

Research Project Proposal

Date: 12/1/1998

Project Title:

Auditory and Visual Functional MR studies in Sedated Children

Start Date: 12/1/98

Amount of Support Requested: 46,600

Completion Date: 12/1/99

Principal Investigator:

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Co Investigator:

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Applicant(s), upon signing below, agree to abide by Miami Children's Hospital Research Program's policies on research grants.

Signature (PI)

Signature (Co PI)

ABSTRACT OF PROPOSAL

Must not exceed one page

Name of Principal Investigator: Nolan R. Altman, MD

Title of Project: Auditory and Visual Functional Magnetic Resonance Imaging (fMRI) Studies in sedated children

AIMS

The specific aims of this project are to:

1. Develop protocols for functional MR imaging to demonstrate auditory and visual (A &V) cortical activation in sedated children.
2. Investigate the normal developmental changes in localization and organization of auditory and visual cortices.
3. Investigate the effects of brain lesions on localization and organization of A&V cortex in infants and children.

Hypotheses

- Functional MR imaging A&V cortices can be reliably performed in sedated children, using the appropriate technology and paradigms.
- Along with normal neurological development there are changes in cortical activation.
- The effects of lesions involving sensory visual and auditory cortex in children, depend on the type of lesion and time of insult.

Significance

- Demonstrate activation of cortical A&V areas in sedated children to provide tools to assess developmental disorders in early childhood improving treatment outcomes.
- The ability to dynamically image auditory and visual functions in children of various ages will provide insight into cortical systems that underlie normal and abnormal spatial, speech and language neural networks.
- Lateralized activation achieved on basic sensory stimuli might be an early marker of language asymmetry, a critical aspect for surgical planning of brain lesions.

Other Research Support

- **CURRENT SUPPORT:** For each professional named in Budget, give source of support, project title, name of principal investigator, individual's percent of effort, period of the time covered, and direct costs for entire period of grant.
- **PENDING SUPPORT:** For each professional named in Budget, list all applications pending. State whether this application is to be considered an "either/or" pending another application.
- **PRIOR SUPPORT:** _____ YES NO

Please list grant number, year, title of project and amount.

Co-investigator of Project

Nolan Altman, MD

Chief, Department of Radiology

Director, Neuroradiology, MCH

Areas of expertise: neuroimaging, functional MRI, developmental disorders.

Byron Bernal, MD

Research Specialist, Department of Radiology

Neurologist

Short title of Project.- Auditory and Visual fMR in sedated patients.

Area of Project Research.- Functional imaging, developmental neuroscience.

Project duration.- 1 year

If the project is approved, when will it start?.- December 1, 1998

Where will the project be carried out?.- Miami Children's Hospital, Radiology Department

Will the participation of other institutions or agencies be required?. - No

Expertise of Investigators

The Neuroimaging Group at Miami Children's Hospital (MCH), headed by Dr. NOLAN ALTMAN, has been involved in the development of paradigms for sensory, motor, and cognitive mapping of the brain for the past two years. They have already purchased and installed scanner hardware necessary to perform functional MR image at MCH and have ongoing close collaborations with physicist, engineers and data managers. The pilot functional MR imaging studies already in progress confirm the feasibility of achieving high quality functional MR imaging at MCH.

Certification for protection of human subjects and care and

treatment of laboratory animals

Name of the principal investigator: Nolan R. Altman, MD

Title of proposal: Auditory and Visual Functional MR studies in Sedated Children

Human subjects: Safeguarding the rights and welfare of human subjects is the responsibility of the Principal Investigator and (if applicable) the sponsor. No applications for research involving human subjects shall be reviewed unless the application for such support has been reviewed and approved by an appropriate institutional review board.

Initial the application statement:

This application does not propose activities involving humans.

This application proposes activities involving humans and has been reviewed and approved by the MCH Institutional Review Board on (date) _____ in accordance with current NIH policy.

Laboratory animals: The proper care and humane treatment of laboratory animal is the responsibility of the Principal Investigator and (if applicable) the Sponsor. No application for research involving laboratory

animal shall be reviewed unless the application has been reviewed and approved by an appropriate institutional, committee.

Initial the applicable statement:

This application does not propose any activities that would involve laboratory animals.

This application proposes activities involving laboratory animals and has been reviewed and approved by our institutional committee on (date) _____ in accordance with current NIH policy. List species of laboratory animals to be used.

Background

Cerebral cortex localization in children

Regional specialization of the cerebral cortex with respect to neurological functions is well established from anecdotal lesional and cortical electrode mapping in adults and children. Primary visual areas are located in the calcarine fissure of the occipital lobes, while secondary areas lie in occipital poles and parietal cortex. The primary auditory cortex is located in the transverse temporal gyrus or Heschl's gyrus, while the secondary auditory cortex is in surrounding regions of the superior temporal gyrus.

These cortical regions function as a system, having important connections with each other as well as with motor, sensory and association cortex. These connections emerge in a stepwise fashion with normal brain maturation characterized by synaptic proliferation, synaptic elimination along with myelination of the white matter.

In visual functions primary areas will serve as foundations for the future visuo-spatial perception skills. The primary auditory functions will facilitate language and verbal skills. It seems clear that early damage or insults to these areas produce pathology in childhood cognitive development, such as learning disabilities.

Lateralization is felt to be a dynamic process in the infant and childhood brain. Functional MR studies have shown in adults for pure tone stimulation there is asymmetry in the function of auditory cortex. (Millen S et al., 1995) Language, that ultimately develops from auditory capabilities, is a lateralized function of the left hemisphere, in most people. In very young children, damage to critical language cortex may cause language function to transfer to homologous areas in the opposite hemisphere, leading to development of normal language (Cummings JL, 1979). In contrast, similar insults occurring in older children and adolescents are not usually associated with recovery of function due to limited brain plasticity. Face recognition and spatial orientation are complex visual functions, and felt to be lateralized to the right hemisphere. It may be possible that these functions can also be transferred if the insult is early. This may be able to be documented with fMR technology. Neuropsychiatric disorders have been investigated with various modalities. Auditory and visual neurophysiologic studies have been found abnormal in hyperactive patients. (Jonkman LM et al. 1997) Previous studies of auditory evoked responses in newborns have shown a high degree of accuracy in prediction of relatively minor deficiencies in language abilities 4 years later (Molfese, 1992). More recently fMR studies of visual function in adults have shown an abnormal pattern in patients with dyslexia (Eden GF et al., 1996).

Functional Magnetic Resonance imaging

Brain activity in fMR is based on the observation that increased neural activity leads to an increase in localized cerebral blood flow, blood volume, and blood oxygenation. In fMRI this technique is referred to as Blood Oxygen Level Dependent (BOLD) contrast. As an area becomes activated i.e. left primary motor cortical activity in relation to right hand finger tapping, there is a surplus delivery of oxygenated blood to the active cortex. This leads to a relative predominance of oxyhemoglobin and a decreased concentration of deoxyhemoglobin. This drop in relative deoxyhemoglobin concentration in turn leads to increased signal detectable by appropriate quantitative analysis of the MR scan data. Application of statistical processing methods to the timed series of signals from each voxel in the brain obtained during

an experiment permits optimal extraction of the signal of interest, i.e., task related activation, from background artifacts and noise (Frackowiak 1997, Bandettini 1993).

In a typical experiment a patient lies within the scanner and cannot receive real-life stimuli. Instead, they are given special goggles and earphones through which they receive visual and auditory stimuli. A subject may also be asked to perform a motor task (for example, to repeatedly tap their fingers in a specific sequence).

During an experiment, a sequence of 3-10 images per second are acquired from the MR scanner. Each image represents a cross section of the subject's brain. Contiguous slices represent volumetric images of the brain. The head must remain totally immobile while collecting the multi-slice images. Four hundred or more consecutive scans of the entire brain are collected during one experiment.

Recent advances in fMRI permit high spatial and temporal resolution mapping of neuropsychological functions, thus increasing our understanding of the relation of specific brain regions to the performance of complex cognitive, language, and sensory motor functions. Computer advances in multimedia tools, virtual reality, and image processing can play an important role in extending the applications of fMRI to routine clinical situations.

Functional Magnetic Resonance in Children and infants

Tasks used in functional magnetic resonance are either active or passive. Active type tasks require the patient cooperation in doing specific motor, attention or discrimination actions. Passive tasks are performed without the patients cooperation..

Commonly adults and children up to 6-9 years of age can perform an active task.. Younger children have problems with cognitive tasks that demand immobility and lengthy fixed attention in spite of the presence of loud noise from the magnet. Infants, of course, can not cooperate at all in this environment..

Several fMRI studies have been published of children older than 5 years of age who were awake during the examination. (Casey B et al., 1998; Chapman P et al., 1995; Zilbovicius et al, 1998; Hertz-Pannier et al, 1998). To our knowledge only two studies have been done in infants and newborns: Sie and coworkers using visual stimulation (Sie LTL, 1998) and Hirsh's group using passive listening of mother voice and, independently, visual stimulation (Hirsh, 1998)..

Functional Magnetic Resonance and sedation

The main concern about fMRI in young children is whether the sedative drugs or anesthesia need to provide a motionless environment will reduce or extinguish the cortical activation. Antognini JF (1997) has found that Isoflurane anesthesia blunted cerebral responses to noxious and innocuous stimuli. In addition anesthetic and sedative drugs might produce reduction of the cerebral blood flow or the brain metabolism. Propofol induces a 35% decrease in CBF velocities and 10% cerebral oxygen extraction (Ederberg S. et al 1998). Phenobarbital decreases the local cerebral glucose utilization in some areas of the brain (Ableitner A et al, 1987) but is not associated with significant changes in cerebral flow velocity (Saliba E. Et al., 1991). Midazolam-fentanyl (an analgesic) reduces cerebral oxygen metabolism rate by 26% (Olsen et al, 1992). Information on the effects of chloral hydrate in brain metabolism or CBF is unknown. Propofol was used successfully by the Hirsch group in infants between 15 and 39 months of age.

In the neurophysiology EEG service at Miami Children's Hospital there has not been observed reduction in EEG amplitudes or significant changes in the evoked potentials with using chloral hydrate or Nembutal (Personal communication).

Functional Magnetic Resonance in MCH

Over the past two years the neuroscience group at MCH has been working to establish protocols for functional MR imaging of motor and expressive language in children and adults using standard neuropsychological tasks and conventional echoplanar imaging (EPI) MR imaging. The verbal task

consists of a paradigm where the subject is asked to think of words beginning with a given letter, while lying motionless with eyes closed in the MR scanner. This protocol has been used to assess language dominance in patients undergoing WADA (intracarotid amytal) testing and epilepsy surgery. This has also been performed in normal volunteers. All subjects showed cortical activation, characteristically in the inferior frontal lobe, the anterior cingulate region and the posterior parietal region. Lateralization was confirmed with Wada testing in the epilepsy patients. In addition, the protocol has been shown to be reliable in retest situations and has been used to study the exact relationship between physiological changes in cerebral blood flow and changes in MR signal. Motor paradigms have been successful showing activation of hand, foot, Broca and eye movement (research investigators). The fMR exams utilized a gradient EPI single shot sequence. (TR 3000/TE 60, 10 mm slice with 2 mm space, 64x64 matrix, 1 NEX, 24x24FOV). Axial or coronal slices are obtained depending of the task.

To date, several cases have been examined with the aim of mapping language or motor areas as a tool useful for both presurgical planning and intraoperative localization. Functional MR has shown so far to be practical and reliable in clinical settings.

Research plan

Equipment and technological aspects

MCH has a General Electric (GE) 1.5 Tesla machine, with EPI capability and appropriate receiver coils. In addition there is a workstation to perform statistical data analysis and image coregistration and display. Currently there is a second mobile GE machine with similar capabilities but some restrictions in connectivity with the local processing net.

The current multimedia equipment for visual and or auditory stimulation shows obsolescence.. Basic auditory stimulus need to be controlled, both in intensity and frequency. To guarantee cortical activation in infants it may be necessary to present mothers voice to the sedated infant. The current technology employs long tubes extending to the earphones which cut off high frequencies and amplitude of the signal. In addition the loud noise of the magnet must be reduced as far as possible in order to prevent cortical saturation. The new device requested provides for digital noise cancellation and mechanical insulation that reduces noise significantly. The current projection screen used to display visual stimulation needs open eyes and active fixation of the patient and offers poor resolution. For stimulation of sedated subjects it is necessary for goggles to provide the necessary strength of the signal. In addition, for stimulation of these cognitive areas it is extremely important that the functional media equipment accept input from a multimedia computer where the tasks have been designed. The computer is also necessary to create, tailor, store and display auditory, visual and cognitive tasks.

Paradigms

Auditory paradigm.- Stimuli will be tones, voices, musical or environmental sounds. An example of a pure tones paradigm is a series of 4 kHz of 500 Ms. (5 Ms. linear rise and decay time) with interstimuli silent time of 200 msc, presented in episodes (epochs) of 30 seconds. Tones will be presented at 70 dB sound pressure level(SPL) to ensure listening. Tones can be presented at different frequencies trying to activate the more extensive areas of the cortex. Each run will consist of 6 cycles with 12 epochs, 6 in activation (ON) and 6 in "rest" (OFF). Each epoch will have 10 sets of images at 4 locations. The total number of images is 480.

Visual Paradigm.- Consists of 8 Hz photic LED stimulation via goggles placed over the child's closed eyes. The number of images and arrangements in cycles and epochs are similar as described above.

Standard statistical techniques for comparison of average baseline and stimulation signals for single voxels will be applied to reveal locations of active cortical areas.

Source and criteria of selection

We propose to study a representative sample of children recruited from patients undergoing MRI at MCH as a diagnostic procedure or follow up, either in otherwise normal or abnormal subjects, younger than 9 years of age. Into the abnormal group will be included patients with seizures, vascular malformations, tumors, dysplastic lesions, but without motor, sensorial, visual, auditory or mental substantial or notorious deficit. The sample will be divided into four age groups: (i) before 1 year, (ii) 1-2 years, (iii) 3-5 years and (iv) after 5 years. These groups are based on current knowledge of brain maturation milestones. Only children with normal vision or hearing will be included in the study. A previous study of evoked potentials will be necessary of all children. Children with metal pacemakers, or a certain type of metallic clips in his/her bodies will be rejected. As in all regular procedures with magnetic resonance, all metallic objects will be removed from the patient prior to approaching the high field strength magnet. The experiment wont be applied in each case of unusual long standing in bore for the requested examination. Similarly, the task will be stopped in any case of insufficient sedation used for the medical purpose of the examination. Informed consent will be obtained from all parents.

Planned studies

1. Development of protocols for functional MR imaging of sedated children activating auditory and visual cortices.

Functional MR imaging will be conducted immediately after the conventional examination requested for the physician. Thus, it will be performed in a single session lasting approximately 10-15 minutes, with the patient still sedated for the initial procedure. Patients will be sedated with Phenobarbital (2-8 mg/kg) or Chloral Hydrate (100-150 mg kg). The paradigms as described above will be initially employed with modification as deemed necessary to obtain the best results. Functional MR data will be analyzed and processed using statistical software developed for functional MR analysis..

2. Investigate the normal developmental changes in lateralization, localization and organization of auditory and visual cortex.

The localization and magnitude of the cortical activations will be averaged into the age groups and compared between the groups looking for patterns of normal development. Cortical activation by chronological age, will also be analyzed with respect to "developmental age". Follow up of cases will demonstrate intrasubject normal developmental changes..

3.- Investigate the effects of brain lesions on localization and organization of A&V cortices in infants and children.

The same paradigms applied to the group of diseased patients will serve to assess cortical visual and auditory activation. These subjects will be recruited prospectively through the neurology, neurosurgery and radiology departments of the Miami Children's Hospital. The V&A activation in this group will be analyzed with respect to location of lesion, type of lesion, age of neurologic insult, presence of seizures and age of the subject. Issues of relocation of the A&V activation as related to these lesional cases and cerebral plasticity will be studied.

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