitamin E fiducial will be placed adjacent to the probe to provide for later correlation with the MRI image voxels. The patient will be allowed to settle to a resting/sleep state. NIRS measurements will be measured using the FORE-SIGHT NIRS system performing the same passive listening task that will be performed during the ASL-MRI measurement with 2 minutes of resting measurements before and after the task. Total measurement time will be approximately 15 minutes. The vitamin E fiducial will be removed after the MRI scan is complete.

5. *Surveys or Questionnaires:*

A questionnaire of neurological history will be administered as a part of pre-recruitment. This will be completed over the telephone by the recruiter and/or project coordinator. The process will be as follows: The recruiter and/or project coordinator will either receive names from the CTO or will receive a phone call from an interested family that has seen a posted flyer. The recruiter and/or coordinator will begin with a four-page questionnaire to determine eligibility. Families will be consented over the phone with a waiver of written consent for the information from this four-page questionnaire to be kept in a database and de-identified for all families, including those who do not participate. If the family meets inclusion criteria and is not ruled out by exclusion criteria, the recruiter and/or coordinator will mail the family a packet of materials which will include a description of the study, the consent form, and a child development questionnaire. In addition, the family will receive an outline of the full-length screening questionnaire, in order to facilitate the second phone call. During the second phone call, the recruiter and/or coordinator will go over the consent form with the family, answer any questions, and then conduct a more thorough screening questionnaire. Upon completion of this full-length questionnaire, eligibility will be determined by the study staff, and eligible participants will be brought in to the IRC facilities. See screening questionnaires attached in ePAS.

In addition, the participants in the longitudinal cohorts will be screened for any changes in their neurological history before scans 2 and 3. See Appendix A.

Sexual maturity data may also be obtained from each subject. Sexual maturation is known to influence development of the body, the brain and the neural circuitry underlying cognitive function. The least intrusive way for us to assess sexual maturity accurately for each participant is via a self-report questionnaire administered to the children (*Archives of Disease in Childhood* 1969 & 1970). This method for Tanner Staging has been found to correlate very highly with pediatrician examination and rating of Tanner Stage (*Pediatrics* 1980). The self-report questionnaire includes photographs and rating scales for each child to circle the number on the photo that best reflects their own body appearance. These questionnaires are included in Appendix B. This approach obviates a physical examination of the genitalia and breasts. Prior to asking the children to complete the self-report, permission is obtained from the parents. This request is included in the Informed Consent form, and the procedure is explained to the parents.

6. *Blood:*
   No blood will be solicited or drawn from the subjects as part of this study.

7. *Research overlap:*
   There are no other studies involving this specific cohort of patients and MRI scans. However, there is no restriction on participants and their families, should they be interested in participating in a concurrent study.

8. *Data Analysis:*
   fMRI BOLD image data sets will be processed on a computer workstation to calculate cortical activation maps on a pixel by pixel basis. A computer program developed by the Imaging Research Center at CCHMC (IRC) will be used to compute the 2D activation maps and to overlay them on anatomical MR images of the same plane. The program, Cincinnati Children's Hospital Image Processing Software (CCHIPS), written in IDL, uses statistical algorithms to estimate the areas of activation and confidence levels from the acquired images.
   A user-friendly package for analysis of ASL data will also be developed. The program will be based on the currently available ASLtbx processing suite [30] written in Matlab on the SPM2/SPM5 platform (Wellcome Dept. of Cognitive Neurology, London, United Kingdom).

   The package will enable analysis and display of results from either data from single subjects, or for groupwise analyses. The routines will be written in Interactive Data Language (IDL; ITT Visual Systems Inc., Boulder, CO) as IDL provides cross-platform capabilities and can run on Windows, Unix/Linux, and Macintosh operating systems. An interactive color display will be made available so the user can define ROIs, look at time courses, and output results in formats usable by Excel or SPSS software.

   The package will be made very user-friendly so as to be applicable to clinical as well as research applications. IDL is chosen, in preference to other high-level programming platforms such as Matlab, due to its superior processing speed, and ability to thread routines through multiple processors.

   EEG data will be acquired in this study. A high sampling rate is beneficial for EEG data collection and for the removal of the echoplanar imaging (EPI) artifact. EEG data reconstruction and analysis will occur using Neuromedia acquisition software for semi-automated removal of EPI and ballistocardiographic (BCA) artifacts and stimulus presentation software are integrated with the system. Curry software is also available (4 licenses) for post-processing of EEG source data, dipole source localization and co-registration with anatomical and functional MRI data.

   Convenient GUI-based routines will be available to implement batch processing (e.g. processing on several subjects, or several routines); the user will also have the option of creating/editing a text file with the details of the processing to be performed.

   Source code will be provided and extensively documented so research users may make their own changes to the code if needed.

NIRS data will be acquired in this study. The NIRS data will be processed using the NIRS Analysis Package (NAP) available in the public domain as a MATLAB toolbox to remove physiologic and movement artifacts from the NIRS background (49). The ASL-MRI data will be analyzed as described previously. The changes in normalized intensities of THb, HbO2, and Hb at the time of the participant's environment changes from resting state to passive listening will be plotted with respect to time and compared with the average ASL-MRI data from the voxels underneath the NIRS probe. Errors in the NIRS measurements will be calculated as the standard deviation of the NIRS signal between runs. The absolute THb, HbO2 and Hb for each participant will be correlated with the ASL-MRI signal intensity using a zero-lag correlation to determine if the ASL measurements most closely follow the HbO2.

9. *CCHMC Facilities:*

The study will be performed in the Imaging Research Center located on the R-level the new research building at the Children's Hospital Research Foundation. Access to the IRC is card reader restricted and only authorized personnel can enter. The recruiter/project coordinator will meet the subject and escort him/her to the IRC. Subjects will be escorted out of the building at the conclusion of the study, as well.

The separate EEG session will take place in the Communication Sciences Research Center (CSRC) located on the first floor of the new research building at the Children's Hospital Research Foundation. The recruiter/project coordinator will meet the subject at the CRSC at commencement of the study and will be escorted out of the building at the conclusion of the study, as well.

10. *Special Considerations:*

a) Radiation Safety – subjects will not be exposed to any ionizing radiation.

b) Investigational Drugs or Devices – no drugs will be used in this study. No device used in this proposed study requires IDE approval.

c) Scan Review and Reporting – The imaging protocol used in this study includes only the minimum MR scanning needed to test the tasks and paradigms research hypothesis for the project, as well as to test the equipment itself. Board-certified radiologists at CCHMC have determined that the limited anatomical images generated are not adequate to diagnose or to rule out pathology. No report will be generated or supplied to the research participants. However, all scans performed for this project will be reviewed for gross abnormalities by a board-certified or board-eligible radiologist through the PACS system. Although no diagnosis will be made, in the event that abnormal findings are identified, the PI be informed and will assume responsibility for notifying the participants. We will collect contact information for the primary care physician of each participant on the first visit. In the case that abnormal findings are identified, the participant's physician will be contacted by the PI, or a designee of the PI and the findings reported. A report generated by the radiologist will be made available to the physician if requested. All radiologists who review the images will be members of the study staff, therefore the only individuals who will have access to these findings will be study staff, and the participant's physician.

11. Withdrawals:

Participants will be made aware of their right to withdraw from the study at any time.

Methods to minimize attrition:

All participants will make three study visits, two for scanning and one for neuropsychological testing. The 45 participants in the 7-9 year old age group will be asked to return for two longitudinal follow-up series of scans at one-year intervals, as well as the 150 participants in the 0-3 year old age group. In any multi-session or longitudinal study, participant retention is crucial. We have found that participant attrition may result from several factors including loss of interest, inconvenience, moving out of town, an unpleasant experience associated with the study, or becoming ineligible due to change in health status. We have developed several strategies to maintain our study cohorts. The first step is in the recruitment process. The study details are fully described to potential participants so that they understand what is involved with participation in the study in terms of time commitment and types of activities. We also ask if they have plans to move from the area before the study is completed. Secondly, we develop ongoing and close contact between the participants and their parents. At each visit, the participant's current address, telephone number and school information and the parent's place of employment will be updated. In addition, the parents of the participant will provide information on one or more close contact individuals who will be likely to know of any changes in address or phone number. We also will provide the family with appropriate information to contact us if they move or if changes in scheduling are necessary. We will contact the family by email or by phone one week prior to the scheduled visit, and again by phone or email 24-28 hours prior to the visit to remind them of the visit and determine if there are any scheduling difficulties. We will send the participants cards each year on their birthday and periodic updates about the study. Incorporated in each of these contacts is the message that they and their ongoing participation are important and appreciated.

Careful choice of staff is also very important in minimizing participant attrition. Most of our research staff has extensive experience in the recruitment and maintenance of large cohorts, and they have been involved with recruitment and execution of several pediatric neuroimaging studies involving young children and adolescents. They have experience in working around busy family schedules and provide maximum flexibility for participants to be studied including evening and weekend appointments. In addition, we will offer an incentive of $50 for each study visit (3 visits total) to help compensate for the inconvenience, time of participation and to defray the cost of transportation. To maximize ongoing participation, we will provide round-trip taxi service for local participants who do not have transportation. Depending on the study population, we have found that up to 10% of participants need assistance with transportation. We have had excellent results in maintaining study cohorts. Our participant retention on our current 10-year study longitudinal study of language development is 84% (27 out of 32 original participants, see [9]).

12. Quality Assurance and Portability of Methods:

In order to complete one main component of NICHD's contract guidelines, we are required to develop methods that can be translated to different sites. In order to do so, quality control measures must be put into place.

In order to test the portability and replicability of our procedures, we plan to test the imaging and behavioral protocols at a second site beginning in year 3. With the assistance of Advisory Board members Dr. Arthur Toga and Dr. Jennifer Levitt, our project protocols as stated in the manual will be implemented at the Laboratory of Neuro Imaging in the Department of Neurology at UCLA. Data will be collected from 30 participants ages 7-9 in order to demonstrate the replicability of our protocols for structural imaging, ASL imaging and fMRI across sites and scanners. In addition, to demonstrate the feasibility of our desensitization protocol in young children, the UCLA site will also scan 10 children in the 0-3 age range.

After beta testing, changes to the procedures documented in the manual will be made, and procedures can be revised and discussed the annual project meeting at the end of year 3. A final version of the manual should be complete during year 4.

UCLA will be creating its own IRB protocol. Therefore, we maintain that this study does not qualify as a multi-site study, because the data is collected independently and no PHI is shared between CCHMC and UCLA. While our methods will be translated to another site, the data collected will be used mainly for quality control purposes. Should data be used as a part of the larger data processing, all identifiers will be removed *before* the data is seen by anyone outside UCLA. Only UCLA personnel will have access to PHI of those participants scanned at UCLA.

VI. Potential Benefits

There is no direct benefit to the participants enrolled in this research study. However, there may be perceived benefit on the part of these participants, as their altruistic participation may positively impact the scientific community as a whole. In addition, there may be perceived benefit in that the study participants receive free MRI scans, as well as medical, neurological and neuropsychological testing.

VII. Potential Risks, Discomforts, Inconveniences, and Precautions

There are no adverse effects identified to date from undergoing functional imaging studies.

1. *Known and Potential Discomforts or Hazards* – The suggested guidelines for the operation of clinical MR systems established by the FDA address three areas of control. They are:

a) Static magnetic field
b) Gradient switching speed.
c) Radio frequency power absorption by the subject.

a. Static Magnetic Field – The 3.0 Tesla static magnetic field strength of the scanners proposed in this protocol is below the 8 Tesla limit for clinical diagnostic MR scanners set by the FDA guidelines. The FDA has concluded that magnetic field below 8 T does not by itself impose a risk to human subjects.[200]

The FDA guideline for *Criteria for Significant Risk Investigation of Magnetic Resonance Diagnostic Devices* issued in 2003 also suggests magnetic field strengths up to 4T should be safe for infants.[45] In short, the FDA has approved the use of magnetic field strengths of up to 4 Tesla for MR scanning of infants and children in a research environment.

b. Gradient Speed – The FDA suggested rate of change of magnetic field (dB/dt) is 20T/sec. A 3T/sec limit is maintained by the scanner's security system on all three gradients. It measures the gradient currents in time steps of 100 microseconds. In the event that the maximum allowed values are exceeded, a signal is given to the operator console and the scan cannot be initiated. The operator must reduce the gradient strengths by increasing the slice thickness and/or the field of view before the scan can proceed.

c. RF Absorption Rate – The FDA guidelines for the specific RF absorption rate (SAR) is set by limiting the patient's core temperature rise to less than 1 degree Celsius. In the absence of core temperature monitoring equipment, the manufacturers have continued to use the previously established FDA limits of 2 W/Kg (average) and 8 W/Kg (peak). The security system of the scanners proposed in this protocol limits the SAR to 1 W/Kg. In order to monitor this value the RF energy at the output of the amplifier is measured over a period of 10 seconds. In addition to the average output power, the peak value is also monitored. In the event that one of these values is exceeded, the transmitter power supply is turned off automatically within 3 to 5 seconds. These measures ensure that the MRI system is well within the current FDA regulations on SAR.

2. *Discomfort –*

a. Mild to moderate discomfort may occur due to noise produced by the MR scanner. Earplugs and sound isolating headphones will be provided to reduce noise exposure to safe levels. In addition, subjects with known claustrophobic tendencies will be excluded. Visual and audio contact will be maintained at all times with the subject to determine the active physical conditions. Any subject who experiences discomfort or exhibits distress will be removed immediately from the scanner.

b. In the combined EEG/fMRI, some participants may experience mild discomfort from the electrode cap after wearing it in the MRI scanner for some time since head motion is limited. Special foam padding will be arranged with the electrode cap to minimize any discomfort. Any participant who experiences discomfort or exhibits distress will be removed immediately from the scanner.

c. For EEG testing, wearing the EEG cap for extended periods of time can cause some discomfort. Should any level of discomfort occur, the cap will be repositioned or removed.

d. During the NIRS testing there is a possibility of minor skin irritation from the NIRS monitor or the Vitamin E fiducial placed to mark the outline of the NIRS monitor on the MR images. There have been no reported rates of skin irritation in studies of neonates using the MC-2000 small sensor. There is also a possibility that the removal of the MC-2000 sensor may cause discomfort, though it has not been a

reported complication. If a participant is unable to tolerate the sensor or experiences discomfort they will not be included in the NIRS portion of the study.

3. *Precautions –*

a. Protection Against Risk –
All subjects and their families will be screened for compatibility with the MRI system using the attached CCHMC MRI Checklist. All subjects will be provided with ear protection in the form of foam ear-plugs plus insulated headphones. In addition, subjects will be given a "panic" button to hold during the scans. In the event that a subject becomes uncomfortable, he or she can press the panic button to notify the operator of the need for immediate attention. Intercom contact will be opened immediately and the subject can be removed from the scanner if needed. All data will be stored in secured storage spaces in the IRC with access to this data given only to the research team.

b. Method of Monitoring Study Conduct –
The study staff will report adverse events to Cincinnati Children's Hospital Medical Center Institutional Review Board using the Adverse Events reporting form found at the IRB website. It will be completed electronically and submitted to the Institutional Review Board in a hardcopy. The sponsor (NIH) and the Pharmacy and Therapeutics Committee, Cincinnati Children's Hospital Medical Center will also be informed of all adverse events.

c. Maintaining Data Quality and Confidentiality –
The main threat to the quality of MR images is patient motion. Each set of images will be checked for motion immediately following the scan. Image frames that are contaminated by motion can be deleted from the data set during the statistical image analysis stage. With regard to neuropsychological and behavioral testing, all test administrators will work under supervision of a licensed pediatric clinical neuropsychologist and work with young children on a daily basis. We do not anticipate any difficulty in obtaining high-quality data from CCHMC's competent and reliable staff. Confidentiality will be maintained by storing all scan data on secure, password-protected servers, which are located behind an electronic "firewall" in the CCHMC data center. Access to all hard copy records is restricted to study related personnel.

4. *Risk/Benefit Analysis* – The study poses minimal risk but provides no direct benefit to participants. There is no known risk to individuals from MRI or EEG under the conditions employed at this site. The benefit to the study is to the community at large and not specifically to the individual subjects participating in the project.

There may be some perceived benefit on the part of subjects and/or their families to receiving free medical, neurological, and neuropsychological examinations and MRI brain scans. This is more so true for subjects who may be friends or siblings of CHMC patients who have a history of neurologic problems. Results of testing and imaging will

be made available to the PCP and in some cases may result in early detection of neurologic illness.

VIII. Data Safety and Monitoring Board

The risks associated with this study are considered minimal and the IRB has classified the MRI imaging studies for research as minimal risk, thereby obviating a DSMP. However, due to the NICHD's contract requirements, a Data Safety Monitor (DSM) *will* be appointed for this protocol.

The risks of this study relate to MRI scanning, neuropsych testing, and confidentiality. In the event that any of these risks or other, unanticipated problems leads to an AE, such events will be reported to the IRB using the appropriate forms designated by the IRB. On a bi-annual basis, or at anytime an AE is filed with the IRB, the DSM will examine research notes and databases associated with the protocol. The study coordinator and PI will work with the DSM to make available data that specifically relates to the length of the MRI procedures, any deviations from the research protocol, and any AE occurrences.

If AEs occur, the DSM will be notified at the same time the events are reported to the IRB. This will trigger an interim data review by the DSM. Data records relevant to the AE will be reviewed with the PI, coordinator and other members of the research team to determine whether an unanticipated risk may have been overlooked by the initial protocol.

Stopping Rules – If the DSM determines that AEs or other unanticipated risks for this study exceed the risk categorization of this protocol by the IRB, then the DSM will convene a panel to determine whether the study should be stopped, pending full review by the IRB. The panel will consist of the PI, DSM, and representatives from the IRC, Pediatrics and Radiology. This 5 member ad-hoc panel will make a recommendation to the PI and the IRB as to whether the study should be stopped.

IX. Privacy and Confidentiality

Participant information and behavioral/neuropsychological data will be kept in a secure location in the Pediatric Neuroimaging Research Consortium at CCHMC, accessible only to study personnel. Imaging data and electronic records of behavioral data will be kept on a secure password-protected server in the Imaging Research Center at CCHMC, also accessible only to study personnel. Each participant's electronic format data will be randomly assigned a unique participant ID number, and the list of ID numbers corresponding to participant names will be accessible only to the PI. The data will be de-identified for those who do not participate.

Strict confidentiality of research records will be maintained by the study personnel in order to protect the privacy of participants. If the results of the study are reported in medical journals or at scientific meetings, research participants will not be named or identified. Information will not be released about the participant's research involvement. The Cincinnati Children's Hospital Medical Center Institutional Review Board may have access to the records from this study.

X. Period of Time Estimated to Complete the Project

This project is expected to be completed in five years, although further data analysis, journal articles, and presentations may be accomplished after this time. All initial preparation and

protocol development is projected to be finished by the end of the second year of funding, and all data acquisition is projected to be completed by the middle of the fifth year. Data analysis and development of generalizable methods will be ongoing throughout the project, but finalization of data dictionary, project documentation, and software development should be completed after five years. During the collection of data, a secure database will be created behind the CCHMC firewall to store data collected throughout the study. This data will be accessible to CCHMC study staff, as well as sub-contract and other sites. No PHI will be included in this database. Upon completion of contract obligations, data will be part of a larger pipeline and repository, which will allow for continued analysis. Upon entrance in this larger repository and pipeline, modeled after UCLA's LONI Pipeline, identifiers will be removed and subjects will be coded using the subject IDs given to them at their entrance into the study. No PHI will be retained in the future repository.

XI. Funding

This study will be funded through an NICHD contract HHSN275200900018C through 2014.

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XII. Payment for Studies

A compensation of $150 dollars will be offered to each family for their participation in this study. Fifty dollars of this compensation will be in the form of a cash reimbursement to the family for travel to and from CCHMC and parking fees in connection with the first two visits for the MRI scanning. For longitudinal participants, $100-150 will be offered to each family each year they participate in the study. Ideally, if they participate all three years, they will receive approximately $350 in total. We believe this compensation will be necessary in order to help families to justify the three visits to CCHMC and approximately five hours of their time required to participate in the study for the cross-sectional cohort, and the seven visits (six scans and one neuropsychological testing session) for the longitudinal cohort.

If the family chooses to participate in the EEG testing, $50 in compensation for travel and parking will be offered.

Participants in the over-21 adult cohort will not be offered monetary compensation for their time.

XIII. Process of Obtaining Consent

Parents of all potential subjects will be informed of the study protocol, risks, and benefits. If they desire to participate and have had all their questions answered, the parents will sign an IRB-approved consent document. This consent also describes the rights of research subjects and patients under the Health Insurance Portability and Accountability Act (HIPAA) and includes a full disclosure of the use of protected health information (PHI) for the purposes of the research study. The parents will be given telephone numbers and email addresses to contact the study team with any questions, concerns, or the desire to withdraw from the study. They will also be provided with the telephone number of the Institutional Review Board. Children age 11 and above will also be asked to sign an Informed Assent Form. Participants who are 18 years old and older will sign Informed Consent for themselves.

XIV. Vulnerable Populations

Children and adolescents (considered a vulnerable population) will be included in this study. We will require both the assent of the child/adolescent and parental consent for participation in the study in order to respect the right of the children/ adolescents not to participate in the study. They (and their parents) will be made aware of their right to withdraw from the study at any time.

XV. Correspondence

Correspondence between participating families will be conducted with the project coordinator and recruiter. Participants will have access to contact information of study personnel through the various recruitment strategies that we employ. Participants may also be referred by physicians during well-child or well-baby visits, in which case permission will be attained from physicians prior to contacting participants and their families.

Copies of the approved research protocol, consent forms, and all correspondence and changes pertaining to the study protocol or consent forms will be maintained in a cabinet in the Pediatric Neuroimaging Research Consortium, Location: S5.100.

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Appendix A: Neurological Questionnaire

Neurological Status Questionnaire

This year we are going to ask you some questions to assess any changes in your child's neurological status. This is in place of the full neurological exam.

Has your child ever:

Taken Ritalin, dexedrine, Adderall	YES	NO
Had speech therapy	YES	NO
Had an IEP or 504 or been in special classes in school?	YES	NO
Repeated a grade	YES	NO
Had hearing loss/hearing aids	YES	NO
Had changes in vision or hearing	YES	NO

Have ever been diagnosed with:

ADHD	YES	NO
Headaches	YES	NO
Seizures	YES	NO
Head injuries	YES	NO
Brain infections	YES	NO
Fainting	YES	NO
Balance or coordination problems	YES	NO
Mood problems such as depression or anxiety	YES	NO
Learning disability	YES	NO
Tics or movement disorder	YES	NO

Comments: (If Yes, write details here)

_____
_____
_____
_____
_____
_____
_____

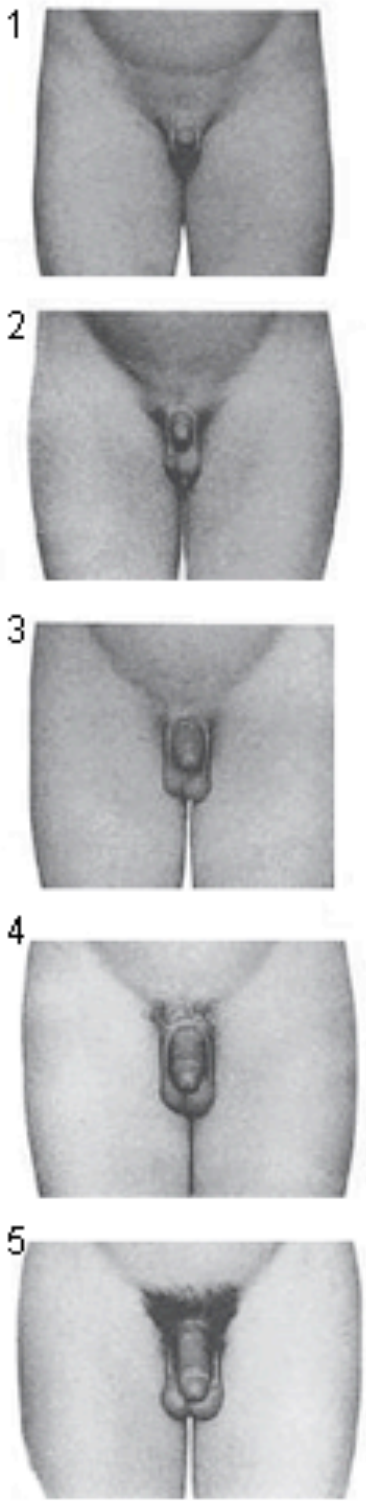
Appendix B: Tanner Staging of Sexual Development

Tanner Scale for Boys

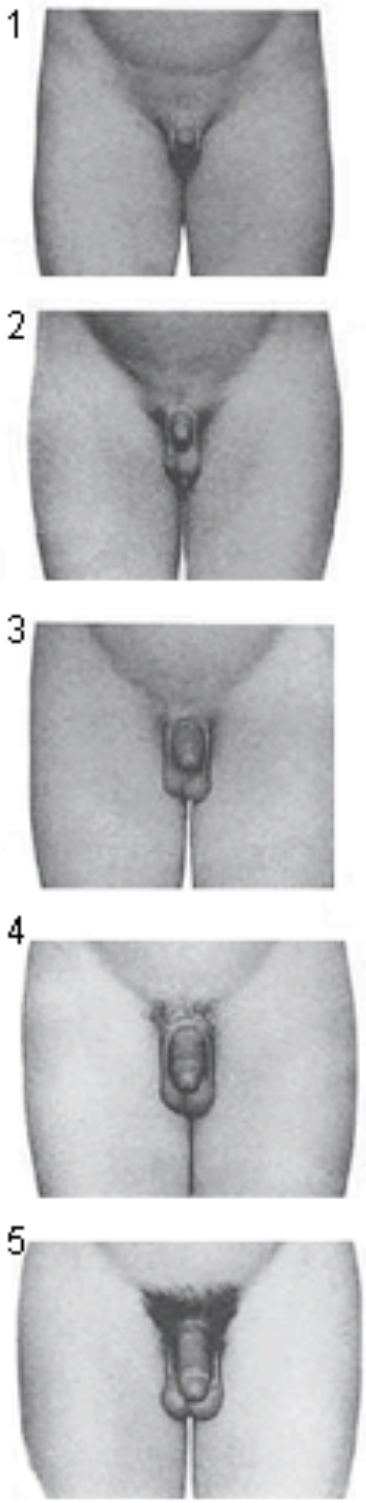
Participant ID:_____

Date:_____

Administered by:_____



Please Circle the Picture that looks most like you



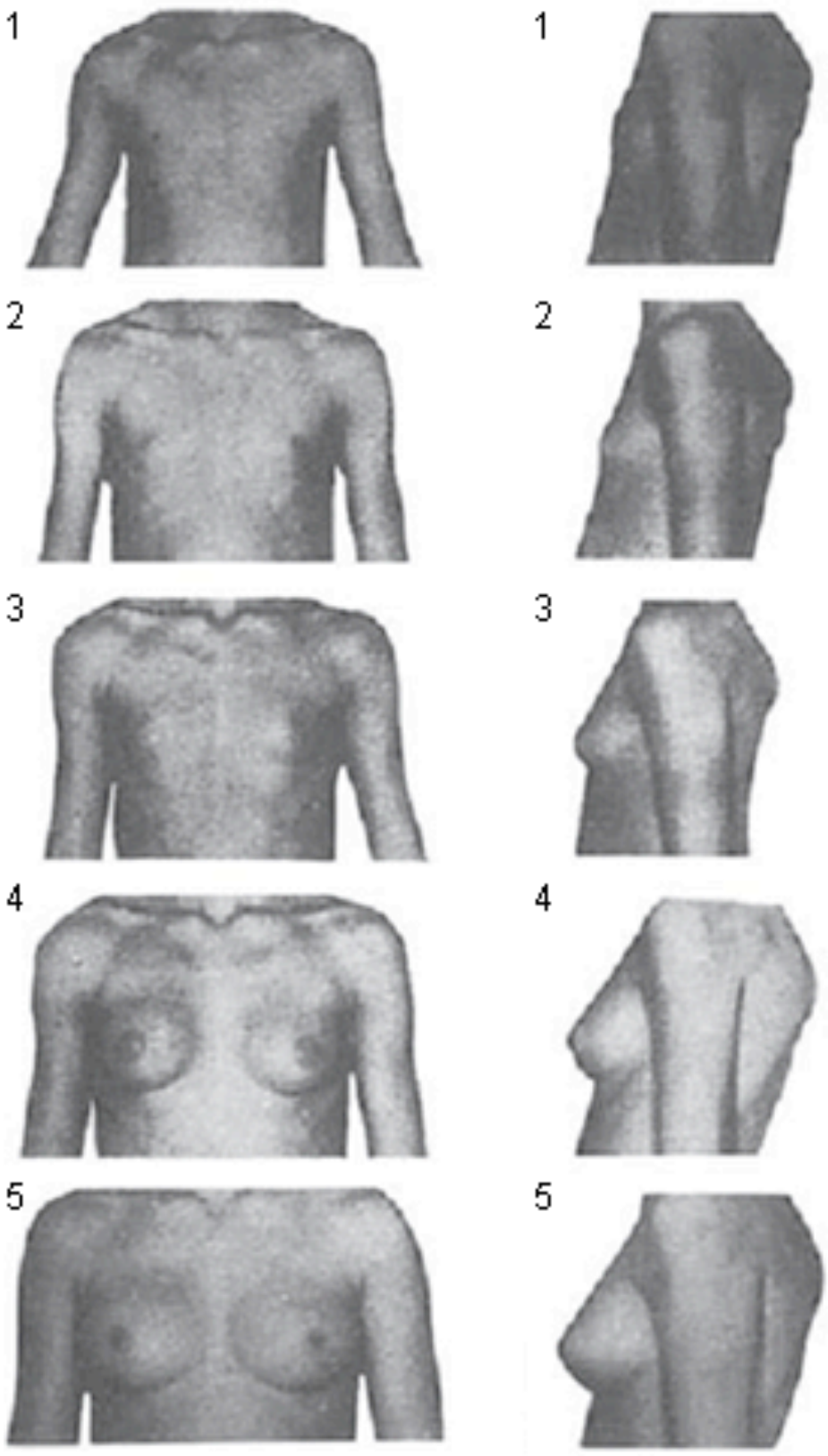
Please circle the picture that looks most like you

Tanner Scale for Girls

Participant ID_____

Date_____

Administered by_____



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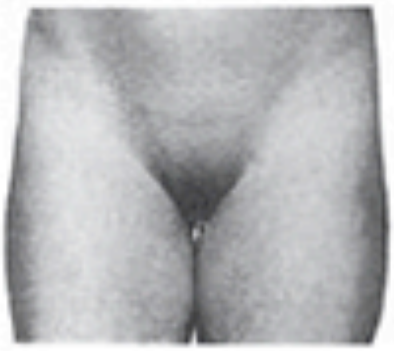

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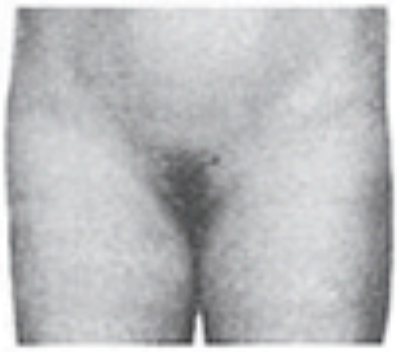

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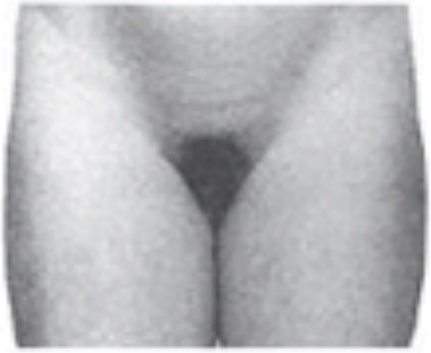

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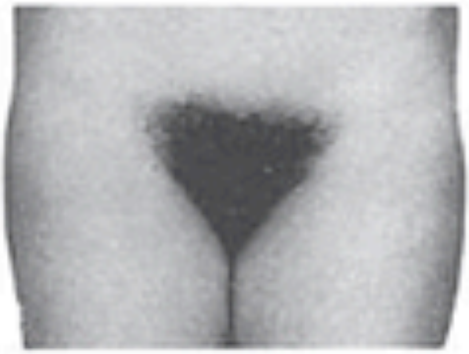

Please circle the picture that looks most like you