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Quantitative Analysis of White Matter Fiber Properties along Geodesic Paths ⋆

Pierre Fillard [a] John Gilmore [b] Joseph Piven [b] Weili Lin [c]
Guido Gerig [a,b,*]

[a] *Dept. of Computer Science, Univ. of North Carolina, Chapel Hill*
[b] *Dept. of Psychiatry, Univ. of North Carolina, Chapel Hill*
[c] *Dept. of Radiology, Univ. of North Carolina, Chapel Hill*

Abstract

Diffusion Tensor Imaging (DTI) is becoming a routine magnetic resonance technique to study white matter properties and alterations of fiber integrity due to pathology. The advanced MRI technique needs postprocessing by adequate image processing and visualization tools. Previous analysis of DTI in clinical studies use manual definition of regions or interest or image matching followed by voxel-based analysis. In contrast, clinical research requires knowledge of white matter integrity along major fiber tracts to describe normal variability and change from normal. This paper presents a novel concept that extracts major fiber bundles by tractography and provides a statistical analysis of diffusion properties *along* fiber tracts which form geodesic paths within the three-dimensional brain image. Fiber bundles extracted from a set of subjects are parametrized by arc-length and mapped to a common coordinate system centered at well-defined anatomical landmarks. Fiber tracking thus serves as an efficient method for defining complex regions of interests along major fiber tracts which are not accessible otherwise. We present preliminary results from an ongoing clinical neonatal MRI/DTI study to assess early brain development.

Key words: Medical Image Analysis, Diffusion Tensor Imaging DTI, Tractography, Brain Development, Neonatal MRI

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* Corresponding author. Address: CB #3175 Sitterson Hall, Chapel Hill, NC 27599
Email address: gerig@cs.unc.edu (Guido Gerig).
URL: http://www.cs.unc.edu/~fillard (Pierre Fillard).

1 Introduction

Diffusion Tensor Imaging (DTI) is an MRI technique which assesses brain tissue properties via diffusivity, initiated by seminal research by Basser, Pierpaoli and others Basser et al. (1994); Basser and Pierpaoli (1996). Water shows restricted diffusivity as a function of material properties, and it tends to show stronger diffusion along oriented tissue such as white matter fibers which is inhibited orthogonally. Therefore, extraction of local diffusion tensors via diffusion tensor MRI and measurements derived from these tensors have become powerful techniques to study the local structure of intra-cellular and extracellular space within brain tissue. Alterations of the density of axons, degree of myelination, and the occurrence of lesions and infiltrating tumors, for example, have strong effects on the magnitude and shape of local diffusion tensors in white matter. The study of local properties of DTI have thus become a standard tool to study white matter disease, for example by calculating the magnitude of local diffusion or the tensor elongation, which serves as a measure of bundling strength. White matter of the human brain is subdivided into fiber tracts based on anatomical and functional criteria. At coarse scale, tracts are subdivided into commissural (left-right), association (anterior-posterior) and projection (inferior-superior) bundles. A finer classification defines the major role of the individual fasciculi. These fiber bundles can be measured in-vivo by techniques commonly called tractography. The simplest methods use trace the vector-field defined by the set of longest tensor axes between source and target regions. This results in curvilinear paths. or streamlines, which likely represent elements of fiber bundles. Research in MRI and Psychiatry even goes a step further and tries to establish a link between diffusion properties and geometric properties of fiber tracts and *brain connectivity*. This could potentially explain changes in functional connectivity as measured by fMRI and lead to a better understanding of neurodevelopmental or neurodegenerative brain changes.

Clinical studies using DTI most often rely on a comparison of regions-of-interest (ROIs) specified by users Zhai et al. (2003) or on voxel-based analysis of registered image datasets Lim et al. (1999). Whereas the former is inherently limited by the problem of reliable specification of small ROIs across a large number of three-dimensional images, the latter requires sophisticated registration and postprocessing techniques to account for local distortion of DTI obtained via echo-planar imaging (EPI), for warping individual brain structures to a template, and to solve tensor re-orientation as part of the non-linear warping Xu et al. (2002).

This paper describes an alternative processing scheme. We use tractography to extract sought fiber tracts from a series of image data. Fiber tracts are stored as sets of curvilinear structures with subvoxel precision and are parametrized by arc-length. These bundles are mapped into into a graph after centering at

a common origin defined by a well-defined anatomical landmark. Statistical analysis of diffusion tensors thus can be performed *along* tracts, which are geodesic paths in the original image data. Concepts for aligning fiber bundles using 3-D curve matching strategies were first presented by Ding et al. Ding et al. (2001). Streamline curves extracted by tractography were bundled to thicker cable-like structures using a metric that describes closeness of curves to a core template. Recently, this clustering has been extended to describe and represent ribbon cables (Corouge et al. (2004)).

The following section 2 describes details of the tractography method and of the calculation of diffusion properties along fiber bundles. Section 3 presents early results from an ongoing clinical study of early brain development. Commissural tracts through splenium and genu of the corpus callosum of newborns (2 weeks old) are compared to those extracted from 2-years old children and to adults.

2 Extraction of Fiber Tracts

Prerequisit to the analysis of diffusion properties along fiber bundles is the extraction of such tracts across a population of subjects. We have developed an integrated software package for efficient processing, fiber tracking, and interactive visualization of DTI data. The DTI analysis tool combines common, well-established tensor calculation methods for DTI data, a recently developed powerful fiber tracking method and interactive scientific visualization into an integrated program. The tool guides a user through the various processing stages including tensor calculation, calculation of fractional anisotropy (FA) and apparent diffusion coefficient (ADC), extraction of fiber bundles between source and target regions of interest, two-dimensional and three-dimensional visualization of diffusion images and fiber tracts, and various choices of output. The tool is fully integrated into the Insight Toolkit programming environment and uses commonly used input and output formats to provide a seemless connection to packages like Analyze and SPM.

Tensor Coefficients Calculation The tensor field calculation is based on an analytical solution of the Stejskal and Tanner's diffusion equation system (a comprehensive description is found in Westin et al. (2002)). The current version is designed to use the common directional coding proposed by Basser et al. Basser and Pierpaoli (1996). The baseline and six directional images are loaded into the program for extraction of the diffusion tensor. The two measures most commonly used in clinical analysis, the "apparent diffusion coefficient" (ADC, trace of tensor) and the "fractional anisotropy" (FA, shape described by tensor), are calculated and can be stored as image data. Non-brain structures are suppressed by a user-defined threshold on the diffusion

baseline image. All the images including the original DTI data and tensor measurement can be selected for multi-planar visualization.

Fiber-Tracking Algorithm The vector field defined by the eigenvectors associated with the largest eigenvalues is assumed to represent a good approximation to local white matter fiber orientation. This simplification fails at branchings and crossings of nearby fiber bundles, which is subject to ongoing research by MR researchers using a larger number of discrete directions or advanced techniques like diffusion spectrum imaging (DSI). The goal of the tracking, also called "tractography", is to find likely paths through the vector field between source and target regions of interest (ROIs). We reimplemented a previously published method Mori et al. (1999) which was later modified by Dongrong Xu et al. (2002) and have integrated the tool into the ITK programming environment. The tractography method makes use of the vector field defined by the local directions associated to the largest eigenvalues. The criteria for judging local continuity include minimal FA value, local curvature (angle difference between consecutive vectors), and local coherence (regularization over local neighborhood). This method provides traces with sub-voxel precision by using a voxel-intercept concept similar to the well-known marching cubes method for surface extraction.

We apply the tracking method with a backward tracking scheme instead of a direct tracking. Direct tracking is a forward processing scheme which has the disadvantages that it can provide only one trace per voxel and that it has to make local decisions for path propagation. The backward scheme as used herein is initialized at each voxel of the full brain or a large user-defined target region. To reduce computational effort, only voxels above a user-specified minimal FA value are considered for tracing. The method traces paths from each target voxel backwards to the source region, and only paths passing through the user selected ROIs are finally kept. This concept, assuming that the target volume is much larger than the source ROI, makes use of the decrease of the complexity during propagating and results in a significantly improved robustness. The choice of a sub-voxel coordinate system is superior to a discrete voxel grid and provides significantly improved fiber representations.

Figure 1 illustrates the processing pipeline with the example of the extraction of the cortico-spinal tract. A user defines source (internal capsule) and target regions (motor cortex) using an interactive 3-D region definition tool SNAP Ho et al. (2002). Our experience shows that these regions can be reliably and efficiently defined on the fractiona anisotropy (FA) image. The fiber tracking tool reads the set of diffusion image channels, calculates the tensor, reads the region of interest image, and performs the tracking. The resulting sets of streamlines are stored as list of polylines which also carry the full tensor information at each polygon point.

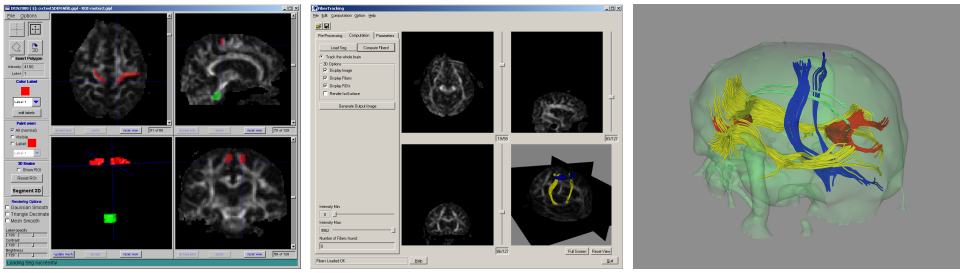

Fig. 1. Example demonstrating the tracking of the cortico-spinal tract. Left: User defined ROIs in the pons and motor cortex using the IRIS/SNAP tool. Middle: Graphical user interface of the Fiber-Tracking tool showing the result of the tracking (yellow) with overlay of source and target regions (blue). Right: Result of the reconstruction of 4 major fibers tracts (cortico-spinal tract, traversal tracts through splenium and genu of corpus callosum, cingulate, longitudinal fasciculi, shown with overlay of the intracranial cavity. DTI are acquired on a GE 1.5T scanner with an EPI sequence and 2x2x2mm3 voxel resolution.

Figure 2 illustrates the reconstruction of the left and right cingulate fiber tracts in an adult case. The ROIs for the tracking (defined with the SNAP tool) are placed in the anterior and posterior regions of the cingulate.

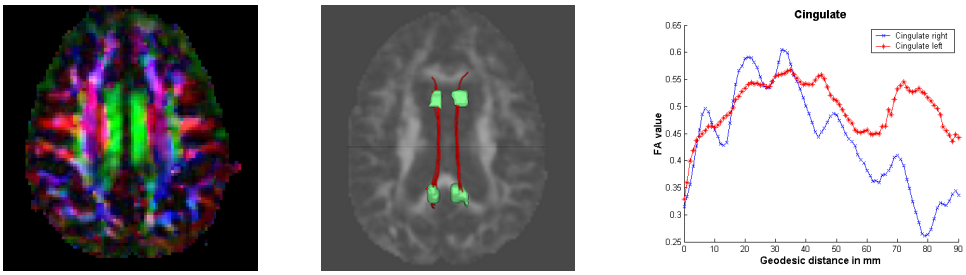

Fig. 2. Reconstruction of the cingulate tract. Left: Color-coded FA image at the level of the left and right cingulate (anterior-posterior, inferior-superior and left-right orientations are shown in gree, blue and red, respectively). Middle: Result of the fiber tracking with source and target regions for initializing the tracking (blobs). Right: FA values for left and right cingulate plotted as a function of geodesic distance, left to right represents posterior to anterior.

The DTI processing package includes the following features:

- Loading input DTI data (GIPL, ANALYZE or DICOM-META format) as sets of baseline and gradient encoding images.
- Extraction of tensors and calculation of ADC and FA values.
- 2-D orthogonal slice visualization of DTI data and of ADC and FA images.
- Loading label image with user-defined ROIs.
- Fiber tracking from target to source volumes.
- 3-D interactive visualization of fiber bundles, FA isosurface, source and target ROIs, and user-selected image channels.
- Storing of fiber bundles as sets of poly-lines (ITK data format for curvilinear structures) or as binary fiber-tract label images.

- Storing of FA, ADC image data and 3-D renderings.

This software has been developed in ITK (NLM sponsored Insight Toolkit Kitware (2002); Ibanez et al. (2004)), a powerfull C++ library dedicated to medical image processing. Currently, the DTI tool is available for Windows PC (Win2000 and XP), Linux, and UNIX Sun Solaris (download at http://midag.cs.unc).

2.1 Mapping of fibers to corresponding coordinate frame

Fiber tractography provides sets of streamlines suitable for visual inspection and scientific visualization. Use of DTI in clinical studies, on the other hand, requires a processing scheme for quantitative analysis of diffusion properties within cross-sections and along fiber tracts. Fiber bundles traced between target and source are stored as sets of curvilinear poly-lines using the standardized data structure provided by ITK Kitware (2002). Within each bundle, the coordinate origin is specified as a key anatomical landmark specified by the user. The specification of such an origin might vary for various types of fiber tracts. Commissural tracts through the corpus callosum, for example, use the midsagittal plane coordinate as the common center. The cingulate, on the other hand, uses the specification of the center of the nearby splenium as an external anatomical landmark to represent the most inferior location for left and right structures.

The curvilinear structures carry FA and ADC values as attributes at each node. This list of attributes can be easily extended upon user's needs, e.g by combining values extracted from structural images. It is straightforward to combine the FA values of the set of single fibers to an average $\overline{FA}$ and to calculate statistics as a function of distance from the origin $FA(d)$:

$$FA_i(d) \quad d \;=\; \{-d_{min}, \cdots, 0, \cdots, d_{max}\} \tag{1}$$

$$\overline{FA}(d) = \frac{1}{n_d} \sum_{i=1}^{n_d} FA_i(d) \tag{2}$$

As bundles vary in local thickness, the number of streamlines to be averaged varies as a function of distance from the origin. Please note that this mapping represents a *geodesic path* in the individual datasets as shown in Figure 2 middle. Fig. 2 right illustrates the FA values for the left and right cingulate fiber tracts as functions of geodesic distance along the tracts. Left to right shows posterior to anterior direction.

We apply the same concept of arc-length parametrization centered at a common origin to combine and compare fiber tracts among different individuals.

We assume that the tracked structures represent comparable anatomical regions.

3 Application to Neonate Study

While it has been hypothesized that brain development is abnormal in neurodevelopmental disorders, there have been very few attempts to study very early brain development in children. Only a few prior quantitative magnetic resonance imaging and diffusion tensor imaging studies of unsedated newborns exist; most of the children in these studies were born prematurely Hüppi et al. (1998a,b); Neil et al. (1998).

In a pilot study to optimize procedures for a much larger full-scale clinical study (Zhai et al. (2003)), 20 unsedated healthy newborns underwent 3 Tesla magnetic resonance imaging (MRI and DTI, 10 males and 10 females; age 16 $\pm$ 4 days [mean SD]). Scans without significant motion were obtained in 13 children. The imaging parameters for the DTI sequence were: TR/TE/TH=4219ms/92.2ms/5mm, inplane resolution = $1.72x1.72mm^2$, 12 averages, and 20 slices. Seven images were acquired for each slice using the directional encoding scheme developed by Basser et al. Basser and Pierpaoli (1996). Due to the pilot character of this study also including scanner pulse sequence optimization, we selected all 13 scans for ROI analysis in one axial slice (see subsection 3), but only a subset of five neonates for the more advanced fiber tracking method.

Quantitative ROI analysis of DTI Eight regions of interest (ROIs) were placed in white matter on a *single* transverse section through the level of the basal ganglia, including the anterior and posterior limbs of the internal capsule (IC), left and right occipital and frontal WM adjacent to the cortical gray matter and the genu and splenium of the corpus callosum Zhai et al. (2003). Group comparisons showed a global elevation of ADC ($p<0.001$) in both GM and WM and a reduction of FA ($p<0.001$) in WM were found in neonates when compared with that in adults. While regional variations of FA and ADC in adults are less remarkable, the central WM in neonates consistently exhibits higher FA and lower ADC than *peripheral WM*. This study clearly demonstrated that user-defined region of interest analysis is by definition limited to simple regions most often defined in only one plane. Moreover, errors are introduced by limited intra- and inter-rater reliability of the region of interest definition and by the selection of intersection planes. Also, statistical analysis within small ROIs including only a few voxels might be very sensitive to partical voluming.

Fiber tract analysis along geodesic paths The study discussed above was limited to measurements within user-defined small regions of interest in only one axial cross-section. We applied our highly automated measurement scheme to assess white matter properties in full 3-D space and tested the hypothesis of FA decrease from interior to peripheral directions. The user interaction is limited to the specification of the splenium and genu of the corpus callosum, used as source regions for fiber tracking. This task can be reliably and efficiently done by loading the FA image into our interactive image editing tool IRIS/SNAP (free download at midag.cs.unc.edu), which allows a user to define 3-D regions of arbitrary shape, e.g. spheres, in volumetric image data. Fiber tracts were traced backwards from the full brain towards these source regions. Figures 3 represent 5 cases with commissural tracts through the splenium and genu regions and qualitatively demonstrates the reproducibility across subjects.

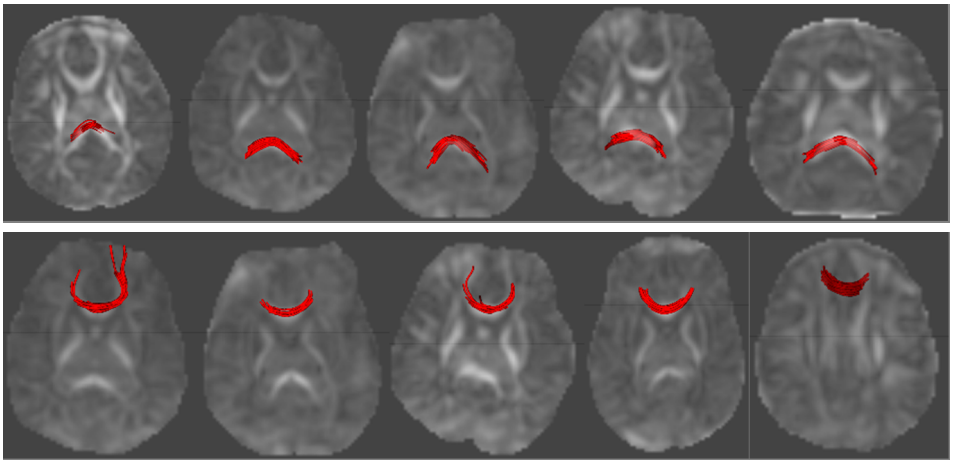

Fig. 3. Tracing of the commissural fiber tracts through the splenium and genu of the corpus callosum shown in five neonates. The regions of interest were specified as a sphere centered at the midsagittal plane. The whole brain with FA larger than 0.1 is specified as the target region. Fibers are traced backwards from target to source.

Mapping of fibers into corresponding coordinate frame The quantitative analysis of fiber tracts follows the procedure outlined in previous sections. The coordinate origin for each fiber bundle was set to the center of the genu and splenium regions within the interhemispheric plane (Fig. 4). Figure 5 illustrates the FA properties of the commissural tracts through the genu (left) and splenium (right) for five neonates. Individual curves (textured) such as average curve (solid blue) are shown in overlay. All curves cover a common distance of $\pm 20mm$ from the origin and clearly show a sharp decrease of FA with increasing distance from origin. Figure 6 illustrates the potential of our new method to address the important clinical question of maturation as a function of age or alterations due to developmental delay. The genu and splenium tracking was additionally applied to DTI of healthy adults and 2-year

old children. Each curve represents an average of several subjects. Given the small number, it would be too premature to draw final conclusions. However, the curves confirm earlier findings of smaller FA values in neonates Hüppi et al. (1998b); Zhai et al. (2003). Interestingly, the 2-year old subjects seem to have FA values in the same range as adults.

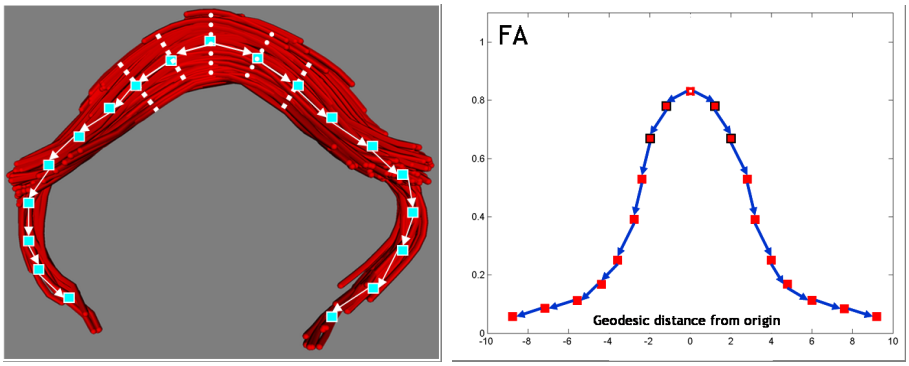

Fig. 4. Schematic diagram illustrating the mapping of diffusion properties along fiber bundles. The left figure shows the example of the fiber tract through the genu of the corpus callosum with origin and sampled cross sections. Resulting average values for each cross-section as a function of arc-length, here of the fractional anisotropy FA, are displayed in the right figure.

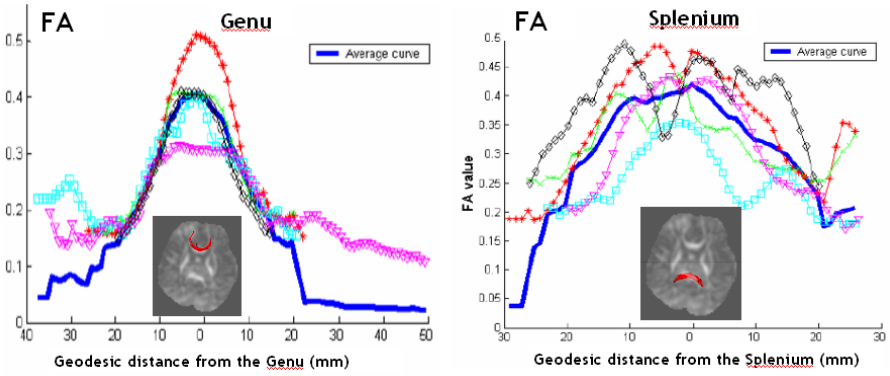

Fig. 5. Fractional anisotropy (FA) measured along commissural tracts through the genu (left) and splenium (right) shown for five neonates. The plots are centered at the position of the midsagittal plane and follow the fiber tracts exteriorly towards the cortex, mostly in anterior (genu) posterior (splenium) directions. The average $\overline{FA}$ curves are shown as a solid, blue lines.

Validation In total, we tested the DTI analysis and fiber tracking tools on over 25 images taken from various ongoing clinical studies. Validation of DTI with comparison of different pulse sequences (EPI and spiral), scanner manufacturers (Siemens 3T, GE 1.5T and 4T), and different spatial resolution is part of an ongoing activity between MRI research at UNC, at Duke University and our neuroimage analysis laboratory. Validation of DTI fiber tracking

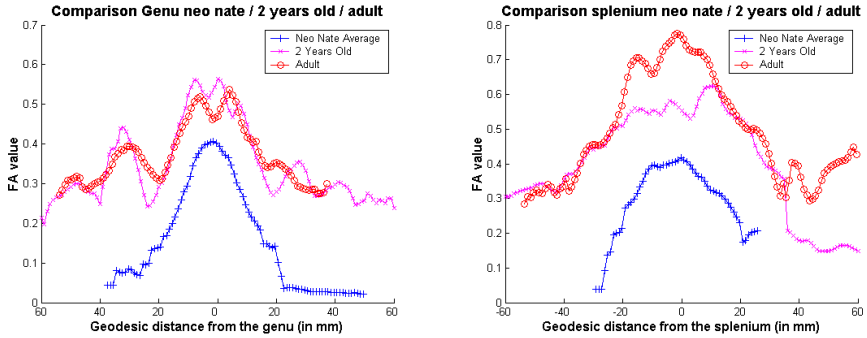

Fig. 6. Fractional anisotropy (FA) measured along commissural tracts through the genu (left) and splenium (right) as a function of age. The average of five neonates (blue) is compared to 2years old subjects (purple) and adults (red). The horizontal axis reflects real distance in mm. Results suggest significantly smaller FA values for neonates and quick decrease towards peripheral regions.

requires simulated data, standardized phantoms and/or animal studies. Providing tools and methodology to assess validity of MR-DTI is part of ongoing efforts of the MRI research community.

Validation in our study was so far limited to assess reliability of the postprocessing methods. Systematic validation studies of user-defined ROI placement in DTI illustrated the problem of limited reliability and was key for the new development presented here. In this validation study with repeated measurements (5 cases with 3 repetitions each, 2 years old children), two manual raters blind to the data placed volumetric ROIs in frontal white matter as seen in ADC images, following a well-defined protocol based on anatomical landmarks. Statistical analysis of the apparent diffusion coefficient (ADC) and fractional anisotropy (FA) resulted in inter- and intra-rater reliabilies of 0.85 to 0.90, which was considered as insufficient. Our new method only requires the placement of two regions to cover the splenium and genu in the FA image. This simple task can be achieved with very high reliability. The remaining fiber tracking procedure with a fixed set of parameters is fully automatic and not subject to any user variability.

4 Discussion

This report describes work in progress towards mapping and parametrizing fiber tracts extracted from a large number of subjects. We present a new approach for measuring white matter diffusion properties along fiber tracts as a function of geodesic distance from specific anatomical landmarks. Fiber tracking and parametrization serve as new methods to establish homology among subjects. The procedure overcomes existing limitations of user-specified region definition or full-brain registration, especially in view of the spatial

distortions faced with high-speed neonatal MRI. The tracking takes only a few seconds on a standard PC. The whole process including ROI specifications, FA calculation, tracking, and storing fibers into a database takes a few minutes per subject. Current research addresses the issues of developing more advanced schemes for fiber tract alignment and validation of fiber bundles obtained by tracking in comparison to co-registered structural image data.

Previous studies in infants and older children find that white matter FA increases and ADC decreases with age Hüppi et al. (1998a,b); Neil et al. (1998); Schmithorst et al. (2002). In the very limited age range available to our study and using regions of interest, we observed a significant increase in FA in the genu ($r2 = 0.3639$; $p = 0.0291$) and splenium ($r2 = 0.5102$; $p = 0.0091$) of the corpus callosum, but not in other white regions. This suggests that the white matter of the corpus callosum is undergoing significant maturation in the period after birth that may represent a window of vulnerability to perinatal insults that have been associated with neurodevelopmental disorders.

The tractography analysis is limited by the relatively small sample size and our findings need to be replicated in a larger sample. As part of our Conte Center to study pathophysiology in schizophrenia, we expect to scan over 120 neonates, some with follow-up scans, over the next 5 years. In combination with the activities of the neurodevelopmental research center, we will also apply our new DTI analysis technique to 2-4 years old children (autistic subjects and controls, N=20+50). Further, we will explore other major fiber bundles known for early myelination like the cortico-spinal tract and bundles known for delayed myelination like the temporal lobes.

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