The NIH MRI Study of Normal Brain Development

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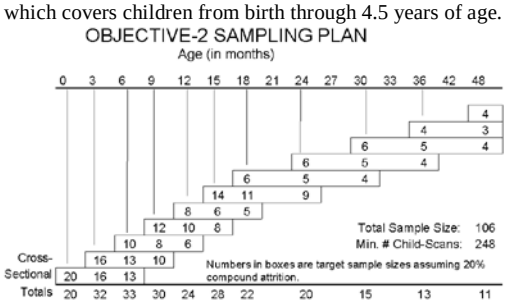
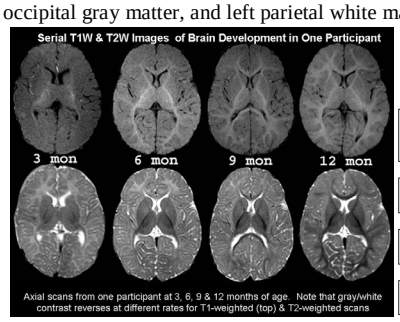
Introduction: The NIH MRI Study of Normal Brain Development is the most comprehensive and rigorous study of human brain and behavioral development ever conducted. This is a multi-site research project using a combined longitudinal and cross-sectional design to map brain-behavioral development of normal children from birth through 18 years of age. The project is funded by NIH (NINDS, NICHD, NIMH, and NIDA), and includes seven Medical Centers (Boston, Philadelphia, St. Louis, Cincinnati, Houston, Los Angeles, and Montreal). This abstract deals with Objective-2 of this project, which covers children from birth through 4.5 years of age.

Methods: A demographically-representative sample of 64 children (to date) have received repeated brain scan plus behavioral studies between birth through 4.5 years of age. Infants and children were recruited via hospitals and community organizations, and each subject received at least three 'scans plus testing' at 3, 6, or 12 month intervals. A comprehensive neurobehavioral testing battery includes age-appropriate standardized and experimental assessments and was administer to each child to validate "normal/typical" neurobehavioral development of the study sample. Neurobehavioral testing: The neurobehavioral testing battery included assessments of neurological status, development, intelligence, cognition, language and verbal fluency, learning and memory (both language and performance), problem solving, and fine-gross motor abilities. In addition, parents provided information about their child's developmental status with regard to behavior, temperament, the parent-child dynamic, as well as the psychiatric status of first degree relatives of the child. MR Scanning: All scans are performed without sedation at 1.5 T using a circularly-polarized radiofrequency head coil. The core of the MR protocol is designed for image segmentation. A 2D T1-weighted multi-slice (MS) spin-echo (SE) is a practical compromise. Images are collected parallel to the AC-PC line with a 1x1x3 mm spatial resolution. Whole brain coverage is accomplished in less than 5 minutes. The T1-weighted scan is given highest priority and if there is subject motion, the scan is repeated until artifact-free data are obtained. The second set of scans for image segmentation are proton density and T2-weighted (PD/T2W) images acquired to match the orientation, spatial resolution and slice locations established by the T1-weighted acquisition. This is accomplished with a fast/turbo spin echo acquisition. The PD/T2W images are generated in less than 5 minutes. Again, the scans must be repeated until they are motion artifact-free before moving to the next phase of the MR protocol. The T1W and PD/T2W images constitute the minimum dataset for a successful MR exam. Following completion of the core structural MR sequences, the protocol emphasis shifts to relaxometry. For T1 relaxometry, an inversion recovery (IR) sequence developed by Haselgrove, et al. (JMRI, 11:360-367, 2000) was adapted for this study. The image acquisition in the IR sequence is single shot fast/turbo spin echo (SSFSE/HASTE) or, less frequently, echo planar imaging (EPI). The images are acquired to match the 3 mm slice orientations and locations established by the T1W and PD/T2W acquisitions. In-plane resolution is reduced to 2 mm as dictated by single shot readout. For T2 relaxometry, good quality multi-component T2 relaxometry could only be performed one slice at a time using 32 or more echoes and at least 6 minutes/slice. This is impractical in a sleeping child. The investigators prioritized whole brain coverage over the established accuracy of the single slice multi echo method. Therefore, the protocol incorporates a dual (effective) echo fast/turbo spin echo acquisition to estimate T2 for a single compartment model throughout the brain. The PD/T2W structural imaging sequence serves double duty in this regard. A second FSE/TSE sequence is added with an intermediate and very long echo time, which improves the T2 estimate in the youngest children who have very long T2 relaxation times. However, this second acquisition is deemed lower priority to the ancillary aims of DTI and MRS. Thus the second dual echo acquisition is acquired as the last element of the imaging protocol. Again the second dual echo image acquisition is acquired to match the orientation, spatial resolution and slice locations established by the T1-weighted acquisition. Imaging time again runs about 5 minutes duration. Diffusion tensor imaging (DTI) data are collected on a subset of the cohort. The images are acquired on a 3x3x3 mm matrix covering the entire brain. Single shot, spin echo diffusion-weighted images are acquired using an echo planar sequence. DTI is obtained in separate acquisitions: b=0, 1000 s/mm2, and b=0, 500 s/mm2. The gradient orientations are the standard 6 direction set. Two acquisitions of the b=0, 1000 s/mm2, two acquisitions of the b=0, 500 s/mm2, and finally two more acquisitions of the b=0, 1000 s/mm2. A subset of the cohort also is studied with MRS. A moderate TE (TE 144 ms) PRESS acquisition, with voxels measuring 15x15x15 mm (3.375 cc), and 64 signal averages produces acceptable SNR spectra in a scan time of ~3 minutes per voxel. Four voxels of interest were identified corresponding to the left frontal white matter, thalamus, occipital gray matter, and left parietal white matter.



Results: Longitudinal MRI studies of individual subjects (see adjacent figure) illustrate dramatically the dynamic maturational changes in anatomical contrast. The table (right) is an example of an Objective-2 Progress Report that is prepared at approximately two-week intervals and is used to track progress of recruitment, screening, exclusions, refusals, and progress for numbers of subjects successfully brain scanned+behaviorally tested. This tracking ensures that a demographically representative sample of subjects is obtained for the project. Approximately 60% of attempted scans result in data suitable for subsequent quantitative analysis. About 30% of the scans fail because the child wakes up. The rest of the scan failures are related to excessive motion of the sleeping subject during the MR acquisitions.



OBJECTIVE–2 PROGRESS REPORT (AS OF 10/01/04)

	Boston	Saint Louis	Totals
SAMPLING PLAN (number of subjects/site)	**46**	**60**	**106**
SCREENED SUBJECTS	1898	1138	3036
TOTAL EXCLUDED	1746	992	2738
% EXCLUDED	**91.9%**	**87.2%**	**90.2%**
TOTAL REFUSED TO PARTICIPATE	127	107	234
% REFUSED	**6.7%**	**9.4%**	**7.7%**
CONSENTED, SCANNED & TESTED	25	39	64
% SUBJECTS	**1.3%**	**3.4%**	**2.1%**
TOTAL NUMBER OF SCANS COMPLETED	**53**	**123**	**176**
AVERAGE NUMBER OF SCANS/SUBJECT	**2.1**	**3.2**	**2.8**

Discussion: Initial segmentation will be performed manually as there are no automated algorithms to accurately segment the MR scans from young children. Volumes obtained will provide data suitable for construction of growth curves that span then entire project (1 week to 18 years of age). Future work will focus on development and validation of automatic image segmentation methods. Established algorithms will be used to quantify T1 and T2 relaxation times. The combination longitudinal and cross sectional design will help establish the definitive reference for relaxation times in children between 1 week and 4 years 5 months of age. The isotropic spatial resolution and whole brain DTI acquisition will allow unbiased characterization of white matter maturation from infancy through adolescence. Analysis of the moderate TE MRS from the voxels in the white matter, cortical gray matter, and thalamus will provide the reference standard for Choline Creatine and N-acetylaspartate throughout brain development.

Conclusion: The results of this project will include determination of normal brain growth curves, and associations among growth of the brain and specific brain regions and neurobehavioral testing performance scores With about 50% of the Objective 2 cohort enrolled and 70% of the scans performed, we have demonstrated definitively that is feasible to obtain high quality MR scans from unsedated children under 5 years old. The database under construction will serve as standard and as a resource for future studies involving MR scanning of young children. Support contributed by NS-92319.