Tract-Based Morphometry

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Abstract. Multisubject statistical analyses of diffusion tensor images in regions of specific white matter tracts have commonly measured only the mean value of a scalar invariant such as the fractional anisotropy (FA), ignoring the spatial variation of FA along the length of fiber tracts. We propose to instead perform tract-based morphometry (TBM), or the statistical analysis of diffusion MRI data in an anatomical tract-based coordinate system. We present a method for automatic generation of white matter tract arc length parameterizations, based on learning a fiber bundle model from tractography from multiple subjects. Our tract-based coordinate system enables TBM for the detection of white matter differences in groups of subjects. We present example TBM results from a study of interhemispheric differences in FA.

1 Introduction

Diffusion tensor magnetic resonance imaging (DTI) provides directional measurements of water diffusion in the brain. DTI tractography [1] follows directions of maximal water diffusion to estimate the trajectories of fiber tracts (major neural connections in the white matter). Clinical and neuroscientific questions regarding white matter pathways may potentially be addressed by analyzing DTI data in regions of specific white matter tracts. Many analyses of tracts [2,3] have calculated the mean (in the entire tract) of a scalar such as the fractional anisotropy (FA). However, due to anatomical factors such as crossing fibers or nearness to cerebrospinal fluid or grey matter, as well as tissue microstructural factors such as packing densities and axon diameters [4], FA varies spatially along tract trajectories. Thus analysis of its mean value may not be optimal for localization of group differences.

The spatial patterns of FA along fiber tracts have not yet been studied in detail due to the difficulty of tractography segmentation and of finding pointwise correspondences along the lengths of fibers from multiple subjects. In this paper we propose a general method for calculation of multisubject fiber arc length

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coordinate systems, enabling tract-based morphometry (TBM), the group statistical analysis of tensors or scalar invariants *along the length* of fiber tracts. Our method first analyzes tractography from multiple subjects, producing a bundle model that gives a prototype fiber. Next, by finding robust pointwise correspondences of all other fibers to the prototype, common arc length coordinates are produced for all subjects. Finally, statistical analysis of the diffusion MRI data (TBM) is performed in the tract-based coordinate system. We illustrate the method with TBM results from an experiment comparing right- and left-hemisphere FA in normal right-handed subjects, showing that significant differences are found in the cingulum bundle and arcuate fasciculus. By mapping these results onto the respective group mean fibers, we demonstrate the anatomical locations of the interhemispheric differences.

2 Related Work

Other groups have described methods for tract-based analysis of DTI. One approach for fiber tract parameterization by arc length required human interaction to define a corresponding point on all fibers [5]. Another approach, demonstrated on the the corona radiata and cingulum of one subject, estimated three level sets to produce a fiber coordinate system [6]. A principled statistical bundle model with arc length coordinates was created in [7]. In [8], a manually segmented arc angle coordinate system specific to the cingulum bundle was applied to a study of interhemispheric FA differences in multiple subjects. A similar method was applied to the pyramidal tract [9]. An approach called tract-based spatial statistics performed voxel-based morphometry of FA data after aligning local high FA values to a group FA skeleton [10]. However, by working in a voxel coordinate system such a method must ignore any tract-derived information. To our knowledge, no existing method for tract-based DTI analysis has both automatically applied a coordinate system to fibers from multiple subjects and demonstrated statistical analysis in this coordinate system.

3 Method: Tract-Based Morphometry

We propose a method for tract-based morphometry, the statistical analysis of diffusion data in a white matter tract coordinate system. We automatically determine a group fiber arc length coordinate system by learning a fiber bundle model using tractography from multiple subjects. The five steps in our method are: fiber bundle definition, prototype fiber calculation, arc length parameterization, measurement of descriptive statistics, and statistical analysis in the group.

3.1 Fiber Bundle Definition

As a preprocessing step, fiber bundle(s) of interest must be defined in all subjects, either automatically [7,11] or interactively [12]. Here we have used congealing normalization [13] and automatic group fiber clustering [11].

3.2 Bundle Modeling and Prototype Fiber Calculation

A distinction between our approach and a straightforward 3D approach such as finding a bundle skeleton or centerline is that our method finds a prototype fiber that is the most representative of the bundle's trajectory across all subjects, according to a fiber affinity metric. For each bundle of interest a fiber bundle model is generated by spectrally embedding all fibers using the affinity metric [11]. Once embedded, each fiber is represented as a point. The embedding of all fibers produces a point cloud whose mean would correspond to a fiber that is most representative of the fiber bundle's trajectory across all subjects. Because we have a high fiber sample size (the total number of fibers in the bundle from all subjects together), we can estimate the mean using the fiber closest to the mean. We refer to this fiber as the *prototype fiber*.

3.3 Arc Length Parameterization by Matching to Prototype Fiber

We propose a simple pointwise matching method (Fig. 1) to produce arc length coordinates for all fibers across all subjects. The basic idea is that the prototype fiber defines the arc length coordinates for the bundle, and these coordinates are propagated to all other fibers by matching each point on the prototype fiber to the closest point(s) on the other fibers.

(a) Method for Matching to Prototype Fiber

(c) Example Result

Fig. 1. Arc length coordinates are produced for each fiber “x” in the bundle via matching to the prototype fiber. First, the matched region (a) is found by matching each point on the prototype with the closest point on fiber x. Dashed lines indicate matches. Non-matched regions at either end of fiber x (gray x’s) are excluded from further analysis. Next, points in the matched region that were skipped are matched to the closest point on the prototype. An example prototype fiber from the uncinate fasciculus is shown in (b) followed by one subject’s matching result (c), with non-matched areas in gray.

The following features of the matching method make it robust to fiber trajectory variation across subjects. First, the method allows partial matching if a fiber is shorter than the prototype fiber. It also rejects any outlier fibers whose matched arc length coordinates are not strictly nonincreasing or nondecreasing. Finally, the TBM analysis is limited to the region that corresponds across subjects: any arc length coordinates that have not matched to fibers from all subjects are excluded.

3.4 Measurement of Descriptive Statistics

For each subject, the statistic of interest (mean FA) is measured in the fiber arc length coordinate system¹. First, for each fiber x , a vector of FA values vs. arc length is calculated using the matching result from the previous section: for each arc length coordinate the point(s) matching to it on fiber x contribute the average of their FA values. Next, for each subject's fibers the mean and standard deviation of the FA are calculated for each arc length coordinate². Using the above method we also compute the mean (x,y,z) coordinate for each arc length, giving a per-subject mean fiber.

3.5 Statistical Analysis in the Group

We now have a per-subject vector of mean FA values versus arc length, for the bundle(s) of interest. For each arc length coordinate, statistics appropriate to the study may be calculated, and multiple comparisons can be corrected for via permutation testing, as described for fMRI data [14]. By averaging the per-subject mean fibers we produce a group mean fiber for visualization of results.

4 Methods for Example TBM Study

We applied TBM to analyze FA differences in the right and left hemispheres in the cingulum bundle and the arcuate fasciculus.

Data. DTI data (EPI, 30 directions + 5B0 images, 2.5mm isotropic voxels) from 35 normal right-handed subjects was seeded with tractography (where $c_L \geq 0.2$ on a 1.5mm grid). FA data was affinely group registered using congealing [13] (no shear terms) and the registration was applied to the fibers.

Fiber Bundle Definition. Tractography clusters, corresponding across hemispheres and across subjects, were automatically identified by group spectral clustering [11]. Bilateral clusters in the arcuate fasciculus (AF) and cingulum regions (CB) were selected to give bundles for further analysis. 10 subjects (AF) and 3 subjects (CB) were excluded due to missing or very short fibers. The total numbers of fibers per bundle were: 1523 (AF L), 1702 (AF R), 4308 (CB L), and 2679 (CB R). The means and standard deviations of the numbers of fibers per subject were: 61 ± 36 (AF L), 68 ± 51 (AF R), 135 ± 47 (CB L), and 84 ± 36 (CB R).

Bundle Modeling and Prototype Fiber Calculation. For each bilateral fiber bundle, one prototype fiber was calculated using the embedding from the clustering step.

Arc Length Parameterization by Matching to Prototype Fiber. Each fiber was matched to the prototype fiber or to its reflection across the mid-sagittal plane, depending on whether the fiber was from the right or the left

¹ We discuss measurement of FA though the measurement would work identically for any other scalar invariant or other local scalar/tensor information.

² All subjects' tensor orientation information is taken into account by using the fiber coordinate system, thus to study FA along fibers we average FA, not tensors.

hemisphere. This gave a consistent arc length parameterization for all fibers, to allow comparisons across subjects and across hemispheres.

Measurement of Descriptive Statistics. The mean FA for each arc length was measured separately for bundles in the right and left hemisphere of each subject. In addition, the mean FA was measured in the entire bundles.

Statistical Analysis in the Group. First, significant interhemispheric FA differences in whole bundles were investigated with a two-tailed paired t-test. Then, in TBM analysis, a two-tailed paired t-test was employed at each arc length coordinate to investigate local differences in right and left hemisphere FA. To correct for multiple comparisons, permutation testing [14] was performed by exchanging the labels for right and left within each subject, and 10000 permutations were used to estimate the distribution of the maximal test statistic. Using this distribution, p-values were calculated for each arc length coordinate and overlaid on the group mean fiber for anatomical localization of group differences.

5 Results

We present example results from each step in the method. Input fiber data, fiber embedding, and the resulting prototype fibers from the bundle modeling

Fig. 2. Group fiber bundle modeling in the arcuate fasciculus (top) and cingulum (bottom). Input fiber bundles (a) with fibers colored by subject. Fiber embedding according to trajectory similarity (b): each fiber is represented as a point and colored according to subject. The embedding produces a prototype fiber for the bundle model (c). In (a) and (b), for visual clarity a random subset of the data is shown. In (b), the original 10D embedding was reduced to 2D for display using multidimensional scaling.

step are pictured (Fig. 2). Next, arc length parameterization results are shown from the matching to prototype fiber step (Fig. 3). Then, from the measurement of descriptive statistics step, example FA measurements from all fibers for a single subject are plotted (Fig. 3). Means and standard deviations of FA measurements in entire bundles were: 0.3992 ± 0.0190 (AF L), 0.3830 ± 0.0252 (AF R), 0.4231 ± 0.0297 (CB L), 0.4016 ± 0.0269 (CB R). In entire bundles, mean left arcuate FA was greater than right ($p = 0.0197$) and mean left cingulum FA was greater than right ($p < .0001$). TBM results from statistical analysis in the group are presented in Figure 4, showing locations of significant interhemispheric differences in the cingulum bundle and arcuate fasciculus, respectively.

Fig. 3. Example arc length parameterizations (a-c) for arcuate fasciculus (top) and cingulum bundle (bottom). Unmatched variable regions (gray) are excluded from analysis. Example FA measurements from one subject versus arc length (d). Each curve gives the measurements from one fiber.

6 Discussion

The success of the method is demonstrated by the results in the cingulum bundle region which reproduce published findings (laterality differences measured using a cingulum-specific arc angle coordinate system [8]). As in [8], differences are localized to the anterior cingulum. The results in the region of the arcuate fasciculus are (to our knowledge) the first demonstration of FA measurements in a tract-based coordinate system in this region. An interesting feature of the mean FA result (Fig. 4 (b)) in the arcuate is that there is significantly lower mean FA in the right hemisphere where the fibers curve from the anteroposterior orientation to the superoinferior orientation. We hypothesize that fiber tractography termination (“broken trajectories”) in this region may be the cause of the lower number of tractography fibers often reported in the arcuate fasciculus in the right hemisphere.

Fig. 4. Left and right hemisphere FA measurements and significant differences for the arcuate fasciculus (top) and cingulum bundle (bottom). For each arc length coordinate, each subject's mean FA value was computed for each hemisphere. The (group) mean and standard error of these per-subject means are shown vs. arc length in mm (a). The left and right group mean FA (b) and p-value for interhemispheric FA difference (c) are overlaid on the group mean fiber. In all plots, anterior is to the left.

There are some potential areas of improvement of the method that are under investigation. First, it is possible that the prototype fiber is a short fiber, and it is of interest to select a longer (and non-outlier) fiber to analyze as much of the bundle's length as possible. Second, the appropriate resolution or scale at which to perform statistical comparisons should be determined. Third, a per-hemisphere prototype (followed by an alignment of the two hemispheres' fibers) might better represent the shape of some structures. Fourth, a non-rigid registration method could improve the pointwise correspondence quality. Finally, a feature of the presented method is that it excludes the ends of the tracts that are not present in some subjects. However, to locate possibly clinically relevant changes in those regions, analysis would be needed at arc length coordinates where fibers from all subjects are not present.

7 Conclusion

We have presented a new method for tract-based morphometry that learns a bundle model from multiple subjects, generates a prototype fiber and an arc length parameterization for all fibers, and enables statistical analysis along fiber bundles of diffusion data from multiple subjects.

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