VOXEL-WISE GROUP ANALYSIS OF DTI

Zhexing Liu[1, 2], Hongtu Zhu[3], Bonita L. Marks[4, 5], Laurence M. Katz[4, 5], Casey B. Goodlett[7], Guido Gerig[7], Martin Styner[1, 2, 6]

[1]Neuro Image Research and Analysis Laboratories, Depts. of [2]Psychiatry, [3]Biostatistics, [4]Exercise and Sport Science, [5]Emergency Medicine, [6]Computer Science, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, , United States
[7]Scientific Computing and Imaging Institute, University of Utah, Salt Lake City, Utah, United States

ABSTRACT

Diffusion tensor MRI (DTI) is now a widely used modality to investigate the fiber tissues in vivo, especially the white matter in brain. An automatic pipeline is described in this paper to conduct a localized voxel-wise multiple-subject group comparison study of DTI. The pipeline consists of 3 steps: 1) Preprocessing, including image format converting, image quality check, eddy-current and motion artifact correction, skull stripping and tensor image estimation, 2) study-specific unbiased DTI atlas computation via affine followed by fluid nonlinear registration and warping of all individual DTI images into the common atlas space to achieve voxel-wise correspondence, 3) voxel-wise statistical analysis via heterogeneous linear regression and wild bootstrap technique for correcting for multiple comparisons. This pipeline was applied to process data from a fitness and aging study and preliminary results are presented. The results show that this fully automatic pipeline is suitable for voxel-wise group DTI analysis.

Index Terms— Diffusion tensor, MRI, Voxel-wise analysis, Group comparison.

1. INTRODUCTION

Diffusion Tensor Magnetic Resonance Imaging (DT-MRI, DTI) [1] is a relatively new but rather fast developing MR imaging modality, aiming to measure the diffusivity of water in tissue. DTIs have been widely used to investigate white matter microstructure and its changes in brain, in vivo including normal brain development, aging and pathological damages. Unlike traditional medical images, DTI at each voxel is a 3x3 symmetric positive definite matrix with 6 independent elements. Then, scalar indices, such as fractional anisotropy (FA), mean diffusivity (MD) and eigenvalues, can be calculated from a tensor. Due to the complexity of tensor images, the processing and analysis of DTI is still under extensive research.

Most statistical analyses of DTI are based on region-of-interest (ROI) methods, which usually involve manual ROI delineations and the statistical analysis of the averaged tensor indices within the ROIs. This kind of analyses often suffers from large intra and inter-person variability and bias in defining meaningful ROIs. In some situations when more spatially localized properties should be considered, voxel-wise analysis as an alternative method may perform better.

Voxel-wise analysis of DTI is characterized by spatial normalization of DTI, hypothesis test at each voxel and multiple comparison correction. The major challenges in voxel-wise DTI analysis include high quality voxel correspondence and multiple comparison correction in hypothesis test. SungWon Chung [2] described a voxel-wise analysis of single-subject serial DTI. This is a longitudinal comparison and intra-subject registration is much easier than the inter-subject group comparison

Currently, there are 2 popular DTI group analysis methods. One is called Track-Based Spatial Statistics (TBSS) [3] method, developed by Stephen M. Smith, et al., in FMRIB, Oxford University. The other is a fiber-tract based analysis method developed by Casey B. Goodlett [4], et al. in University of Utah. In TBSS, B-spline based nonlinear registration is used to bring all the FA images into a specific template space. All the registered FA images are averaged and a skeleton of the mean FA image is created. Each subject's aligned FA values are projected from the nearest relevant tract center onto the skeleton, attempting to solve the voxel correspondence and smoothing problems. Then, statistical analysis is done at each of the voxels on the FA skeleton. With TBSS, it is easier to test whole brain than ROI based methods. However, only a very small amount of "voxels" on the skeleton are tested and this is not a true voxel-wise method. Group difference may also be reduced or eliminated during the FA based nonlinear registration procedure. In the fiber tract based method, a study specific unbiased tensor image atlas is first computed via a fluid-based nonlinear registration method [5]. Fiber tracking is done in the atlas tensor image and then, the diffusion properties are parameterized along the fiber tracts from all the aligned subjects' tensor images. Finally, group comparison is conducted on the on-tract diffusion properties. Limitations of this method include manual interventions in

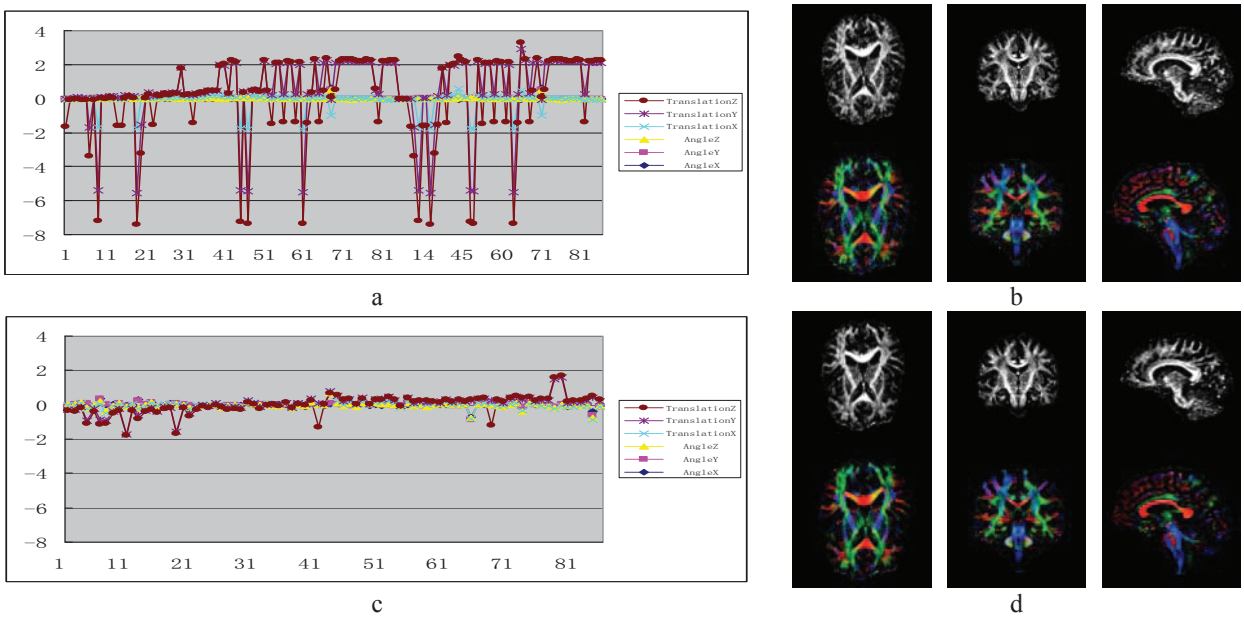

Fig. 1. DWI quality control and artifact correction. a. Rigid registration parameters between each gradient and baseline image of the original DWI. b. FA and color coded FA images before eddy-current and motion correction. c. Rigid registration parameters between each gradient and baseline image of the corrected DWI. d. FA and color coded FA images after eddy-current and motion correction.

specifying ROIs for fiber tracking in atlas and fiber tracts cleaning before parameterizing. Both methods do not consider the whole brain images.

We present here a fully automated pipeline for voxel-based DTI group analysis, with no need to delineate ROIs and ability to investigate localized changes anywhere in the brain. Correlation studies can also be conducted. This pipeline consists of preprocessing, unbiased DTI atlas computing, voxel-wise statistical modeling and multiple comparison correction.

2. METHODS

2.1 Preprocessing

First, diffusion weighted images (DWI) in dicom format were converted into a NRRD file format using DicomToNrrdConverter, a 3D Slicer plug-in tool (slicer.org, v3.2). The NRRD format stores all the necessary image and diffusion information and is used by NAMIC as DWI and DTI data format. Second, DWI image quality checking was performed on each of the subjects' DWIs to check if the DWIs contained large slice brightness artifacts, intra-gradient Venetian blind artifacts and motion artifacts using a locally developed tool. If slice brightness and/or Venetian blind artifacts were/was found, the whole gradient data would be discarded. If large motion artifacts were found, corresponding gradient data would also be excluded. Only small motion artifacts between different gradients were allowed to reside in the DWIs fed into an eddy-current and motion artifact correction tool (developed by P. Thomas Fletcher and Ran Tao at the University of Utah). Fig. 1. shows the motion artifact check results before and after eddy-current and motion correction, as well as the corresponding FA and color coded FA images. After artifact correction, all the motion remnants were all at the level of subvoxel. Third, diffusion tensor images were estimated using a weighted least square method. DTI FA and MD maps were computed. Skull stripping is performed automatically via a brain mask computed from baseline images with itkEMS. Masking out the non-brain tissues stabilizes the following registration step. All DTI tools and itkEMS are part of the NeuroLib (www.ia.unc.edu/dev/).

2. 2 Unbiased DTI Atlas Building

All the DTIs needed to be spatially normalized to get voxel correspondence across all subjects for group comparison. Like most voxel-based analysis methods, registration accuracy is crucial for identifying meaningful group differences so that a large deformation non-linear registration algorithm is needed. We used a nonlinear fluid deformation based high-dimensional, unbiased atlas computation method [6]. The atlas building procedure is initialized by affine registration and followed by nonlinear registration of a feature image which is sensitive to the geometry of white matter and is similar to methods proposed in the literature for modeling white matter by its medial sheet [3, 7]. With the deformation field data, we warped each of the tensor images into the unbiased space

and got the aligned DTIs. After averaging all the registered DTIs, a study specific unbiased DTI atlas was created. The tensor warping and averaging were conducted in a Log-Euclidean space. Fig. 2 shows the schematic view of the DTI atlas computation.

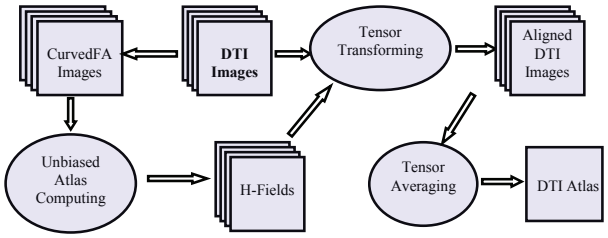

Fig. 2. Scheme of unbiased DTI atlas computing

2.3 Voxel-wise analysis

Scalar indices (FA, MD, et al.) were then calculated from the aligned tensor images. After minimal Gauss smoothing with variance=1, the images were fed into the statistical comparison tool. The brain regions other than white matter were masked out before the statistical modeling and testing. This reduced not only the unnecessary computation but also the number of multiple comparisons, and thus increased the statistical power in detecting the group difference. The white matter mask was made up by all the voxels where FA values were larger than 0.2 in the DTI atlas.

For the DTI voxel-wise analysis, there is currently no standard statistical framework. Due to the non-Gaussian nature of DTI data, semiparametric statistical methods without assuming any specific parametric distribution are more suitable. Two non-parametric techniques were applied for the DTI statistical testing. One is bootstrap, and the other is permutation-based. Both techniques have shown the ability to sample and conduct the group difference significance testing. We used a heteroscedastic linear model for statistical modeling and a robust test procedure based on the wild bootstrap method for correcting multiple comparisons developed by Hongtu Zhu [8]. Finally, the multiple-comparison corrected significance map was produced. Fig. 3. illustrates this statistical procedure.

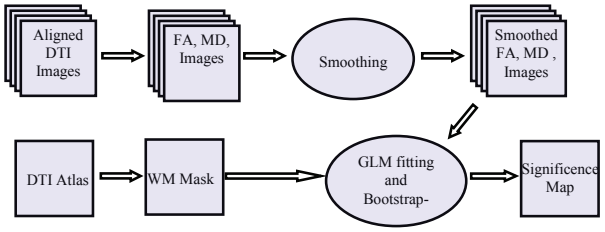

Fig. 3. Voxel-wise group comparison scheme

2.4 Correlation analysis

Voxel-wise Pearson correlations were calculated between FA and the subject's Oxygen consumption (VO2). The correlation significance was also tested with the same wild bootstrap technique as for group testing described in 2.1.3.

3. EXPERIMENTS

3.1 Subjects

Fifteen older adults between 60 - 76 years of age (8 males, 7 females) completed the testing procedures. All were college educated, healthy, without orthopedic, metabolic cardiopulmonary or cognitive limitations. Subjects reported participating in either aerobic exercise for a minimum of 180 min/wk for the past 10 years or less than 90 min/wk for the past 10 years. Aerobic fitness was verified with a peak aerobic capacity test on a treadmill. This research was approved by UNC's Biomedical IRB for Human Subjects.

For this preliminary study and hypothesis generation, one subject was excluded and the rest were divided into 2 groups based on self-reported aerobic activity participation. Group 1 is more aerobically active (n=7, 5m, 2f), and averaged 65.3 years. Group 2 is less aerobically active (n=7, 2m, 5f) and averaged 68 years

3.2 Diffusion Tensor Imaging

Images were acquired with a head only 3.0 Tesla MRI unit (Allegra Siemens Medical Systems) with a maximum gradient strength of 40 mT/m and a maximum slew rate of 40 mT/m/msec. A spin echo diffusion tensor weighted sequence was used to acquire the MR images. A baseline (b=0) image and 21 directional images (b = 1000s/mm^2) were acquired (4 NEX) at an isotropic resolution of 2mm.

3.3 VO2Peak Assessment

Oxygen consumption (VO2) was measured using the PARVO TrueMax VO2 Metabolic Cart System (ParvoMedics, Salt Lake City, Utah). Subjects underwent a physician-supervised, ECG-monitored ramped peak exercise stress test on a treadmill (TM) utilizing Duke's Modified Pepper Protocol.

4. RESULTS

The pipeline described above was used to analyze this aging and fitness study dataset. While doing voxel-wise group analysis, age and gender influence were corrected as covariants in the heteroscedastic linear model. Pearson correlation was computed with the raw FA values and the peak VO2, both of which were not corrected for age and gender influence as the peak VO2 is highly gender variable.

Fig. 4. shows the group comparison and correlation analysis results of FA images. In 4a., FA group difference significance maps (in red, $p<0.05$) were overlaid on the atlas FA images. In 4b., correlation significance maps (in

red, $p<0.05$) were overlaid on the Pearson correlation images with non-white matter areas masked out. Group differences were found within the areas of cingulum, splenium, arcuate, and the corpus callosum (CC). Significant positive correlations were found in genu, splenium, and CC.

Due to the low the sample size and self reported grouping, much care needs to be taken when drawing any conclusions.

5. CONCLUSIONS

We have described a complete pipeline for voxel-wise group DTI analysis. This pipeline is fully automatic and thus is very suitable for DTI data sets as illustrated in a fitness and aging study. All processing tools will be made available as open source within the UNC NeuroLib.

6. ACKNOWLEDGMENT

We thank Tom Fletcher and Ran Tao at the University of Utah for their Eddy current and motion correction tool. Funding for this work was provided by UNC Neurodevelopmental Disorders Research Center HD 03110, National Alliance for Medical Image Computing (NAMIC), NIH Roadmap U54 and a seed grant from UNC's Biomedical Research Imaging Center awarded to Dr. Bonita L. Marks, principle investigator for the research, "Role of Recreational Sport Participation on Cerebral White Matter Integrity in Older Adults".

7. REFERENCES

[1] Basser, P., Pierpaoli, C., "Microstructural and physiological features of tissues elucidated by quantitative DT-MRI," Journal Magnetic Resonance, 111 (3), 209-219, Jun. 1996.

[2] Chung SungWon, "Whole brain voxel-wise analysis of single-subject serial DTI by permutation testing," NeuroImage 39, (4), 1693-1705, February, 2008.

[3] Smith, S. M., Jenkinson, M., "Tract-based spatial statistics: Voxelwise analysis of multi-subject diffusion data," NeuroImage 31 (4), 1487-1505, 2006.

[4] Casey B. Goodlett, "Group Analysis of DTI Fiber Tract Statistics with Application to Neurodevelopment," NeuroImage, inpress.

[5] Joshi, S., Davis, B., Jomier, M., Gerig, G., "Unbiased diffeomorphic atlas construction for computational anatomy." NeuroImage 23 (Supplement1), S151-S160, Nov. 2004.

[6] Goodlett, C., Davis, B., "Improved Correspondance for DTI population studies via unbiased atlas building," MICCAI Vol.4191 of LNCS. Springer-Verlag, pp. 260-267, 2006.

[7] Kindlmann, G., Tricoche, X., Westin, C.-F., "Delineating white matter structure in diffusion tensor MRI with anisotropy creases," Medical Image Analysis 11 (5), 492-502, 2007.

[8] Hongtu Zhu, Joseph G. Ibrahim, "A Statistical Analysis of Brain Morphology Using Wild Bootstrapping." IEEE Transactions on Medical Imaging 26, no. 7: 954-966, 2007.

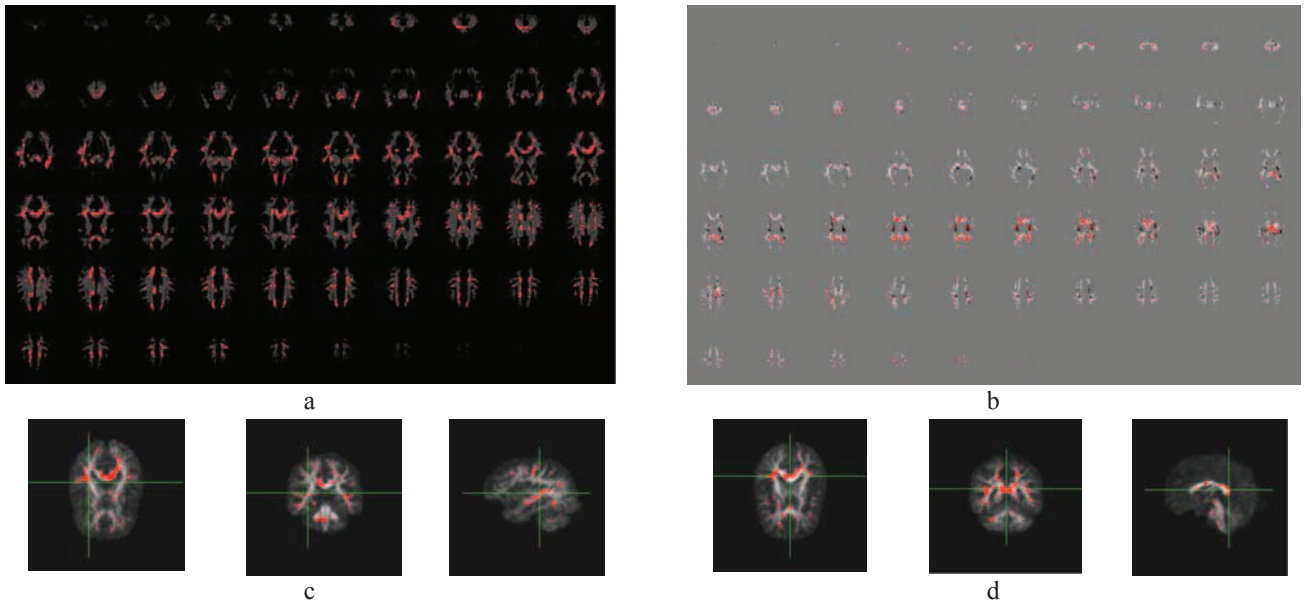

Fig. 4. Voxel analysis results. a. Axial view of significance maps (in red, $p<0.05$) overlaid on FA images of the unbiased DTI atlas. b. Axial view of correlation significance maps (in red, $p<0.05$) overlaid on a white matter masked Pearson correlation images. Within the correlation maps, correlation equals 0 where the color is gray as in back ground, white equals 1 and black equals -1. c. and d. are zoomed in views of a. at the Arcuate and Splenium area.