Bootstrap-based Longitudinal Analysis of DTI Estimates (BLADE): Applications in Clinically Isolated Syndrome Patients

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Introduction: Numerous studies have shown that diffusion tensor MRI (DTI) and other quantitative MRI methods are sensitive to changes in the normal appearing white matter as well as in the lesions of multiple sclerosis (MS) patients[1, 2]. Longitudinal imaging studies on MS patients is crucial to understand disease evolution and to monitor treatment effect, and DTI can be a powerful tool for this by providing information about changes in microstructural integrity of white matter. Most longitudinal studies have focused on large region (whole brain normal appearing tissue or predefined regions of interest) analysis and do not provide information on regional changes. Therefore, outstanding questions remain with regards to the origin of normal appearing white matter (NAWM) changes: i.e. distal effects of focal, lesions or global pathology. In this study, a novel scheme of voxel-based longitudinal analysis is introduced, incorporating bootstrap-based uncertainty measurement of DTI indices to get the significance level of changes over time. This method was validated in control studies and preliminary results in application of this method illustrate NAWM abnormalities correlated with distal lesions in the earliest stage of MS.

Methods: 25 patients with clinically isolated syndrome (CIS) who often progress to relapsing-remitting MS were scanned at 3 months post presentation and at 3 month interval up to 2 years. 10 healthy subjects were scanned as well for three or four separate time points. For the study presented here, data was analyzed for three patients in addition to control analyses. DTI was acquired on the 1.5T GE Signa MR Scanner with 4G/cm gradients and standard quadrature head coil, with the single-shot spin echo EPI sequence and TR/TE = 7s/100ms, 9NEX, 256x128 matrix, 440x220mm FOV, 1.7x1.7x2.1mm voxel size (no gap between slices), 6 non-collinear diffusion-encoding gradients (b=2000s/mm^2) in addition to b=0s/mm^2 image. Data averaging in the scanner was done up to 3NEX to come up with 3 repetitions of 3NEX data which can be used for bootstrap analysis. Bootstrap analysis is a non-parametric statistical method which was shown to be a powerful tool to characterize uncertainties in DTI data[3]. Bootstrap was performed on a voxel-by-voxel basis, with 3 repetitions and 100 iterations to come up with 100 bootstrap sample FA volumes in each time point. All these samples were registered to the FA volume of the last time point independently by affine transformation using FLIRT (part of FSL package) and mean and variance of fractional anisotropy (FA) were calculated in each voxel using 100 registered volumes, effectively representing the distribution of FA in each voxel for the specific time point after registration to the last time point. T statistic, representing the difference of two point estimates scaled by square root of sum of variance, was calculated for each voxel between time point 1 and 2, time point 1 and 3, and so on. These T statistic maps were evaluated for the pattern of spatial distribution, and DTI tractography, based FACT[4], deterministic streamline method, was utilized to further evaluate the connectivity between relatively significantly changing voxel clusters.

Results: Figure 1 shows the absolute values of T statistic map of the control subject between arbitrarily chosen two time points. T scores were observed to be randomly distributed in the volume with few noticeable structural features, implying that the variance in each voxel for two time points were properly estimated, effectively scaling the difference between two time points. The T scores in the entire brain were found to be distributed similar to normal distribution with mean of zero and standard deviation of 1, supporting appropriate estimation of the variance since it is known that T distribution with large number of samples is known to approximate standard normal distribution. Figure 2 shows the T scores $p<0.01$ overlaid over mean FA map in the same slice and same time points as figure 1. Increases (red) and decreases (blue) in FA over time is shown, with brighter color meaning higher T scores. Random events dictate that 1% of the voxels will exceed this T threshold and these supra-threshold voxels are randomly scattered around, without any definite patterns. Figure 3 shows the T statistic maps and corresponding T1-weighted images for a CIS patient, between time point 1 (baseline) and 2 (3 months after). Similar differences were observed for the next subsequent 4 time points. Clusters of voxels with increasing FA (red clusters) were identified at the site of an acute T1 lesion (not shown) and also superiorly in NAWM voxels related by fiber tracking (yellow arrow). This suggests the possibility of acute NAWM changes and improvement related to acute lesions. Clusters of voxels with decreased FA (blue clusters) were found in NAWM (blue arrow), which were connected by fiber tracking to a chronic T1 lesion (blue arrow) possibly degeneration of NAWM undetectable by conventional imaging. These results illustrate the richness of information that can be investigated with this methodology.

Discussion: By calculating bootstrap-based uncertainties for the longitudinal analysis of MS patients that provide the confidence level in the changes of DTI indices of interest over time on the voxel level, we were able to detect local changes that could not be easily captured by histogram or ROI analysis. Longitudinal analysis is relatively free from registration complications that cross-sectional studies face, making voxel-based analysis more reliable. The ability to follow up each patient individually, either by searching for clusters with certain size or larger changing statistically significantly over time or even single voxels in case of higher SNR and good registration between different time points, may have a great potential in monitoring the disease progression and treatment effect in multiple sclerosis and other white matter diseases as well. Future studies of optimizing the procedure and quantitative correlation with chronic and acute lesions using the information of connectivity provided by DTI tractography will be helpful.

References: 1. Castriota Scanderbeg, A., et al., AJNR Am J Neuroradiol, 2000. 21(5): p. 862-8. 2. Henry, R.G., et al., J Magn Reson Imaging, 2003. 18(4): p. 420-6. 3. Pajevic, S. and P.J. Basser, J Magn Reson, 2003. 161(1): p. 1-14. 4. Mori, S., et al., Ann Neurol, 1999. 45(2): p. 265-9.