Quantitative Comparisons of Measurement Uncertainty in Human Brain Data with Different DTI Protocols Using a Wild Bootstrap Method

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Introduction: Selection of DTI protocols to minimize the measurement uncertainty has been addressed previously by several groups [1, 2]. Criteria for proper protocol selections were also proposed in these studies which rely mostly on numeric simulations, such as Monte Carlo (MC) methods. However, to our knowledge, verification of these criteria on real human DTI images has not been reported, partly due to complexity of human brain but also due to lack of robust estimators for DTI measurement uncertainty. In this report, we applied wild bootstrap (WBS) [3,4], a novel non-parametric statistical method for uncertainty estimation, on human brain DTI data obtained with three clinical DTI protocols from a group of subjects. Measurement uncertainties of different protocols were quantitatively evaluated and brain regions where uncertainties of DTI metrics are sensitive to protocol selection were depicted by VBM analysis on uncertainties of DTI metrics among groups.

Methods: *Subjects:* 13 healthy normal volunteers were scanned on a GE 1.5T scanner (Excite11). *DTI protocols:* For each volunteer, DTI images were obtained using three protocols with different numbers of DW directions (= 6, 21 and 31). Other DTI parameters are: 2x2x3.5 mm voxel size with 128x128x28 matrix, TR/TE=6000/80 ms and b-value=1000s/mm^2. In order to keep the same SNR level (≈25 for non-DW images in this study), average numbers were varied for different protocols and the total numbers of images were kept approximately the same. Scan time for each protocol was less than 10 minutes. Additional high resolution T_1 SPGR images were acquired for aid of spatial normalization. *WBS method*: Mathematically, tensor calculation is a progress of linear regression which minimizes the fitting residuals. Instead of a need for multiple acquisitions for conventional bootstrap (BS), WBS creates the data resampling y_i* or variability by multiplying the fitting residuals μ_i with a two-point distribution function ε_i which has mean zero and unit variance, as illustrated in equation [y_i*= $(B\_matrix*D)_i$+ $a_i\mu_i\varepsilon_i$, $i=1\ldots N$]. Measurement uncertainty can be estimated from the standard errors of certain parameter, e.g. FA, from all WBS samples (750 samples used in this study) to finally generate the standard error map of DTI metrics in each brain voxel. We have evaluated the performance of WBS quantitatively, which is reported in another abstract for this conference. *Modified WBS for six-direction data*: Since fitting residuals μ_i are inseparable for linear regression on six-direction DTI data, a modified WBS was used. In brief, we added white noise in quadrature [2], according to SNR level of DTI data, to original six-direction data and generate "noisy" DTI set. Differences between calculated ADC images from "noisy" and original set were then used as the fitting residuals μ_i for WBS procedure. We applied numeric simulation to compare modified WBS with MC simulation results (***Fig.2***). *Image Processing:* Custom-built software based on C++ and Matlab was used. Before DTI parameter calculation, additional corrections for motion and eddy-current artifacts were performed. *VBM analysis:* Custom-built software packages based on SPM tools were used for spatial normalization (between T1 and b=0 image) and VBM analysis. The processing pipeline followed the optimized VBM strategy [5]. Transformation was then applied to standard error maps of DTI metrics which were generated by WBS method. *Evaluation Criteria*: Measurement uncertainty of DTI protocol was evaluated from two perspectives. First, VBM analysis was applied on normalized standard error maps from 13 subjects. ANOVA analysis was performed on data from three protocols and followed by paired t-test on each protocol pairs. Voxel-wise signification level was set to be p<0.01 with FDR method for multiple comparison correction. Secondly, for standard error maps in native space, we categorize the brain tissue into 8 subgroups according to the FA value from 0.1 to 0.9, with the stepwise increment of 0.1. A two-factor ANOVA analysis was performed on standard deviation of standard error (SE) of DTI metrics, over all pixels within the different subgroups. This statistical analysis quantitatively evaluates the potential dependence among DTI measurement uncertainty, anisotropy level (Factor A) and different protocol selection (Factor B).

Results: Performance of modified WBS (mWBS) is illustrated in ***Fig.2*** as the comparison between Std of FA estimated from mWBS (blue plot) and from MC simulation (red plot). Underestimation exists and becomes worse with small FA level, which may introduce bias in uncertainty estimation for six-direction data. VBM analysis on standard error maps of FA and Mean Diffusivity (MD) across 13 subjects identifies brain regions which are sensitive to proper DTI selections (***Fig.1***). As for uncertainty of both FA and MD, Protocol 21 always has equivalent or larger uncertainty in comparison to Protocol 31. Regions with larger uncertainty are showed on glass brain as well as the superimposing with T_1 normal template in ***Fig.1***. Regions with higher uncertainty are located in gray matter or fiber crossing regions in white matter, such as Left Sub-lobar, Insula, Gray Matter, Brodmann area 13 and Right Frontal Lobe, Sub-Gyral,White Matter. Due to the underestimation issue for mWBS discussed above, estimated FA and MD uncertainty of Protocol 6 by mWBS is smaller than Protocol 21 and 31 for about 70% of brain voxels. Although still underestimated from the true value, several regions, especially many gray matter regions (***Fig.1***), showed worse FA and MD uncertainty with comparison to P21 and P31. Two-factor ANOVA analysis on standard deviation of standard error (SE) of DTI parameter over subgroups shows that there are significant differences between subgroups. Further, one-way ANOVA as well as paired t-tests detected the significant dependency among measurement uncertainty, anisotropy level and protocol selections. As for FA uncertainty, P31<P6 (p=0.0311) at anisotropy level 0.7<FA<0.8 and (P31, P21) <P6 (p=0.0051) at anisotropy level of 0.8<FA<0.9. For MD uncertainty, there is no significant difference among three protocols, except for a subgroup with 0.1<FA<0.2, where P6<P31.

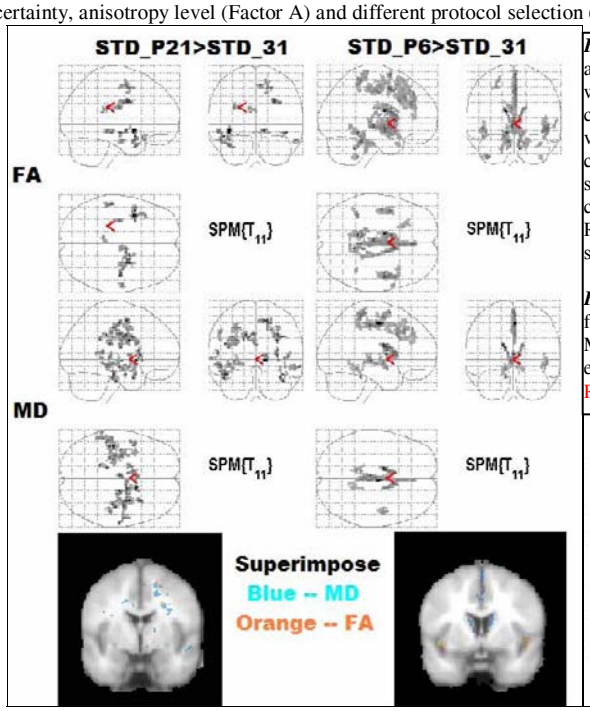
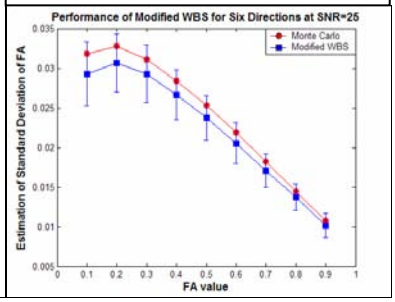


Fig.1. (***Left***): VBM analysis of uncertainty among three DTI protocols. Significant areas were detected by criteria: p<0.01 with FDR correction and with cluster size larger than 30 voxels. Left column: P21 vs. P31; Right column: P6 vs. P31. Similar regions with smaller cluster size were detected for comparison between P6 and P21. Bottom row: Regions from the top two rows are superimposed to a standard brain (MNI152).

Fig.2. (***Bottom***) Performance of modified WBS for the six-direction data, with comparison to MC simulation results. Standard deviations estimated at different FA levels were plotted. Red: MC results, Blue: Modified WBS results.



Discussions: Wild bootstrap was applied on a set of real human brain DTI data to quantitatively compare the DTI measurement uncertainty from three clinical protocols. Previously reported uncertainty pattern based on numeric simulations has been observed here by WBS method, and similar conclusions are drawn regarding requirements for reliable measurements such as at least 20 gradient directions for less FA uncertainty [2]. Furthermore, brain regions where uncertainty is sensitive to protocol selections have been identified. Advanced topics on fine-tuning performance of WBS for clinical applications, such as selection of different HCCME functions of WBS, will be subjected to future studies.

References: [1]. Skare S et.al. MRI 2000; 18:659-69; [2]. Jones DK et.al. MRM 2004; 51(4):807-15; [3]. Whitcher B et.al. Proc. ISMRM 13th Annual Meeting. Miami, 2005; 1333. [4]. Chung S et.al. NeuroImage 2006; 33(2): 531-41; [5]. Good CD et.al. NeuroImage 2001; 14: 21-36.

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