SPatial REgression Analysis of Diffusion tensor imaging (SPREAD) for longitudinal comparison of neurodegenerative disease progression in individual subjects

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Introduction: Diffusion tensor imaging (DTI) technique [1] has been applied to achieve more robust early detections of neurodegenerative diseases and more effective monitoring the progression of disease-related abnormalities in white matter (WM) longitudinally. For diseases that usually affect common WM structures among the diseased population, advanced group-based statistical comparisons, including voxel-based morphometry (VBM) [2] and tract-based spatial statistics (TBSS) [3], can be used to achieve adequate statistical power. However, two major limitations exist in these analyses. For several neurodegenerative diseases, such as multiple sclerosis (MS) and mild traumatic brain injury (mTBI), the brain abnormality has strong subject-dependent or time-dependent heterogeneous patterns. Moreover, most existing analyses for DTI do not take into consideration of the intrinsic spatial/intensity correlation of neighboring voxels. In this study, we propose a novel statistical analysis approach for DTI based on a nonparametric spatial regression fitting of DTI data among neighboring voxels. Using nonparametric resampling methods, statistical inference can be made for both group comparison among individuals and longitudinal comparison within the same individual. Effectiveness of this approach on group comparison was compared with the VBM approach through numerical simulations. The longitudinal analysis of a single MS patient with progressive MS lesions was conducted for the purpose of concept proof.

Methods: ***(I). Theory***: Neighboring voxels naturally belong to the same anatomical structure and are potentially affected by the common pathophysiological changes. This abundant information of spatial correlation in DTI can be used for a) detecting longitudinal abnormalities of a single subject from just one pre and one post brain scan; b) boosting statistical power for traditional group comparisons. The proposed method includes three parts. (1) A nonparametric spatial regression to fit the fractional anisotropy (FA) values as a spatial function. In this study the Nadaraya-Watson kernel regression with Gaussian kernel was used. (2) A non-parametric group comparison. The difference (or mean difference in group comparison) between pre and post FA maps is used to quantify FA changes. To simulate the distribution of FA values under the null hypothesis (no longitudinal change is present in the FA maps), we randomly permuted the time label of FA value at each voxel for 1000 times and re-run kernel regression for each permutation. A resampling based *p*-value was obtained for each voxel. (3) A multiple testing procedure to control a suitable type I error rate such as familywise error rate (FWER) or false discovery rate (FDR). We applied a tailored Westfall-Young procedure to control FWER at 0.05 level in this study. ***(II). Simulations for Group Comparison***. A DTI dataset (isotropic 2x2x2 mm voxel, 60 diffusion gradient directions with b=700 s/mm^2) of a healthy subject was selected. Gaussian noise determined by the SNR level of the original DTI was added to generate two groups of DTI data, simulating two serial data of the same subject. For each time point, the numbers of repeat measurements of DTI (*r*) investigated were 3,4,5,6. For simulated data of the 2nd time point, we added different effect sizes (*es*) to the largest eigenvalue (λ_1) of each voxel within a cubic region (5x5x3 voxels) at the center of splenium corpus callosum, where *es* took values of {0%,10%,20%,30%,40%} of the mean λ_1 value over all voxels within the selected region from the original DTI map. This 5x5x3 region simulated a diseased area (Fig.1A). For each combination of *r* and *es*, 100 simulated datasets were generated. Two-sample *t*-tests were conducted using the VBM analysis in the SPM package and the proposed approach. Performance of two approaches was compared through the Receiver-Operating-Characteristic (ROC) analysis among 100 simulated datasets. ***(III). Longitudinal Analysis of the Progression of a MS Patient***. Four datasets of a MS patient acquired within a year (average time interval between scans: 3 months) were analyzed. Each dataset included a DTI scan (2x2x3mm voxel, 24 diffusion directions with b=1000 s/mm^2), a FLAIR scan and a T1 contrast enhanced scan (2x2x3mm), and a high-resolution T1 SPGR scan (1x1x1.5mm). At the 2nd scan (6th month after baseline), T1 contrast images showed an active lesion at the left posterior thalamic radiation. This lesion became chronic (normal appearance in T1 contrast scan but hyperintensity in FLAIR scan) since the 3rd (9th month) time point with progressively reduced size. A nonlinear registration between the non-diffusion weighted images (b=0) at the baseline and at each of follow-up time points was performed to achieve better spatial registration, followed by reslicing DTI data, adjusting diffusion weighting vectors, artifacts correction and tensor calculation using the FSL package. Lesion masks from the 2nd to 4th time points were manually created by an experienced neuroradiologist as the gold standard to evaluate significant changes detected by the proposed approach. Two quantitative measures, True Positive Ration in Lesion (TPR_L) and False Positive Ratio within Non-Lesion white matter (FPR_NL), were calculated as quantitative criteria for evaluation.

Results: A smoothing kernel of FWHM=2x2x2voxel was used in estimation of the nonparametric spatial regression model of DTI. To make direct comparisons with the new approach (red asterisk in Fig.1B), the VBM analysis of SPM was performed on both non-smoothed (black cross) and smoothed (blue circles) data. From Fig. 1B, the new method is directly comparable to the VBM approach if multiple scans in each time point were available for conducting a group comparison. ROC curves show that the new method performs better than VBM when the number of scans per group is small (r<5). While the VBM analysis requires at least three repeated DTI measurements at each time point to enable a valid longitudinal comparison of DTI data for a patient, our method, on the other hand, detected significantly decreased FA from only one DTI scan per time point for the MS patient with progressive lesions (Fig.2). Compared to the gold standard lesion mask, the TPR_L values associated with each longitudinal comparison from our method were: 85%, 69% and 70%. The FPR_NL values were 1.6%, 0.8% and 0.7%, well under the acceptable 5% level.

Discussion and Conclusions: Imaging data are unique in that they present exquisite spatial details with a large number of voxels for each subject but often with only a small number of subjects or a few follow-ups of each subject due to financial or patient recruitment constraints. Taking advantage of the abundant information of intrinsic spatial correlation in DTI data, we present a statistical analysis approach that can achieve sufficient statistical power for longitudinal analysis of DTI data even for an individual patient with only one DTI acquisition at each longitudinal image exam. When pathological changes of neurodegenerative disease are heterogeneous among population and during disease progression, our method provides a potentially better way to assess individual abnormality by establishing a within-subject baseline to determine more directly how the brain has changed as a result of disease/injury.

References: [1]. Basser, P., et al., 1994,Biophy J, 66:259-267. [2]. Ashburner, J., et al., 2000, Neuroimage, 11:805-821. [3]. Smith, S.M., et al., 2006,Neuroimage, 31:1487-1505.

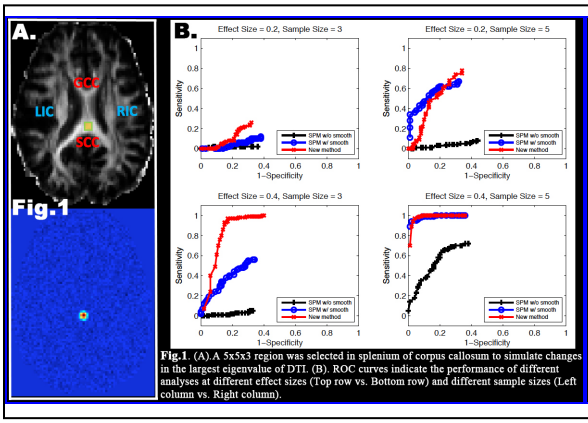

Fig.1. (A).A 5x5x3 region was selected in splenium of corpus callosum to simulate changes in the largest eigenvalue of DTI. (B). ROC curves indicate the performance of different analyses at different effect sizes (Top row vs. Bottom row) and different sample sizes (Left column vs. Right column).

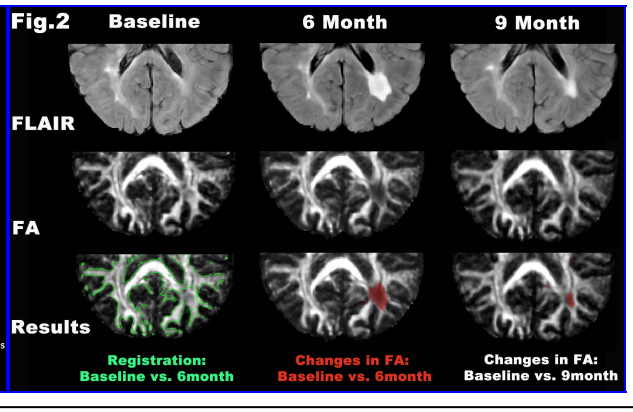

Fig.2 Longitudinal analysis of lesion progression of a MS patient within a 9-month period. Lesions are visible with both FLAIR (hyper intensity in 1st row) and FA map (hypo intensity in 2nd row). Significant changes in FA detected by the new approach are indicated in red color, superimposing on FA maps (3rd row). Efficiency of nonlinear registration is illustrated by superimposing the contour line (FA=0.3) of the baseline onto FA maps of following time points.