Automatic Tractography Segmentation Using a High-Dimensional White Matter Atlas

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Abstract—We propose a new white matter atlas creation method that learns a model of the common white matter structures present in a group of subjects. We demonstrate that our atlas creation method, which is based on group spectral clustering of tractography, discovers structures corresponding to expected white matter anatomy such as the corpus callosum, uncinate fasciculus, cingulum bundles, arcuate fasciculus, and corona radiata. The white matter clusters are augmented with expert anatomical labels and stored in a new type of atlas that we call a high-dimensional white matter atlas. We then show how to perform automatic segmentation of tractography from novel subjects by extending the spectral clustering solution, stored in the atlas, using the Nystrom method. We present results regarding the stability of our method and parameter choices. Finally we give results from an atlas creation and automatic segmentation experiment. We demonstrate that our automatic tractography segmentation identifies corresponding white matter regions across hemispheres and across subjects, enabling group comparison of white matter anatomy.

Index Terms—Atlas, clustering, diffusion magnetic resonance imaging (MRI), tractography, white matter.

I. INTRODUCTION

IFFUSION magnetic resonance imaging (MRI) is presently the only technique that allows measurement of white matter fiber orientation in the human brain in vivo. The power of diffusion MRI lies in the fact that the diffusion of water molecules probes tissue structure at very small scales, much smaller than the voxel resolution. This allows measurement of the voxel-averaged effects of collisions of water molecules with cellular components such as membranes. In tissues which have an oriented fibrous structure, such as white matter and muscle, water diffusion is anisotropic (varies with direction), and the direction of fastest diffusion parallels the fibrous structure. There is a large difference in size between macroscopic MRI voxels and microscopic neurons, as many thousands of axons can fit in a volume corresponding to one image voxel. However, diffusion imaging can measure the orientation of axons in white matter fiber tracts because the distance diffused by a water

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TABLE I SIZE SCALES OF DIFFUSION IMAGING

Quantity	Measurement
axon packing density (corpus callosum)	$338,000/mm^2$ [12]
axon diameter (central nervous system)	0.2 to 20 µm [13]
voxel size in diffusion MRI	pprox 2 imes 2 imes 2 mm
mean water diffusion distance	1-15 µm (in 50-100 ms) [14]

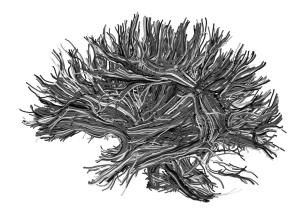


Fig. 1. An example of whole brain white matter tractography, with fiber trajectories colored random shades of gray. This data is the input to our method.

molecule during imaging is approximately an axon diameter (Table I).

Diffusion MRI can be used to create a representation of white matter tracts in the brain via a process called tractography [1]–[5] that estimates white matter tract trajectories by following likely tract directions. The two main tractography strategies are probabilistic (an attempt to describe all possible fiber trajectories [6]–[8]) and streamline (which locally chooses the most probable fiber trajectory [2]–[5]). Tractography methods have been adapted to various representations of diffusion and fiber tract orientation data, including diffusion tensor MRI (DTI), q-ball [9], and multiple tensor models.

The most common combination of diffusion data and fiber tractography method today is DTI and streamline tractography. In DTI, a tensor model is used to represent diffusion [10] and the major eigenvector of the tensor (principal diffusion direction) is associated with the fiber tract direction. The streamline method of tractography estimates entire fiber trajectories by stepping along the major eigenvector direction, usually for a predefined step size (around 0.5 mm) and using the Runge-Kutta numerical integration method of order 2 or higher [2], [3], [11].

When performed in the entire brain, tractography outputs many thousands of fiber trajectories per subject (Fig. 1). These trajectories are not immediately useful to clinicians or researchers: they must first be organized into anatomically meaningful structures. We refer to this as the tractography segmentation problem. After segmentation, tractography then becomes useful in applications such as the localization of specific tracts for surgical planning and the definition of tract regions of interest for quantitation of diffusion in clinical studies of diseases that affect the white matter. Our goal, therefore, is to perform automatic segmentation of tractography data to enable further clinical and research applications of tractography.

In this paper, we propose a method for white matter atlas building and automatic white matter segmentation. Because we have access to tractography data from multiple subjects, we have designed our method to learn common white matter structures that are present across subjects. These white matter structures are found by simultaneously clustering registered (rigidly aligned) tractography from all subjects. The clustering is performed in a high-dimensional spectral embedding space where each fiber trajectory is represented as a point. Then the clusters are visualized and expertly labeled with anatomical names, creating an anatomical model of white matter structures that we call a high-dimensional white matter atlas. We use the atlas to perform automatic segmentation of tractography from new subjects by embedding the new fiber trajectories as points in the atlas spectral embedding space, then labeling the fibers according to the nearest cluster centroid.

In Section II, we relate background information on tractography segmentation approaches and goals. Section II describes related work in the machine learning literature. Next, we describe each step of our method in detail. Then we present atlas and automatic segmentation results from an application of our technique, as well as results regarding choices of parameter settings and stability of the method. Finally, we conclude with a discussion of the method.

II. BACKGROUND: TRACTOGRAPHY SEGMENTATION

A. Existing Techniques

Existing tractography segmentation approaches can be divided into three categories: interactive methods, automatic clustering methods, and automatic atlas-based methods.

1) Interactive: In interactive tractography segmentation approaches, fiber selection and anatomical labeling are done using expert knowledge. These methods, also known as "virtual dissection," select fibers that pass through user-defined regions of interest (ROIs) [3], [15] and have been employed to create a fiber tract atlas [16] and in clinical studies [17]–[19]. In fact, Partridge *et al.* found tractography-based definitions of a pyramidal tract ROI to be more reproducible than manual ROI drawing [19]. Interactive methods are currently the most commonly used, but require extensive knowledge about complex 3-D white matter fiber tract anatomy.

2) *Clustering:* Most published automatic tractography segmentation methods have used clustering approaches (algorithms that group similar items) to organize the large number of fiber trajectories into clusters, or fiber bundles. However, few of these methods have attempted to automatically attach anatomical labels to the clusters or to find corresponding clusters across subjects.

In order to perform clustering, first a mathematical definition of fiber similarity (or more commonly a fiber distance) must be specified. Then, pairwise fiber distances may be calculated and used as input to a clustering algorithm such as hierarchical clustering [20]–[22] or spectral clustering [23]–[26].

Various fiber distances have been proposed in the literature, all based on the assumption that fiber trajectories that begin near each other, that follow similar paths, and that terminate near each other should belong to the same anatomical structure. Early work by Brun et al. performed spectral embedding based on distance between fiber endpoints, then colored fibers using their embedding coordinates to give a soft visual perception of connectivity [27]. Later Brun et al. introduced a 9-D tract shape descriptor vector, defined as the mean and lower triangular part of the covariance matrix of the points on a fiber, and computed the Euclidean distance between shape descriptors [23]. Gerig et al. and Corouge et al. proposed distances that employed pointwise comparison of tract shapes: they defined three measures related to the Hausdorff distance including the mean closest point distance we employ [20], [21]. In work by Jonasson et al. (who used fiber trajectories through high angular resolution diffusion data) a similarity measure was calculated based on the number of times two trajectories shared the same voxel [24]. The preceding methods all used streamline tractography as input, however the method of Johansen-Berg et al. employed probabilistic tractography and connectivity matrix reordering to find the boundary between the supplementary motor area and the presupplementary motor area [28].

There is convergence in the literature with respect to the choice of fiber distance measure, as multiple authors have employed some type of mean closest point distance [20], [21], [22], [26], [29], [30] and it was found to be the most effective in a small study where the ground truth clusters were known [31]. The mean closest point measure has also been applied to trajectory clustering in outdoor video [32].

3) Atlas-Based: Automated fiber grouping via atlas-based labeling of tractography was described by Maddah *et al.* [33] who used manual interactive methods to create a tractography atlas and gave an algorithm for transferring its labels to a novel subject. Their further work created an atlas of the corpus callosum using labeled tractography from several subjects and used an electromagnetic (EM) framework to classify fibers from novel subjects [34]. Their atlas contained statistical models of tractography in subregions of the corpus callosum (the average and standard deviation of fibers in each region) and the fibers were represented using spline coefficients [34]. A different application of an atlas was presented in [30], where a gray matter atlas was used to initialize clustering, then the mean closest point and Hausdorff distances were used to group fibers.

B. Techniques for Corpus Callosum Parcellation

One application of our tractography segmentation method is the subdivision of the corpus callosum into regions. Subdivision of the corpus callosum is of interest because many studies have localized intersubject differences to specific regions of the corpus callosum, for example in callosal atrophy with age [35] and in fractional anisotropy (FA) changes in Alzheimer's disease [36]. DTI-based approaches have mostly aimed to parcellate according to whether corpus callosum tractography goes to temporal, occipital, frontal, or parietal regions [37]–[39] though one approach employed a statistical model of tractography [34], and another used functional MRI (fMRI) visual field maps [40].

C. Goals of Tractography Segmentation

Ideally, an automatic tractography segmentation algorithm should satisfy several goals: grouping of like trajectories into fiber bundles (for further processing or visualization), bundle correspondence across subjects (for cross-subject comparison), and anatomical labeling of bundles (for analysis of specific white matter structures). The first goal (grouping) is satisfied by the clustering and atlas-based algorithms. The second goal (bundle correspondence) has been approached by cluster postprocessing and matching [22], [41], by simultaneous clustering of multiple subjects [25], and by labeling using an atlas [33], [42]. Finally, the third goal of anatomical labeling of bundles has been satisfied by atlas-based approaches [30], [33], [42].

It is clear that atlas information is beneficial to satisfy the automatic segmentation goals. However, the construction of an atlas itself requires tractography segmentation, with the inherent challenges of the large number of fiber trajectories per subject and the three-dimensionality, anatomical complexity, and intersubject variability of the data. Consequently, here we propose a unified approach to atlas creation and subsequent tractography segmentation that takes advantage of a clustering method to identify common white matter structures across subjects and uses expert input to anatomically label those structures.

III. BACKGROUND: EXTENDING SPECTRAL CLUSTERING TO NEW DATA

Our automatic segmentation method uses the results of a spectral clustering solution (stored in the high-dimensional white matter atlas) to classify novel data. Related work exists in the machine learning literature, where using spectral clustering for embedding novel data was proposed by Bengio et al. in 2004 [43]. They describe how to embed out-of-sample (nontraining) data using the Nystrom method, for various methods of spectral embedding including normalized cuts and multidimensional scaling (MDS), but they do not discuss use of clustering results in the embedding space for labeling or segmenting the out-of-sample points. Other related work is the Nystrom extension to normalized cuts by Fowlkes et al. [44] on which our approach is based. However, Fowlkes et al. discuss eigenvector approximation of a matrix where all data is at hand, not the use of the method for embedding new data. It has also been pointed out that the embedding of new data via the Nystrom method is equivalent up to scale factors to the method of projection onto eigenvectors of kernel principal component analysis (PCA) [45].

In contrast to related work, our approach segments novel data using spectral embedding and the results of an existing clustering solution, and we augment the learned cluster model with additional anatomical information specific to our segmentation problem. In this paper, we show specifically how to embed novel data using the framework for normalized cuts spectral clustering and matrix normalization of Fowlkes *et al.* [44], and we show

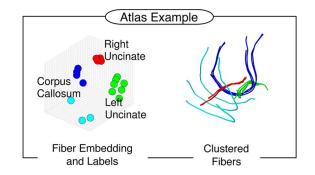


Fig. 2. Toy example of atlas creation. For purposes of illustration all points and fibers are colored according to cluster. The fibers (right) were embedded as points (left). The image on the left shows the first three dimensions of the actual embedding space. Then the points were clustered (cluster membership is indicated by color), and finally the clusters were given expert anatomical labels (shown in left image).

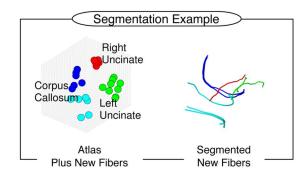


Fig. 3. Toy example of automatic segmentation using spectral embedding. For purposes of illustration all points and fibers are colored according to cluster. The new fibers (right) were segmented by first embedding them as points in the atlas embedding space (left) and then assigning each point to the closest atlas cluster.

that our tractography data can be segmented according to its distance to existing atlas cluster centroids.

IV. METHOD

A. Overview

Our method has two parts: atlas generation and automatic segmentation. The atlas contains a high-dimensional model of white matter structure. It differs from traditional digital (voxel-based) atlases because it represents long-range connections from tractography rather than local voxel-scale information.

The high-dimensional atlas is constructed via a process called spectral embedding, where each fiber is represented as a point in an atlas embedding space. Common white matter structures (across subjects) are identified as clusters in this space, then the clusters are inspected and given expert anatomical labels. Fig. 2 shows the actual spectral embedding for a very small example dataset.

Automatic segmentation of tractography is achieved by first spectrally embedding the new fibers as points in the atlas embedding space, then assigning the points to the existing atlas clusters. This process is shown visually for a few new fibers (Fig. 3), using the atlas from Fig. 2.

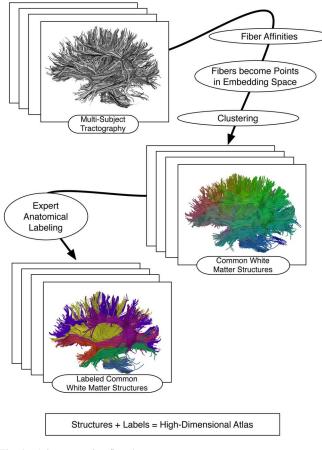


Fig. 4. Atlas generation flowchart.

 TABLE II

 CONTENTS OF THE HIGH-DIMENSIONAL ATLAS

Atlas Data	Description
reference image	Group mean FA image
fibers	Random subset of fibers used for affinity compu-
	tation
D_{param}	Fiber distance parameters: symmetrization type,
	midsagittal reflection on/off (eqs. 2, 3)
σ	Parameter in conversion of distances to affinities
	(eq. 4)
$\mathbf{A}^{-1}\mathbf{b}_r$	For affinity matrix normalization (eqs. 6, 10)
$\mathbf{a}_r + \mathbf{b}_r$	For affinity matrix normalization (eqs. 6, 11)
$U\Lambda^{-1}$	Basis vectors for embedding space (eqs. 8, 13)
centroids	Cluster centroids in atlas embedding space
labels	Anatomical information associated with each cen-
	troid
colors	Colors for display of each cluster and anatomical
	tract

Now we describe the atlas generation and automatic segmentation parts of the method in detail.

B. Atlas Generation Procedure

The sequence of steps in the atlas generation procedure is: group image registration, multiple subject whole brain tractography, fiber affinity calculation, fiber spectral embedding, fiber clustering, and expert anatomical labeling (Fig. 4). The full contents of the atlas are listed in Table II for reference. In the rest of this section, each step will be explained.

1) Group Image Registration: The following steps assume that all subjects' tractography is in a common coordinate

TABLE III Parameters for Whole Brain Tractography

Threshold	Description	Useful Values
T _{seed}	start tractography where $C_L > T_{seed}$	0.1 to 0.3
$T_{\rm stop}$	stop tractography where $C_L < T_{stop}$	0.1 to 0.2
T_{length}	cull fibers whose length $< T_{length}$	10 to 50 mm
N	cluster N randomly sampled fibers	>= 10,000

system. We have employed the congealing algorithm [46] for rigid (rotation, translation, and scaling) group registration of subject FA images. Then we have applied the registration to subject tractography data. The congealing algorithm is an unbiased group registration technique that does not at any point register to a subject in the group. The mean FA image from group registration defines the coordinate system of the atlas and it is stored as the reference image for registration of future subjects to the atlas.

2) Multiple Subject Whole Brain Tractography: Our method is applicable to any tractography data that is represented as trajectories in three dimensions. Specifically in this paper, we consider whole brain tractography from streamline integration in DTI data, because this is currently the most common type of tractography and data. We generate tractography in the entire white matter of the brain of each subject, using Runge-Kutta order two tractography [2], [11] with a fixed step size of 0.5 mm.

We have three threshold parameters for tractography: T_{seed} , T_{stop} , and T_{length} . The first two are anisotropy thresholds based on the linear anisotropy measure (C_L) [47]

$$C_L = \frac{\lambda_1 - \lambda_2}{\lambda_1} \tag{1}$$

where λ_1 and λ_2 are the largest two eigenvalues of the diffusion tensor, sorted in descending order. The goal of the anisotropy thresholds is to limit tractography to the white matter. We seed (initiate) tractography in every voxel in the brain with C_L higher than the threshold T_{seed} . Tractography stops when C_L on the fiber falls below T_{stop} , indicating gray matter or areas of planar anisotropy. We have chosen the C_L measure rather than the FA [48] because FA can be relatively high in regions of planar anisotropy, which can indicate tract crossings or branchings [49]. The third threshold is a length threshold T_{length} used to remove very short fibers from the clustering. The thresholds vary by application, generally higher (less inclusive) if only the major tracts are desired, and lower (more inclusive) for neurosurgical visualization where one would like to see "everything."

Depending on the subject, the seeding resolution, and the various thresholds, whole brain tractography produces between 10 000 and 100 000 fibers per subject. In practice, we randomly sample from these fibers to obtain a practical number, where approximately 10 000 fibers per subject is reasonable for visualization of a subject's white matter. All random sampling of fibers is performed without replacement. Useful ranges for the thresholds and random sampling are listed in Table III.

3) Fiber Affinity Calculation: The next step in the method calculates information about the subjects' fiber trajectories. As described in Section III, the assumption of all fiber clustering

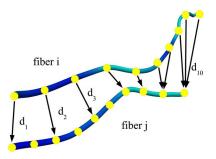


Fig. 5. Illustration of computation of mean closest point distance measure between two fibers. In this example each fiber is represented by 10 yellow points. The directed closest point distances (from fiber i to j) are represented with black arrows.

methods is that fibers which follow similar trajectories belong to the same anatomical structure. We quantify pairwise fiber trajectory similarity by first computing a pairwise fiber distance, then converting it to a pairwise fiber affinity. We employ the mean closest point distance d_{mcp} , which is defined as the mean distance between pairs of closest points on two fibers. This measure is often used in fiber clustering ([20], [21], [22], [26], [29], [30]). To compute this distance from fiber *i* to fiber *j*, first for each point on fiber *i*, the closest point on fiber *j* is found, and the distance is stored. After computing the distances from all points on fiber *i*, the distances are averaged

$$d_{\mathrm{mcp}_{ij}} = \frac{1}{n} \sum_{k=1}^{n} d_k \tag{2}$$

where *n* is the number of points on fiber *i*, and d_k is the distance between point *k* on fiber *i* and the closest point on fiber *j*. Note that this is a directed distance so $d_{\text{mcp}_{ij}} \neq d_{\text{mcp}_{ji}}$. Fig. 5 illustrates the computation of this distance measure.

Practically, it is not necessary to use all points on each fiber to compute the distance measure. In the interest of decreasing computation time, before computing the distance measure we represent each fiber using 15 equidistant points (where distances are computed along the trajectory of the fiber), including both endpoints. Then the mean closest point distances are computed using only these 15 points. As the fiber lengths range from around 10 mm (20 points) to 150 mm (300 points), using only 15 points per fiber significantly decreases computation time.

The clustering requires a symmetric distance, so we symmetrize the mean closest point distance by taking the minimum of the two possible distances $d_{\text{mcp}_{ii}}$ and $d_{\text{mcp}_{ii}}$

$$d_{ij} = \min(d_{\mathrm{mcp}_{ij}}, d_{\mathrm{mcp}_{jj}}).$$
(3)

We have also employed the mean of the two distances, and we find that the minimum performs qualitatively better when clustering using bilateral matching (described below), while the mean is generally better when doing standard clustering. The minimum encourages the grouping of shorter fibers with longer fibers, if they run parallel for some distance; this is beneficial for clustering similar anatomy in both hemispheres.

Optionally, we can obtain cluster correspondence across hemispheres to facilitate both visual and quantitative comparison of anatomical structures that are present bilaterally. A modification to the distance computation allows us to consider

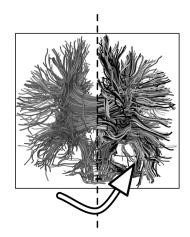


Fig. 6. Optional midsagittal reflection enables bilateral (both hemispheres) clustering to find corresponding anatomical structures.

symmetry across hemispheres. First, the midsagittal plane is defined by anterior commissure-posterior commissure (AC-PC) alignment of the group mean FA image. Then, before computing the distance metric, we create a reflected version of all fibers by reflecting the brain across the midsagittal plane. The directed pairwise fiber distance from fiber i to j now becomes the minimum of the distance from i to j and the distance from i to the reflected j. Distances are then symmetrized as described above. This modification of the method allows fibers with similar shapes and locations in either hemisphere to cluster together, automatically giving anatomical correspondences (Fig. 6).

The bilateral clustering is a new approach in clustering of tractography. We find that this method produces better separation of some difficult anatomical structures, for example the inferior parts of the cingulum from the inferior parts of the fornix. We believe the improvement in clustering is because reflecting across the midsagittal plane effectively doubles the number of prototype brain examples input to the clustering process. Note that our clustering/atlas creation method is not dependent upon this reflection approach, however, the bilateral matching is a useful additional property that we can obtain.

The parameters of the distance computation method must be stored in the atlas so that when performing segmentation these fiber distances are computed in the same way as during atlas creation. For generality (as other distance measures may be tested in the future), we refer to these parameters collectively as $D_{\rm param}$. Specifically for the mean closest point distance measure, the method for symmetrization of distances (minimum or mean) is stored in $D_{\rm param}$. In addition, whether or not midsagittal reflection was used in atlas generation is stored in $D_{\rm param}$.

Next, the distance measures are converted to affinity measures suitable for spectral clustering. Each distance (d_{ij}) is converted to an affinity measure (\mathbf{W}_{ij}) via a Gaussian kernel

$$\mathbf{W}_{ij} = e^{-d_{ij}^2/\sigma^2} \tag{4}$$

a method that is frequently employed in the clustering literature [50]–[52]. Since the distances are symmetric, this conversion produces a symmetric affinity matrix for clustering.

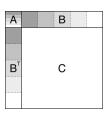


Fig. 7. Diagram of the parts of the multisubject fiber affinity matrix **W**, for an example five-subject clustering problem. The regions within **A** and **B** represent individual subjects. **C** is the part of the matrix that does not need to be calculated when using the Nystrom method.

The role of σ in (4) is to define the size scale of the problem by setting the distance over which fibers can be considered similar. We standardly choose σ based on our clustering experience to be 30 mm with bilateral matching (and minimum symmetrization), and 60 mm in standard clustering (with mean symmetrization). For smaller clustering problems (not the whole brain), values as low as 10 mm can give better clusterings. Note that a larger value of σ incorporates more information from anatomically neighboring structures. A benefit of this affinity measure is that the clustering is insensitive to small registration errors and to small anatomical differences across subjects due to the capture range of the mean closest point distance and the Gaussian kernel.

The entire pairwise fiber affinity matrix W contains affinities for all pairs of fibers across all brains. Because W is too large to compute, we use an approximation called the Nystrom method [44]. Instead of calculating all pairwise affinities, we randomly choose a subset of the fiber trajectories (sampling an equal number from each subject), and then compute affinities from all fibers to just that subset. This produces two affinity matrices, one that holds the subset's pairwise affinities (A), and another (B) that holds affinities of the rest of the fibers to the subset. The layout of the affinity matrix for group clustering is illustrated in Fig. 7. Note that the A and B matrices contain information from all subjects together.

4) Fiber Spectral Embedding: Next a spectral embedding of all fibers is created based on the fiber affinity values. In the embedding space each fiber is represented as a point, and nearby points in general correspond to similar fiber trajectories. The advantage of this space is that similarity relationships are represented spatially, so that clusters can be more easily found. The embedding is calculated using the eigenvectors of the multisubject fiber affinity matrix.

Specifically, the Nystrom method is employed to estimate the leading eigenvectors of the normalized affinity matrix

$$\mathcal{W} = \mathbf{D}^{-(1/2)} \mathbf{W} \mathbf{D}^{-(1/2)}.$$
 (5)

In the above equation, W is the full multisubject pairwise affinity matrix for all fiber pairs across all brains, and normalization is performed using D, a diagonal matrix containing the row sums of W. The effect of this normalization is to divide each element of W by the square root of the row and column sum at that location. We denote matrices using boldface and their normalized counterparts using italics. The row and column sums needed for normalization of the A and B matrices, to give A and B, are estimated using the following formula [44]

$$\hat{\mathbf{d}} = \begin{bmatrix} \mathbf{a}_r + \mathbf{b}_r \\ \mathbf{b}_c + \mathbf{B}^T \mathbf{A}^{-1} \mathbf{b}_r \end{bmatrix}$$
(6)

where \mathbf{a}_r and \mathbf{b}_r are column vectors containing the row sums of \mathbf{A} and \mathbf{B} , and \mathbf{b}_c is a column vector containing the row sums of \mathbf{B}^T . Once $\hat{\mathbf{d}}$ is computed, the known elements of \mathbf{W} (the values in \mathbf{A} and \mathbf{B}) are normalized as in (5)

$$\mathcal{W}_{ij} = \frac{\mathbf{W}_{ij}}{\sqrt{\hat{d}_i \hat{d}_j}}.$$
(7)

Next the eigenvectors of \mathcal{W} (the quantities needed for embedding) are estimated using the eigenvectors of \mathcal{A} . The eigenvectors \mathbf{U} and diagonal eigenvalue matrix $\mathbf{\Lambda}$ of the normalized matrix \mathcal{A} are first calculated, and the population eigenvectors $\mathbf{\bar{U}}$ are then estimated via projection of normalized affinity values in \mathcal{B} onto the eigenvector basis from \mathcal{A} . $\mathbf{\bar{U}}$ is estimated via the following formula [44]

$$\bar{\mathbf{U}} = \begin{bmatrix} \mathbf{U} \\ \mathcal{B}^T \mathbf{U} \mathbf{\Lambda}^{-1} \end{bmatrix}.$$
 (8)

In (8), the ordering of the rows of $\overline{\mathbf{U}}$ is such that those corresponding to rows of \mathcal{A} are first, followed by those corresponding to rows from B^T . (Note $U = \mathcal{A}U\Lambda^{-1} = \mathcal{A}^T U\Lambda^{-1}$ has the same form as $\mathcal{B}^T U\Lambda^{-1}$ in (8), showing that the rows of both matrices, \mathcal{A} and \mathcal{B}^T , are projected onto the orthogonal basis $U\Lambda^{-1}$. This basis defines the embedding space.)

Finally, spectral embedding vectors \mathbf{E} are calculated for each fiber using the rows of the eigenvector matrix, giving

$$\mathbf{E}_{j} = \frac{1}{\sqrt{\mathbf{D}_{jj}}} (\bar{\mathbf{U}}_{j,2}, \bar{\mathbf{U}}_{j,3}, \dots, \bar{\mathbf{U}}_{j,n})$$
(9)

where the eigenvector ordering is in descending order according to the eigenvalue. This generates a coordinate system, the spectral embedding space, where each fiber is represented as a point, and similar fibers are generally embedded near each other. (Note that because the rows of the normalized W matrix sum approximately to 1, the vector of all constant values is an eigenvector but does not provide information for clustering. To discard this uninformative vector, the embedding begins with the second eigenvector as indicated in (9).)

5) Fiber Clustering: By simultaneously performing clustering in a group of registered subjects, we find population clusters which represent common structures present in tractography. The clustering is performed in the embedding space using the k-means algorithm to find k clusters. The k-means algorithm, a simple iterative method for finding a local minimum of the sum of squared distances to cluster centroids, is commonly used in spectral clustering [44], [50].

After clustering, each of the k population white matter clusters is likely to contain fibers from all or most subjects. Therefore, when viewed or analyzed on a per-subject basis, the clusters correspond across subjects.

For visualization purposes, cluster colors are assigned automatically and also correspond across subjects. We color each cluster according to the location of its cluster centroid in embedding space. As proposed by Brun *et al.* [27], we scale the first three embedding coordinates to fit into the interval [0, 1] and use them to determine red, green, and blue (RGB) values. (The first three embedding coordinates correspond to the eigenvectors with the second, third, and fourth largest eigenvalues.) An example of these colors can be seen in the atlas creation flowchart (Fig. 4). These colors are used for display of all subjects' tractography during the expert labeling step.

6) Expert Anatomical Labeling: The final step in atlas creation is the use of expert information to perform anatomical labeling. After cluster generation, k clusters have been defined in each subject, and these clusters correspond across subjects. For example, this means that cluster number 10 represents approximately the same region for every subject, because cluster 10 was created as a single cluster in the multiple-subject embedding space. Thus, providing higher-level anatomical information is reduced to the problem of defining a label for each of the k clusters.

Cluster labeling is performed as follows. The tractography clusters are visualized using three dimensional graphics and the color scheme discussed previously. Cluster(s) are selected with the mouse and given an anatomical label that is defined by the expert. In addition, a unique color is chosen for display of each anatomical structure. Theoretically the cluster labeling could be done by inspecting the k clusters in only one subject, but due to anatomical or tractography differences, a small number of clusters are generally empty in each subject. We find the simplest approach is to label one subject, then transfer the cluster labels to the next subject. Working through all subjects in this manner ensures that at the end all clusters have a high-level anatomical description. Due to the fact that tractography may cross from one anatomical structure to another, these expert anatomical labels represent the best approximate description of the white matter regions discovered in group clustering.

C. Automatic Segmentation Procedure

Once an atlas has been created, it can be used for automatic segmentation of whole brain tractography from novel subjects. To apply the atlas to segment a novel subject, each new fiber is embedded in the same atlas embedding space in which clustering was performed originally. Then cluster labels and anatomical information are assigned according to the nearest cluster centroid. The steps in this process (Fig. 8) are registration to the atlas, fiber affinity calculation, fiber spectral embedding, and fiber cluster assignment.

1) Registration to the Atlas: To segment a novel subject using the atlas, the subject's FA image should first be rigidly registered to the reference image from atlas registration (the group mean FA image).

2) New Fiber Affinity Calculation: To generate affinity values for a new fiber, its mean closest point distance (2) is first

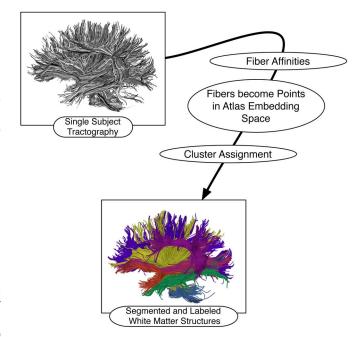


Fig. 8. Automatic segmentation flowchart.

A	В	S
B	с	D
S	D ^T	

Fig. 9. Diagram of the parts of the affinity matrix for extension of spectral embedding to new data. The upper left part of the matrix was generated in the atlas creation step (Fig. 7) but is not stored in the atlas. S contains affinities for embedding a new subject and D is not computed. S is shown as having a large size to emphasize that we can label a large number of fibers per subject with this approach, without the overhead of actually clustering that many fibers using k-means in the embedding space.

measured to each fiber stored in the atlas, using the distance parameters stored in $D_{\rm param}$. If the atlas was created with midsagittal reflection for bilateral matching, the new subject is first reflected across its midsagittal plane, as described above (Fig. 6). The distances are then symmetrized (3) using the method (max/mean) stored in $D_{\rm param}$. Next, the distances are converted to affinities (4) using σ from the atlas. To summarize, in the affinity calculation step, the following contents from the atlas (Table II) are used: the stored random subset of fibers originally used for affinity computation, the parameters for distance computation ($D_{\rm param}$), and σ .

Fig. 9 shows the parts of the multisubject fiber affinity matrix with a novel subject included: **S** holds affinity values for the new subject. The affinity values for each new fiber are stored in a new row in the affinity matrix for the novel subject (a row of \mathbf{S}^{T} in Fig. 9).

3) New Fiber Spectral Embedding: To perform embedding using the normalized cuts framework, the affinity matrix must be normalized by division of each element by the square root of the row and column sums at that location [44]. The required row sums for the new fibers are estimates of the row sums of $[\mathbf{S}^T \mathbf{D}^T]$ in Fig. 9, which can be calculated as

$$\hat{\mathbf{d}}_{\text{row}} = [\mathbf{s}_c + \mathbf{S}^T \mathbf{A}^{-1} \mathbf{b}_r]$$
(10)

where \mathbf{s}_c is a column vector containing the row sum of \mathbf{S}^T . For normalization of each row of \mathbf{S}^T by column sum, we employ the column sum from the original matrix

$$\hat{\mathbf{d}}_{\rm col} = [\mathbf{a}_r + \mathbf{b}_r]. \tag{11}$$

The above two normalization equations use information from the atlas (Table II): $\mathbf{A}^{-1}\mathbf{b}_r$ and $\mathbf{a}_r + \mathbf{b}_r$. Once $\hat{\mathbf{d}}_{row}$ is computed, the elements of \mathbf{S}^T are normalized:

$$S_{ij}^{T} = \frac{\mathbf{S}_{ij}^{T}}{\sqrt{\hat{d}_{\mathrm{row}_{i}}\hat{d}_{\mathrm{col}_{j}}}}.$$
(12)

Performing the scaling in this way makes sense for two reasons. First, if we re-embed a fiber that we have already seen (whose information was in **A** or **B**) it will be mapped to the same location in the embedding space, because the matrix normalization will be the same. This is why the column sum (11) should not be updated with new information from **S**. Second, we would expect that each individual new fiber (row of S^T) would not significantly change the column sum if it were present in the original atlas affinity matrix due to the fact that thousands of fibers are used in creation of the original atlas affinity matrices. Thus, the scaling applied to a novel fiber (row of S^T) is basically the same as that which would have been applied if it were part of the original clustering problem.

After normalization of the S matrix, the eigenvectors are estimated using the Nystrom method

$$\bar{\mathbf{U}}_S = \mathcal{S}^T \mathbf{U} \mathbf{\Lambda}^{-1} \tag{13}$$

and the normalized cuts embedding vectors are given as the rows of $\bar{\mathbf{U}}_S$, each divided by the square root of the corresponding row sum from $\hat{\mathbf{d}}_{row}$ [as in (9)]. This is the same as the embedding process employed for the **B** matrix in atlas creation.

4) New Fiber Cluster Assignment (Segmentation): Finally, automatic segmentation is performed according to the cluster centroid information from the atlas. The new subject's embedding vectors are each classified according to the nearest atlas cluster centroid, giving a cluster label for each fiber. Then the rest of the atlas cluster information is applied to the segmented fibers. This includes the per-cluster expert anatomical labels and the chosen colors for display of clusters and of expert-labeled anatomical regions.

V. RESULTS

We first present experiments regarding the stability of the spectral embedding and the number of clusters in the white matter. Then we present results from an atlas generation and automatic segmentation experiment, demonstrating the anatomical structures found, illustrating the use of the method for corpus callosum subdivision, and showing some challenges to the method.

Two datasets were used in the experiments, Population I (LSDI data acquired with 6 directions of diffusion weighting) and Population II (EPI data acquired with 30 directions of diffusion weighting). Further details about data acquisition are located in the Appendix.

A. Embedding Stability Experiment

The reproducibility of clustering is directly related to the reproducibility of the spectral embedding. Considering the embedding problem as a Nystrom eigenvector approximation, successive eigenvector approximations can be compared to test if the embedding is stable. (The reason all of the eigenvector approximations are not identical is that they are calculated by extending the eigenvector solutions computed for different small random subsets of the data.)

The normalized Frobenius matrix norm

$$\frac{1}{N_E} \|\mathbf{U}^T \mathbf{V}\|_F \tag{14}$$

where U and V are two matrices containing N_E eigenvectors, is high when the N_E selected eigenvectors span the same subspace [44]. If two sets of eigenvectors span a similar subspace, the two embeddings are similar. The eigenvector basis can rotate when eigenvalues are near each other, so the important thing is that the same subspace is described.

We used this embedding stability measure to determine how large \mathbf{A} should be for stable embedding. We would like to select a random sample size that is just large enough to produce reproducible embeddings. The drawback of choosing a large random sample of fibers (when forming A) is the increase in run time of the method, because every fiber's distance must be computed to each of the randomly sampled fibers. In addition, the \mathbf{A} matrix must fit in memory and its eigenvectors must be computed. Practically with the 32-bit matlab software available during these experiments, the maximum random sample size was 4000.

To investigate how large \mathbf{A} should be for stable embedding, we performed spectral embedding for various sizes of the \mathbf{A} matrix, for several random selections of \mathbf{A} per size. For each size of \mathbf{A} , the mean and standard deviation of the reproducibility value (matrix norm) were computed using all unique pairs of embeddings. In addition, we repeated the experiment using several different numbers of eigenvectors (where the number of eigenvectors determines the dimensionality of the embedding space). We performed this embedding stability experiment first for a single subject and then using a 10 subject dataset. The DTI data used was from Population I.

1) Single Subject Experiment: Fig. 10 shows the result of the embedding stability experiment in the single subject dataset. 10 embeddings were performed for each size of **A** (with parameters of $\sigma = 60$ and mean symmetrization). For this dataset, stability is highest when using approximately 20 eigenvectors, indicating that the cluster information is represented well in 20 dimensions. This has motivated our use of 20 eigenvectors for the

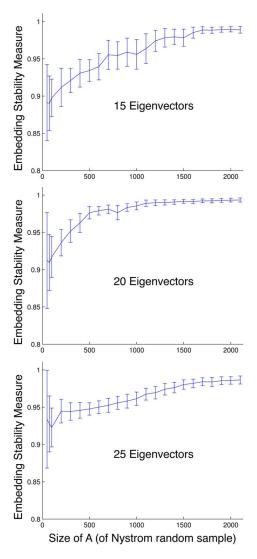


Fig. 10. Embedding stability measure versus the size of the A matrix, for different numbers of eigenvectors (dimensionalities of the embedding space). A of size 1500×1500 or greater with 20 eigenvectors is optimal for this single-subject dataset.

atlas creation results presented later. Stability for any number of eigenvectors is highest when using 1500 or more fibers when creating the \mathbf{A} matrix. For this reason, 1500 is our recommended minimum number of fibers for creation of \mathbf{A} .

2) Atlas Experiment: Fig. 11 demonstrates that the embedding is stable for the atlas, even though multiple subjects are being analyzed simultaneously. There were 10 subjects used in the atlas embedding stability experiment, with 3000 fiber trajectories each. Embedding was performed five times for each size of the **A** matrix (with parameters of $\sigma = 30$ and minimum symmetrization). In this experiment, the random sample of fibers used to form **A** came from all subjects (with an equal number of random fibers from each), and embedding was performed for all fibers from all subjects.

B. Number of Clusters Experiment

Interesting anatomical clusters exist at many size scales so choosing the number of clusters k is not trivial. In our applica-

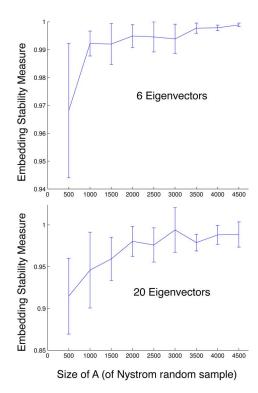


Fig. 11. Embedding stability measure for atlas data versus the size of the ${\bf A}$ matrix.

tion, the number must be large enough to avoid combining dissimilar fibers. In addition, we would like to choose the smallest k that is experimentally shown to produce good quality clusters, because the run time increases with k. (The spectral clustering method uses the k-means algorithm to locate cluster centroids in embedding space, and each k-means iteration computes k cluster means.)

We investigated the inherent number of clusters present in a single brain by measuring the quality of the clustering solution for various numbers of clusters. The DTI dataset used was from Population 1 (see Appendix I), and the mean closest point distance measure was used with mean symmetrization and σ of 60. A worst-case cluster measure, the maximum sum of point-to-centroid distances over all clusters, is shown versus number of clusters in Fig. 12. According to this measure, there are more than 100 clusters inherent in a single subject. In fact, the cluster quality is slightly better if more than approximately 200 clusters are found. This motivated our choice of 200 clusters for the following atlas generation experiment.

C. Atlas Generation and Automatic Segmentation Experiment

1) Whole Brain Tractography Generation: DTI data from Population II (see Appendix I) was analyzed for 15 subjects. Tractography was performed in each subject using Runge-Kutta order two integration, with the following parameters: seeding threshold T_{seed} of $c_L 0.25$, stopping threshold T_{stop} of $c_L 0.15$, step size 0.5 mm, and minimum length T_{length} of 25 mm.

Group registration of subject FA images was performed using the congealing algorithm [46] to calculate rotation, translation, and scaling (no shear terms). Rigid registration without shear was chosen so that the registration would have the same effect

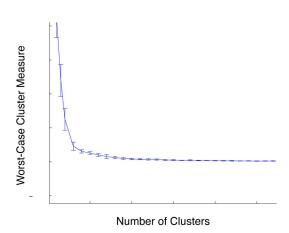


Fig. 12. Worst-case cluster measure (the maximum cluster centroid distance sum) versus number of clusters, indicating that 100 or more clusters are present in this single-subject dataset.

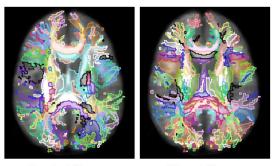
if applied to the tensors or to the tractography. This registration was then applied to the fiber trajectories generated via tractography. For simplicity in the experiments presented here, this registration was performed by congealing training and test subject FA images together, thus placing them all in the coordinate system of the group mean FA image.

2) Parameters of Atlas Creation and Automatic Segmentation: The dataset was divided into 10 training subjects (used in atlas creation) and 5 test subjects (used only for automatic segmentation). To create the atlas, 3000 fibers were randomly selected from each of the 10 subjects as input to the clustering, giving 30 000 total fibers to cluster. For affinity computation we used the mean closest point distance, σ of 30 mm, and minimum symmetrization. The size of the random sample used to create the **A** matrix was 2500, 20 eigenvectors were used for embedding, and k = 200 clusters were generated.

First, an experiment was done to compare the midsagittal reflection method (bilateral clustering) with standard clustering. The same 30 000 fibers were clustered using each method, and the resulting clusters were used to label the voxels of an image volume for visualization of the difference between the methods.

Next the final atlas was generated. We used the midsagittal reflection method for distance computation, where the midsagittal plane was defined using the average group registered FA image. The 200 atlas clusters from each subject were visually inspected and labeled with anatomical names.

We then performed automatic segmentation of tractography from all 15 subjects using the atlas. We labeled 10 000 fibers from each of the 15 (10 used in atlas creation plus five novel) subjects using the atlas. This 10 000 was a random sample from the total tractography for each subject, which contained between 80 000 and 100 000 fibers. (Note that in the 10 training subjects, this random sample was unlikely to contain many of the 3000 fibers which were used for clustering during atlas creation, so performing segmentation of the 10 000 fibers was not the same as reclassifying the original data.) The 10 000 labeled fibers per subject were then used to produce the automatic segmentation result images shown next.



Standard Clusters

Bilateral Clusters

Fig. 13. Comparison of standard and bilateral clustering (using midsagittal reflection). Note the increased right-left symmetry in the bilateral clustering result. However note that the conversion of the atlas to voxels (for visualization) is imperfect because the atlas is not voxel-based. The atlas may represent any number of structures inside the volume of a voxel, thus when one structure is selected for visualization information is lost.

TABLE IV MAJOR WHITE MATTER STRUCTURES IN ATLAS

Structure	Color (Figs. 14-19)
corpus callosum	navy blue
arcuate fasciculus region	purple
cerebral peduncle/internal capsule/corona radiata	yellow
uncinate fasciculus	orange
middle cerebellar peduncle	light blue
inferior occipitofrontal fasciculus	pink
inferior longitudinal fasciculus	green
superior cerebellar peduncle	light pink
cingulum bundle	magenta
fornix	lime green

3) Bilateral Clustering Comparison: The images in Fig. 13 demonstrate the difference between the bilateral clustering (with midsagittal reflection) and the standard clustering.

4) Automatic Tractography Segmentation Results: Segmented structures and their display colors are given in Table IV.

Figs. 14–16 demonstrate automatic segmentation of tractography from all 15 (training and test) subjects. First, all major structures are shown in a view from the left (Fig. 14) and an inferior view (Fig. 15). These images demonstrate the ability of the method to identify white matter structures such as the corpus callosum, uncinate fasciculus, cingulum bundles, arcuate fasciculus, inferior occipitofrontal fasciculus, and corona radiata. The colors in the images correspond to the expert anatomical labels, and most colored structures contain multiple clusters.

Next, selected regions are displayed. Fig. 16 shows two fasciculi: the uncinate (containing several clusters) and arcuate (containing one cluster). Then Fig. 17 demonstrates the six individual clusters discovered by the method in the region of the cingulum, as segmented in the test subjects.

5) Corpus Callosum Subdivision Results: Our atlas can be used to identify the corpus callosum fibers and to subdivide the corpus callosum according to the clusters discovered during atlas creation. (In the atlas clustering result, anatomical structures are generally divided into multiple clusters.) Fig. 18 shows the corpus callosum parcellation for all subjects. Note especially that the fibers going to the temporal lobe (yellow) are successfully segmented.

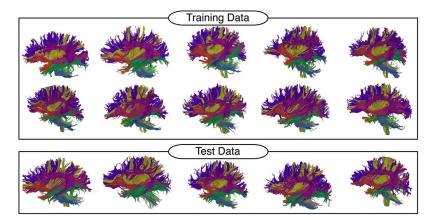


Fig. 14. Result of automatic segmentation of training (top) and test (bottom) subjects (view from left). Structures and colors are as in Table IV.

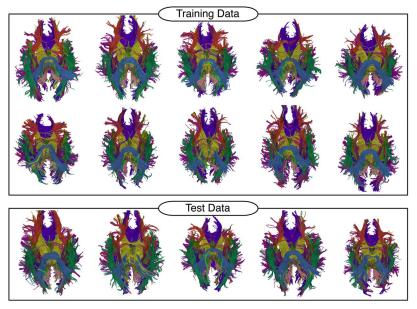


Fig. 15. Result of automatic segmentation of training (top) and test (bottom) subjects (inferior view). Structures and colors are as in Table IV.

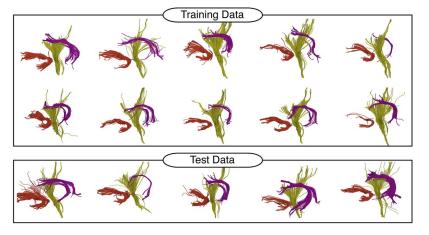


Fig. 16. Automatic segmentation of uncinate (orange) and arcuate (purple) fasciculi, with part of cerebral peduncle/internal capsule/corona radiata (yellow). The arcuate is one cluster.

VI. DISCUSSION

When labeling tractography with anatomical names, it is important to note that the correspondence between tractography and anatomical regions is imperfect. For instance, a fiber trajectory may cross structures by traversing part of the arcuate fasciculus and part of the external capsule. Tractography that crosses from one structure to another can be seen in the limbic system segmentation results (Fig. 19). Some fibers in the fornix region (green) cross structures to follow part of the corona radiata (see anterior part of fornix, to the left in the images). In addition, fibers in the cingulum (purple) are shown entering and leaving this structure. Anatomically, the cingulum bundle is the core of the purple structure,

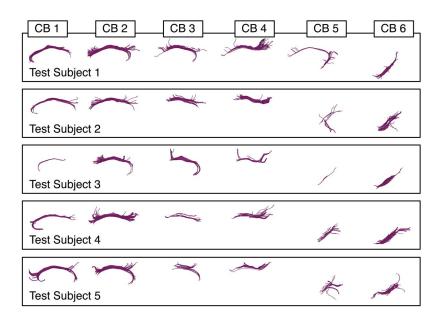


Fig. 17. The six individual clusters discovered in the cingulum region, segmented in the test data. Some clusters (second from right) are more variable.

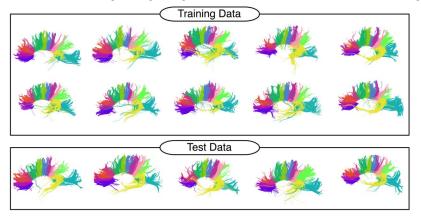


Fig. 18. Automatic corpus callosum segmentation and subdivision result. The fibers to the temporal lobe (yellow) are distinct from those to the occipital lobe (light blue).

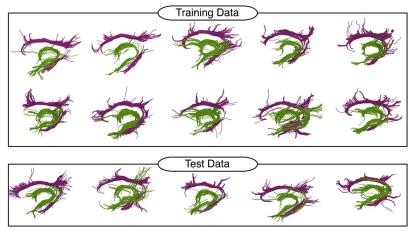


Fig. 19. The limbic system, including the fornix (green) and cingulum bundles (magenta) is a challenge to the method due in part to tractography that crosses anatomical structures.

but axons enter and leave the bundle all along its length. The diffusion MRI measurements reflect this and consequently the tractography enters and leaves the cingulum region. The limbic system also presents a challenge to the atlas clustering due to the proximity and similar shapes of the inferior parts of the cingulum (purple) and fornix (green), as well as the general noisiness of tractography in this region. The detection of uncommon fiber trajectories, possibly caused by noise or by crossing from one structure to another, merits further investigation.

Due to the fact that the diffusion tensor model is ambiguous in regions of fiber crossing, it is known that some anatomical structures (such as the lateral connections of the corticospinal tract to the face motor area) cannot be traced using DTI streamline tractography. Consequently, it will be of interest in the future to apply our method to tractography from diffusion data reconstructed with a model (such as Q-ball or PAS-MRI) that can represent fiber crossings. It would also be of interest to map the white matter atlas to a standard anatomical space such as the Talairach coordinate system.

VII. CONCLUSION

In this paper, we have presented a new method for automatic tractography segmentation. The method learns a model of the anatomical organization of white matter pathways from a population of subjects, using an unsupervised spectral clustering method. It produces a quantitative description of white matter architecture in the form of a cluster, and a quantitative model of white matter architecture in the group. Each cluster is annotated with an expert anatomical label, creating a high-dimensional white matter cluster atlas. We have shown how to embed novel data in the spectral clustering framework (normalized cuts with the Nystrom method) of Fowlkes and Malik, and we have applied this technique to perform automatic segmentation of new tractography data. We have demonstrated that the method is able to identify known white matter anatomical structures including the corpus callosum, uncinate fasciculi, cingulum bundles, arcuate fasciculi, inferior occipitofrontal fasciculi, middle cerebellar peduncles, and corona radiata. Our work enables statistical white matter analysis using tractography. By segmenting corresponding white matter regions across subjects and across hemispheres, we allow neuroscientific hypotheses to be tested regarding group differences and questions of symmetry.

APPENDIX DATA ACQUISTION

Population I: MR diffusion scans were performed with a quadrature head coil on a 1.5 T GE Echospeed system (General Electric Medical Systems, Milwaukee, WI), which permits maximum gradient amplitudes of 40 mT/m. Coronal LSDI scans were acquired perpendicular to both the AC-PC line and interhemispheric fissure. To increase the precision of the acquisition alignment, instead of one 3-D localizer, a set of three 2-D T1-weighted localizers (sagittal, axial oblique aligned to the AC-PC line, and another sagittal oblique aligned to the interhemispheric fissure) were acquired. Finally, the last sagittal oblique T1W image served as the localizer for the LSDI coronal scans. For each section, six images with high (1000 s/mm^2) diffusion-weighting along six noncollinear directions [e.g., relative amplitudes, (Gx, Gy, Gz) =(1,1,0), (0,1,1), (1,0,1), (1,1,0), (0,1,1)(1,0,1) and two with low (5 s/mm^2) diffusion-weighting have been collected. The following scan parameters were used: rectangular field of view (FOV) $220 \times 165 \text{ mm}^2$; $128 \times 128 \text{ scan matrix}$ (256 \times 256 image matrix); slice thickness 4 mm; interslice distance 1 mm; receiver bandwidth T4 kHz; TE (echo time) 64 ms; effective TR (repetition time) 2592 ms; scan time 60 s/slice section. A total of 31-35 coronal slices covering the entire brain (depending upon brain size) were acquired. The total scan time was 31–35 min.

Population II: DTI images were acquired using a SENSE head coil on 1.5 T whole-body MR scanners (Philips Medical Systems, gyroscan NT) equipped with explorer gradients (40 mT/m). For acquisition, an eight-element arrayed RF coil, converted to six-channel to be compatible with the six-channel receiver, was used. For DTI acquisitions, a single-shot spin echo-echo planar sequence (SE-EPI) was used, with diffusion gradients applied in 30 noncollinear directions and $b = 700 \text{ s/mm}^2$. Five additional reference image with least diffusion weighting ($b = 33 \text{ s/mm}^2$) was also acquired. Fifty to sixty axial slices were acquired to cover the entire hemisphere and the cerebellum, parallel to the AC-PC line. The field of view, the size of the acquisition matrix, and the slice thickness were 240×240 mm/96 \times 96/2.5 mm. X and Y resolutions were then zerofilled to 256×256 . Other imaging parameters were: TR 7000 ms and TE = 80 ms; and SENSE reduction factor = 2.5. To improve the signal-to-noise ratio, three datasets were acquired, leading to a total acquisition time of 12–15 min. T2-weighted images with TE = 40 and 100 ms were separately acquired with the same EPI acquisition scheme to ensure the accurate coregistration. For anatomical image, MPRAGE with higher resolution (1.25 mm isotropic) was also acquired.

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