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The Diffusion Tensor Imaging (DTI) Component of the NIH MRI Study of Normal Brain Development (PedsDTI)

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Abstract

The NIH MRI Study of Normal Brain Development sought to characterize typical brain development in a population of infants, toddlers, children and adolescents/young adults, covering the socio-economic and ethnic diversity of the population of the United States. The study began in 1999 with data collection commencing in 2001 and concluding in 2007. The study was designed with the final goal of providing a controlled-access database; open to qualified researchers and clinicians, which could serve as a powerful tool for elucidating typical brain development and identifying deviations associated with brain-based disorders and diseases, and as a resource for developing computational methods and image processing tools.

This paper focuses on the DTI component of the NIH MRI Study of Normal Brain Development. In this work, we describe the DTI data acquisition protocols, data processing steps, quality

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assessment procedures, and data included in the database, along with database access requirements. For more details, visit http://www.pediatricmri.nih.gov.

This longitudinal DTI dataset includes raw and processed diffusion data from 498 low resolution (3mm) DTI datasets from 274 unique subjects, and 193 high resolution (2.5mm) DTI datasets from 152 unique subjects. Subjects range in age from 10 days (from date of birth) through 22 years. Additionally, a set of age-specific DTI templates are included. This forms one component of the larger NIH MRI Study of Normal Brain Development which also includes T1-, T2-, proton density-weighted, and proton magnetic resonance spectroscopy (MRS) imaging data, and demographic, clinical and behavioral data.

Keywords

diffusion; DTI; database; NIH; MRI; multicenter; longitudinal; pediatric

1. Introduction

The NIH MRI Study of Normal Brain Development (PedsMRI; www.pediatricmri.nih.gov) sought to characterize typical brain development in a population of infants, toddlers, children and adolescents/young adults, covering the socio-economic and ethnic diversity of the population of the United States. It was a multi-center, longitudinal study, jointly funded by several NIH institutes, specifically the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), the National Institute on Drug Abuse (NIDA), the National Institute of Mental Health (NIMH) and the National Institute of Neurological Disorders and Stroke (NINDS). The study began in 1999 with data collection commencing in 2001 and concluding in 2007. The study was designed with the final goal of providing a controlled-access database; open to qualified researchers and clinicians, which could serve as a powerful tool for elucidating typical brain development and identifying deviations associated with brain-based disorders and diseases, and as a resource for developing computational methods and image processing tools.

Longitudinal data were collected from un-sedated, medically healthy, psychiatrically normal children, adolescents, and young adults (up to age 22) at six sites across the United States using an epidemiological sampling strategy, stratified by age and sex, and matched to the U.S. Census on family income and race/ethnicity. The participating sites, coordinating centers, data processing centers and investigators are listed at www.pediatricmri.nih.gov/ nihpd/info/participating_centers.html. Data acquisitions included multiple magnetic resonance imaging (MRI) modalities and comprehensive, age-appropriate clinical, cognitive and behavioral measures collected at each time point. All subjects were to have a minimum of 3 visits with the first scan occurring at any age between 10 days (from date of birth) through 18 years 3 months of age. There was no preset limit on the number of visits for those under 4.5 years. The maximum number obtained on a single subject was 10 visits. The study was organized into 2 objectives. Objective 1 included subjects aged 4 years 6 months and older at enrollment, studied at two-year intervals for three visits, while objective 2 included subjects that were younger than 4 years 6 months of age at enrollment, studied at intervals ranging from three months to one year for up to ten visits. T1-, T2- and proton

density-weighted imaging were the primary MRI modalities of the study. Ancillary modalities included proton magnetic resonance spectroscopy (MRS) and diffusion tensor imaging (DTI). For a more detailed overview of the study, see (Evans, 2006) and (Almli et al., 2007).

This paper focuses on the DTI component of the NIH MRI Study of Normal Brain Development (PedsDTI). DTI was acquired at five out of the six sites (1.5T; 2 Siemens scanners, 3 GE scanners). All DTI data assessment, quality control, and pre-processing were handled by the DTI-processing center (DPC) at the NIH.

This project provided one of the first publicly-available pediatric DTI databases for typical development from ages newborn to young adult, and resulted in the development of novel DTI image processing algorithms (Chang et al., 2005; Chang et al., 2012; Rohde et al., 2004; Wu et al., 2008) and tools publicly released in the TORTOISE software package (http://tortoisedti.org) (Pierpaoli et al., 2010). It also provided a dataset including phantom and human brain data for evaluating cross-site reliability in a multisite/multi-scanner pediatric DTI study (Walker et al., 2013), a standardized quality assessment method for multi-center DTI studies (Nayak et al., 2011), the development of age-specific brain templates covering birth through young adulthood (Figure 1), and a method of registering brains from this wide age range into a common template space (Pierpaoli et al., 2012), a proposed method of semi-automated ROI placement (Nayak et al., 2012), and the ability to assess the contributions of experimental factors on DTI studies of developmental trajectories (Sadeghi et al., 2015).

2. DTI Acquisition Protocol

Two DTI protocols were acquired on all subjects where possible. These are referred to as "conventional" DTI, or simply DTI, and "extended" DTI (eDTI).

The conventional DTI protocol was designed such that it could be acquired very quickly to accommodate un-sedated children, and conformed to typical DTI studies (as of 1999). For objective 1 scans, the protocol included 6 diffusion directions at b=1000s/mm² plus 1 b=0s/mm², repeated 4 times, totaling 28 brain volumes. For objective 2, we acquired an additional 6 b=500s/mm² plus 1 b=0s/mm² repeated twice, for a total of 42 brain volumes. The full protocol called for a spin echo EPI sequence with minimum repetition time (TR) = 3s, minimum achievable echo time (TE) with full echo acquisition, axial slices (i.e., perpendicular to the z axis of the magnet, not oblique), field of view (FOV), matrix, and slice thickness adjusted to give $3 \times 3 \times 3$ mm³ voxels, with the FOV and matrix size adjusted depending on the head size of the child with approximately 48–60 contiguous slices (no slice gaps). Images were to be reconstructed at their native resolution, without zero filling or interpolation, no cardiac gating.

A total of 498 conventional DTI scans from 274 unique subjects (139 female, 135 male) are included in the database after quality assessment. Longitudinal age distribution separated by gender is shown in Figure 2. The largest number of successful DTI scans on a single subject was six.

b=0 s/mm²; 9 images (GE), 10 images (Siemens)

b=100 s/mm²; 10 images

b=300 s/mm²; 10 images

b=500 s/mm²; 10 images

b=800 s/mm²; 30 images

b=1100 s/mm²; 50 images

The full protocol requirements for eDTI were similar to the DTI protocol with the following changes: Full brain coverage using 60 slices, 2.5mm slice thickness, FOV= 240mm with a 96×96 matrix resulting in $2.5 \times 2.5 \times 2.5$ mm³ voxels.

A total of 193 eDTI scans from 152 unique subjects (82 female, 70 male) are included in the database after quality assessment. Longitudinal age distribution separated by gender is shown in Figure 3.

Both DTI and eDTI were acquired on subjects when possible. There were 133 timepoints from 110 unique subjects which had both DTI and eDTI scans successfully acquired during the same visit.

3. Image Post-processing steps

All DWIs underwent the same set of post-processing steps.

Step 1) Computation of transformation for motion and eddy distortion correction with appropriate reorientation of the b-matrix of each image to account for the applied rotation of the coordinate system (Rohde et al., 2004).

Step 2) Computation of transformation for susceptibility induced EPI distortion correction. The first step in this correction consists of registering the first b0 image to a T2 weighted structural image with a second order model, in native DWI space. This step was applied to all datasets. The second step in this correction uses a b-spline image registration method (Wu et al., 2008). This method has different levels of success depending on age of the subject and amount of distortion. Due to this fact, this type of EPI correction was only applied to data with severe distortion. Generally, this was only applied on GE data for children above the age of 5 years. In all other data, b-spline correction use applied on a case-by-case basis and assessed for quality of improvement post correction. Use of this type of EPI distortion correction is indicated in the metadata contained in the database.

Step 3) Computation of transformation for reorientation to a common anatomical orientation. This step was accomplished by registering the first non-diffusion weighted (b=0s/mm²) image of the DTI dataset to a properly reoriented T2 weighted structural image of the same subject. This T2 image was produced by applying the Talairach transformation (as was done for the T2W images available in the database) but with the scaling terms set to zero. This image, which is named "tal noscale", was provided by the data coordinating center (DCC), but was not included in the structural MRI data release. The tal noscale images are created from structural images from the PedsMRI data (release version 3, from 2009). The DTI data does not match either the native space or Talairach space images provided in the structural data releases, but instead matches the tal noscale images which are included with the corresponding DTI data.

Additional structural images were used for registration in cases where the structural scans failed to pass all stages of quality control required for inclusion in the structural MRI portion of the database. In these cases, the T2W image was assessed for use in the DTI pipeline. If a T2W image was deemed un-usable, or was otherwise unavailable, a T1W image was used in its place. In these cases, no b-spline EPI correction is performed (step 2 above).

Step 4) Application of all transformations, rotation of b-matrices (Leemans and Jones, 2009; Rohde et al., 2004), and production of the raw corrected DWIs. All transformations were combined and applied as a single transformation in order to have only a single interpolation. For the corrected DWI images, noise variance is estimated and images of a variance modulating factor (Irfanoglu et al., 2011) are produced. In the database, we provide transformation matrices (See http://science.nichd.nih.gov/confluence/display/nihpd/ Transformation+Files for full description of the transformation matrices), noise variance images, and the T2W structural image used as target image.

After corrections of the DWIs, either conventional nonlinear least squares tensor fitting, RESTORE robust tensor fitting (Chang et al., 2005), or iRESTORE robust tensor fitting (Chang et al., 2012) is performed, and all tensor derived quantities are created, as described in section 4.1.

4. Data Available in the Database

4.1 Imaging Data

Users are able to download uncorrected raw diffusion weighted images (DWIs) as originally acquired from the MRI scanner, raw corrected DWIs after motion, eddy current and echo planar imaging (EPI) corrections were applied (as described in section 3), and finally computed diffusion tensors (DT) and tensor derived variables.

In order to provide both complete datasets as acquired at the scanner, as well as data which are more comparable to traditional DTI acquisitions, we provide the eDTI protocol data including only the b=0s/mm² and b=1100s/mm² volumes (total of 59 (GE) or 60 (Siemens) brain volumes) as well as the full acquisition with all intermediate b-values included (119 (GE) or 120 (Siemens) brain volumes).

Derived variables are available for download in NIFTI format (file naming acronyms indicated in parentheses):

- Directionally encoded color maps (DEC) (Pajevic and Pierpaoli, 1999)
- Eigenvalues (EV) (Basser et al., 1994) as a 4D image file with volumes in the order of λ_1 , λ_2 , λ_3
- Fractional anisotropy (FA) (Basser and Pierpaoli, 1996)
- Lattice index (LI) (Pierpaoli and Basser, 1996)
- Relative anisotropy (RA) (Basser and Pierpaoli, 1996)
- Trace of the diffusion tensor (TR) (equal to 3*Mean Diffusivity) (Basser et al., 1994)
- Chi-Squared map of the fitting (CS). A measure of the goodness of fit of the tensor model (Pierpaoli et al., 2010).
- Outlier map (OUT). From RESTORE (Chang et al., 2005) or iRESTORE (Chang et al., 2012) fitting only. Indicates the percentage of data points identified as outliers and removed from the tensor fitting on a voxel-by-voxel basis.
- Brain mask (MS)

Raw images are provided in a raw floating point format readable by the TORTOISE DTI software (www.tortoisedti.org), organized as:

- Slice by slice images in raw floating point format
- A text readable header file (.list) which describes the essential information about the images including resolution, slice thickness, etc.
- A text readable B-matrix file (.bmtxt) which contains 6 columns by n-rows, where n is the number of image volumes contained in the dataset (b0 images and DWI images). The 6 columns are (from left to right) bxx 2*bxy 2*bxz byy 2*byz bzz
- A text readable file of pointers to the raw data (.path) which contains the relative path to each slice in the order of 1st slice for all volumes, then 2nd slice for all volumes, ... then nth slice for all volumes

Additional data available for download include:

- Structural target images used in registration steps
- Noise variance images
- Transformation matrices derived from post-processing steps

4.2 Template Data Available in the Database

Age-specific atlases were created using the highest quality eDTI data, spanning the full age range of the study (see sample templates in Figure 1). We provide two types of atlases, both in NIFTI format:

- morphologically faithful average brains in which each computed average tensor map has the average morphology for the group of subjects included in that age range
- morphologically normalized average brains in which each age group has the same morphology which is representative of the population

4.3 Clinical Data Available in the Database

Clinical, behavioral, and demographic information is downloadable in text (.txt) format. All subjects have complete demographic data. Every effort was made to provide complete (age appropriate) behavioral data, which includes:

Demographics: age, sex, parental education, family income, race/ethnicity

Physical neurological exams: motor functions, physical measurements, developmental milestones

Hormonal measures: cortisol, DHEA, estradiol, testosterone

Structured psychiatric interviews: Family Interview for Genetic Studies, Computerized Diagnostic Interview for Children (DISC) – Parent and Youth versions, DISC Predictive scales

Tests: Bayley Scales of Infant Development, California Verbal Learning, CANTAB, Differential Ability Scales, Handedness, Verbal Fluency, Preschool Language Scales-3, Purdue Pegboard, Wechsler Digit Span, Digit Symbol and Coding, Wechsler Abbreviated Scale of Intelligence (WASI), Woodcock-Johnson Tests of Achievement-III

Behavioral Rating Scales: Behavior Rating Inventory of Executive Function, Cary Temperament Scales, Child Behavior Checklist, Parenting Stress Index

5. Quality Assessment

With DTI data collected at 5 different sites, using 2 different scanner manufacturers (Siemens or GE), and with multiple imaging protocols, we felt it was important to implement a standardized procedure for quality assessment of the data (Nayak et al., 2011). For consistency, all assessments were carried out by one individual, author A. Nayak, supervised and spot checked by author L. Walker. The assessment was broken down into 2 categories: deviations from protocol and data quality. Quality assessment scores are included in the database, so the user can choose to work only with data of the highest quality, or depending on end goal, include differing levels of quality as desired.

5.1 Quality Assessment Criteria

Deviations from Protocol: Scoring: 0 – according to protocol, 1 – not according to protocol

• number of volumes (b0 and DWIs of appropriate weightings)

- number of slices
- resolution (voxel size and slice thickness)
- no zero filling used
- no averaging (NEX) used
- axial slice orientation is used
- echo time consistency between different b-value series (e.g. for objective 2 conventional DTI, b=500s/mm² series and b=1000s/mm² series should have same echo time)
- scaling difference between image series (e.g. were b=500s/mm² and b=1000s/mm² series scaled differently by the scanner)

Data Quality: Scoring: 0 – no issue, 1 – minor, 2 – moderate, 3 – severe Items inspected in uncorrected data:

- proper brain coverage: top of the brain
- proper brain coverage: bottom of the brain
- severity of ghosting
- artifacts affecting signal, such as spike noise, RF artifacts, or reconstruction artifacts
- motion resulting in signal dropouts
- motion with within volume (interleave) misregistration
- severity of eddy current distortions
- severity of susceptibility induced (geometric) EPI distortion
- pervasiveness of cardiac pulsation artifacts

Items inspected in corrected data and tensor derived quantities:

- quality of motion and eddy distortion correction
- quality of susceptibility induced EPI distortion correction
- visual assessment, performed for overall and regional quality of tensor derived quantities in:
 - frontal
 - parietal
 - occipital
 - temporal
 - cerebellum / brain stem
 - central brain

- top of the brain
- overall

Note that "top of the brain" refers to the top-most slices of the cerebral cortex and "bottom of the brain" refers to the bottom-most slices of the cerebellum and brainstem, rather than a specific anatomic landmark. This notation reflects that the top/bottom few slices of brain are occasionally cut-off during acquisition and that acquisition in children is typically done with the head positioned comfortably rather than with a strict position, leading to some variability in the anatomical definition of "top" and "bottom" of the images.

A detailed guide to our quality assessment procedure, including a series of images showing the different scoring levels used in this project, is available at www.pediatricmri.nih.gov/nihpd/info/protocols.html.

5.2 Results of Quality Assessment

After quality assessment, best efforts were made to correct for artifacts and distortions. If a single diffusion weighted image (DWI) volume suffered from artifacts but the overall dataset was of high quality, individual affected volumes were removed prior to tensor fitting. Therefore, it is possible that the number of DWIs may vary from subject to subject. The number of DWI and b0 volumes used in each dataset is indicated in the metadata of the database. Datasets that were acquired with severe deviations from the prescribed protocol and datasets that suffered from pervasive artifacts were not included in the database. After quality assessment, 380 of 878 acquired low resolution DTI datasets were not included, while only 8 datasets out of 201 acquired eDTI datasets were not included (Table 1).

The rejection rate of the low resolution DTI protocol (43%) can be explained largely by experimental design aspects of this portion of the PedsMRI project. The primary focus of the PedsMRI was the acquisition of structural MRIs (T1, T2, and proton density weighted images); which were systematically reviewed soon after acquisition and had to be reacquired if they did not pass QC. The structural MRI acquisition was mandatory for all sites and all sites needed to be technically capable of acquiring structural MRIs according to the prescribed protocol. On the contrary, the low resolution DTI acquisition was designed as an "ancillary" project which some of the sites volunteered to perform by adding a diffusion MRI acquisition at the end of the structural scan if the subject was still sleeping. This ancillary portion of the project received no additional funding for image acquisition. Each site tried its best to comply with the agreed upon protocol but in certain cases this proved to be difficult because of the lack of standardization of the DTI sequences available, and the lack of resources dedicated to correct problems. The ancillary nature of the DTI scans also implied that there were no on-site OC procedures and that the transfer of the data was given low priority because there was no plan to repeat the scan in case of corrupted data. Essentially, all data was transferred to the DTI processing center with no prior local QC resulting in the apparently high rate of rejection for the low resolution DTI scans.

Data rejection due to problems with the protocol accounted for >90% of rejection. Quantities from the diffusion tensor are known to be sensitive to voxel size/resolution, so consistent voxel sizes are needed for inclusion in a standardized database. In addition,

artifacts in the presence of protocol errors frequently resulted in data that could not be corrected.

Motion is often a big concern in DTI data acquisition, however, using TORTOISE we were able to correct for isolated motion in most cases. 22 datasets were rejected due to severe motion and/or motion further confounded by protocol errors. Of these 22 datasets, 8 occurred in children under 1 year of age. Figure 4 shows the distribution of rejection for motion with age, as a percentage of acquired datasets.

The higher resolution protocol had a much lower rejection rate. This has to be attributed in part to the fact that the eDTI protocol was implemented only by sites whose scanners were technically capable of acquiring this demanding protocol. However, another important factor is the larger number of DWIs acquired. The increased data redundancy allowed for more flexibility in correcting and/or rejecting individual volumes affected by artifacts, leaving adequate data for tensor computation. So, one lesson we have learned is that, although at face value a longer acquisition protocol may appear problematic for pediatric DTI, its higher redundancy provides significant benefits to the final quality and usability of data.

6. Database

This database is static, including data only from the NIH MRI Study of Normal Brain Development acquired between 2001 and 2007. No new raw subject-level data are accepted from outside users, and no significant changes to the database are expected as of the date of this publication.

All imaging, clinical/behavioral and metadata are stored in the PedsMRI database accessible through http://www.pediatricmri.nih.gov. This dataset shares the infrastructure created for the NIH's National Database for Autism Research (NDAR) and is also accessible through https://ndar.nih.gov, along with several other NIMH datasets recently added that utilize the NDAR platform. All data, including demographic, imaging (DTI as well as anatomical MRI and MRS), and clinical/cognitive/behavioral measures are immediately available once access is granted. Access can be requested through either of the two websites (PedsMRI or NDAR). Qualified researchers studying normal brain development, disorders or diseases, and/or who are developing image processing tools can apply for access using a Data Use Certification form. Accounts remain valid for 1 year, after which progress reports and a new Data Use Certification should be submitted for continued access.

Additional information about the PedsMRI project as a whole can be found at www.pediatricmri.nih.gov. A downloadable brochure includes a list of data types and numbers of datasets available for each MRI modality (www.pediatricmri.nih.gov/nihpd/info/Documents/PedsMRI_Brochure_June2012.pdf). White papers for each of the imaging modalities and the neurobehavioral components of the project are available through both the PedsMRI and NDAR websites.

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Abbreviations:

PedsMRI	NIH MRI Study of Normal Brain Development	
PedsDTI	DTI component of the NIH MRI Study of Normal Brain Development	
DPC	DTI-processing center	
DEC	directionally encoded color map	
eDTI	extended DTI	
DCC	data coordinating center	
DT	diffusion tensor	
NDAR	National Database for Autism Research	

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Highlights:

We describe the DTI component of the NIH MRI Study of Normal Brain Development Longitudinal study of typical brain development from birth through 22 years of age Database includes anatomical MRI, MRS, DTI and demographic/clinical/behavioral data Standardized post-processing and quality assessment of DTI data are discussed



Figure 1. DTI Templates

Examples of directionally encoded color (DEC) maps computed from age specific average brain DTI templates obtained using diffeomorphic tensor based registration of the DTI data of the individual subjects (Zhang et al., 2007; Zhang et al., 2005). Two types of DTI templates are available for download from the database: Morphologically Faithful templates, which represent the average morphology of the subjects included in each age group (top row), and Morphologically Normalized templates in which the average brain is further warped to the morphology of the 18-20 year old group (bottom row).



Figure 2. Age Distribution of "conventional" low resolution DTI Age and gender distribution of all conventional DTI scans. Each line represents a single subject, and each dot represents a single scan, such that a single line tells you the number of scans for that subject and the subject age at the time of the scan.



Figure 3. Age Distribution of "extended" high resolution DTI Age and gender distribution of all eDTI scans. Each line represents a single subject, and

Age and gender distribution of an eD IT scans. Each line represents a single subject, and each dot represents a single scan, such that a single line tells you the number of scans for that subject and the subject age at the time of the scan.



Figure 4. Age Distribution of Data Rejected for Motion Contamination

Percent of datasets rejected due to uncorrectable motion per 6-month age period, calculated as (number of rejected scans / number of acquired scans in that age range)x100. More motion is seen in children less than 10 years of age. The lack of motion related rejections during the 2-5 year age range is primarily attributed to the low sampling in that age range.

Table 1:

Data rejection reasons by imaging protocol

Reason for Rejection	DTI (3mm)	eDTI (2.5mm)
Motion with or without protocol errors	22	1
Artifacts (spike noise, ghosting, etc)	32	0
Artifacts combined with protocol errors	22	0
Uncorrectable eddy current distortions combined with protocol errors	135	0
Incorrect image matrix size/resolution	77	0
Other protocol errors (including incomplete acquisition)	92	7
Total	380	8