

Automated Voxel-Wise Brain DTI Analysis of Fitness and Aging

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Abstract: Diffusion Tensor Imaging (DTI) has become a widely used MR modality to investigate white matter integrity in the brain. This paper presents the application of an automated method for voxel-wise group comparisons of DTI images in a study of fitness and aging. The automated processing method consists of 3 steps: 1) preprocessing including image format converting, image quality control, eddy-current and motion artifact correction, skull stripping and tensor image estimation, 2) study-specific unbiased DTI atlas computation via diffeomorphic fluid-based and demons deformable registration and 3) voxel-wise statistical analysis via heterogeneous linear regression and a wild bootstrap technique for correcting for multiple comparisons. Our results show that this fully automated method is suitable for voxel-wise group DTI analysis. Furthermore, in older adults, the results suggest a strong link between reduced fractional anisotropy (FA) values, fitness and aging.

Keywords: Diffusion tensor imaging, DTI atlas, voxel-wise analysis, nonlinear warping, aging and aerobic fitness.

1 INTRODUCTION

Diffusion Tensor Imaging (DTI) is increasingly being used to investigate the microstructure, integrity and changes of white matter in normal, developing, aging and pathological brains [1-5]. Theoretically, DTI uses a "diffusion coefficient" to quantify the rate and directionality of water displacement in various brain tissues and has been developed as a tool to determine structural integrity of underlying tissues and fiber tracts pathways in white matter [6].

DTI uses a tensor model estimated at each voxel position using linear or nonlinear regression methods given at least 6 gradient directions. Diffusion sensitizing gradients measure signal attenuation of water diffusion by a second order tensor matrix. The most commonly used scalar property maps of DTI are fractional anisotropy (FA) and mean diffusivity (MD), which are calculated from the tensor eigenvalues. Other scalar maps include geodesic anisotropy (GA), parallel/axonal diffusivity (PD/AD), and orthogonal/radial diffusivity (OD/RD). The principal eigenvector of a tensor determines the overall direction of the fiber structure at the voxel under investigation. DTI fiber tractography can be

computed to determine the structures and pathways of major white matter fiber bundles. In this study, we focus on the use of FA images, which is the most commonly employed DTI map in neuroimaging studies. FA measures the degree of diffusion anisotropy and is usually highest in regions of tightly aligned, highly myelinated fiber bundles.

In clinical DTI literature, analytic DTI approaches vary from region-of-interest (ROI) based analysis to voxel based group analysis in neuroimaging studies. ROI analysis typically uses manual or automatically determined ROIs that define white matter structures, followed by statistical analysis of the average tensor indices within those ROIs [7]. ROI methods are probably the most commonly applied method due its simplicity, e.g. for the study of normal development [8-10], schizophrenia [11] or Krabbe's disease [12]. The major drawbacks of ROI analysis suffer from large intra and inter-rater variability and bias in defining meaningful fiber regions, which identify the long and curved shape of fiber bundles. Furthermore, the distribution of DTI property values such as FA within white matter regions is non-Gaussian and thus simple averaging over large ROIs is non-optimal.

In contrast, voxel-wise analysis of DTI is a highly localized analysis methodology that is able to differentiate structures. Voxel-wise analysis has been applied in DTI studies including autism [13] and schizophrenia [14, 15]. These methods are characterized by spatial normalization of a

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population of DTI images, hypothesis testing at each voxel position and multiple comparison corrections. One reason for discrepancies across voxel-wise analysis techniques lies in the difficulty of appropriate anatomical registration of DTI data. This limitation of the established voxel correspondence is pointed out by Chung *et al.* [16], as they reported superior voxel-wise analysis reliability based on intra-subject registration compared to inter-subject registration. Due to their ease of use, voxel-based methods have become quite common in the last years, especially as a first-line tool for hypothesis generation.

One of the most popular voxel-based analysis frameworks was developed by Smith S.M. *et al.* [17], called Track-Based Spatial Statistics (TBSS). TBSS brings all the FA images into a specific template with B-spline based non-linear registration. Registered FA images are then averaged and skeleton of the mean FA images is extracted. Each subjects' aligned FA values are projected to the nearest relevant tract center on the extracted white matter skeleton, where the local maximum FA is computed as the main analysis feature. This procedure compensates for the imprecision in the voxel correspondence and solves the smoothing problems so that statistical analysis can be done on each voxel of the white matter skeleton. In TBSS, only a very small number of voxels in the skeleton are thus tested as compared with a full brain voxel-wise method. The TBSS technique has been used to study preterm infants and adolescent development [18, 19], patients with schizophrenia [20], fetal alcohol syndrome [21] and Alzheimer's disease [22]. While this technique reduces the number of statistical tests and simplifies multiple comparison problems, multiple fiber bundles close to intersection areas are likely to be mixed on the skeleton and thus can significantly increase measurement variability. Limited warping quality especially close to the cortical regions due to the large inter-subject variability in brain shape may further limit the utility of TBSS, although this is an issue for most voxel-based analysis methods. In addition, the use of the projected FA maximum values is considered to result in reduced test/retest reliability, as maximal values are more susceptible to noise.

As a complement to DTI voxel-wise analysis, fiber-tract based analysis has been proposed to investigate group differences in DTI [23]. A DTI atlas is created via a fluid-based nonlinear registration method [24] and fiber tracking is performed on the atlas tensor image. The diffusion property profiled are extracted along the parameterized fiber tracts from all the atlas-aligned subjects' tensor images so group comparisons can be performed on these fiber tract diffusion profiles. Several steps in this procedure still need to be performed manually (such as fiber tract source selection), thus limiting the level of automation. While fiber based analysis yield commonly the best compromise between locality and regional average, it is ill-suited for hypothesis generation.

There is great interest in the public health sector to identify biological factors within the central nervous system (CNS) that are associated with cognitive aging and brain structural changes [1,2,25-30]. Epidemiological studies suggest that cardiovascular fitness and education may

protect the brain from degradation associated with aging [31-34] and Alzheimer's disease [35, 36]. Along these lines, voxel-based morphology (VBM) has been used in high resolution structural MRI images including T1 and T2 images [33] and more recently, DTI analysis has been developed to investigate the role of aerobic fitness on white matter integrity in the aged [37-39]. The related studies have found a decline of FA and an increase of MD in several white matter regions in normal aging [1-4].

In this study, we developed a fully automatic methodology for voxel-wise group DTI analysis based on our previous work [40], which requires no manual intervention, while being able to investigate localized changes anywhere in brain. We investigated the relationship between aerobic fitness and white matter integrity in older adults using this methodology. This includes voxel-wise brain white matter group comparisons and voxel-wise correlation studies between DTI properties.

2. MATERIALS AND METHODS

2.1. Subjects and Grouping

Fifteen older adults between 60 - 76 years of age (8 males, 7 females) were involved in this study. This study was approved by the University of North Carolina at Chapel Hill's Committee on the Protection of the Rights of Human Subjects. All subjects provided informed written consent for participation. All subjects were college educated, healthy without orthopedic, metabolic, cardiopulmonary, cognitive or MRI scanning limitations. None were on anti-depressants or on medications that would alter the heart rate response to exercise.

Subjects were divided into two groups based on their aerobic fitness according to fitness classifications for men and women aged 60 years and older [41]. Group 1 subjects were aerobically active and reported participating in aerobic exercise for a minimum of 180 *min/wk* for the past 10 years. Group 2 subjects were aerobically inactive and reported participating in aerobic exercise less than 90 *min/wk* over the past 10 years. Aerobic fitness was verified with a physician-supervised, peak exercise (walking) test on a treadmill utilizing Duke's ramped Pepper Treadmill Protocol [42]. The oxygen consumption (VO_2 peak) was measured using the PARVO TrueMax VO_2 Metabolic Cart System (ParvoMedics, Salt Lake City, Utah). The grouping and VO_2 peak cut-off values for the groups are listed in Table 1. The gender composition between the two groups were comparable, however there was a significant age difference between them ($p < 0.00001$).

Whole-head DW 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 echoplanar diffusion tensor weighted sequence ($\text{TE} = 79$ *ms*, $\text{TR} = 9200$ *ms*, acquisition matrix = 128×104 , $\text{FOV} = 256 \times 208$ mm^2 , slice thickness=2 mm and number of slices =80 with no gap) was used to acquire the DWI images. A baseline ($b = 0$ *s/mm*², non diffusion-weighted) image and

Table 1. Aerobic Fitness Classifications per age and Gender. [*Males in the active group had significantly greater VO₂ peak values than males in the inactive group (1-Way ANOVA, $F(1,6) = 5.73, p = 0.05$). **Females in the active group had significantly greater VO₂ peak values than females in the inactive group (1-Way ANOVA, $F(1,5) = 14.51, p = 0.01$), the unit of VO₂ peak is ml/kg/min

Active Group (Age: 62.11 ± 2.57 yrs.)	Above Average	Means	(SD)
Males (n = 5)	VO ₂ peak ≥ 33	42.02	(7.8)*
Females (n = 4)	VO ₂ peak ≥ 26	29.25	(4.36)**
Inactive group (age: 72.33 ± 2.66 yrs.)	Below Average	Means	(SD)
Males (n = 3)	VO ₂ peak ≤ 32	30.83	(1.1)
Females (n = 3)	VO ₂ peak ≤ 25	17.6	(3.4)

21 directional DW images ($b = 1000 \text{ s/mm}^2$) were acquired (4 NEX) at an isotropic resolution of $2 \times 2 \times 2 \text{ mm}^3$

2.2. Preprocessing

The preprocessing procedure for our methodology consists of the following steps: DICOM to NRRD format conversion, DWI quality control, skull stripping and DTI computations. The dicom files were first converted into NRRD format¹ using DicomToNrrdConverter, which is a command line module in Slicer². DWI quality control was performed using DTIPrep [43]³, (see below for more detail). Skull stripping was then conducted using an atlas based tissue segmentation tool called ABC applied to both the baseline image and the isotropic diffusion weighted image⁴. The tensor images were then estimated using a weighted least squares method [44]. Finally, fractional anisotropy (FA), color coded FA and other property maps were computed straightforwardly from the tensors. DTI estimation and computation was conducted using the DTIPProcess toolkit⁵.

2.2.1. DWI Quality Control

Artifacts are common in DTI acquisitions. Signal changes produced by severe artifacts result in erroneous diffusion tensor values. Due to the inherent low signal to noise ratio (SNR) and relatively long scanning time of the multi-direction DWI acquisition, compared to common MRI modalities, DWI suffers from eddy-current, head motion and bed vibration artifacts. Even if the artifact in DWI is just a few pixels out of balance, they result in estimation errors of tensors and give confusing artifactual appearances in tensor-derived scalar maps and may result in bias throughout DTI analysis. Quality control procedures are of great importance for stable estimation of tensor fields. Currently, most of the quality control procedures are conducted manually by visually checking the DWI data set in a gradient by gradient and slice by slice method. The results often suffer from low

consistency across different data sets because of insufficient QC inter-rater reliability. Our DWI quality control methodology is fully automatic and provides a crucial piece for robust DTI analysis in our study that may reduce the manpower needed for large DTI studies. As far as we know, DTIPrep [43] is the first comprehensive preprocessing tool for DWI quality control with protocoling, reporting and data correction capabilities.

2.3. DTI Spatial Normalization

All the DT images were spatially normalized to acquire voxel-wise correspondence across all subjects for meaningful voxel-wise group comparison. DTI spatial normalization was composed of 2 steps. In the first step, we used an unbiased atlas computation method [45] based on nonlinear fluid deformation to initially create an unbiased DTI atlas. In this step, based on our previous work on DTI atlas building [46], we used intensity normalized FA images instead of the curvature of FA image [24] to avoid introducing any bias in subsequent group FA comparison analysis for registration process. Also, intensity normalized FA images outperform curvature FA image in terms of model generalization and specificity in atlas space [46]. The intensity normalized FA images were first smoothed using Gaussian kernel with $\sigma = 2 \text{ mm}$, which corresponds to the full width at a half maximum (FWHM) of 4.6. The atlas building procedure was initialized by an affine registration and followed by fluid-model based nonlinear registration of the intensity normalized FA image which is sensitive to the geometry of white matter, white matter/gray matter and white matter/cerebrospinal fluid (CSF) boundaries. Using the computed deformation field information, we warp each of the individual tensor images into the data specific unbiased space and compute the aligned DT images. After averaging these registered DT images, the first-step DTI atlas was created. Tensor warping and averaging were conducted in a Log-Euclidean space [47-49].

To further improve the voxel-wise correspondence quality, we conducted a second mapping step. In this step, we used the pair-wise diffeomorphic demons algorithm [50] to re-map each of the individual DT images to the unbiased atlas created in the first step. The demons algorithm was also initialized with an affine transformation. The DTI transformations were performed the same way as in the first step. After all the DT images were warped, the atlas was updated by averaging the newly warped DT images. In this step, we again used the intensity normalized FA as the driving property map. Fig. (1) shows the schematic view of our novel methodology of the unbiased atlas computation in the first step via applying fluid-based atlas building and the second step after using demons registration algorithm.

Both FA and color coded FA maps show very good smoothness and sharpness within white matter boundaries of the atlas. Structures in the brain stem and pyramidal system are well defined. Overall, visual assessment of the atlas images implies a good alignment among all the subjects. Fig. (2) shows the color coded FA maps of the unbiased atlas created in the first and second mapping step. For the atlas created in the first step, smoothness within most parts of white matter and sharpness at white matter boundaries are obtained, while in some white matter regions, noise-like

¹<http://teem.sourceforge.net/nrrd>

²<http://www.slicer.org>

³<http://www.nitrc.org/projects/dtiprep>

⁴<http://www.nitrc.org/projects/abc>

⁵<http://www.nitrc.org/projects/dtiprocess>

Caution should be used when extrapolating the clinical relevance of the results presented here in Fig. (4) and Fig. (6), as well as the differences between Fig. (4) and Fig. (6) since the small sample size has the potential to create unstable results and produce correction errors in the linear model.

3.2. Voxel Wise Correlation Analysis

Fig. (8) shows the voxel-wise Pearson correlations between FA and the corrected VO₂ peak values overlaid on a FA map in different views. Only the positive correlations are showed (red) for clarity. The correlation significance was also tested with the same wild bootstrap technique as for group testing. Significantly correlated ($p < 0.05$) voxels are displayed in violet. In most white matter regions, positive correlations can be seen as expected. Scattered significant voxel can also be seen, with significant correlations between FA and corrected VO₂ peak values in the genu, internal capsule and brain stem. As in the previous study, it is noteworthy that these results have been determined on a small sample and thus clinical interpretation should be performed cautiously.

Fig. (8). Voxel-wise correlations between FA values and corrected VO₂ peak values in the axial and sagittal views in inferior-superior and right-left orders. Positive correlations are shown in red. The significance map is shown in violet where corrected $p < 0.05$, WarmTint color mapping is used.

4. DISCUSSION

4.1. DTI Normalization and Unbiased Atlas Computing

Currently, DTI spatial normalization can be classified into 2 categories based on DTI properties driving the matching process: 1) scalar map based [51] and 2) whole tensor based methods. Scalar map based methods have been intensively investigated and well evaluated. These methods can be directly used to estimate the deformation field between DTI images. Whole tensor information based methods are relatively new and lack applications in clinical studies due to the Riemannian/non-Euclidean analysis space for tensors. The overall performances of both methods are comparable at image level, while the whole tensor based methods provide better local tensor corresponding where the orientation information is taken into account. With the development of tensor based registration methods, there is improved matching quality at both image and voxel levels. For spatial nor-

malization of group data sets, a well established brain atlas is used as a registration template. All the subjects are transformed into the atlas space and analyzed in that space.

The advantage is the results are presented in a familiar coordinate space to readers, thus it is easier to understand and interpret. The disadvantage is that the warped subjects are biased in shape to the template. Moreover, to map to a standard template, very large deformations may need to be estimated for some subjects, which is one of the major challenges the matching algorithms faces. Compared to a fixed template though, unbiased atlases uses the average space as the center of all the subjects in an unbiased fashion where the overall deformation is minimized. The method is limited in that any change in the data sets will result in a new atlas space. We propose a 2-step normalization strategy, first using the unbiased atlas computing method to build an unbiased atlas, then second, combining the pair-wise registration and average position optimization to enhance warping voxel-wise correspondence.

4.2. Voxel-Wise Analysis

Once all the subjects are transformed into atlas space, voxel-wise analysis can be easily conducted for any scalar maps. We presented the FA analysis results in this paper, but it can be applied for any other scalar maps such as MD, PD, RD, etc. Because we used a heteroscedastic linear model for statistical modeling in this paper, it is very easy to incorporate other factors as co-variants by defining a proper design matrix. This elderly fitness study focused on demonstrating the application of a new automated DTI analysis methodology rather than testing clinical hypotheses related to the fitness parameters. Despite the inherent statistical limitations of sample size and issues of age imbalance, application of this new methodology to this unique population provides some valuable results compared to previous related studies. In order to investigate the effects of fitness exercise on cerebral white matter integrity in older adults, Heo *et al.* [39] examined a one-year long aerobic training program and determined longitudinal differences in FA values in 70 older adults. They found that improved aerobic fitness is associated with superior white matter integrity specifically in the prefrontal and parietal brain regions. In our paper, while we observed different specific-region effects, we also found similar results with respect to the genu (prefrontal) and cerebrospinal tract (parietal). More related clinical results which corroborate our results can be found in Colcombe *et al.* [34, 61].

In line with our results, a multiple sclerosis study [35] found a positive association between fitness and the white matter integrity in the right anterior corona radiata. We found similar regions with respect to the cerebrospinal tract (right anterior corona radiata).

An important limitation of our study, as acknowledged before, is most of the group differences were eliminated when age and gender influences were taken into consideration. This may partially be due to the small sample size as well as the difference in mean age between the two groups. The average age for the inactive group was approximately 10 years older than active group. A larger sample size with less age disparity between groups may improve the ability to

detect significant group differences. Furthermore, we are aware of sensitivity limitation in voxel-wise analysis, as we have also observed in this study a null finding in the cingulum region whereas we found a significant correlation with regional analysis in previous work [38].

5. SUMMARY

In summary, we describe an automated methodology for voxel-wise group DTI analysis in an older adult population. This methodology is composed of automated preprocessing, normalization and hypothesis testing, which may also be suitable to run on large sample DTI data sets. Our results indicated the improved cardiovascular fitness is associated with mostly prefrontal and parietal brain regions.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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