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The NIH MRI study of normal brain development (Objective-2): Newborns, infants, toddlers, and preschoolers

C.R. Almli,[a] M.J. Rivkin,[b,*] and R.C. McKinstry[c]
Brain Development Cooperative Group[1]

[a]*Developmental Neuropsychobiology Laboratory, Departments of Neurology, Psychology, Programs in Neuroscience, Occupational Therapy, Washington University School of Medicine, Saint Louis, MO, USA*
[b]*Departments of Neurology, Psychiatry and Radiology, Children's Hospital Boston, Harvard Medical School, Boston, MA, USA*
[c]*Mallinckrodt Institute of Radiology and St. Louis Children's Hospital, Washington University Medical Center, Saint Louis, MO, USA*

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The Magn. Reson. Imaging (MRI) study of normal brain development currently conducted by the *Brain Development Cooperative Group* represents the most extensive MRI study of brain and behavioral development from birth through young adulthood ever conducted. This multi-center project, sponsored by four Institutes of the National Institutes of Health, uses a combined longitudinal and cross-sectional design to characterize normal, healthy brain and behavioral development. Children, ages newborn through 18-plus years of age, receive comprehensive behavioral, neurological and multimodal MRI evaluations via Objective-2 (birth through 4-years 5-months of age) and Objective-1 (4-years 6-months through 18 years of age and older). This report presents methods (e.g., neurobehavioral assessment, brain scan) and representative preliminary results (e.g., growth, behavior, brain development) for children from newborn through 4-years 5-months of age. To date, 75 participants from birth through 4-years 5-months have been successfully brain scanned during natural sleep (i.e., without sedation); most with multiple longitudinal scans (i.e., 45 children completing at least three scans, 22 completing four or more scans). Results from this younger age range will increase our knowledge and understanding of healthy brain and neurobehavioral development throughout an important, dynamic, and rapid growth period within the human life span; determine developmental associations among measures of brain, other physical characteristics, and behavior; and facilitate the development of automated, quantitative MR image analyses for neonates, infants and young children. The correlated brain MRI and neurobehavioral database will be released for use by the research and clinical communities at a future date.
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Introduction

Knowledge of structural and functional development of the human brain is advancing through evolution of magnetic resonance (MR) technology, and the development and refinement of analytical methods for anatomical MR imaging (aMRI and Diffusion Tensor Imaging [DTI]), MR Spectroscopy (MRS), and functional MR imaging (fMRI) (e.g., Ball, 2000; Barkovich, 2000; Giedd, 2004; Huisman et al., 2002; Huppi, 2001; Martin and Marcar, 2001; Neil et al., 1998; Poldrack et al., 2002; Rivkin, 2000; Sowell et al., 2004). Reports using MR to describe and characterize 'typical' brain development of children from school

* Corresponding author. Pavilion 154, Department of Neurology, Children's Hospital Boston, 300 Longwood Avenue, Boston, MA 02461, USA. Fax: +1 617 730 0618.
E-mail address: michael.rivkin@childrens.harvard.edu (M.J. Rivkin).

[1] Investigators from the pediatric study centers are as follows: *Children's Hospital Boston*, Principal Investigator Michael J. Rivkin, MD, Investigators Deborah Waber, PhD, Robert Mulkern, PhD, Sridhar Vajapeyam, PhD, Peter Davis, BS, Julie Koo, BS, Sandra Kosta, BA, Jacki Marmor, MA, Richard Robertson, MD, Heidelise Als, PhD, Gloria McAnulty, PhD; *Washington University in St. Louis*, Principal Investigator Robert C. McKinstry, MD, PhD, Co-Principal Investigator C. Robert Almli, PhD, Investigators Aaron A. Wilber, MS, Asif Moinuddin, MD, Tina M. Day, BA, Jennifer L. Edwards, MSW. The Principal Investigator of the data coordinating center at *McGill University* is Alan C. Evans, PhD, Investigators Rozalia Arnaoutelis, BS, G. Bruce Pike, PhD, D. Louis Collins, PhD, Gabriel Leonard, PhD, Tomas Paus, MD, Alex Zijdenbos, PhD, and Research Staff Samir Das, BS, Vladimir Fonov, PhD, Luke Fu, BS, Jonathan Harlap, Ilana Leppert, BE, Denise Milovan, MA, Dario Vins, BC, and at *Georgetown University*, Thomas Zeffiro, MD, PhD and John Van Meter, PhD Nicholas Lange, ScD, *Harvard University/McLean Hospital*, is a biostatistical study design and data analysis investigator to the data coordinating center. The Principal Investigator of the Clinical Coordinating Center at *Washington University* is Kelly Botteron, MD, Investigators C. Robert Almli, PhD, Cheryl Rainey, BS, Stan Henderson, MS, Tomoyuki Nishino, MS, William Warren, Jennifer L. Edwards, MSW, Diane Dubois, RN, Karla Smith, Tish Singer and Aaron A. Wilber, MS. The Principal Investigator of the diffusion tensor processing center at the *National Institutes of Health* is Carlo Pierpaoli, MD, PhD, Investigators Peter J. Basser, PhD, Lin-Ching Chang, ScD, and Gustavo Rohde, PhD. The Principal Collaborators at the *National Institutes of Health* are Lisa Freund, PhD (NICHD), Judith Rumsey, PhD (NIMH), Laurence Stanford, PhD (NIDA), and from NINDS, Katrina Gwinn-Hardy, MD, and Giovanna Spinella, MD.

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and adolescence ages have been increasing at a relatively rapid rate since the early 1990s (e.g., Blanton et al., 2001; Blatter et al., 1995; Courchesne et al., 2000; Giedd et al., 1996; Gogtay et al., 2004; Jernigan et al., 1991; Kanemura et al., 2003; Lange et al., 1997; Mukherjee et al., 2001; Paus et al., 1999; Pfefferbaum et al., 1994; Schaefer et al., 1990; Schmithorst et al., 2002; Sowell and Jernigan, 1998).

Fewer MR studies of brain development from newborn through preschool ages are available (e.g., Ashikaga et al., 1999; Barkovich, 1998; Barkovich et al., 1988; Holland et al., 1986; Martin et al., 1991; McGraw et al., 2002; Mukherjee et al., 2001; Neil et al., 1998), and many of those studies have used clinical populations of sedated infants and young children. Consequently, the currently available studies do not provide MR data for this young age range that can confidently be accepted as representative of truly healthy brain development. This gap in our knowledge of early, healthy brain development is not limited to MR imaging studies. Indeed, the anatomical brain data derived from autopsy specimens of young children (which are few in number for the < 5 year old age range) are not strictly representative of 'normal or healthy,' since death was generally caused by, or related to, some type of pathology (e.g., Benes et al., 1994; Brody et al., 1987; Dekaban and Sadowsky, 1978; Dobbing and Sands, 1973; Huttenlocher and Dabholkar, 1997; Yakovlev and Lecours, 1967).

MRI has become the premier tool for the quantitative, noninvasive study of childhood brain development. Developmentally accurate MR data are critically needed to determine the actual ranges of variation in brain structure and function that can be expected for healthy infants and young children. Achievement of such an MR data resource would provide standards to permit clinicians and researchers to better identify and define brain pathology that is associated with behavioral, neurological, and/or psychiatric disorders for infants, children, and adolescents.

The NIH has recognized that the scientific and clinical communities have a need for a developmental neuroimaging and behavioral database for normal, healthy children ranging in age from birth through adolescence. In 1999, NIH funded the current, ongoing multi-center project to provide research and clinical communities with a correlated MRI and behavior database that would be demographically diverse and generally representative of gender, race, ethnicity, and income level established by the United States Census Bureau (2000) and United States Department of Housing and Urban Development's Office of Policy Development and Research (2003). Six Pediatric Study Centers (PSCs) serve as principal recruitment and data acquisition sites and are located at Children's Hospital Boston, Children's Hospital Medical Center of Cincinnati, University of Texas Health Science Center at Houston, University of California-Los Angeles, Children's Hospital of Philadelphia, and Washington University Medical Center in Saint Louis. A Data Coordinating Center (DCC; Montreal Neurological Institute, McGill University) coordinates the imaging and database aspects of the project. A Clinical Coordinating Center (CCC; Washington University Medical Center in Saint Louis) coordinates and maintains quality control for the sampling plan, screening and recruitment, and neurobehavioral measures. Centralized data analysis of DTI data is provided by a Diffusion Tensor Imaging Data Processing Center (DTI-DPC; NIH, NICHD, Intramural Program). Spectroscopy data is processed at the University of California-Los Angeles by the Magnetic Resonance Spectroscopy Data Processing Center (MRS-DPC). All of the Centers listed above participate as full scientific partners in this research endeavor.

The overall project comprises two objectives which span the entire period of childhood development from birth through early adulthood. Objective-1 recruits children between the ages of 4-years 6-months through 18 years, while Objective-2 recruits from birth through 4-years 5-months of age. Notably, children advancing to 4-years 6-months of age and older are transferred to Objective-1 for their further participation in the project. Similarly, children who enter Objective-1 in late adolescence (e.g., 18 years of age) continue to participate in the project through their early twenties. As a result, the entire developmental epoch from birth through early adulthood is represented in the combined Objective 1 and 2 samples of participants. This project will yield a correlated brain MRI and neurobehavioral database for healthy brain and behavioral development from birth through young adulthood that will be made accessible to the scientific and clinical communities for use in research studies and clinical practice. It is anticipated that the process of releasing brain and behavioral data to the public will begin in the near future.

The remainder of this report describes the methodology and preliminary results for Objective-2, which is being conducted by the Boston and Saint Louis sites only. An overview report, generally describing the sample and methods of the entire project, is available (see Brain Development Cooperative Group, 2006).

Methods

Objective-2 combines both *cross-sectional* and *longitudinal* designs to characterize normal, healthy development of the pediatric brain and behavior from the neonatal period through 4 years of age (Fig. 1). The sample comprises 11 cohorts of children that enter the study at predetermined ages, i.e., the cross-sectional component. Each of the 11 cohorts is re-evaluated at least two additional times at specified ages, i.e., a minimum of three scans for the longitudinal component.

Participants

A sample of at least 106 normal, healthy children (newborn through 4-years 5-months of age) is being enrolled in Objective-2 (Fig. 1). The sample is diverse and reflects the demographics of the population of children established by the United States Census Bureau (2000). All participants recruited are born full term (>37 weeks, 3 days), with equal representation of males and females. Race, ethnicity, and income are distributed in a demographically-balanced sample to mirror proportions defined by the United States Census Bureau (2000, see Table 1). Measures of family income level, parental education level, and parental occupations serve as indices of socioeconomic status. Income levels are corrected for geographical region and family size based on United States Department of Housing and Urban Development's Office of Policy Development and Research (2003). At least 60 children are being recruited in Saint Louis, MO, and at least 46 children are being recruited in Boston, MA. Institutional Review Board (IRB) approval of the project has been obtained at both sites, and signed informed consent is obtained from parents at *each* of their child's study time-points (i.e., ages at which brain and neurobehavior evaluations take place).

Age calculations and representations

Ages of all participants are adjusted to a 40-week gestational age baseline (even though all children are born 'full term'). This

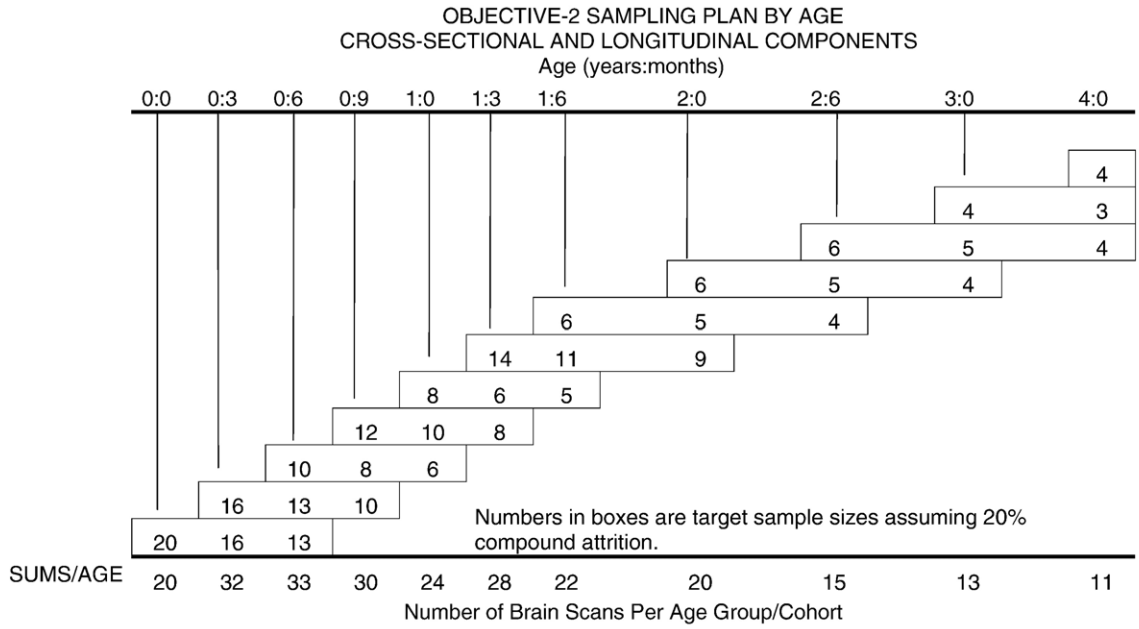

Fig. 1. Objective-2 sampling plan showing the number of participants recruited and studied (left-hand side of horizontal rectangles) for the 11 age-cohorts from 0:0 (neonatal) through 4:0 (4 years). Independent groups of participants were recruited, tested and scanned at each of the 11 age cohorts (cross-sectional component), and each participant received at least three testing-scanning sessions (longitudinal component). The second and third numbers within each age-cohort rectangle represent the anticipated participant attrition rate of 20% over the second and third testing ages. The sampling plan provided for a minimum of 106 participants receiving at least 248 brain scan plus behavioral testing sessions across the 11 age-cohorts.

adjusted age is based on the child's "due date" (i.e., Expected Date of Confinement, EDC), and is applied to all age calculations from birth through 4-years 5-months of age for Objective-2. Further, throughout this report, EDC-adjusted age is represented in the "years:months" format, such that "1:3" represents an EDC-adjusted age of "1-year 3-months of age." Using this notation, the age of a newborn infant would be represented as "0:0". However, the actual "target" age used for the newborn scan and neurological exam is 10–14 days post-EDC. This delayed target age for the newborn time-point was selected to allow for physiological adaptation to the extra-uterine environment. To ensure that all newborn infants received an adaptation period, the scan/exam time-point could not occur earlier than 7 days post-delivery.

Sampling plan

The overall sampling plan is stratified by four factors: (1) *age* (11 cohorts), (2) *gender* (approximately equal numbers of male and females), (3) *income* (divided into low, medium, or high income level by PSC site and family size based on United States Department of Housing and Urban Development's Office of Policy Development and Research (2003)), and (4) *race/ethnicity* (see Table 1), to provide a diverse and demographically-balanced sample of participants based on the United States Census Bureau (2000, Table 1).

Table 1
Race/ethnicity distribution for US census-2000 and Objective-2 sampling plan

Race/ethnicity	%Census	%Sampling plan
White/Caucasian	69.1	69
Black/African American	12.1	12
Asian	3.6	4
American Indian/Alaska native	0.7	1
Native Hawaiian/other Pacific Islander	0.1	1
Hispanic or Latino (of any race)	12.5	13
Some other race + Two or more races	1.9	–
	100%	100%

In laying out the design for Objective-2, there were no appropriate data available for children in this age range to allow calculation of power or effect sizes. Thus, the design adopted was influenced by practicalities with respect to sampling frequency and participant number given the constraints of conducting non-sedated brain scans with a demographically-balanced sample of normal healthy infants and young children to the age of 4-years 5-months.

Fig. 1 presents the Objective-2 sampling plan and demonstrates the age cohorts and their respective numbers. Both cross-sectional and longitudinal design features are evident. The cross-sectional component consists of 11 age groups ranging from newborn (0:0) through preschool (4:0–4:5) ages (see staggered horizontal rectangles in Fig. 1). The minimum total number of children at each age is presented at the bottom of the figure along the *X*-axis and is the sum of the numbers in rectangles above this number. The longitudinal component is represented by each of the staggered 11 cohorts viewed horizontally, wherein each child receives full evaluation (i.e., MRI, neurological and behavioral testing) a minimum of three times during the project.

The time intervals between individual age-cohorts range from only 3 months for the youngest children (i.e., 0:0 through 1:6 cohorts) to 12 months for the oldest children (i.e., 3:0 to 4:0/4:5 cohorts), with larger sample sizes for children of younger ages whose developmental epochs of brain growth and structural change are expected to be most rapid. The longitudinal component of the design allows for an individual child to be evaluated at multiple time-points (i.e., >3 time-points), thereby increasing the number of

Table 2
Exclusion categories and examples of exclusion factors

I. Demographic
Child adopted; Both Parents uncomfortable reading and understanding English documents; Medical history of biological parents unknown

II. Pregnancy
Maternal birth age <16 years or >44 years; Intrauterine exposure (Smoking [>10 cigarettes/week], Alcohol [>2 drinks/week], Medications with known/suspected CNS effects [steroids], Drugs of abuse [marijuana]); Medical conditions (Antepartum hemorrhage, Pre-eclampsia, Infections); Pre-delivery hospital admission; General anesthesia

III. Delivery
Multiple births; Malpresentation; C-section with fetal or maternal distress; High forceps or Vacuum extraction

IV. Birth-neonatal
Born <37 weeks 4 days or >42 weeks 3 days; Growth measures <5%; Apgar score <8 (5 min); Hyperbilirubinemia requiring treatment; Anemia; Respiratory distress; Admitted for specialized care; Chromosomal/Congenital anomalies; Infections (ToRCHeS); Tumors

V. Child development
Child growth measures <5%; Non-fluent in English; Major surgery; Congenital anomalies; Heart problems; Seizures, CNS Infection or radiotherapy, Head injury, Hearing/Visual impairment requiring treatment; Significant language/learning disorder; Lead treatment; Muscle disease; AD/HD; Tic disorder; Mood/conduct disorder; Exclusionary maternal medications during breastfeeding

VI. Family psychiatric history—1st degree relatives
Schizophrenia; Bipolar/manic disorder; Major depression; Pervasive developmental disorder; Alcohol dependence; AD/HD; Inherited neurological disorder; non-traumatic mental retardation

VII. Child behavioral testing/Parental reports
Poor scores (>2 sd below mean) on developmental, language, intelligence testing; High scores (>70, CBCL) parental report indicating child behavior problems

VIII. Child neurological exam
Facial dysmorphisms; Dystonia; Strabismus; Dysmetria; Ocular motility, Strength <4/5; Tics

children that are being evaluated at each of the ages indicated in Fig. 1. Notably, the sampling plan represented in Fig. 1 is open to increasing numbers of children and increasing numbers of time points for data acquisition per child. Indeed, our preliminary results indicate that the sampling plan of 106 children receiving 248 time-point evaluations over the duration of the project will be exceeded (see Results and discussion section). Power and effect sizes will be reported in subsequent reports following completion of data acquisition for Objective-2.

Procedure

Recruitment and screening of child and family

Objective-2 children are recruited to fill specific, predetermined cells (based on age, gender, race/ethnicity, and income factors) of the sampling plan in order to achieve a demographically-balanced sample corresponding to the United States Census Bureau (2000). Only one child from a given family is eligible to be recruited into the study. Participant recruitment within the greater Boston and Saint Louis metropolitan regions is conducted using a community-based strategy that includes hospital venues (e.g., maternity wards and nurseries, satellite physician offices, and well-child clinics),

Table 3
Child neurobehavioral testing battery

Name of Test/Scale	Administration ages [a]	Function/ability assessed
Neurological Examination (NEURO)	0:0 to 4:5	Neurological development
Bayley Scales of Infant Development-II (BSID-II)		
Mental Scale	0:3 to 2:6	Mental development
Motor Scale	0:3 to 3:0	Motor development
Behavior Rating Scale	0:3 to 2:6	Behavioral development [b]
Preschool Language Scale-3 (PLS-3)		
Auditory Comprehension Subscale	0:3 to 4:5	Receptive language
Expressive Communication Subscale	0:3 to 4:5	Expressive language
Total Language	0:3 to 4:5	Total language
Differential Abilities Scale (DAS)		
Block Building	3:0 to 3:5	Fine motor, visual perceptual
Verbal Comprehension	3:0 to 4:5	Receptive language
Picture Similarities	3:0 to 4:5	Reasoning, recognition
Naming Vocabulary	3:0 to 4:5	Expressive language
Pattern Construction	3:6 to 4:5	Visual–spatial orientation
Early Number Concepts	3:6 to 4:5	Math concepts/skills
Copying	3:6 to 4:5	Fine motor, visual perceptual
General Conceptual Ability	3:0 to 4:5	Intelligence
Handedness-1:0 (HAND-1)	1:0 to 2:11	Hand preference
Handedness-3:0 (HAND-3)	3:0 to 4:5	Hand preference
Verbal Fluency (NEPSY)	3:0 to 4:5	Semantic fluency
Purdue Pegboard (PEG) Half-Board Version	3:0 to 4:5	Fine motor coordination
Cambridge Neuropsychological Test Automated Battery (CANTAB)		
Motor Screening	4:0 to 4:5	Reaction time/accuracy
Spatial Span	4:0 to 4:5	Figure/sequence memory
Spatial Working Memory	4:0 to 4:5	Memory/plan/monitor
Big Circle–Little Circle	4:0 to 4:5	Category rule/reversal
Intra/Extra Dimensional Set-Shift	4:0 to 4:5	Rule shifting/interference

[a] Administration Ages—years:months (e.g., 2:6 = 2-years, 6-months).
[b] Behavioral development includes: attention, engagement, emotional regulation, motor quality, etc.

community organizations (e.g., day-care centers, schools, churches, and other types of community centers), and siblings of children participating in other studies.

Once signed informed consent is obtained, a comprehensive screening process is conducted with the parents to ensure that the candidate child and family do not possess medical and/or family histories that exclude them from participating in the project. Table 2 presents eight major areas of participant screening and exclusion, with examples of specific criteria that exclude a child/family from participation in the project (see www.bic.mni/mcgill.ca/nihpd_info, for a complete inclusion/exclusion listing). In addition, questionable brain scan findings are reviewed by two board certified neuroradiologists, plus the neuroradiologist at the specific site of the brain scan, and agreement that the finding is abnormal or pathological leads to child exclusion. Other questionable conditions/situations that have the potential to be exclusionary are reviewed by a group of physician investigators to determine inclusion or exclusion by simple majority.

Each successfully enrolled child receives 'full evaluation' at a series of pre-selected ages (i.e., time-points) that are defined by the child's age-cohort (see Fig. 1). Full evaluation at each time-point includes: (1) a re-screening evaluation of the child and family (Table 2), (2) behavioral and neurological evaluation of the child (Table 3), (3) evaluation of the child and family via parental questionnaire (Table 4), and (4) MR evaluation of child's brain (Table 5). A child may be excluded from the study if a relevant child or family member exclusion factor is determined to be present for any of the four evaluation areas listed above, at any of a child's full evaluation time-points (ages shown in Fig. 1). The comprehensive and strict nature of the screening-exclusion criteria, and the repeated and ongoing screening-exclusion process at each evaluation time-point, serves to ensure that the final study sample is representative of normal, healthy brain and behavioral development. The exclusion/inclusion factors are very similar between Objectives 1 and 2.

Age "Windows" for evaluation time-points

Age windows for full evaluations at selected time-points (Fig. 1) were established to maintain specificity of the age cohorts and age time-points. For the newborn time-point (0:0), an extra 7 days is added to the time-point age-range of 10–14 days post-EDC, yielding a window of 10–21 days post-EDC. A ±2-week window is used for the time-points between 0:3 and 1:3 (e.g., 2 months and 2 weeks through 3 months and 2 weeks defines the boundaries of the 0:3 time-point), and a ±4-week window is used for the 1:6 to 3:0 time-points. The 4:0 time-point boundaries range from 3:11 to 4:5. The window size around a specific cohort age is age dependent, such that narrower windows are designated for the younger infants/children undergoing more rapid brain growth rates (e.g., ±2 weeks for 0:3). These windows are designed and used to ensure adequate separation of the 11 target age-groups (cohorts) in Objective-2, and to allow for statistically valid data analyses of discrete age-groups (see 'Sampling plan' section, and Fig. 1). The "extra" number of days added to time-point windows carries a practical implication by providing some latitude for rescheduling of neurobehavioral testing and/or brain scans due to family or child illness, a failed brain scan, transportation difficulty, and so on.

Superimposed on the "age windows" defined above, a maximum time interval for completion of neurobehavioral plus neuroimaging data acquisition events is defined as the *data acquisition window*. For newborns, the neurological exam and the brain scan must be completed within a 7-day epoch (e.g., if the neurological exam was administered at 10 days post-EDC, the brain scan had to be completed by 17 days post-EDC). The data acquisition window for the 0:3 through 2:6 cohorts is 2 weeks, and within 4 weeks for the 3:0 and 4:0 time-points.

Table 4
Parent questionnaire battery

Name of questionnaire	Administration ages [a]	Function/ability assessed
Family Interview for Genetic Studies (FIGS)	0:0 to 4:5	Family psychiatric history
Family Biographical History (FBH)	0:0 to 4:5	Family demographics
Carey Temperament Scales (CAREY)		
Early Infant Temperament (EITQ)	0:3	Child temperament
Revised Infant Temperament (RITQ)	0:6 to 0:9	Child temperament
Toddler Temperament (TTS)	1:0 to 2:6	Child temperament
Behavioral Style (BSQ)	3:0 to 4:5	Child temperament
Parenting Stress Index (PSI)	0:3 to 4:5	Parent–child relationship
Child Behavior Checklist (CBCL)	1:6 to 4:5	Child behavior style

[a] Administration ages—years:months (0:0 is the age code for "newborn" infants, 0:3 is zero years:three months).

Child testing battery

Associated with each evaluation time-point (Fig. 1), a child receives a comprehensive, age-appropriate neurobehavioral test battery (including neurological examination). The behavioral testing battery used in Objective-2 is outlined in Table 3, accompanied by the child age-ranges at test administration, and the behavioral domains assessed by each test. All Objective-2 behavioral tests have standardized administration and scoring procedures.

While assembling the behavioral testing battery during protocol development, it was deemed important that the tests selected for Objective-2 provide comprehensive characterization of behavioral development, and that the testing battery could be completed in a timely fashion, i.e., less than 3 h for the oldest children, less than 90 min for children 1:0 and younger, and within approximately 20 min or less for newborn infants. Rest, bathroom, play, snack and drink breaks are provided as appropriate. The tests selected should also have a strong history of widespread use in both clinical assessment and research on child behavioral development, and the instruments need to be readily available for future studies. It was also important that the results of the behavioral testing could be used for determining brain–behavior correlations. Finally, some of the behavioral tests had to serve the purpose of ensuring that the study sample reflects normal, healthy neurobehavioral development (i.e., a screening-exclusion function).

Exclusionary behavioral assessments include the Bayley Scales of Infant Development-II (BSID-II; Bayley, 1993), the Preschool Language Scale-3 (PLS-3; Zimmerman et al., 1992), and the Differential Abilities Scale (DAS; Elliott, 1990) which are all standardized and normed assessments. Scores greater than two standard deviations below the mean of 100 (i.e., scores <70) are exclusionary for those assessments (see www.bic.mni/mcgill.ca/nihpd_info). The four, age-appropriate Neurological Examinations

Table 5
MR protocol for Objecitve-2

	Sequence	Sequence timing	Resolution and coverage	Purpose
1	Axial T1W	TR 500 ms TE 10 ms	1 × 1 × 3 mm; 1NEX; WU:256 × 192 matrix, FOV; CHB:256 × 192 matrix, FOV 250(0.75) to cover the entire brain, skull and overlying skin	Structural Scan for image segmentation
2	Axial PD/T2W	TR 3500 ms TE1 17 ms TE2 119 ms Echo Train Length 5 Bandwidth 130 Hz/pixel	1 × 1 × 3 mm; 1NEX; WU:256 × 192 matrix, FOV; CHB:256 × 192 matrix, FOV = 250 (0.75), to cover the entire brain, skull and overlying skin	a. Structural Scan for image segmentation b. T2 relaxometry
3	Axial IR HASTE (WU) SSFSE (CHB)	TR > 10,000 ms TE 47 ms (effective) (WU) TE 35 ms (effective) (CHB) TI 150, 500, 750, 1000, 1500, 2000, 4000 ms	1NEX WU:2 × 2 × 3 mm, FOV = 256 × 192, matrix 128 × 96 CHB:1.5 × 1.5 × 3 mm, FOV = 240 × 240, matrix 160 × 160 to cover the entire brain, skull and overlying skin	T1 relaxometry
4A	DTI	TR > 6000 ms TE 80 ms (or minimum) 6 directions: (*x*,*y*,*z*) {(1,0,1), (−1,0,1), (0,1,1), (0,1,−1), (1,1,0), (−1,1,0)}	3 × 3 × 3 mm WU: either FOV192 × 192, matrix 64 × 64 or FOV 384 × 384, matrix 128 × 128; CHB: FOV 380 × 380, matrix 128 × 128 to cover the entire brain, skull and overlying skin	For computation of the diffusion tensor
4B	MRS (CHB)	TR 1500 ms TE 144 ms 64 averages(i.e., 64NEX) 6–20 min	Single Voxel PRESS 1.5 × 1.5 × 1.5 mm 1. Left frontal white matter 2. Left thalamus 3. Occipital gray matter which straddles the mid-line (visual cortex) 4. Left parietal white matter	For brain metabolic maturation
5	T2W dual contrast	TR 3500 ms TE1 80 ms TE2 160 ms Echo Train Length 7 Bandwidth 83 Hz/pixel	1 × 1 × 3 mm; NEX = 1; WU:256 × 192 matrix, FOV; CHB:256 × 192 matrix, FOV = 250(0.75), to cover the entire brain, skull and overlying skin	For T2 relaxometry

WU = Washington University, CHB = Boston Children's Hospital Boston.
Scan priority rank: 1 = highest through 5 = lowest.
Scans 1 and 2 required for minimal data set, i.e., a successful brain scan session.
Scans 4A (DTI) and 4B (MRS) were optional.

are also exclusionary for certain items, in addition to their provision of neurologic data that characterizes the sample (M.J. Rivkin, P. Filipek, and J.J. Neil, unpublished neurological assessments, 2003; Capute et al., 1986). Examples of exclusionary factors include selected facial dysmorphisms, dystonia, strabismus, and hypotonia, as well as height, weight or head circumference <5th percentile (Chen, 2000; National Center for Health Statistics, 2000; Nellhaus, 1968; see www.bic.mni/mcgill.ca/nihpd_info, for a complete description of the examinations and exclusion factors). The choice and effect of exclusionary criteria "cut-offs" is discussed in the Results and discussion section of this report.

Additional tests used for Objective-2 are presented in Table 3, and those tests (plus the DAS) also extend into Objective-1 through at least the age of 5:11. Two versions (based on age) of handedness tests are used to evaluate development of hand use and lateralization (C.R. Almli, unpublished handedness assessments, 1999, see Table 3). The Handedness-1:0 test presents 8 trials of reaching and grasping an object, while the Handedness-3:0 version presents 10 trials of bimanual manipulations. Handedness can be scored in graded fashion for both test versions, e.g., a child using the right hand on all eight trials to reach for and grasp presented objects on the Handedness-1 test would be classified as "strong" right handed, while use of the right hand to reach and grasp objects on five of eight trials would be classified as "weak" right handed (see www.bic.mni/mcgill.ca/nihpd_info, for a complete description of administration and scoring of the hand use assessments). The half-board version of the Purdue Pegboard is used to assess fine motor dexterity, speed and coordination (Gardner and Browman, 1979; Lafayette Instrument Company, 1985; Wilson et al., 1982). The Semantic Verbal Fluency test of the NEPSY: A Developmental Neuropsychological Assessment (Kemp et al., 2001; Korkman et al., 1998) is used for assessing verbal fluency (i.e., child generates of names of "animals" or "things to eat or drink"). The Cambridge Neuropsychological Test Automated Battery (CANTAB; Cambridge Cognition Limited, 2004; CeNeS Limited, 1999) is a computerized assessment that was selected for this project based on research reporting that individual CANTAB tests were sensitive to cortical (e.g., frontal lobe) and subcortical (e.g., basal ganglia) functions or injuries, and can be used with children as young as 4:0 (e.g., Lee et al., 2000; Luciana, 2003; Luciana and Nelson, 1998, 2000, 2002; Owen et al., 1996).

The behavioral tests (Table 3) used for Objective-2 offer the potential to yield data that can be used for calculating developmentally dependent brain structure–behavior correlations using quantitative, whole or regional brain measures. For example, developmental correlations can be computed between: hand

preference scores and hemispheric volumes; CANTAB "working memory" scores and frontal lobe volumes or cortical thickness; and between Purdue Pegboard scores and motor cortex volume or cortical–spinal tract white matter intensities.

Parental questionnaire battery

Table 4 presents a listing of the parental questionnaires used for Objective-2, as well as the child's age at administration and the general history and behaviors assessed. Collectively, these questionnaires provide additional background information for characterizing child and family history, and two serve an exclusionary function, and all may prove useful for computing brain–behavior correlations.

The Family Interview for Genetic Studies (FIGS; Initiative NSaBDG, 1992; Maxwell, 1992) and the Child Behavior Checklist for Ages 1½–5 (CBCL; Achenbach and Rescorla, 2000) are used for screening and exclusion for familial or child psychopathology (see Tables 2 and 4; see also www.bic.mni/mcgill.ca/nihpd_info). The Parenting Stress Index (PSI; Abidin, 1995), Carey Temperament Scales (CTS; Medoff-Cooper et al., 1995), as well as the CBCL, are included for Objective-2 because of their widespread use for clinical and research characterization of child behavior, child temperament, and parent–child interactions.

A Family Biographical History questionnaire was developed specifically for Objective-2, and is the mechanism by which family demographic and child historical information is acquired. Information gathered includes family composition and income, parental education and occupation, parent and child race/ethnicity, as well as specific child development information, such as infant breast and bottle feeding experiences, child care and assistance programs used (e.g., day care, baby sitter, Parents-as-Teachers, Head Start, preschool programs; see www.bic.mni/mcgill.ca/nihpd_info, for detailed description).

Adaptation and habituation to the MR brain scan process

The neurobehavioral testing, neurological exam, and the MR scan are conducted during one or more visits to the medical center, depending on parental preference. Preparation of the child and parents for the brain scan process is typically accomplished during a visit to the medical center and/or during parent–child interactions within the family home. The fact that no participants could be sedated for brain scans presented challenges that are addressed as follows.

Newborn infants (i.e., 0:0 [10–14 days post-EDC]), and infants at 0:3, are scanned during daytime or nighttime sleep. Generally, these young infants are fed, swaddled, prepared with sound protection (ear plugs) and monitoring equipment (pulse oximetry), and then the supine infant's head is positioned within the magnet coil. The infant is visually monitored by staff throughout the scan process (e.g., McKinstry et al., 2002; Neil et al., 1998).

Older infants (e.g., 0:6) and children through 4:5 are less likely to fall asleep in the strange environment of the scanner room during the day or night, i.e., they are more challenging to scan without sedation than are neonates. As a result, infants and children ranging in age from 0:6 through 4:5 generally receive adaptation protocols that prepare them for the scan, and the scans are conducted at the child's normal night bedtime, i.e., during natural sleep.

Adaptation protocols were designed to maximize the child's (and parent's) comfort with the MRI procedures, so that the child would be able to fall asleep in the scanner room, tolerate application of sound protective materials and head positioning into the quadrature coil, and not awaken in response to the sudden onset and loud volume of scanner noises. Parental education about the scan and testing process is provided via verbal descriptions and a brochure developed for this project that outlined and pictured the scan process (see www.bic.mni/mcgill.ca/nihpd_info). In addition, the parents actually assist with the scan adaptation process for their child while at home. For example, parents are provided with CD or audio tape of the MRI sounds to play for the child at home during the child's sleep and waking (e.g., feeding, playing). This experience serves to habituate the child (and parents) to the scanner sounds. In addition, ear plugs (sponge or wax) are provided so that the parent could place the plugs in the child's external ear canal during play and sleeping for the purpose of habituating the child to the ear plug placement process and the resulting sound changes. Parents are instructed to make "games" of these activities at home and they are encouraged to be a major source of comfort for their child in advance of, during, and following the MR scan.

Two forms of mock scanner environments are made available to the child and family during medical center visits. A 'play-scanner' is made up of a table covered with a sheet to make a bore-like opening, with a "mechanic's creeper" representing a scanner bed. The child can play with this equipment while the scanner sounds are played on CD. The parents and child can also play on a 'mock-scanner' (i.e., the external shell of a real MR scanner, complete with a movable bed platform and a head coil). A Polaroid photograph of the child playing on the mock scanner may be given to the child to take home. As appropriate, the parent and child also visit the actual MR scanner and control room that will be used for the child's scan, as well as see the parking locations that will be available for them during the nighttime scan. The parents are informed about what to bring, or not bring, to the scan appointment. These experiences help the parents feel comfortable prior to and during their child's scan, and help to minimize distress in older infants and children who happen to awaken in the darkened scanner room during scanning.

Preparation for brain scanning

Prior to entering the scanner room, an MRI Safety Screening Form (signed by adults) is discussed for each person (children and adults) entering the scanner room. In addition, all parties (including the child) are further screened for materials on their person that are unsafe within the magnetic field of the scanner. A plastic rocking chair and small crib/playpen (both magnet-safe) are available in the darkened scanner room for use by the parent to feed, comfort, and put the child to sleep.

The children are generally brought by the parents to the MRI facility in their pajamas and ready for a nap or bedtime. As quickly as possible, the child and parents are moved into the darkened scanner room to put the child to sleep. One parent generally takes responsibility for getting the child to sleep (e.g., feed and/or rock the child, put the child in crib, etc.). If the child has not fallen asleep and still appears wide-awake after 90–120 min in the darkened scanner room, the scan is typically cancelled. If the parents are agreeable, a "re-scan" is scheduled if there is sufficient time available within the child's time-point window. Otherwise, the child is scheduled for the next time-point age, e.g., no sleep or failed scan at 1:0, child advanced to 1:3 (see Fig. 1).

Once soundly asleep, the child is moved to the scanner bed and may be swaddled or blanketed, as per child preference. Sound

protection is applied (e.g., sponge or wax ear plugs placed in the external ear canals, foam cosmetic pads placed over the ears and held in place by a knit hat). The child is then moved to position the head within the magnetic coil. Additional sound protection is applied (e.g., head phones or ear muffs [Avotec, Inc., Jensen Beach, FL] are placed over the ears and secured with rolled towels and ace bandages around the head, or, are secured by custom designed Styrofoam bead bags that fit snugly around the child's head when air is removed from the bag [separate sizes for newborn, less than 2:0, and less than 4:6; S and S X-ray, Houston, TX]). The rolled towels, ace bandages, and bead bags gently hold the child's head in position, limit head movements, and provide for sound protection. Generally, the child is supine with the head on midline during the scan, however, lateral decubitus (side-lying) or prone positions are also used (depending on child sleeping-position preferences).

Throughout all brain scanning, the child is visually monitored by the staff through the scanner bore for movement, waking, or any signs of distress. Monitoring of younger infants also includes pulse oximetry. If necessary, the child can be removed from the scanner bore within 5 s. At the completion of the brain scan, the child is removed from the scanner and given to a parent. The child and parents are provided with a toy, brain picture, payment for their expenses (e.g., travel, parking, meals, etc.), and they are escorted to their car.

Magnetic resonance brain scans of normal, healthy infants and children

Brain maturation over the first few postnatal years appears to be rapid (Mukherjee et al., 2001), thereby presenting challenges in the design of an MR protocol. For example, MR relaxation rates fall dramatically over the first 12 to 18 months, necessitating modifications to an MR protocol that would be suitable for older children and adults (Jones et al., 2004; Nowell et al., 1987). Moreover, white matter microstructure and brain metabolic changes that occur during normal, healthy brain development have never been characterized uniformly, and are likely to be dramatic.

The MRI protocol for Objective-2 (Table 5) is designed to gather structural MRI data for segmentation and parcellation studies of brain throughout early childhood, to characterize brain maturation throughout early childhood using T1 and T2 relaxometry, to characterize the normal, healthy developmental change in white matter microstructure with diffusion tensor imaging (DTI), and to elucidate a profile of brain metabolic maturation using magnetic resonance spectroscopy (MRS). MR scanners from two different vendors are used for Objective-2 (General Electric at Boston, Siemens at Saint Louis), however, both are 1.5 Tesla (T) field strength. The MR pulse sequences, timing parameters and image resolution are selected so that comparable image contrast and quality is achieved across both imaging centers.

Neuroimaging data are acquired at 1.5 T field strength. Sample design, recruitment method, as well as neurobehavioral, neurologic and neuroimaging protocols were planned to provide relevant reference data for both clinical and research domains independent of the field strength employed for imaging. In addition, while imaging at 3 T field strength has entered the clinical domain, the 1.5 T MRI scanner is likely to remain the predominant field strength used for MR imaging for some time. Finally, the imaging protocols employed in the current research were optimized to produce maximum contrast among constituent brain tissues scanned at 1.5 T field strength. Despite differences in T1 and T2 relaxation times, MR spectra and diffusion times found at different magnet field strengths, the methods of optimizing features of pulse sequences in order to maximize contrast between component tissues described in this study remain relevant irrespective of the field strength employed (Huisman et al., 2006).

All Objective-2 MRI scans are acquired without sedation, and since natural sleeping periods may be short due to environmental novelty for the child, or because of scanner noise, the constituent pulse sequences of the protocol are prioritized to ensure that critical portions of the scan protocol are obtained soon after the child has fallen asleep. Thus, neuroanatomical acquisitions (T1-weighted, proton density and T2-weighted scans) are followed by T1 relaxometry, then either DTI or proton MRS, and finally supplemental T2 relaxometry scans.

In order to achieve continuity with Objective 1 of the project, the core of the MR protocol is designed for image segmentation. A 2D T1-weighted multi-slice spin-echo (SE) data set is acquired first (Table 5, Fig. 2). While not a volumetric acquisition, this pulse sequence produces neuroanatomical data in less time than a 3D T1W protocol in subjects that are predisposed to movement during the scan. Images with $1 \times 1 \times 3$ mm spatial resolution are acquired

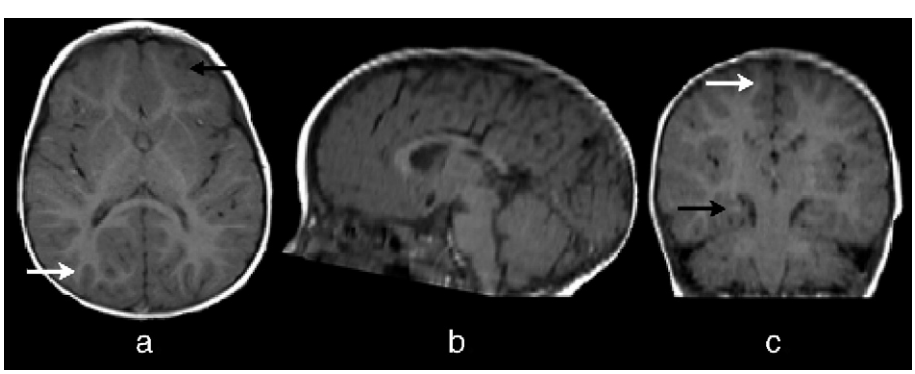

Fig. 2. T1-weighted structural MR images from a toddler (female) at 18 months of age (1:6). (a) Axial image oriented parallel to the anterior/posterior commissure line at the level of the Foramen of Monro and the basal ganglia. (b) Sagittal and (c) coronal images obtained by reformation from the axial images centered on the brainstem. Note that by 18 months of age, the gray/white matter contrast in the parietal lobes has already attained the adult-like pattern (white arrows). An immature pattern of myelination is noted in the subcortical regions of the frontal lobe and in the mesial temporal lobes (black arrows). Note that the same child is presented in this figure and Figs. 2–7, and that radiologic convention is followed for presentation of axial and coronal images in which the left side of the image corresponds to the right side of the participant.

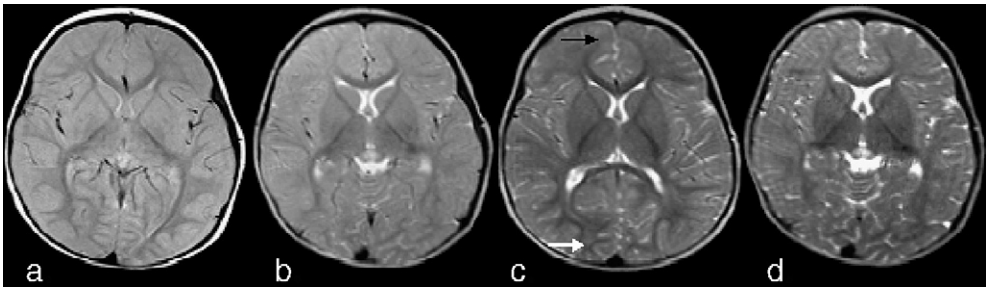

Fig. 3. Proton density and T2-weighted images for segmentation and T2 relaxometry. Images from 18 month old (same child as in Fig. 2) obtained parallel to the anterior/posterior commissure line at the level of the Foramen of Monro and basal ganglia. Two dual (effective) echo turbo spin echo image pairs are shown. The first acquisition (a and c) was performed after the T1-weighted structural images (see Fig. 2). The echo times, TE of 17 and 119 ms, are the same as those used with the older children under study in Objective-1 of the project. This will facilitate image segmentation and provide the necessary images to estimate the slow component of T2 relaxation. The second acquisition (b and d) was performed as the last series. The echo times, TE 83 and 165 ms, improve the estimate of T2 relaxation times in younger children where T2 values are much greater. The black arrow in (c) illustrates an immature pattern of myelination with ill-defined gray/white contrast in the subcortical region of the right frontal lobe. The white arrow in (c) demonstrates a mature, adult-like pattern of myelination in the occipital lobe.

parallel to the AC–PC line to cover the vertex of the skull through the foramen magnum in less than 5 min. The T1-weighted (T1W) scan is given highest priority and should unacceptable subject motion occur, the scan is repeated until acceptable data are obtained (see also, 'quality confirmation process').

The second set of scans for image segmentation includes a dual-echo series consisting of proton density and T2-weighted (PD/T2W) fast/turbo spin echo images that are acquired to match the orientation, spatial resolution, and slice locations established by the T1-weighted acquisition (Table 5, Fig. 3). The PD/T2W images are generated in less than 5 min. Again, the scans are repeated until 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 examination.

Following completion of the core structural MR sequences, T1W relaxometry is performed (Table 5, Fig. 4). For T1 relaxometry, an inversion recovery (IR) sequence developed by Haselgrove et al. (2000) was adapted for this study. A few participants recruited early in the study were scanned with the IR echo planar imaging (EPI) sequence. Since then, the image acquisition in the IR sequence has been a single shot fast/turbo spin echo. 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.

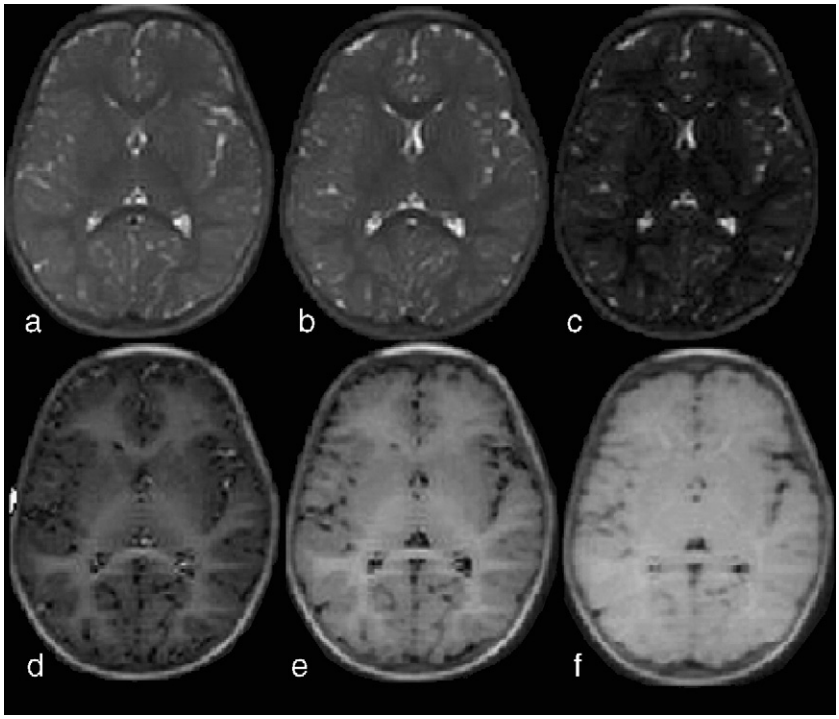

Fig. 4. Inversion recovery images for T1 relaxometry. Image oriented parallel to the anterior/posterior commissure line at the level of the Foramen of Monro and the basal ganglia (same 18 month old toddler as Fig. 2). Varying the inversion time (TI) allows for the computation of the T1 relaxation time in each voxel. (a) No inversion, (b) TI = 50 ms, (c) 400 ms, (d) 800 ms, (e) 1200 ms, (f) 2000 ms.

Good quality, multi-component T2 relaxometry can only be performed one slice at a time using 32 or more echoes and at least 6 min/slice. This is impractical for a sleeping child, and whole brain coverage is prioritized 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 the T2 relaxation time for a single compartment model throughout the brain. The PD/T2W structural imaging sequence serves double duty in this regard (Table 5, Fig. 3). A second double echo 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 (Table 5, Fig. 3). However, this second acquisition is deemed lower priority to the DTI and MRS protocols. Thus, the second dual echo acquisition is acquired as the last element of the overall 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 is about 5 min duration.

Diffusion tensor images (DTI, Table 5, Fig. 5) are acquired to cover the whole brain with 3 mm isotropic voxels. Single shot, spin echo diffusion-weighted images are acquired using an echo planar sequence. Since diffusion is faster in the brains of the youngest children, a single diffusion-weighting (b value) is not optimal. As such, DTI is obtained in separate acquisitions: $b=0$, 1000 s/mm^2, and $b=0$, 500 s/mm^2). The gradient orientations are the standard 6-direction set originally established by Pierpaoli et al. (1996) and subsequently implemented by the MR vendors [x, y, z gradient unit vectors: (1,0,1), (−1,0,1), (0,1,1), (0,1,−1), (1,1,0), (−1,1,0)]. In recognition of the likelihood for subject motion, signal averaging is not employed. Rather, separate acquisitions are repeated, i.e., two acquisitions of the $b=0$, 1000 s/mm^2, two acquisitions of the $b=0$, 500 s/mm^2, and finally two more acquisitions of the $b=0$, 1000 s/mm^2. Cardiac-gating, which improves data quality, is deemed impractical for this study as it increases scan duration and complexity.

At the outset of the current study, acquisition of DTI data in children ranging in age from the newborn to 4:5 years was designed to provide quantitative assessment of diffusion tensor attributes such as mean diffusivity and fractional anisotropy during normal brain development in young human subjects. This goal is being met. Importantly, in a supplementary study of the current sample, additional DTI data sets are being acquired using 6 different b-factors and a maximum of 50 unique directions. These data will certainly provide opportunity for quantitative fiber tract analysis and will be the subject of subsequent manuscript(s).

Single voxel magnetic resonance spectroscopy (MRS) is also performed at Children's Hospital Boston (Table 5). Spectroscopy is performed using four single voxel acquisitions as the time required for multi-voxel spectroscopy is too great for use with this non-sedated cohort of sleeping children. Spectra are acquired from left frontal white matter, left thalamus, bi-occipital gray matter and left parietal white matter. A moderate TE (TE 144 MS) PRESS acquisition, with voxels measuring 15 × 15 × 15 mm (3.375 cc), and 64 signal averages produces acceptable SNR spectra in a scan time of less than 3 min per voxel.

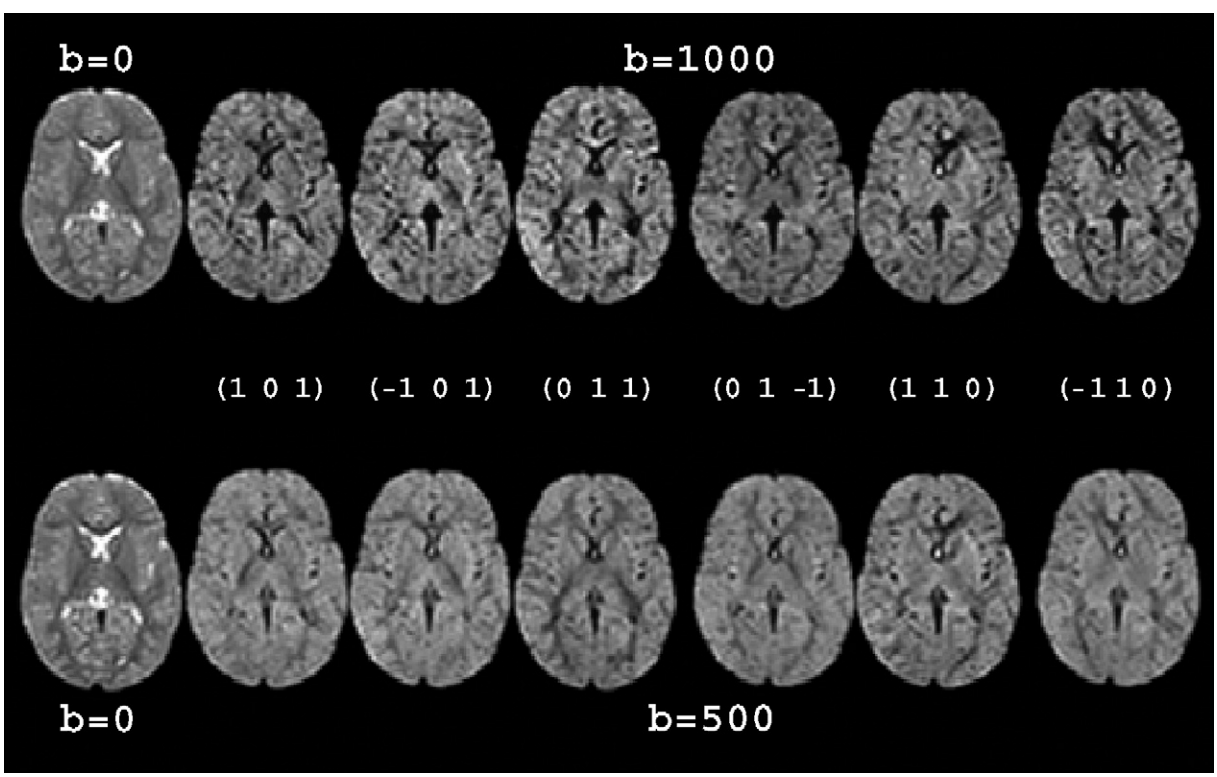

Fig. 5. Diffusion weighted images from an 18 month old (same toddler as Fig. 2). Images were acquired in the axial plane at the level of the Foramen of Monro and basal ganglia. Two separate acquisitions are employed. The top row acquired $b=0$ s/mm^2 and 6 directions of $b=1000$ s/mm^2. The second acquisition acquired $b=0$ s/mm^2 and the same 6 directions of $b=500$ s/mm^2. The numbers in parentheses are the diffusion gradient directional unit vector (x, y, z). The first acquisition was repeated twice, then the second acquisition was repeated twice, finally, the first acquisition was repeated twice more. The 6 separate acquisitions were used to compute the diffusion tensor at each voxel location.

In summary, the highest priority of the Objective 2 MR protocol is the collection of structural MR images similar to those obtained in Objective-1. As such, T1W and PD/T2W acquisitions are deemed critical, and constitute the *minimal acceptable dataset*. Both sequences are repeated until satisfactorily acquired, otherwise the scan session is aborted. The remaining protocol steps are prioritized as follows: T1 relaxometry, DTI or MRS, and a second dual echo acquisition for T2 relaxometry. If no repeats are necessary, the minimum Objective-2 MR protocol is obtained in under 15 min, and the full Objective-2 MR protocol is obtained in under 45 min.

Quality confirmation process

Quality confirmation (QC) methods and procedures used by Objective-2 are outlined in Table 6 and described in detail on the project website (www.bic.mni/mcgill.ca/nihpd_info). The QC processes for behavioral instruments (i.e., neurobehavioral tests and neurological exams; Table 3) and the Family Interviews for Genetic Studies-FIGS (Table 5) are administered through the Clinical Coordinating Center (CCC; Saint Louis). The QC processes for brain images and database data input are administered through the Data Coordinating Center (DCC; Montreal).

The QC process for the administration and scoring of the *behavioral instruments* (Tables 3, 4 and 6) is conducted to insure that the data acquisition sites (Boston and Saint Louis) are administering and scoring all instruments in a consistent and accurate fashion; thereby yielding test results that are comparable, valid, and reliable across sites and participant age-ranges. All behavioral testers and interviewers are provided with training sessions (including written materials and video tapes) for administration and scoring of all behavioral instruments used in Objective-2.

QC evaluation is conducted from test/interview booklets and videotape (tests and exams) or audiotape (interviews). Initially, "practice children" are assessed, and once achieving passing status, "real Objective-2 participants" can be seen. Performance for neurobehavioral test administration and scoring of each test is graded as: Administered and Scored Correctly-Passing (i.e., ≥90% accuracy for administration and scoring by the tester), Provisionally Passing (≥90% accuracy for administration and scoring by the tester, but potentially significant errors, e.g., borderline passing accuracy of 90–92%), or Not Administered and/or Not Scored Correctly–Not Passing (≤89% accuracy for administration and scoring by the tester). Performance on the neurological examination is graded as passing (i.e., >95% accuracy for administration and scoring) or not-passing. Passing on the FIGS interview is a rating of >80% agreement with the CCC rater for administration of the interview (Kappa>.80, Cohen, 1960). Written feedback about an individual's performance is provided to the site for each tester and instrument undergoing QC evaluation. If QC does not yield a passing grade or rating, working with practice children is re-instituted until passing status is re-achieved, and then real participants can again be seen. The CCC maintains a database for behavioral instrument QC evaluation results, and archives the QC materials.

The DCC administers the QC process for *database data entry*, and provides training sessions and written materials for database staff at both sites for the data entry for all behavioral instruments. Three levels of data entry QC are utilized (Table 6): (1) Sites double-check their own data entry, and compare their hand scoring of instruments with the automated scoring provided by the database. (2) The database itself is designed such that the data entry is completed on a computer monitor screen image that resembles the record booklets and scoring pages of individual instruments, and data input is automatically checked by the database for valid types, ranges, and completeness. (3) Hard copies of all instrument booklets and scoring forms are sent to the DCC for one in every three (quasi-random) "real participants" assessed by a site. QC evaluation includes direct comparison hard-copy data with the data entered into the database. The sites correct any errors in data entry discovered by the DCC, and repeated data input errors elicit additional training as appropriate.

QC for the *brain images* is conducted by both the site and the DCC (Table 6). Each site visually checks the images at the time of

Table 6
Quality confirmation (QC): areas and procedures

I. *CCC: Neurobehavioral Tests*
- A. Criterion for QC (as determined from videotape and scoring record of testing):
  1. Passing: ≥90% accuracy for administration/scoring of individual subtests
  2. Age-groups: 0:0 to 0:11, 0:12 to 2:11, and 3:0 to 4:5
- B. *Initial* QC for new testers
  1. Use "practice" children at each of the three age-groups
  2. Continue #1 until "passing status" achieved for all subtests/ages
  3. Promoted to testing "real" participants (requires QC on first five participants)
- C. *Ongoing* QC for testing with "real" participants
  1. QC evaluation of every sixth real participant for duration of project

II. *CCC: Neurological Examinations*
- A. Criterion for QC (as determined from videotape of examination and scoring)
  1. Passing: >95% accuracy for administration and scoring of each exam
  2. Age-groups: 0:0 to 0:1, 0:2 to 0:11, 1:0 to 2:11, and 3:0 to 4:5
- B. QC evaluation: Videotape of practice child being examined submitted for QC
- C. Examiners maintain passing status for each exam/age group

III. *CCC: Family Interviews for Genetic Studies (FIGS)*
- A. Criterion for QC (as determined from audiotape of interview)
  1. Passing: Kappa>.80 (>80% agreement for interview administration)
- B. *Initial* QC for new interviewers
  1. Audiotapes of five interviews with "practice" parents
- C. *Ongoing* QC for interviewers achieving passing status with real participant parents
  1. QC evaluation for randomly selected real participant for duration of project

IV. *DCC: Database Data Entry*
- A. Hard copies of all behavioral tests, examinations, and interviews for one in three participants studied by the site are compared to database entry for accuracy
- B. Database input errors are corrected by the site
- C. Once database for participant is corrected, participant's data is approved
- D. Remediation training plans are developed for PSC sites with data entry problems

V. *DCC: Brain Images*
- A. Evaluated initially at acquisition site, then transferred to DCC for QC evaluation:
  1. Protocol compliance and image quality are evaluated
- B. Images evaluated for artifacts and quality and "passed" or "failed"
  1. If images pass: scan child at next time-point
  2. If images fail: rescan child, if age-window remains open
  3. If images fail: scan child at next time-point, if current age-window closed

acquisition, and re-checks the images with 3D display software following data transfer to the site's local, study work station. The image data are then transferred to the DCC where they are checked for integrity, completeness, and accuracy of acquisition parameters. Finally, the images are also checked for quality, both visually and with quantitative indices at the DCC. If the minimum MR data set is not achieved at a given time-point because the images failed DCC QC, the scan is either repeated (if within the child's window), or the child merely advances to the next time-point for subsequent scanning.

Comparability of image characteristics, contrast and quality has remained a critical and continuous focus of effort while conducting this multicenter study. In the current work, while a 1.5 T MRI scanner is used in each of the two centers acquiring imaging data, the center in Boston uses a General Electric product while the center in Saint Louis uses a Siemens scanner. At both sites, monthly scans of all imaging pulse sequences used in the current study are acquired using the standard American College of Radiology (ACR) phantom. In addition, each site scans the same human subject (who traveled between both sites) at regular intervals so that data sets can be acquired from the same human brain for quality assurance purposes. Both ACR and human phantom data sets are analyzed by the DCC.

The entire MR protocol is applied to the phantoms. Automated analysis procedures (L. Fu, V. Fonov, B. Pike, A. Evans, and L. Collins, unpublished, 2006) for estimation of signal-to-noise ratio (SNR), percent uniform intensity (PUI), and geometric distortion (D) are applied to each T1w,T2w and PDw phantom scan. These data are analyzed using JMP (SAS Institute, version 5.0.1.2) to determine if there are significant differences between sites or if drifts occur over time. Two image correction procedures have been developed to reduce acquisition artifacts. The first corrects for scanner-dependent intensity inhomogeneity. The second corrects for scanner-dependent geometric distortion. Image non-uniformity correction fields are estimated for each subject using N3 (Sled et al., 1998). The fields for all subjects acquired on a given scanner are averaged together in the scanner coordinate system to create a scanner-specific bias field that is used to correct the image data before processing. A geometric distortion map is modeled by estimating the parameters of the spherical harmonic equations mapping an ideal numerical ACR phantom to the acquired images of the phantom.

Evaluation of participant images from the two centers was performed initially on a qualitative basis to ensure that contrast and image qualities were similar in both imaging centers. Region of interest intensity analysis of grey and white matter regions demonstrated no significant differences in subjects tested. Second, an image processing pipeline, applied to the MRI data, results in automatically defined regions of interest that include total GM and WM in the intracranial cavity. When these volumes were used in a general linear model with site, scanner, age and sex as explanatory variables, only age and sex emerged as statistically significant in the regression.

Results and discussion

As data collection is still in progress, the results presented below are preliminary. These preliminary results are being presented for the purpose of providing an indication of the project's progress, as well as a preliminary preview of the scope of the neuroimaging and neurobehavioral data that are being collected.

Weekly progress report

Table 7 presents a representative copy of an Objective-2: Weekly Progress Report (the report is the actual project report for a recent week). The report shows the number of candidates: screened, excluded within specific exclusion categories, and the total excluded (note that an excluded child/family is only represented in a single exclusion category, as screening was terminated as soon as the first exclusion criteria was met). Also included are the numbers of candidates that refused to participate in the project or are "in progress" (but not yet scanned). In addition, the number of participants making up the sampling plan are shown, as well as the number of participants completing their first scan (which is equal to the current participant '*N*'), and subsequent sequential scans (2nd through 5th plus), and the total number of completed scans (all scans for all participants).

As the numbers in Table 7 reveal, 17.6% of the Objective-2 candidates *pass* the screening and exclusion process to date (Boston = 17.0%, Saint Louis = 18.4%). This relatively low percentage of children passing the screening/exclusion process is most likely due to the very comprehensive and rigorous exclusion criteria that are being used to assure that participants are 'normal and healthy.' Notable and consistent with the comprehensive screening and exclusion criteria is the finding that *none* of the 75 Objective-2 participants completing brain scans to date has displayed brain injury or abnormality as per neuroradiology review.

Similar to these findings for the younger children of Objective-2, Objective-1 (Brain Development Cooperative Group, 2006) also reports a relatively low percentage of candidates passing the screening/exclusion process (i.e., 1 = 15.1% versus 2 = 17.6%). Further, Objective-1 has completed brain scans on approximately 400 children from ages 4:6 to 18:0, and only *one* has displayed a

Table 7
Sample Objective-2: weekly progress report

	Boston	Saint Louis	Totals
Screened candidates	2103	1767	3870
Exclusions based on:			
Demographic factors	193(9.2) [a]	47(2.7)	240(6.2)
Pregnancy complications	314(14.9)	494(28.0)	808(20.9)
Delivery complications	275(13.1)	321(18.2)	596(15.4)
Birth—neonatal child factors	746(35.5)	553(31.3)	1299(33.6)
Development—child factors	86(4.1)	4(0.2)	90(2.3)
Psychiatric history (family, child)	132(6.3)	22(1.2)	154(4.0)
Child testing—parental interviews	0(0)	0(0.0)	0(0.0)
Neurological exam—child	0(0)	1(0.1)	1(0.03)
Total candidates excluded	1746 (83.0)	1442 (81.6)	3188 (82.4)
Refusals/loss of contact	127	164	291
Candidates in progress (NO-SCAN)	202	114	316
Sampling plan: target "*N*"	46	60	106
Participants completing 1st SCAN	28[60.9] [b]	47[78.3]	75[70.8]
Completing SCAN—2	21[45.7]	40[66.7]	61[57.5]
Completing SCAN—3	14[30.4]	31[51.7]	45[42.5]
Completing SCAN—4	2[4.3]	20[33.3]	22[20.8]
Completing SCANS ≥ 5	0[0.0]	15[25.0]	15[14.2]
Total completed scans	65	153	218

[a] ( ) Percentage of screened candidates excluded.
[b] [ ] Percentage of participants enrolled and completing their first scan.

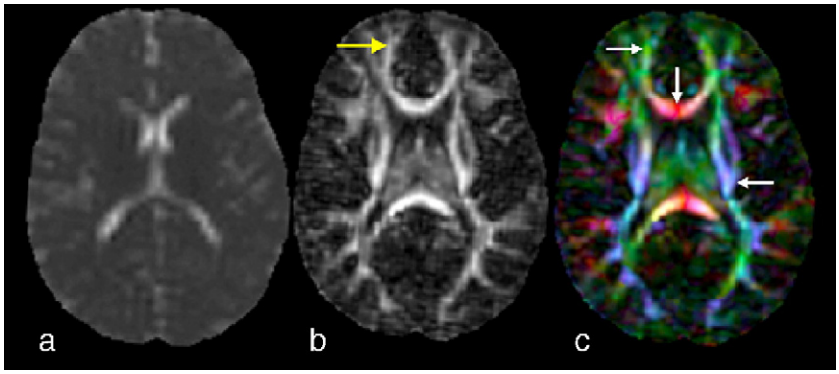

Fig. 6. DTI scalar parameter maps (same 18 month toddler as shown in Fig. 2). After computation of the diffusion tensor, scalar parameter maps were derived to characterize average diffusion and diffusion anisotropy. (a) Mean diffusivity is a measure of average (total) diffusion. (b) Fractional anisotropy is greatest in highly ordered, tightly packed white matter tracts. The yellow arrow (in b) highlights that fractional anisotropy contrast precedes the contrast changes on T1-weighted (see Fig. 2, black arrow) and T2-weighted images (see Fig. 3, black arrow). (c) Color fiber maps indicate the orientation of white matter tracts: green for fibers oriented anterior to posterior (upper arrow), blue for fibers passing through the image plane (lower arrow), red for fibers oriented left to right (middle arrow).

brain abnormality, as per neuroradiology review (i.e., 1 = 0.3% versus 2 = 0%). The similar findings between the two Objectives are likely related to the comprehensive and rigorous screening and exclusion criterion that they share for this project.

The decision to exclude participants for low (but not high) child test scores and/or child growth indices for this project deserves comment. The goal of this project is to obtain brain and behavioral data from a sample of truly healthy children. Generally, young infants and children scoring extremely low on standardized/normed behavioral assessments and/or displaying retarded or depressed growth measures are at risk for developmental delay, although high test scores (e.g., high IQ scores) and high growth scores (e.g., cerebral gigantism or Canavan's disease) may or may not be indicative of health. Nevertheless, no child has been excluded from this project based on low behavioral test scores (e.g., <70 on developmental or IQ testing) indicating that the truncated lower range cut-off for normed behavioral testing has not been brought into play. It is likely that children that would have scored low on the exclusionary behavioral tests were already excluded by other exclusion factors, such as medical history. Likewise, no child with high growth indices (e.g., large head circumference) has been excluded for low behavioral test scores (see preliminary results). This indicates that that sample that we have currently recruited would be the same even if we had not included a behavioral testing exclusion factor.

In comparison to the sampling plan (Fig. 1, Table 7), 71% of the targeted participant sample in the plan (i.e., 75 of 106) has successfully completed at least one time-point (which comprises a brain scan, neurobehavioral testing, neurological examination, and parental questionnaires). Eighty-eight percent of the total targeted scan time-points (i.e., 218 of 248 time-points) have already been completed (Fig. 1 and Table 7). The numbers of brain scans completed for each of the 11 cohort ages (Fig. 1) ranges from a low of 2 scans at 1:6 to a high of 20 scans at birth (0:0). Further, over 42% of the targeted sample (i.e., 45 of 106) has already undergone the required 'three longitudinal' scans, and 21% of the targeted sample (22 of 106) has already completed four or more longitudinal scans. The current sample of 75 participants is also demographically-balanced and diverse with regard to gender (half of sample is female), race/ethnicity (each of the six race/ethnicity groups shown in Table 1 are currently represented in the sample), and income level (low, medium and high) as per national statistics (United States Census Bureau, 2000; United States Department of Housing and Urban Development's Office of Policy Development and Research, 2003). It is highly anticipated that the numbers in the original sampling plan (Fig. 1) will be far exceeded by the final numbers of participants and longitudinal scans obtained.

Brain scan success

Approximately two-thirds of the MRI scan attempts with Objective-2 participants are successfully completed. This success rate spans the age range from neonates through 4:5. Successful scans are defined as those that include at least the minimum MRI data sets, i.e., T1W and PD/T2W (Table 5) which pass the brain image QC process at the DCC (approximately 90% of scans passing).

The safety of all children was monitored from their arrival to the scanner site through completion of the brain scan. The scanner room was maintained at a comfortable temperature and the children were swaddled or blanketed to maintain comfortable sleeping temperature. Pulse oximetry was used at each center to monitor subjects during the scan. Also, the children were directly observed by one or two trained members of the research staff posted at one or both ends of the magnet bore throughout the scan. With rare exception, one or both parents accompanied the child in the scanner room throughout the scan, and the scan operator was in continuous voice and visual contact with the staff in the scanner room. Greater than 200 scans have been completed as part of this study without a single adverse event involving the child or parents at either center.

Given that the scans in this project have been safely performed on non-sedated, sleeping infants and young children, it is likely that similar non-sedation studies could be performed on naturally sleeping children with underlying neurologic and psychiatric deficits. As described above, the provision of techniques for scanner acclimation and allowing sufficient time for the onset of deep sleep will facilitate the success rates for non-sedated scanning of special populations of young children.

The key for successful, non-sedated scanning is to have both the child and the parent comfortable enough for the child to sleep in the scanner room.

Unsuccessful scans are most frequently due to: (1) the child not falling sufficiently asleep (i.e., sleeping deeply) to tolerate preparation for the scan (e.g., placement of ear plugs, positioning the head within the magnet coil, head stabilization), (2) the child waking-up and/or moving during the actual scanning process (e.g., in response to high noise levels, vibration of the scanner bed, or (3) scanning equipment failure or malfunction (e.g., scanner booting problems). Based on our experience with Objective-2 aged infants and children, hunger, teething, stuffy nose or cough, stomach distension/bowel movements, fever, or having had an "atypical day" are likely to alter a child's sleeping patterns, and make it difficult to complete the brain scan protocol.

Sample MR image data

Typical T1-weighted images from a toddler (female, 1:6) are shown in Fig. 2. By 18 months of age, the T1-weighted images already have a myelination signal pattern that is very similar (but not identical) to the adult pattern. At this age, most of the white matter is hyperintense to the cortical gray matter (white arrows). However, the subcortical white matter of the frontal and temporal lobes is not as well myelinated as in the adult (black arrows). Both the differences and similarities between the young cohort and adults constitute the strength and promise of the Objective 2 database. Sagittal (Fig. 2b) and coronal (Fig. 2c) orientations are generated from axial images (Fig. 2a) using multiplanar reformation. Note that all brain images shown in Figs. 2–7 are of the same participant, and that for all brains, left-side of image is right-side of patient, as per radiological convention.

The images in Fig. 3 serve two purposes. Figs. 3a and c are PD and T2W images that match the sequence timing parameters of the Objective 1 protocol for older children. The PD and T2W scans are necessary for image segmentation of brains with a mature contrast pattern. Figs. 3b and d are the second, dual echo acquisition included to improve T2 relaxometry in younger children. The images from this 18 month old (same toddler as Fig. 2) show an adult-like, myelination pattern in the corpus callosum, internal capsule, and in the optic radiations (e.g., Fig. 3c, white arrow). An immature pattern of myelination is seen in the subcortical regions of both frontal lobes (Fig. 3c, black arrow).

Relaxometry is a unique aspect of the Objective 2 study design. Relaxometry is a quantitative imaging technique used to compute MR relaxation times for each voxel in the brain. Quantitation is important because there are dramatic qualitative changes in image contrast during the brain maturation process. These changes confound standard image segmentation algorithms. The quantitative techniques employed in this protocol will facilitate research on image segmentation, on water and myelin content, and on brain structure–behavior correlations in children in this young age range. Fig. 4 illustrates the T1 relaxometry data set (same 18 month toddler as Fig. 2). The first image (a) was obtained without inversion. The inversion time was increased subsequently from 50 ms to 2000 ms as indicated in the figure caption. Inversion

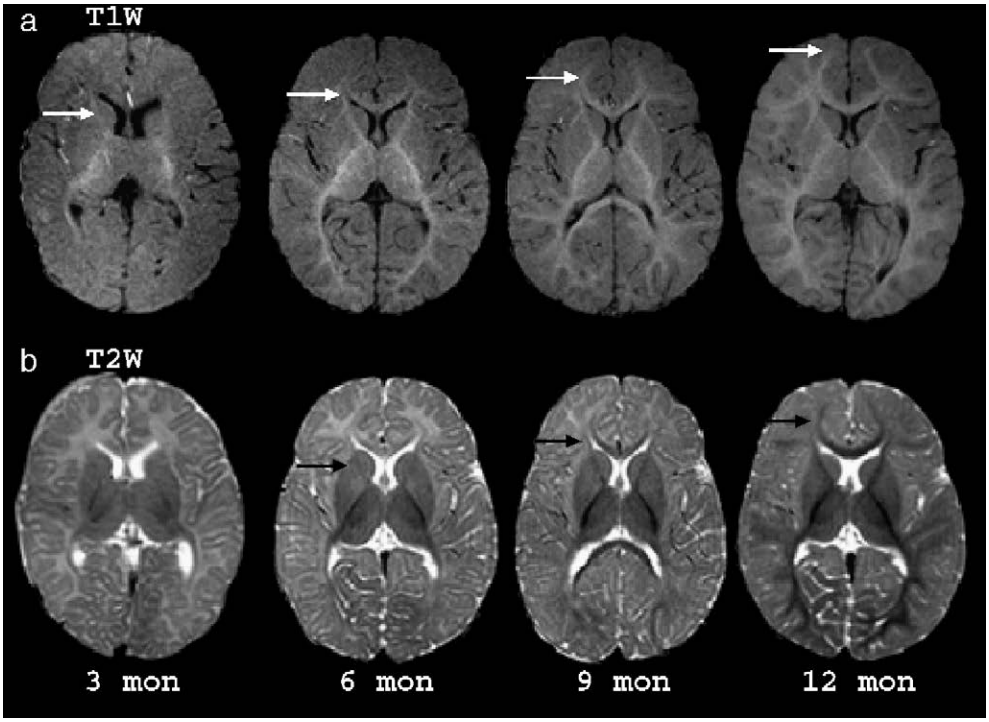

Fig. 7. Brain maturation illustrated on T1W and T2W MR images from a single participant at 3, 6, 9 and 12 months of age (same toddler as in Fig. 2). The images shown were acquired parallel to the anterior/posterior commissure line at the level of the Foramen of Monro. Row 'a' T1W images show maturational trends of increasing myelination from occipital to frontal lobes (caudal-to-rostral), and from central to subcortical white matter (medial-to-lateral) as the subject ages. As myelin matures, T1 shortens and the T1W signal in white matter increases. Note the progression of myelination into the frontal lobe as indicated by the white arrows. Row 'b' T2W images show a similar, but delayed trend with age. T2 shortens as myelin matures (black arrows), which manifests as signal reduction in mature white matter. At 12 months, the frontal subcortical white matter is hyperintense. In contradistinction, T2W signal in the subcortical frontal white matter is isointense to gray matter.

Recovery (IR) preparation allows for computation of T1 relaxation times.

The diffusion weighted images of an 18 month old (same participant as Fig. 2) are shown in Figs. 5 and 6. Fig. 5, top row, illustrates $b=0$ and 6 directions of $b=1000$ s/mm^2. The bottom row illustrates $b=0$ and the same 6 directions of $b=500$ s/mm^2. These data are used to compute the diffusion tensor within each voxel. From the diffusion tensor, one can compute scalar quantitative parameters, such as mean diffusivity (Fig. 6a), fractional anisotropy (Fig. 6b) and color coded white matter orientation maps (Fig. 6c). Note that the subcortical white matter myelination of the frontal lobes is clearly evident in the 18 month old brain on qualitative inspection of the fractional anisotropy map (Fig. 6b, yellow arrow). This is in contradistinction to the T2-weighted scan, which shows ill-defined gray/white contrast at this age (Fig. 3, black arrow). This example illustrates the vast range of image data and brain development covered by the project. Future analysis will focus on the role of each scan (e.g., T1W, PD/T2W, DTI) for understanding the brain maturational process.

The longitudinal nature of The MRI study of normal brain development is evident in Fig. 7. The same participant (same as Fig. 2) was imaged serially at 3 months, 6 months, 9 months and 12 months of age. Note that, in general terms, gray/white matter contrast reverses at different rates for the T1-weighted scan (top row) and the T2-weighted scan (bottom row). As a specific example, examine the deep white matter of the frontal lobe (forceps minor) on the T1-weighted images (top row, 3rd from the left). The white arrows demonstrate progressive myelination with advancing age in the frontal lobe white matter. The T2-weighted images show immature myelination in the forceps minor until 12 months of age (bottom row, 4th from the left.). The black arrows illustrate that there is an approximate 3 month lag in T2 contrast relative to the T1 contrast (white arrows in row a).

The process of developing quantitative analysis techniques for Objective-2 brain images has begun. Included are processing of the anatomical images (T1W, PD/T2W), T1 relaxometry data, a second dual echo pair to compute T2 relaxometry, MRS and DTI data. For example, processing of anatomical (e.g., T1W, PD/T2W) images obtained from birth through approximately 4:5 needs to be developed and validated. This processing includes: Registration (Linear inter-modal, Linear stereotaxic, Non-linear intra-subject, Non-linear stereotaxic inter-subject); Classification; Cortical surface extraction; Structure segmentation and Volumetrics. Processing of MRS and DTI data will follow and parallel the anatomical data processing. Development of these new analytic methods is likely to be most difficult and time demanding for images obtained from children less than 2 years of age due to the rapid and relative changes in signal intensities of gray matter and white matter that attend the rapid advancement of myelination during this period.

Examples of preliminary data for selected measures of growth and behavior

To provide an estimate of growth and behavior characteristics of our sample to date for this report, the following measures were selected for preliminary evaluation on a sample of 24 participants that have successful brain scans (i.e., representing approximately 23% of the targeted sample of 106 participants). Twelve participants (6 females and 6 males) between the ages of 0:3 through 2:6 were randomly selected from the available Boston sample, and those 12 participants were matched for age and gender by 12 participants selected from the Saint Louis sample.

Fig. 8 presents preliminary data (mean ± standard deviation, as appropriate) for: a representative growth measure, i.e., *Occipital–Frontal Circumference* (OFC [$n=24$], head circumference percentile; Chen, 2000; National Center for Health Statistics, 2000), and three representative behavioral measures, i.e., *Handedness-1* ($n=16$, ages 1:00 to 2:6 [$n=8$ were less than age 1:0 and do not receive handedness testing],; *Bayley Scales of Infant Development-II* (BSID-II [$n=24$], Mental Developmental Index and Psychomotor Developmental Index scores; Bayley, 1993); and *Preschool Language Scales-3* (PLS-3 [$n=24$], Total Language Score; Zimmerman et al., 1992).

These growth and behavioral measures were statistically analyzed to compare Boston and Saint Louis sites, and to compare males and females. There were no statistically significant differences between sites ($p>0.05$), or between genders ($p>0.05$). Therefore, the percentiles, percentages, and standard/normed scores for specific growth and behavioral measures were pooled for the combined sites and genders and are presented in Fig. 8. Mean head circumference (OFC) of children ages 0:3–0:30 was at the 59th percentile (range = 19th–98th percentile for individual participants, Fig. 8) based on national norms (Chen, 2000; National Center for Health Statistics, 2000).

For hand preference/use, 9 of 16 participants (56%) at 1:0–2:6 were classified as displaying a "right-hand (R-H) preference" (Fig. 8). Nine children displayed weak (5 of 8 trials using right-hand) through strong (8 of 8 trials using right-hand) right-hand preferences. The remaining seven children used the right hand on fewer than 5 trials (i.e., used a combination of left hand or both hands used on 5 trials or more). This preliminary hand preference result is consistent with other research reporting a slight tendency for very young children to show a 'right hand' preference over a 'non-right hand' preference (e.g., Gabbard et al., 1993; Kaufman et al., 1978; Michel et al., 1985; Tan, 1985).

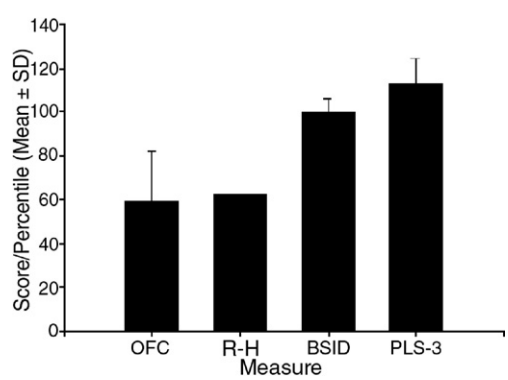

Fig. 8. Means (+standard deviations, S.D.) for: Occipital–Frontal Circumference (OFC [head circumference], percentile); Right Hand Preference (percentage preferring the Right Hand [R-H]); Bayley Scales of Infant Development-II (BSID-II, data shown are mean standard scores [mean ± S.D. = 100 ± 15] of the combined Mental Developmental and Psychomotor Developmental Indexes), and Preschool Language-3 standard scores (Total Language score: mean ± S.D. = 100 ± 15) for 12 participants each at Boston and Saint Louis. The participants included equal numbers of males and females ranging in age from 0:3 through 2:6. Twelve participants were randomly selected from the Boston participant pool, and they were matched for age and gender by 12 participants from the Saint Louis pool.

BSID-II data presented in Fig. 8 are based on averaged standard scores (mean ± standard deviation, sd) from the Mental Developmental Index [normed mean = 100 ± 15] plus Psychomotor Developmental Index [normed mean = 100 ± 15]; Bayley, 1993). These BSID scores ranged from 88 to 108 across all participants, with an overall mean of 100.2. The mean Preschool Language Scales-3, Total Language Score (PLS-3 [normed mean of 100 ± 15]; Zimmerman et al., 1992) was 112.0 (range of 90–133).

These preliminary growth and behavioral results are interesting in that they are generally consistent with and indicative of the relatively broad data distributions and measures of central tendency that are representative of "normal/typical" performance, despite the extremely comprehensive, rigorous and strict exclusion factors used for Objective-2. Although preliminary, the only measure that appears to be biased towards higher scores is the behavioral measure of language ability, where the mean of the sample (mean = 112) is almost one standard deviation above the normative mean of 100, and the highest score (score = 133) exceeds two standard deviations above the normed mean of 100. It is noteworthy, however, that the score of 133 is from a single, extremely verbal 2 year old, and this extreme score increased the group mean score by approximately 5 points. Overall, these preliminary growth and behavioral are quite consistent with general expectations that continuously healthy children will display good growth and behavioral development.

Conclusions and contact information

Objective-2 researches broad aspects of brain MRI (e.g., T1 relaxation, T2 relaxation, DTI, MRS) and behavioral (e.g., sensory-motor, cognitive, language, emotional) development of normal, healthy children from ages birth through 4-years 5-months. To our knowledge, this effort represents the first developmental MRI and behavior study that applies such a comprehensive, rigorous and strict set of biological and behavioral exclusion factors, as well as a US Census-based, demographically-balanced sample. This project also provides the first longitudinal DTI data for this age-group. A major goal of this research is to assemble a correlative brain–behavior development database that will facilitate the creation of automated, quantitative MR image analyses that can be used to generate developmentally valid brain templates and growth curves for normal, healthy infants and young children. The database can be used by clinicians and researchers to support accurate identification and definition of pathologies and abnormalities of the brains of infants and children with disease or disorders of sensory-motor, cognitive, language, behavioral, and/or emotional development. Like its sister study of children extending in age from 4-years 6-months into young adulthood (Objective-1), the stringency of screening during the subject candidacy phase of Objective-2 was designed to exclude children with medical, psychologic, and cognitive features not characteristic of healthy development. Availability of brain atlases, templates and growth curves for normal, healthy brain development will advance understanding of the normal, healthy "variability" range of whole- and regional brain structure during development, and will further the ability to identify relationships among measures of brain and behavioral development. Finally, knowledge of the healthy brain is imperative for identification and understanding of brain pathology that may be associated with special clinical populations, such as children with motor dysfunction, visual processing deficits, learning disabilities, or attentional problems.

The overall MR database being assembled by Objective-1 and -2 is designed to facilitate knowledge and understanding of brain development from birth into early adulthood that will serve to improve the diagnosis, treatment, and quality of care of infants, children, adolescents, and young adults with suspected brain dysfunction or abnormality. It is anticipated that portions of the Objective-1 database will be released to become available for use by clinical and research communities in the near future. Later, following the development of brain image measurement methods for the very young infants and children, portions of the Objective-2 database will also be released to the clinical and research community.

Additional information about "The NIH MRI Study of Normal Brain Development: Objective-2," can be obtained at the project public website (www.brain-child.org), via our protocol document (register for protocol document release via rozie@bic.mni.mcgill.ca), or from project procedure documents available at www.bic.mni/mcgill.ca/nihpd_info.

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