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/mm^2 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/mm^2 images, and functioned as a temporary template. The DT data from all subjects were then registered to that template using high-dimensional elastic registration (DTI-GUI, SBIA, UPenn, PA) [3].

N datasets from the group of 60 subjects were randomly selected ($Group_N$). In each voxel, the tensors from $Group_N$ were averaged and a brain template (T_N) was produced. The primary eigenvector ($\varepsilon 1_N$), FA (FA_N) and trace ($trace_N$) values were estimated for all voxels in T_N. Additional templates based on N subjects were produced following a bootstrap approach. More specifically, N datasets from $Group_N$ were randomly selected with replacement. A template T_{Ni}, and the corresponding $\varepsilon 1_{Ni}$, FA_{Ni}, $trace_{Ni}$ were estimated. The same procedure was repeated 100 times. Maps of the standard deviation of FA (FA_{std}) and trace ($trace_{std}$), and the 95% cone of uncertainty (COU) [4] were produced from the 100 templates. The N was then modified (between 10-60) and the whole process was repeated. Finally, the percentage of white matter voxels with $FA_{std}<0.05*FA_N$, $trace_{std}<0.05*trace_N$, COU<5º were plotted as a function of N.

Results and Discussion: The FA_{std}, $trace_{std}$, 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_{std} was similar for grey and white matter in DT templates with N=10 (Fig.1A). However, for N=60, FA_{std} in most of white matter was lower than that in grey matter, similar to the behavior of the standard deviation of FA in single-subject data [5]. The $trace_{std}$ was lower in white matter compared to grey matter for N=10 (Fig.1B). However, for N=60, $trace_{std}$ was relatively similar in white matter and most of grey matter, and significantly lower than that in cerebrospinal fluid (CSF), as shown in single-subject data [5]. COU was lowest in white matter with high FA_N, and increased for decreasing FA_N (Fig.1C), due to eigenvalue sorting in the presence of noise, similar to what has been observed in single-subject data [4].

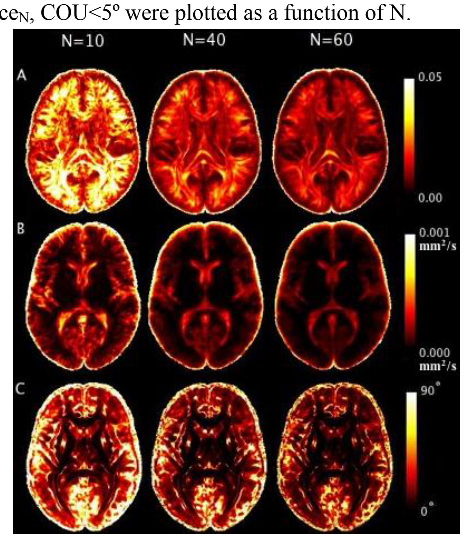

Figure 1. A) FA_{std}, B) $trace_{std}$, and C) COU for DT templates developed using 10 (left column), 40 (middle) and 60 (right) subjects.

The percentage of white matter voxels with $FA_{std}<0.05*FA_N$, $trace_{std}<0.05*trace_N$, COU<5º increased for increasing N (Fig.2). This was due to our earlier finding of decreased FA_{std}, $trace_{std}$, and COU, throughout the brain, for increasing N. Figure 2A shows that, when only 30 subjects were used to build a template, almost 100% of voxels with $0.6<FA_N\leq1$ had an FA_{std} that was less than 5% of FA_N, 97% of voxels with $0.6<FA_N\leq1$ had a $trace_{std}$ that was less than 5% of $trace_N$, and 95% of voxels with $0.6<FA_N\leq1$ had a COU that was less than 5º. Therefore, DT templates with only 30 subjects demonstrated a significantly increased stability in tensor properties of voxels with $0.6<FA_N\leq1$. For a wider range of FA_N values, more subjects were required to reach the same levels of stability in terms of FA_{std} and COU (Fig.2B,C). For example, at least 60 subjects were required to build a template in which more than 93% of voxels with $0.4<FA_N\leq1$ had an FA_{std} that was less than 5% of FA_N, and more than 82% of voxels with $0.4<FA_N\leq1$ had a COU that was less than 5º (Fig.2B). This is due to the fact that, for voxels with low FA_N values, (e.g. FA_N=0.2), misregistration between individual subjects, and eigenvalue sorting in the presence of noise lead to high FA_{std} and COU between templates. In contrast, independent of the range of FA_N considered ($0.6<FA_N\leq1$ or $0.2<FA_N\leq1$), the percentage of voxels with $trace_{std}<0.05*trace_N$ remained higher than 95% for templates with at least 30 subjects (Fig.2A,B,C). This was due to the fact that the mean and standard deviation of trace are relatively uniform throughout brain tissue.

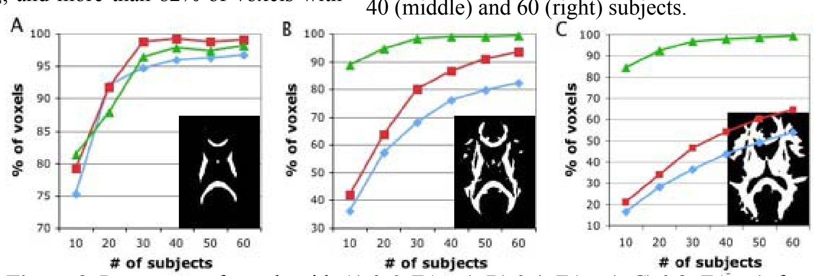

Figure 2. Percentage of voxels with A) $0.6<FA_N<1$, B) $0.4<FA_N<1$, C) $0.2<FA_N<1$, for which $FA_{std}<0.05*FA_N$ (red curve), $trace_{std}<0.05*trace_N$ (green) and COU<5º (blue).

In conclusion, the variability of tensor properties in DT templates decreased as the number of subjects used in the development of these templates increased. Furthermore, DT templates constructed from 30 subjects demonstrated high stability in tensor properties of voxels with FA_N=(0.6,1]. For a lower number of subjects, the variability in tensor properties of the resulting templates 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 $FA_{std}<0.05*FA_N$ and COU<5º. 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.

References: [1] Peng H et al., Neuroimage 2009;46:967-980. [2] Ardekani BA et al., J Neurosci Methods 2005;142:67-76. [3] Yang J et al., Proc. of SPIE Med. Imaging 2008. [4] Jones DK, MRM 2003;49:7-12. [5] Carew JD, et al., ISMRM 2007;p.1598.