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Atlas-Based Analysis of Neurodevelopment from Infancy to Adulthood Using Diffusion Tensor Imaging and Applications for Automated Abnormality Detection

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Abstract

Quantification of normal brain maturation is a crucial step in understanding developmental abnormalities in brain anatomy and function. The aim of this study was to develop atlas-based tools for time-dependent quantitative image analysis, and to characterize the anatomical changes that occur from 2 years of age to adulthood. We used large deformation diffeomorphic metric mapping to register diffusion tensor images of normal participants into the common coordinates and used a pre-segmented atlas to segment the entire brain into 176 structures. Both voxel- and atlas-based analyses reported structure that showed distinctive changes in terms of its volume and diffusivity measures. In the white matter, fractional anisotropy (FA) linearly increased with age in logarithmic scale, while diffusivity indices, such as apparent diffusion coefficient (ADC), and axial and radial diffusivity, decreased at a different rate in several regions. The average, variability, and the time course of each measured parameter are incorporated into the atlas, which can be used for automated detection of developmental abnormalities. As a demonstration of future application studies, the brainstem anatomy of cerebral palsy patients was evaluated and the altered anatomy was delineated.

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Introduction

Magnetic Resonance Imaging (MRI) has been one of the most widely used imaging modalities to describe the macroscopic anatomical changes during the development process because of its capability to capture the anatomy three-dimensionally, quantitatively, and non-invasively. Using MRI, dynamic changes can be characterized *in vivo* on a larger sample size. Previous studies have described a biphasic development of the brain - rapid growth in the first two years of life, followed by slower and more subtle developmental changes. During the first two years of life, histological studies have described the classical temporo-spatial gradients of myelination. In the first months of life, the signal intensities of gray and white matter in T1- and T2-weighted images are the reverse of those seen in an adult brain. As the white matter (WM) myelinates, it changes from hypointense to hyperintense relative to the gray matter in T1-weighted images, and from hyperintense to hypointense relative to the gray matter in T2-weighted images (Ballesteros, Hansen, Soila 1993; Barkovich et al., 1988; Konishi et al., 1993; van der Knaap and Valk 1990).

Although these patterns are generally true, the information they provided on brain maturation is limited (Barkovich 2000; Brody et al., 1987; Kinney et al., 1988; Petanjek et al., 2008). Recently, diffusion tensor imaging (DTI) has been shown to provide additional information about the changes in the brain's microstructure with maturation (Alexander et al., 2007; Bartha et al., 2007; Cascio, Gerig, Piven 2007; Ding et al., 2008; Dubois et al., 2006; Engelbrecht et al., 2002; Gilmore et al., 2007; Hasan et al., 2007a; Hasan et al., 2007b; Hasan et al., 2008; Hermoye et al., 2006; Huang et al., 2006; Huppi and Dubois 2006; Le Bihan 2003; Moseley 2002; Mukherjee et al., 2001; Mukherjee et al., 2002; Neil et al., 1998; Snook et al., 2005; Stegmann et al., 2006). Taking advantage of anisotropic diffusion, DTI can demonstrate brain axonal organization in detail beyond the resolution of conventional MRI (Mori and Zhang 2006). By increasing the contrast within the WM, regional connectivity can be investigated in both normal and pathological conditions.

After the second year, the developmental changes become much more subtle. The average brain weight at two years old has already reached approximately 80% of that of adults weight, and at five years old, there is no significant difference (Dekaban and Sadowsky 1978; Lenroot and Giedd 2006). In terms of MR contrasts, T1-weighted imaging studies found changes in a confined area of the brain (Paus et al., 1999; Snook et al., 2005; Thompson et al., 2000a). DTI is sensitive enough to show a pattern of maturation with considerable regional variation, generally characterized by an increase in fractional anisotropy (FA) and a decrease in mean diffusivity (Dubois et al., 2008; Hasan et al., 2007a; Hasan et al., 2007b; Hasan et al., 2008; Klingberg et al., 1999; Lebel et al., 2008; Qiu et al., 2008; Snook et al., 2005). Previous studies are primarily based on measurements in pre-defined brain regions, and a comprehensive whole-brain spatio-temporal study has not been undertaken.

In this study, we investigated developmental changes in the WM after the second year using DTI. Characterization of brain development by MRI consists of five dimensions: one for time; three for locations; and one for measured parameters, which include volume, FA, apparent coefficient of diffusion, and radial/axial diffusivities. For the location information, the finest unit is the voxel. In voxel-based analyses, we can establish standard voxel coordinates and monitor anatomical changes at each voxel. However, this type of analysis is based on the assumption that the brain normalization procedure (identification of corresponding voxels between the standard brain and individual brains) is accurate, and also, often suffers from poor statistical power due to the high level of noise. An alternative approach based on regions of interest (ROIs) ameliorates these shortcomings by grouping the anatomically related voxels within the same anatomical unit, thus systematically reducing the location information from hundreds of thousands of voxels to a limited number of ROIs. By manually defining the ROIs,

severe inaccuracy issues can also be avoided. The manual ROI-based analyses, however, is known to have reproducibility issues (manual ROI drawing is not perfectly repeatable), and it is not suitable for the whole-brain analyses (too time-consuming to define a large number of 3D ROIs). In this study, we adopted a voxel-based and an atlas-based analysis, in which the entire brain was automatically segmented to 176 anatomical units after normalization. For each defined area, the time courses of various MR parameters were characterized. For the standard coordinates, we used our JHU-DTI-MNI single subject atlas (also known as the “Eve Atlas”) (Mori et al., 2008), which consists of multiple MR contrasts (T1/T2/DTI) and 176 pre-segmented regions (Oishi et al., 2008). The relatively small anatomical changes after the age of two allowed us to use the adult atlas for the standard coordinates.

We expect that this type of five-dimensional analyses would generate complex and often difficult-to-interpret results; some regions may not have any time-dependent change in one parameter (e.g., FA), while there is a clear age-related change in another parameter (e.g., ADC). Such behavior may be completely different in the adjacent anatomical areas. While this type of information will provide further insight into brain development, one of our primary goals is to enrich the brain atlas. Characterization of the normal development process would provide the average values and the degree of normal variability of each measured parameter at each location. This, in turn, allows us to perform power analysis to detect abnormalities in brain growth. This would be an essential step toward automated detection of abnormalities in the future. To demonstrate the utility of the enriched atlas, DTI data from cerebral palsy patients were analyzed for automated detection of abnormalities.

Methods

Subjects

Data from a total of 35 subjects from a pediatric database (lbam.med.jhmi.edu) (Hermoye et al., 2006) were used in this study. This included nine healthy pediatric volunteers (> 4 years-old) and 17 pediatric patients referred for a clinical MR examination for extracranial symptoms (14 male; > 2 years-old; mean age: 6.7 years). The clinical indications were pathologies related to the internal ear, the orbits, the spine, epilepsy, trauma, infectious disease, genetic disease, and vascular/cisternal malformation. The clinical history of each patient was carefully reviewed by a pediatric neurologist to exclude associated neurological disorders. All the subjects were full-term. In all the patients, the cerebral anatomy was normal. These pediatric data were obtained at two different sites (Johns Hopkins Hospital, US, 14 subjects, 5-18 years-old, and St. Luke Hospital, Belgium, 12 subjects, 2-4 years-old) after the setup of the common imaging protocol, as described in a previous paper (Hermoye et al., 2006). The present study also includes image data from nine healthy adult volunteers (five males, ages ranging from 22 to 40 years-old; mean age: 30 years) and 13 patients with cerebral palsy (eight males, ages ranging from 3.3 to 13.9 years old; mean age: seven years). This study was approved by the Institutional Review Board of each participating site, and written, informed consent was obtained from each adult or from the child's parents.

MRI data

Images were acquired using a SENSE head coil on a 1.5 T whole body MRI scanner (Philips Medical Systems, Best, The Netherlands), equipped with explorer gradients (40 mT/m) at both sites. For acquisition, an eight-element arrayed radio frequency coil, converted to a six-channel to be compatible with the six-channel receiver system, was used. For DTI acquisitions, a single-shot spin echo-echo planar imaging (EPI) was used, with diffusion gradients applied in 32 non-collinear directions and $b = 700 \text{ s/mm}^2$. One reference image with least diffusion weighting ($b = 33 \text{ s/mm}^2$) was also acquired (called the b_0 image in this paper). Fifty axial slices were acquired, parallel to the AC–PC line. The field of view (FOV), the size of the acquisition matrix,

and the slice thickness were $220 \times 220 \text{ mm}/96 \times 96/2.3 \text{ mm}$ for subjects between two and five years-old and $240 \times 240 \text{ mm}/96 \times 96/2.5 \text{ mm}$ for older subjects. All images were zero-filled to the final reconstruction matrix of 256×256 . Other imaging parameters were: TR = 7859 ms; TE = 80 ms; and SENSE reduction factor = 2.5. To improve the signal-to-noise ratio, two datasets were acquired, leading to a total acquisition time of 9 min. The healthy volunteers (> 4 years-old) were scanned without sedation and the pediatric patients with the extra-cranial indications (> 2 years-old) were anesthetized. The anesthesia was induced and maintained by inhalation of sevoflurane.

Image processing

The raw diffusion-weighted images (DWIs) were first co-registered to one of the least DWIs and corrected for eddy current (Andersson and Skare 2002; Zhuang et al., 2006) and subject motion using a 12-mode affine transformation of Automated Image Registration (AIR) (Woods et al., 1998). The warping was applied to all raw DWIs. The six elements of the diffusion tensor were calculated for each voxel with multivariate linear fitting (Basser, Mattiello, LeBihan 1994; Jiang et al., 2006a). After diagonalization, three eigenvalues and eigenvectors were obtained. For the anisotropy map, FA was used (Pierpaoli and Basser 1996). The eigenvector associated with the largest eigenvalue (v1) was used as an indicator of fiber orientation. All data processing was performed using DtiStudio (H. Jiang and S. Mori, Johns Hopkins University, Kennedy Krieger Institute) (Jiang et al., 2006b). Before the normalization procedure, the skull was stripped using the b0 images and a skull-strip tool in RoiEditor software (Li, X.; Jiang, H.; Yue, Li.; and Mori, S.; Johns Hopkins University, www.MriStudio.org or www.kennedykrieger.org). The skull stripping method used is a modified version of the active contour method described by Chan and Vese (Chan and Vese 2001). From a given seed point, in this case defined in the origin, the mask corresponding to the brain definition grows towards and stops on the boundary where the contrast between tissue and non-tissue is strongest. The ratio of weightings between inward and outward forces depends on the subject and empirically sets between 0.9 and 1.1. The weighting of inner energy was 0.01. Minimal manual corrections were performed in regions where the automated skull stripping failed, excluding cerebral parenchyma or including skull.

A representation of the subsequent normalization process, performed using DiffeoMap (Li, X.; Jiang, H.; and Mori, S.; Johns Hopkins University, www.MriStudio.org or mri.kennedykrieger.org), is shown in Fig. 1. The images were first normalized to the ICBM-DTI-81 coordinates (Mori et al., 2008) using a 12-parameter affine transformation of AIR. For the affine transformation, b0 images were used for both the subject data and the ICBM-DTI-81 template. After this initial alignment and the brain size normalization by linear transformation, the images were further transformed non-linearly to a single-subject template. For the template, the JHU-DTI-MNI “Eve” atlas was chosen which is a single-subject template in the ICBM-DTI-81 space and is extensively segmented and labeled to 176 gray and WM regions (Nilsson et al., 2008; Oishi et al., 2009). For the non-linear transformation, dual-contrast Large Deformation Diffeomorphic Metric Mapping (LDDMM) (Miller et al., 2005) was employed, in which both b0 and FA images were used to register the subject data to the template. We employed the same approach described in Ceritoglu et al., 2009, using a single α/γ ratio at 0.005 (Ceritoglu et al., 2009). Once completed, the transformation matrix was applied to the co-registered tensor fields using a method described by Xu et al., 2003 (Xu et al., 2003). From the normalized tensor fields, the DTI-based parameters, such as FA, ADC, and eigenvalues, were obtained. As a quantitative metric of local volume changes, we used Jacobian maps calculated from the gradient of the deformation field. The Jacobian maps indicate local tissue expansion (Jacobian>1) or shrinkage (Jacobian<1) relative to the template (Chung et al., 2001; Riddle et al., 2004; Thompson et al., 2000b).

To test the accuracy of our transformation, we manually delineated seven structures (corpus callosum, bilateral external capsula, bilateral corticospinal tract in pons level, and bilateral cingulum) on pre-determined five FA image slices. Two evaluators repeated this process three times with a more than two weeks interval. Then, automated and manual measurements were compared, as well as the measurements done by the same evaluator (intra-evaluator) and by the two different evaluators (inter-evaluator). The indices of agreement regarding the voxel classification were estimated by Kappa coefficient (Landis and Koch 1977).

Measurements

Total brain volume and FA-based brain segmentation—The whole brain boundary was defined by a simple threshold followed by manual correction, including midbrain, the brainstem, and the cerebellum. The extra-cerebral spaces, including ventricles, sulci, and cisterns, were defined and excluded by an ADC threshold at $0.0015 \text{ mm}^2/\text{s}$. Once the brain was defined, the WM compartment was defined by an FA threshold at 0.25. The remaining tissue was defined as the gray matter compartment. There are several important issues to be pointed out regarding these definitions of the compartments. First, these compartment definitions are not the same as classical anatomical definition of the gray and WM defined by histology or T1-weighted images. The threshold of $\text{FA} > 0.25$ is conservative, meaning some WM tissue beneath the cortex could be included in the gray matter compartment. Some regions in the thalamus contain a high concentration of axons with relatively high anisotropy ($\text{FA} = 0.30 - 0.35$) and, therefore, they were included in the WM compartment. Interpretation of the compartment volumes, thus, requires caution.

Voxel-based analysis—After the subject data were normalized to the template (Fig. 1), linear regression analysis was performed at each voxel for Jacobian maps and for four types of image contrasts: FA; ADC; ‘axial diffusivity’ ($\lambda_{\parallel}$, the primary eigenvalue); and ‘radial diffusivity’ ($\lambda_{\perp}$, the average of the secondary and tertiary eigenvalues). For each voxel, measured parameters (the Y axis) were plotted against age (the X axis) in a logarithmic scale. No spatial filtering was used for the statistical analyses. The values of linear regression slopes, correlation coefficients (R^2), and p -values were obtained for each voxel (MatLab 6.1, The MathWorks, Inc., U.S.A.). To identify voxels with a significant correlation with age, we generated a binary map by applying a threshold of $R^2 > 0.3$. The p -values of all these voxels were smaller than 0.01, corrected for multiple comparison by False Discovery Ratio (FDR). We then used these binary maps to mask the slope and R^2 maps that resulted from linear regression.

Atlas-based analysis—The atlas-based analysis was performed using a WM parcellation map (WMPM) of the Eve atlas, as described in a previous article (Oishi et al., 2009)(Fig. 1). Briefly, the brain was parcellated into 130 regions based on anatomical labeling, including both the gray and WM. Because of the reciprocal nature of the LDDMM, the transformation results can be used to warp the WMPM to the original MRI data, thus automatically segmenting each brain into the 130 sub-regions. This is basically a “reverse transformation” compared to the voxel-based analysis. These initial segmentation results (130 regions) were further segmented to separate the cortex and the associated peripheral WM, as shown in Fig. 2D, using the FA threshold ($\text{FA} \geq 0.25$). The anatomy of the cortex is highly variable among subjects and we do not expect good matching between the subjects and the atlas, even after the highly nonlinear LDDMM-based normalization. Therefore, it was not possible to automatically segment the cortex by simply transferring the cortical definition from the atlas to individual brains. Using the method described in Fig. 2D, we segmented the 46 atlas regions that contain the cortex into the cortical and WM compartments in each subject. This approach is denoted the Type II WMPM method in Oishi et al. (Oishi et al., 2009). Accuracy measurement of the automated segmentation is described in our previous article (Oishi et al., 2008; Oishi et al.,

2009). Fig. 2 demonstrates the accuracy level of brain normalization by LDDMM, and also the final segmentation of the cortical and white matter compartments using the FA threshold, which ensures accurate WM definition for the highly variable regions in each subject.

Linear regression analysis was carried out for each ROI, and the horizontal axis corresponded to age (logarithm scale) and the vertical axis corresponded to the intensities of FA, ADC, $\lambda_{\parallel}$, $\lambda_{\perp}$, or volume. The vertical axis was a natural scale except for the volume, which was represented by a logarithmic scale so that the slope measurements were independent of each ROI volume. We took into consideration the fact those regions with an $R^2 > 0.3$ had a significant volume or intensity age-dependency. All these regions had a *p-value* less than 0.003, FDR-corrected.

Results

Macroscopic analysis of brain volumes

Linear fitting showed statistical significance for the logarithmic age-dependent increase in the whole brain, WM, and cerebrospinal (CSF) volumes (Fig. 3), although the correlation for the whole brain volume was weak ($R^2 = 0.3$). At age two, the average brain volume was $1,076,727\text{mm}^3$, 78% of the adult's mean volume. After five years of age, there was no significant time dependency (*p-value* > 0.05) and the average brain volume was $1,179,396\text{mm}^3$. The WM compartment ($\text{FA} \geq 0.25$) increased, with a slightly higher age-dependence ($R^2 = 0.48$). We saw a strong correlation ($R^2 = 0.55$) between the CSF volume and age. Because the total brain volume shows no age-dependency after five years of age, the increases in the CSF and the WM compartment lead to a different time-course of the gray matter compartment ($\text{FA} < 0.25$), where volume is modeled by a polynomial curve in Fig. 3, with the peak at 10 years of age.

Atlas-based analysis

The overall Kappa for the intra-evaluator comparison was 0.84; for the inter-evaluator was 0.77 and for the comparison of automated vs. manual method is 0.78. These kappa values are similar to those found before for adult and aged populations (Oishi et al., 2009), supporting the use of the adult template for the pediatric population older than 2 years old. The table in the Appendix contains the slopes, R^2 , and *p-values* of the linear curve that best fitted the data in each region in the atlas-based analyses. Again, regions with an $R^2 > 0.3$ (that also had a *p-value* < 0.003, FDR-corrected) are shown. Three-dimensional representations of the results are shown in Fig. 4 with color coding, summarizing the logarithmic age-dependent slopes of each area for volume, FA, and ADC measurements. Depending on the measured properties (volume, FA, or ADC), different areas showed characteristic time-dependencies, which were, in general, highly symmetric.

Fig. 5 shows several representative axial slices for the results of volume increases measured by the atlas-based analysis (Fig. 5A: slopes, 5B: R^2 s). The regional analyses showed a time-dependent volume increase that was mostly uniform across the WM, although regions that are rich with projection fibers (e.g., the corona radiata, the internal capsule, the cerebral peduncle, and the corticospinal tract in the pons) tend to have higher time-dependent slopes as well as R^2 values. There were no areas with decreasing volumes with age. Fig. 6 shows examples of actual data points and the fitting results of the atlas-based analysis at representative areas with high (upper row) and low (bottom row) time-dependency.

The diffusivity index analyses revealed positive FA time-dependence in the WM (Fig. 7). In addition to the brainstem and midbrain WM, the thalamus and the anterior limb of the internal capsules had the largest time-dependent FA increase. The peripheral WM, particularly in the

frontal and parietal regions, also had increased FA over time. In contrast, some gyri in the left hemisphere (inferior frontal, superior temporal, pre-cuneus, angular, post-central, and supra marginal), as well as the cortex of the cingulum gyrus (bilateral), had negative time-dependence.

ADC, $\lambda_{\parallel}$, and $\lambda_{\perp}$ had a negative time-dependence (Fig. 8). Age-related changes were widespread in the WM. The frontal WM showed a time-dependence slightly stronger than in other regions. Comparing $\lambda_{\perp}$ and $\lambda_{\parallel}$, $\lambda_{\perp}$ shows larger areas of linear correlation with age, with steeper slopes. Most cortical compartments had no age-related changes on diffusivity images, except for the medium and inferior temporal gyri, the insulas, the left fusiform, and the cortex of the left cingulum, where $\lambda_{\parallel}$ decreased over time.

In Fig. 9, three brain regions with different characteristics for time-dependent changes are demonstrated. These are the CST, the anterior corona radiata (ACR), and the WM of the superior occipital gyrus (SOG). These three areas have high, low, and no significant time dependency of FA, while all three areas have a clear and significant ADC decline. The increase in FA of the CST and the ACR is due to a decrease in $\lambda_{\perp}$, while the concomitant decrease of in $\lambda_{\parallel}$ the ACR led to a less steep FA increase. The $\lambda_{\perp}$ and $\lambda_{\parallel}$ of the SOG decreased in parallel, leading to a non-significant time dependency of FA. This type of diffusion characteristic was found in many peripheral WM regions, including the posterior corona radiata, and the centrum semi-ovale.

Comparison between atlas-based and voxel-based methods

For the volume measurements, the atlas-based and voxel-based methods agreed very well, except for peripheral WM area close to the cortex; the statistically significant areas are confined to the deep white matter regions in the voxel-based method (Fig. 10A). The significant FA changes were detected in various brain regions by the atlas-based analysis (Fig. 10B), while the voxel-based analysis showed only a small number of voxels with significant differences in the brainstem (CST), the midbrain, the thalamus, and deep right WM. With regard to ADC, $\lambda_{\parallel}$ and $\lambda_{\perp}$, both methods had good agreement, but, again, the atlas-based analysis showed more widespread differences in the peripheral WM. One exception is the thalamus, in which only the voxel-based analysis detected a cluster of voxels with statistically significant age-dependency.

Discussion

Macroscopic analysis of brain development

In Fig. 3, macroscopic characterization of brain development is displayed. The time-dependency of the brain, WM, gray matter, and CSF volumes closely follow the results in previous publications (Hasan et al., 2007c; Hua et al., 2009; Wilke, Krageloh-Mann, Holland 2007). It is well known that the human brain grows rapidly during the first two years of life, by which time it has achieved 80% of its adult weight and, at five years of age, it is approximately 90% of the adult weight (Dekaban and Sadowsky 1978; Lenroot and Giedd 2006). In our study, the brain volume at two years of age was already approximately 78% of an adult's volume and after five years of age, as expected, there were almost no significant time-dependent changes.

Also in agreement with previous data are the strong, positive, linear correlations between age and WM and CSF volumes (Good et al., 2001; Paus et al., 1999; Sowell et al., 2003). Other studies had already shown that the WM volume does not begin to decrease until the fourth decade (Giedd et al., 1999; Paus et al., 1999; Reiss et al., 1996). With regard to the CSF volumes, the recognition of its normal increase with age is an important consideration when

interpreting reports of increased ventricular volumes in several neuropsychiatric conditions (Benedict and Bobholz 2007; Bigler et al., 2002; Bigler et al., 2004).

In the gray matter, the correlation between age and volume was not monotonic. The cortical growth is known to obey more complex curves, usually following an “inverted U” developmental course, with volumes peaking at different times in different lobes, most of which peak between 10 and 17 years of age (Giedd et al., 1999; Shaw et al., 2008). In our case, the curve describing the global gray matter compartment peaked around 10 years of age (Fig. 3).

Regional analyses

Although there are a plethora of publications about MRI-based brain development studies, our paper is one of the first reports of comprehensive regional analyses of the WM using DTI and the highly elastic brain normalization technique. For the regional volume and diffusivity indices, the entire WM undergoes a similar time course: an increase in the volume and a decrease in diffusion constants, while there was a small tendency toward a steeper volume increase in the WM regions rich with projection fibers. The regional differences in the amount of decrease in the $\lambda_{\parallel}$ and $\lambda_{\perp}$ led to significant FA increases in a confined number of brain regions, which included the CST, the frontal WM, and the thalamus. These changes may be related to the changes in axon diameters and the amount of myelination in these regions. It has been suggested that the diameter of the thickest fibers in the CST increases linearly as a function of body height (Eyre, Miller, Ramesh 1991). To maintain passive cable conduction, dendrites need to increase four times in diameter when they double in length (Kandel, Schwarz, Jessel 2000). This expansion requires an increase in myelination and, as a result, the increased volume of the insulating sheaths surrounding axonal fibers bulks up the volume of the WM compartment. Moreover, significant shortening of the central conduction time during childhood and adolescence observed in the motor pathway (Armand et al., 1997; Muller, Homberg, Lenard 1991; Nezu et al., 1997) functionally supports the myelinization and organization of CST fibers that occur in this phase, and are plausible explanations for both the increase in volume and FA due to the decrease in $\lambda_{\perp}$ (Figs. 8, 9 and 10).

A positive relationship between FA and age was also present in the peripheral WM of the frontal and parietal lobes, as well as in the superior temporal gyrus of the right hemisphere. In these areas, both $\lambda_{\parallel}$ and $\lambda_{\perp}$ decrease, although $\lambda_{\perp}$ consistently had a steeper decline compared to $\lambda_{\parallel}$, explaining the FA increase (Fig. 9). In other regions, such as the posterior corona radiata, the centrum semi ovale, and the WM of the SOG, $\lambda_{\parallel}$ and $\lambda_{\perp}$ proportionally decreased while FA remained stable (Fig. 9). Decreases in both $\lambda_{\perp}$ and $\lambda_{\parallel}$ might indicate that those regions are under a process of myelination and increasing compactness, but with an additional component of increasingly ‘complex’ fiber structural design (Pierpaoli et al., 2001).

Among these ‘complex’ subcortical areas, the frontal lobe presented bigger slopes (in absolute value) and R^2 in both volume (Fig. 5 and 6) and diffusivity analyses (Fig. 8). It is possible that the different trends we detected represent distinct maturation patterns, in which higher-order association areas mature after the lower-order sensorimotor regions they integrate. This heterogeneous compartment has been previously described for the cortex (Gogtay et al., 2004); (Sowell et al., 2001) and for the WM of older adults (Salat et al., 2005), but not for the WM of younger subjects. However, since the gray and WM have inseparable connections and share lifelong reciprocal relationships (Barres and Barde 2000; Du and Dreyfus 2002; Fields and Stevens-Graham 2002), it is not surprising that we detected the same maturation pattern in the WM.

In agreement with our findings, previous studies have consistently reported brain maturation during adolescence in the internal capsule, the arcuate fasciculus, and the CST (Barnea-Goraly et al., 2005; Ben Bashat et al., 2005; Paus et al., 2001; Schmithorst et al., 2002). Some of these

recent studies have described not linear but mono-exponential equations that modulate the components of the WM diffusivity over time (Ben Bashat et al., 2005; Lebel et al., 2008). Nevertheless, those studies covered a different age range, some including subjects as old as 80 years of age. But, in fact, they are unanimous in concluding that WM FA does not begin to decrease (and mean diffusivity does not begin to increase) until the fourth decade.

Limitations of our quantification approach and data interpretation

It is important to keep in mind that since we used FA to determine the boundaries of the WM compartments, the results are directly influenced by changes in the FA of the peripheral brain regions. In early infancy (< 5 years old), when the total brain volume is visibly expanding, we observed a tendency in the cortex and the WM to enlarge; nevertheless, after 10 years of age, the cortex showed a tendency to shrink while the WM continued to expand (Figs. 3, 4, 5, and 6). This cortical “loss” has been described often (Gogtay et al., 2004; Shaw et al., 2008; Sowell et al., 2003), but the cortex shrinking while WM expands may indicate not only changes in volume (cortical shrink may be driven, at least in part, by a component of synaptic pruning, glial and vascular changes, and cell shrinkage (Morrison and Hof 1997)), but also continuous myelination and/or other microstructural mechanisms that cause an FA increase in the subcortical layers, resulting in a shift of the gray-WM border in the cortical direction. This type of coupling of the “anatomical definition” and “intensity shift” is a common issue in MR image analyses, which require careful interpretation.

In this study, a decrease in FA was found in several cortical compartments of the left hemisphere (Figs. 4 and 7). The time-dependent decrease in cortical FA has been reported in human and animal neonates (Baratti, Barnett, Pierpaoli 1999; Maas et al., 2004; McKinstry et al., 2002; Mori et al., 2001; Neil et al., 1998; Thornton et al., 1997), which was attributed to the increased complexity of the cellular architecture of the cortex. It could be a subject of debate whether our observation supports such a process in much later stages of brain development. There are at least several alternative possibilities that could explain the FA decrease in the cortical compartments. As mentioned in the Methods section, the cortical compartments may contain partial volumes of the CSF, and therefore, the decline in the FA values could be caused by the expansion of the CSF spaces. However, during the same time period, the ADC of the same compartments did not change, suggesting the partial volume effect may not be a significant contribution. Another possibility is the shift of the gray-WM boundary defined by an $FA \geq 0.25$ due to an increase in FA, which would exclude more WM from the cortical segments. However, in most parts of the peripheral WM of these compartments, we did not detect a significant increase in FA with age.

One possible source of inaccuracy in our study is image distortion due to B0 susceptibility, which is common for the single-shot EPI (Chen, Guo, Song 2006). In our previous study (Huang et al., 2008), we mapped the amount of image distortion for DTI images acquired with parallel imaging. A significant amount of distortion (more than two voxels) was found in the anterior pole of the frontal and temporal lobes and the brainstem. In small confined areas in the frontal and temporal lobes, voxel degeneration (more than two voxels are merged) were observed. For the normalization-based study, this distortion is treated as part of the anatomical differences among individuals. Except for the areas with the voxel degeneration, we believe that the impact of this distortion on intensity measurements (FA and diffusivity) should be minimum. In fact, the widely used post-processing distortion correction can be considered part of the normalization process. On the other hand, the time-dependency of the volume measurements could be influenced if the degree of the distortion is also time-dependent (e.g., a younger brain has more or less distortion for some reason). In this regard, we would like to point out that the highly time-dependent brain regions (e.g., the internal capsule and the corona radiata for the size increase) are mostly far from the distorted brain regions. Nonetheless, it

would be beneficial to employ more advanced parallel imaging technologies and/or accurate post-processing distortion correction to increase the accuracy of size measurements in the future.

The way DTI data are transformed also deserves attention because there are multiple ways to perform it with slightly different outcomes, which includes tensor transformation and interpolation (Xu et al., 2003; Zhang et al., 2006). In this study, the tensor field in the native space was transformed to the common space and then various MR contrasts such as FA, trace, and eigenvalue maps were generated. In this way, the full tensor information can be carried to the common space and compared across subjects. However, the tensor transformation and interpolation do not have a single solution and require a certain degree of simplification and assumption. Alternatively, the tensor field could be first converted to a scalar metric of interest (e.g. FA map) and then transformed by a scalar-based method, which would be simpler and free from the issues related to the tensor manipulation. There is still a room for investigation about the impacts of the methods of choice on the final quantitative outcomes.

Finally, there are several possible shortcomings of our database to evaluate the age-dependent changes, which should be mentioned. First, the database consists of data came from two sites, which tend to cover different age ranges. Second, the image resolutions are not consistent throughout the development. The latter is a complicated issue. If the spatial resolution (voxel size) is fixed, the SNR tends to be consistent but the anatomical resolution (the total number of voxels within the brain) reduces for smaller brains, which would lead to larger partial volume effect (i.e. FA may artificially decrease). If the spatial resolution is changed to keep the same anatomical resolution, the voxel size would become smaller for younger brains and the SNR would decrease (i.e. FA may artificially increase). In this study, the voxel size was slightly reduced (2.3 mm vs. 2.5 mm) for the subjects between 2-5 years old to compensate the slightly smaller brains. This might have led to decreased SNR and thus possible increase in FA (Pierpaoli and Basser 1996). This, however, counteracts with our observation that FA tends to be lower in the younger population. Third, the database contains data from “clinically normal” pediatric (< 4 years) cases as described in Hermoye et al (Hermoye et al., 2006). Combined all these possible compounding factors, we cannot deny the possibility of a certain degree of artificial contributions contaminating our observation of the age-dependent observation. Another important point is that the number of our data points is somewhat limited (35 subjects across 38 years). In addition, subjects older than 4 years-old were not sedated and the data from younger populations (e.g. 4-8 years old) may have more artifacts due to motion.

Comparison between the atlas and voxel-based analysis

In this study, a majority of the quantitative reports were derived from the atlas-based approach, in which the pre-segmented atlas was warped to the original MR images, followed by definition of the gray-WM boundaries by the FA threshold in each subject. For normalization-based approaches, it is much more common to use a voxel-based analysis, in which all individual MR images are transformed to the atlas coordinates, and statistical analyses are performed at each voxel. Using the LDDMM-based transformation, both the forward and backward transformations are available, and comparisons using forward and backward transformations are mathematically equivalent. However, there are several important differences between the two approaches.

First, the atlas-based approach groups voxel values within a segmentation. While there are more than one million voxels within a brain, they are reduced to only 176 areas. This reduction (voxel averaging) could lead to higher statistical power. It is known that one of the shortcomings of the voxel-based methods is the low statistical sensitivity of each voxel. This low sensitivity is often ameliorated by using spatial filtering that averages the values of the surrounding voxels (Lee et al., 2009). This uniform filtering, however, does not reflect the WM

anatomy, which often has a sharp boundary between two anatomically distinct axonal bundles. The pre-segmented atlas, therefore, can be considered anatomy-based filters. If anatomical changes follow such anatomical boundaries or are disperse and widespread, the atlas-based analysis could provide higher statistical power. This can be appreciated from the time-dependent FA changes, in which the voxel-based analysis could not provide statistical correlation with time in any regions (Fig.10). The atlas-based approach, however, becomes less useful when changes do not follow the anatomical boundaries defined in the atlas (e.g., stroke that follows the vasculature structures, not the axonal structures), or are confined in a small area (only a portion of a segment). In these cases, the voxel-averaging based on the pre-segmentation may dilute the effect. We believe this is the reason the atlas-based analysis failed to detect the significant decrease in diffusivities in a portion of the thalamus, which was detected by the voxel-based analysis. Therefore, these two approaches should be considered as complementary tools.

The second difference is the way the peripheral WM underneath the cortex is handled. This is the area where there is a high degree of individual variability, and we cannot expect even the highly elastic LDDMM transformation to register the structures accurately across subjects. Consequently, the voxel-based analyses in such areas would be contaminated by the mixture of the voxels in the CSF, the cortex, and the WM. In the atlas-based analysis, after the entire brain was segmented into 130 areas, the cortex and the peripheral white matter were separated by the FA threshold in individual brains. The defined white matter compartments are, therefore, not contaminated by the CSF and the cortex, as much as with the voxel-based method. This could explain why the peripheral white matter areas tend to have statistically significant time-dependency in the atlas-based, but not in the voxel-based analyses.

An approach called TBSS is widely used as one of the normalization-based analyses (Smith et al., 2006). This method approaches this issue by skeletonizing the WM and condensing the nearby WM information into the skeleton. This is a clever way to ameliorate the problems related to the pixel-based analysis described above and, in terms of the amount of pixel grouping, it situates between the pixel and atlas-based analysis. It is theoretically possible to combine TBSS and the atlas-based segmentation to provide anatomical labeling to the TBSS results. Another interesting question is the possibility of finer anatomical segmentation beyond the 176 structures defined in this study. The more segmentation is provided, the more region-specific information we can obtain. Apparently the extreme of the finer segmentation is each pixel, which is equivalent to the pixel-based analysis. The optimum number of the anatomical segmentation, however, should be defined by the contrast in MRI/DTI. Namely, it does not make much sense to provide fine segmentation within a structure that cannot be distinguished by MRI. It is difficult to normalize the locations of such indistinguishable structures across subjects and, thus, the normalization-based analysis would become unreliable. The 176 structures defined in our atlas are based on those definable in the population-averaged DTI data (Mori et al., 2008; Oishi et al., 2008).

Utility for future neurological studies

Our report is largely descriptive, and it is difficult to extract firm cellular-level conclusions about how the brain develops, as long as we rely on the physical and chemical properties of water molecules. For example, as described above, the boundary between gray and WM compartments, defined by an $FA = 0.25$, could be artifactual and may not reflect the true changes in the gray — WM boundary during development. However, as long as we apply the same quantitative tools throughout the development process, the observations could provide useful information about how the brain develops and detect differences among populations. The tools described in this paper could effectively bring our attention to appropriate locations and time in the vast five-dimensional space.

We believe that this is an important step toward quantitative and automated diagnosis of MR images. Namely, the WMPM in the atlas effectively reduces the vast 3D spatial information into a manageable size (176 regions), in which two-dimensional information about the normal time course (and the degree of variability) of various parameters are contained. For demonstration purposes, we applied this atlas, enriched by normal development data, for the quantitative detection of abnormalities in the brainstem of cerebral palsy patients (Fig. 11). In this figure, z-score maps of the size and FA values of three representative patients are shown. The z-score maps use the WMPM, in which the amounts of deviations from the normal values are color-coded. These kinds of maps can be created for each patient, allowing quantitative evaluation of their anatomy at a glance. Here, our interest is the anatomy of the brainstem to evaluate the status of motor pathways. Visual inspection of the FA maps of the patients show smaller CSTs, with possibly lower FA values compared to the control (Fig. 11A, first line). However, it is not straightforward to determine whether these maps are beyond the normal range of variability. After applying the same atlas-based analysis, we compared the FA values and volumes from the FA maps of patients with those of control subjects. For each segment, time-dependence and reliability range can be calculated from the control data, and deviations can be delineated by z-scores, as shown in Fig. 11A, second and third lines. The actual fitting results for the left CST are shown in Fig. 11C. Our results indicate that all 13 CP patients (yellow squares) have the same or smaller FA and volumes as the average control value. Patients #2 and #3 have FA values lower by more than two standard deviations than controls, while all three representative patients have a smaller volume than the average, but within the two standard deviations. Here again, the volume and intensity measurements are coupled; if the CSTs were defined smaller, the FA may become higher. From MRI, we cannot derive any conclusions about the true anatomical status. Therefore, it is important to measure both volumes and intensities and interpret the results carefully. To apply this type of technique for real clinical use, there are many more factors to be considered, such as the impact of differences in imaging protocols and scanner types. In addition, our current data is based on only 35 subjects, which should be increased for more robust abnormality detection. However, our initial evaluation introduced in this paper seems promising for future clinical use.

Conclusion

LDDMM and atlas-based analyses of DTI allowed us to detect brain anatomical changes from two years of age to adulthood, and provided a comprehensive investigation of brain development. Each brain area followed a temporally distinct maturational trajectory in both size and diffusivity of water molecules. The quantitative and regional characterization of the normal maturation process is the first step in characterizing abnormal brain development. The reported tools and data provide important information about the regional normal values and variability among normal subjects, which are essential for experimental designs of future studies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Schematic diagram of the image normalization process. The two images in the boxes framed in blue are initial images for the image analysis; the subject original MRI and the atlas with the white matter parcellation map (WMPM). For the “forward” transformation, the subject image was first linearly normalized (affine transformation) followed by non-linear normalization (LDDMM). After this procedure, all subject images were transformed to a shape similar to that of the atlas. For the “backward” transformation, the WMPM was transformed to the original MRI using the same deformation fields used for the forward transformation. This allows automated segmentation of the original images into 130 subregions. For cortical areas where there is a large amount of anatomical variability, the cortex and the white matter were further divided using a threshold ($FA > 0.25$) for each subject, resulting in a total of 176 subregions. The final images used for statistical analyses are framed by red boxes.

Figure 2.

Demonstration of the normalization process and accuracy. (A) The Eve atlas used as the normalization target image. (B) A subject image warped to the atlas using the linear normalization. (C) A subject image after LDDMM normalization. Structures that are not accurately registered after the linear transformation are indicated by arrows, which are well-registered after LDDMM. (D) The final segmentation of the cortex and the associated white matter using an FA threshold (0.25).

Figure 3.

Scatterplots of the volume of total brain tissue, CSF, white matter, and gray matter compartments as a function of age. The data are fitted by a linear model except for the gray matter, which is modeled by an equation: $\text{volume} = \text{intercept} + \beta_1 * \text{age} + \beta_2 * \text{age}^2$. The orientation of the slices follows the radiological convention (L=left, R=right).

Figure 4.

Three-dimensional views of the atlas-based results overlaid in the rendered brain surface from the JHU-DTI-MNI single-subject Atlas (deepness of ROI visualization=100%). Colors represent the slope of the linear fitting between age (measured in years, in logarithmic scale) and volume (A); FA (B); and ADC (C) in each region. Regions with an $R^2 > 0.3$ are visualized. In many regions, the volume and the FA increase with age (except for FA in some cortical regions) while ADC decreases with age.

Figure 5.

Maps of slopes (A) and R^2 s (B) of the volumes measured by the atlas-based analysis. Larger, positive, time-dependence is observed in the white matter that contains projection fibers, such as in the corticospinal tract at the pons level (CST), the cerebral peduncles (CP), the internal capsules (IC), and the corona radiata (CR). The orientation of the slices follows the radiological convention (L=left, R=right). Slice positions are $z = -55, -45, -35, -25, -15, -5, 5, 15, 25$, and 35.

Figure 6. Actual fitting results (volume (mm³) vs. age (years, logarithmic scale)) at representative locations with high (upper row) and low (bottom row) time-dependence. The orientation of the slices follows the radiological convention (L=left, R=right). Slice positions are $z = -30, -15, 0$, and 25 .

Figure 7.

Maps of slopes (A) and R^2 (B) of the FA measured by the atlas-based analysis. A larger, positive, time-dependence is observed in the brainstem WM, the thalamus (Th), the anterior limb of the internal capsules (IC), and the frontal and parietal WM (FWM and PWM, respectively). Some cortical areas have negative time-dependence. The orientation of the slices follows the radiological convention (L=left, R=right). Slice positions are $z = -55, -45, -35, -25, -15, -5, 5, 15, 25$, and 35 .

Figure 8.

Map of slopes (A, B and C) and R^2 (D, E and F) of ADC, $\lambda_{\parallel}$, and $\lambda_{\perp}$ respectively, measured by the atlas-based analysis. Most white matter regions show a significant decrease in all three diffusivity measures. Regions such as the corticospinal tract (CST), the cerebral peduncles (CP), and the superior longitudinal fasciculus (SLF) showed significant time-dependence of $\lambda_{\perp}$, but of $\lambda_{\parallel}$. The orientation of the slices follows the radiological convention (L=left, R=right). Slice positions are $z = -55, -45, -35, -25, -15, -5, 5, 15, 25$, and 35 .

Figure 9.

Actual fitting results for the FA (first line), ADC (second line, in mm^2/s), $\lambda_{||}$, and $\lambda_{\perp}$ (third line, in mm^2/s) values by age (in years, logarithmic scale) at representative locations. In the corticospinal tract (CST, first column), the FA increase can be explained by the $\lambda_{\perp}$ decrease. In the anterior corona radiata (ACR, second column), the age-related changes in the $\lambda_{||}$ cause a weaker time-dependent FA change. In the WM of the superior occipital gyrus (SOG, third column), the parallel decreases in both $\lambda_{||}$, and $\lambda_{\perp}$ lead to no significant changes in FA. The orientation of the slices follows the radiological convention (L=left, R=right). Slice positions are $z = -58, -8$, and 13 .

Figure 10.

Map of slopes measured by the voxel- (A) and atlas-based analyses (B) for the volume, FA, and diffusivity values. Note the overall agreement between the two methods. Th=Thalamus. The orientation of the slices follows the radiological convention (L=left, R=right). Slice positions are $z = -58, -30, -13, 2,$ and 24 .

Figure 11.

Demonstration of automated abnormality detection using the atlas enriched by a normal database of developing brains. (A) FA maps of one control and three CP patients at the pons level ($z = -57$), revealing the CST, FA, and volume Z-score maps that show the degree of deviation from control values. These maps are shown in the atlas space, with which abnormal WM tracts can be identified at a glance. (B) Actual data in the enriched atlas (green dots), and the values from 13 CP patients (yellow squares) for the FA and volume. Linear regression of FA and volume of the left corticospinal tract (arrows) of normal subjects are shown by green dots. Shaded area is 95% confidence interval of the curve and dashed lines are the prediction interval for z-scores of ± 2 (gray and red lines, respectively), -3 (blue line), and -4 (yellow line). Yellow squares are the results from CP patients. The color surrounding the images and circle colors in the scatterplots identify the subjects.