Variability of diffusion tensor characteristics in human brain templates: Effect of the number of subjects used for the development of the templates

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Introduction: Development of a diffusion tensor (DT) template that is representative of the diffusion characteristics of the healthy human brain, and is not biased by the properties of a single subject, requires spatial normalization and averaging of the DT information from multiple subjects [1]. However, the effect of the number of subjects on the variability of tensor properties in the resulting template has not yet been investigated. The significance of such information lies in the fact that a template with reduced variability of tensor properties is more reliable and less biased by the characteristics of individual subjects. Therefore, the purpose of this study was to investigate using a bootstrap approach the standard deviation of FA and trace, as well as the uncertainty in the principal diffusion direction of mean tensors in templates developed by averaging DT information from different numbers of subjects. This is the first study on the effect of the number of subjects on the variability of the properties of diffusion tensor brain templates.

Methods: Turboprop-DT data were acquired on 60 healthy subjects using a 3T GE MRI scanner (General Electric, Waukesha, WI). Brain extraction, motion correction, and tensor estimation were performed. In this work, the variability of tensor properties was investigated for ICBM DT templates. Therefore, the b=0 s/mm² volume from each subject was first registered to the ICBM-152 template with rigid-body registration, and then with high-dimensional non-linear registration using the Automatic Registration Toolbox (ART) [2]. The subject with the lowest total deformation was identified. The DT data from that subject were transferred to ICBM-152 space using the spatial transformation applied to the corresponding b=0 sec/mm² images, and functions as a temporary template. The DT data from all subjects were then registered to that template using high-dimensional elastic registration (DTI-GUI, SBLA, UPenn, PA) [3].

N datasets from the group of 60 subjects were randomly selected (GroupN). In each voxel, the tensors from GroupN were averaged and a brain template (TN) was produced. The primary eigenvector (ε1), FA (FAN) and trace (tracen) values were estimated for all voxels in TN. Additional templates based on N subjects were produced following a bootstrap approach. More specifically, N datasets from GroupN were randomly selected with replacement. A template TN was created from each N datasets. The N was then modified (between 10-60) and the whole process was repeated. Finally, the percentage of white matter voxels with FA<0.05*FAN, trace<0.05*traceN, COU<5° increased significantly. In addition, when considering voxels with a wide range of FA values (e.g. 0.4-1 or 0.2-1), more than 60 subjects were necessary in order to develop a template in which more than 95% of these voxels had FA<0.05*FAN and COU<5°. Finally, it should be noted that template tensor variability is strongly dependent on the accuracy of tensor matching achieved by the registration algorithm. High-dimensional elastic registration was used in this work. Further, improvements in registration accuracy will reduce tensor variability in DT templates, and will thereby reduce the number of subjects required for their development.

Results and Discussion: The FA, trace, and COU decreased throughout the brain in templates with increasing N (Fig.1). Thus, templates produced from a large number of subjects have more similar tensor characteristics than those generated from few subjects. This is due to the fact that the information contained in templates produced from a small number of subjects is heavily influenced by the DT properties of these subjects.

The FA, trace, and COU are lower in white matter compared to grey matter, reflecting the lower FA and trace values in white matter compared to grey matter. Therefore, the purpose of this study was to investigate using a bootstrap approach the standard deviation of FA and trace in white matter, as well as the uncertainty in the principal diffusion direction of mean tensors in templates developed by averaging DT information from different numbers of subjects. This is the first study on the effect of the number of subjects on the variability of the properties of diffusion tensor brain templates.

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