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Intersubject variability in the analysis of diffusion tensor images at the group level: fractional anisotropy mapping and fiber tracking techniques

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Abstract

Introduction: Diffusion tensor imaging (DTI) provides comprehensive information about quantitative diffusion and connectivity in the human brain. Transformation into stereotactic standard space is a prerequisite for group studies and requires thorough data processing to preserve directional inter-dependencies. The objective of the present study was to optimize technical approaches for this preservation of quantitative and directional information during spatial normalization in data analyses at the group level.

Methods: Different averaging methods for mean diffusion-weighted images containing DTI information were compared, i.e., region of interest-based fractional anisotropy (FA) mapping, fiber tracking (FT) and corresponding tractwise FA statistics (TFAS). The novel technique of intersubject FT that takes into account directional information of single data sets during the FT process was compared to standard FT techniques. Application of the methods was shown in the comparison of normal subjects and subjects with defined white matter pathology (alterations of the corpus callosum).

Results: Fiber tracking was applied to averaged data sets and showed similar results compared with FT on single subject data. The application of TFAS to averaged data showed averaged FA values around 0.4 for normal controls. The values were in the range of the standard deviation for averaged FA values for TFAS applied to single subject data. These results were independent of the applied averaging technique. A significant reduction of the averaged FA values was found in comparison to TFAS applied to data from subjects with defined white matter pathology (FA around 0.2).

Conclusion: The applicability of FT techniques in the analysis of different subjects at the group level was demonstrated. Group comparisons as well as FT on group averaged data were shown to be feasible. The objective of this work was to identify the most appropriate method for intersubject averaging and group comparison which incorporates intersubject variability of the directional information.

Keywords: Magnetic resonance imaging; Diffusion tensor imaging; Fractional anisotropy mapping; Fiber tracking

1. Introduction

Diffusion in human brain white matter (WM) can be noninvasively mapped by diffusion tensor magnetic resonance imaging (DTI). By DTI, the directional dependence of diffusion in each voxel can be characterized by the so-called diffusion tensor $\vec{\vec{D}}$. The eigenvectors ($\vec{v}_1, \vec{v}_2, \vec{v}_3$) and eigenvalues ($\lambda_1$, λ_2, λ_3) of the 3×3 matrix $\vec{\vec{D}}$ reflect the diffusivity of water in each direction. This can be used to quantify the diffusivity by so-called fractional anisotropy (FA) maps on a voxelwise basis [1–3]. The directional information can be used as the basis for reconstruction of the interconnectivity of brain regions by following the fiber pathways by fiber tracking (FT) techniques. The basis of FT is the consecutive connection of neighbored tensors along their principal directions. Basically, the FT techniques can be divided into two groups: streamline or deterministic FT [4–7] and probabilistic FT [8–14].

The objective of the present study was to optimize the technical approach for the preservation of quantitative and directional information contained in diffusion weighted images/DTI data in order to provide a framework for the comparison of FT of subject groups with defined anatomical

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WM alterations and groups of normal subjects. To find a difference between two subject groups may eventually assist the diagnosis in finding ways to categorize a subject to one of the group based on some discrimination metric.

The prerequisite for this comparison of subject groups was the transformation of the basic DTI data into a stereotactic standard space, e.g., the Montreal Neurological Institute (MNI) space [15]. After this normalization, a comparison at the group level might be performed in several ways:

(i) FA maps of different subject groups could be compared, while the directional information within these maps is not considered.
(ii) FT results of group-averaged data sets could be qualitatively compared by neuroimaging experts on the basis of standardized human brain atlases [16,17]. The result images were judged in terms of the three factors directionality, cortical projection areas and homogeneity of fiber bundles.
(iii) Skeletons that consist of fiber tracts could be used for quantitative comparison on the basis of the directional dependence.

In order to show the validity and power of the different techniques, the following questions were to be addressed:

- How could intersubject averaging and group comparison be performed and which were the most appropriate methods to quantify differences between subject groups?
- How to consider intersubject variability of the directional information?

Like in other advanced magnetic resonance imaging (MRI) methods, DTI- and FT-based studies pursue the ultimate goal to categorize individual patients' brain morphology in order to facilitate the diagnostic process based on some discrimination metric. In the present study, the standardization of technical approaches to group-based analyses of certain brain pathologies can be considered the prerequisite for the identification of pathological patterns of altered brain anatomy. As an example for a groupwise comparison, differences between patients with atrophy of the corpus callosum (CC) and age-matched healthy controls were mapped. As a model of CC alteration, subjects with the neurodegenerative disease of complicated hereditary spastic paraparesis were investigated as a prototype of morphological alterations (thinning) along the whole structure of the CC [18,19]. The CC was chosen as the most appropriate structure in the brain to be analyzed since it is one of the white matter structures with the most strongly directed fibers [20].

2. Data recording and data preprocessing

2.1. Data recording and standard data preprocessing

All DTI data were acquired on the same 1.5T scanner (Symphony, Siemens Medical, Erlangen, Germany). Six healthy controls (three men, three women, average age 32.7±4.5 years), and six patients with thinned CC (tCC) (three men, three women, 32.5±12.1 years old) underwent the MRI protocol.

All DTI acquisitions consisted of 13 volumes (45 slices, 128×128 voxels, slice thickness 2.2 mm, in-plane voxel size 1.5×1.5 mm), representing 12 gradient directions and one scan with gradient 0 (b_0). Echo time (TE) and repetition time (TR) were 93 ms and 8000 ms, respectively. b was 800 s/mm^2, five scans were k-space-averaged online by the Siemens SYNGO operating software. As an anatomical background, a high-resolution T_1-weighted, magnetization-prepared, rapid-acquisition gradient echo (MPRAGE) sequence was used (TR=9.7 ms, TE=3.93 ms, flip angle 15°, matrix size 256×256 mm^2, voxel size 1.0×0.96×0.96 mm^3), consisting of 160–200 sagittal partitions depending on the head size.

All analyses were performed by the software package (Tensor Imaging and Fiber Tracking) [21]. Standard image processing procedures such as eddy current correction and transformation to iso-voxels and smoothing have already been described previously [21,22]. Also, the spatial normalization protocol to MNI standard space has also been described in [21]. All data sets were preprocessed and normalized accordingly.

2.2. MNI normalization and storage of major eigenvectors

Basically, a complete nonlinear MNI normalization consisted of three deformation components (DC):

- DC 1: a rigid brain transformation to align the basic coordinate frames. The rotation angles had to be stored in a rotation matrix $\vec{\vec{R}}$.
- DC 2: an affine deformation according to landmarks. The six affine deformation parameters for the different brain regions had to be stored in an array with 6 components $\vec{S}$.
- DC 3: a non-affine normalization equalizing non-linear brain shape differences. The 3D vector shifts were different for each voxel leading to a separate transformation for each voxel of the 3D voxel array (a 5D transformation array $\vec{\vec{T}}$ with indices image row, image column, image slice, dilation matrix row, dilation matrix column) (details see below, Eq. 3).

Consequently, for normalized data the resulting diffusion tensor $\vec{\vec{D}}_i$ of each voxel i had to be rotated according to all the rotations listed above.

- A rotation resulting from the aligning to the basic coordinate frame (corresponding to DC 1) had to be applied

$$\vec{\vec{D}}_i' = \vec{\vec{R}} \cdot \vec{\vec{D}}_i \tag{1}$$

- The components of the eigenvectors $(\vec{V}_1, \vec{V}_2, \vec{V}_3)$ had to be adapted according to the six affine