# A preliminary study of DTI Fingerprinting on Stroke Analysis

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***Abstract*—DTI (Diffusion Tensor Imaging) is a well-known MRI (Magnetic Resonance Imaging) technique which provides useful structural information about human brain. However, the quantitative measurement to physiological variation of subtypes of ischemic stroke is not available. An automatically quantitative method for DTI analysis will enhance the DTI application in clinics. In this study, we proposed a DTI Fingerprinting technology to quantitatively analyze white matter tissue, which was applied in stroke classification. The TBSS (Tract Based Spatial Statistics) method was employed to generate mask automatically. To evaluate the clustering performance of the automatic method, lesion ROI (Region of Interest) is manually drawn on the DWI images as a reference. The results from the DTI Fingerprinting were compared with those obtained from the reference ROIs. It indicates that the DTI Fingerprinting could identify different states of ischemic stroke and has promising potential to provide a more comprehensive measure of the DTI data. Further development should be carried out to improve DTI Fingerprinting technology in clinics.**

## I. Introduction

DTI (Diffusion Tensor Imaging) is a remarkably valuable clinical MRI technology to measure the restricted diffusion of water in white matter tissue, in order to form fiber tract imaging [1]. One popular application of DTI in clinics is tract-specific localization of white matter lesion such as brain tumor [2-4]. Researchers also focus on the assessment of white matter in development, pathology and degeneration with DTI technology. Current quantitative analysis of DTI data is sensitive to the lesion location but not the physiological changes in nature. However, DTI images not only provide structural information but also contain physiological meanings [5]. Further development on the quantitative analysis of physiological characterization on DTI data will benefit both neuroscience research and clinical practice.

For DTI neural analysis, the measurements of diffusive anisotropy, such as FA (Fractional Anisotropy) and ADC (Apparent Diffusion Coefficient) have remained for over 20 years [6], being mainly restricted to low imaging resolution in a cross section and inaccurate qualitative spatial localization of fiber tracts. Moreover, the identification of hyperintense or hypointense areas on DTI images is not enough for explanation of disease evolving mechanism. On the other hand, tractography as another primary DTI application can only calculate the magnitude and orientation of the primary axis or vector rather than the full set of tensor properties of interest, which fails to provide quantitative indication of the severity of brain disease states. In 2013, Ma proposed MRF (Magnetic Resonance Fingerprinting) technology [7] permitting quantitatively detecting and analysis of complex signal changes that can represent physical alterations of a neural material or early indicators of disease. Inspired by this idea, non-invasive quantification of brain tissue on DTI could be promising to overcome the DTI existing limitations.

In current study, a new technology named DTI Fingerprinting, is proposed to identify the comprehensive physical and physiological features of stroke lesion. Instead of depending on pure recognition of diffusive anisotropy intensity contrast, successive acquisition of DTI data can be characterized by a certain pattern of the signal, which is a fingerprint of the DTI dataset. The fingerprint will be the unique identity for the specific brain tissue with different physiologies. Region of interest (ROI) in diffusion images from patients and normal controls were drawn manually and defined automatically (e.g. tract based spatial statistics, TBSS). The unique signal patterns corresponding to different neural tissues is the key assumption underlying the DTI Fingerprinting technology. The preliminary result in the present study demonstrates the promising potential of DTI Fingerprinting technology in quantification of neural physiology, which is beyond the spatial localization of most existing quantitative analysis methods of DTI data. It is evident that by the clustering process, such technology can assess neural physiological changes, which will assist clinical diagnosis with a comprehensive measure.

## II. Methodology

### A. Data acquisition and Preprocessing

Nineteen subjects (13 men and 6 women, mean age 49 ± 19 years) participated in the therapeutic trails were included in the current study. In these 19 subjects, there were eight healthy people (4 male and 4 female, mean age 31 ± 4 years), eight with fresh stroke lesion (6 male and 2 female, mean age 64 ± 15 years), and three with stroke sequela (3 male, mean age 58 ± 8 years). The diagnostic reports were issued by two neurologists in Peking University Shenzhen Hospital. All the

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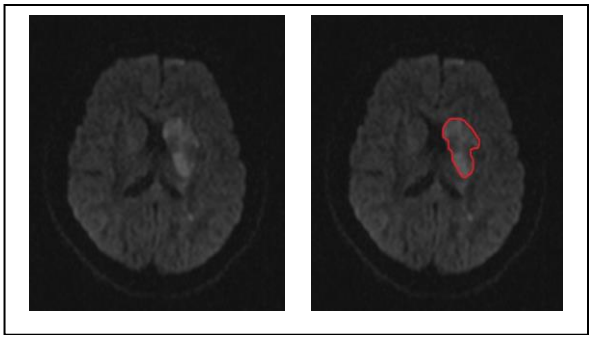

Figure 1. Manual ROI drawing of stroke lesion on DWI images. The stroke lesion was observed in the brain DWI image. A hand-drawing red region was marked on stroke lesion to obtain ROI fingerprints.

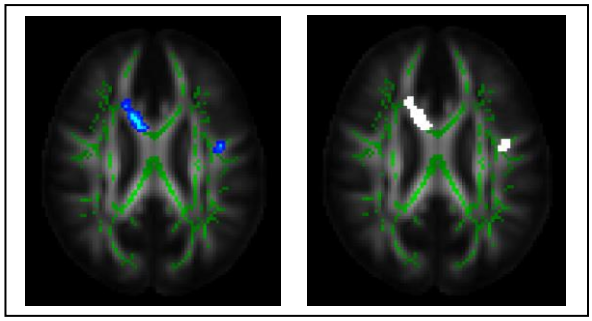

Figure 2. TBSS mask calculation on FA map by FSL software. Blue regions showed significantly decreased FA ($p<0.005$) in patients with stroke relative to normal controls. White regions showed the corresponding lesion mask. Green regions represented the mean FA skeleton.

subjects underwent MR imaging with 1.5T Siemens Sigma System (Siemens Medical Systems, Peking University Shenzhen Hospital). The typical MRI protocol consisted of fast T2-weighted sequence (TE=89ms, TR=4000ms, Flip Angle=150°, acquisition matrix=768×624, FOV=230×187 $mm^2$) and diffusion tensor imaging sequence (TE=88ms, TR=2700ms, Flip Angle=90°, acquisition matrix=256×256, FOV=250×250 $mm^2$, b0=1000 $s/mm^2$). Diffusion weighting was consist of 20 non-collinear directions, and a non-diffusion tensor image whose b0=0 $s/mm^2$. Nineteen axial sections of scanning in 5mm thickness without gap, covering the whole brain were obtained.

The DICOM data of 21 DWI images in each subject was imported into the SPM8 software (Welcome Trust Centre, UCL) for preprocessing. Images were realigned automatically and then normalized into the standard MNI (Montreal Neurological Institute) space. Meanwhile, the Gaussian filter of 3-fold voxel size was employed in order to improve SNR.

### *B. Manual ROI and TBSS Mask*

Acquisition of diffusion weighting signals from the infarct brain volume required accurate location. Therefore, ROIs of stroke lesion on DWI images were drawn independently by another neurologist blinded to clinical symptoms as shown in Figure 1, which was set as a reference for other automatic ROI definition. The signals from the normal control group were also selected manually in the high occurrence areas of infarct. The clear delineation of the landmarks on T2-weighed images facilitated correction by comparing the initial and follow-up images and justified the use of T2-weighed instead of DWI images for the final infarct location. For all manual ROIs, a mirror ROI placed in the contralateral regions was generated by software. Thus the ratio value between infarct areas and the mirror normal areas was obtained for all the subjects.

As an objective alternative to ROI delineation, which is time-consuming and labour-intensive, an automatic ROI definition method based on TBSS was proposed [8-10]. After obtaining all the participants' FA (Fractional Anisotropy) maps using DTIStudio software [11], TBSS analysis was performed using FMRIB software library (FSL 4.1.9; www.fmrib.ox.ac.uk/fsl) by the following procedures:

1) ICBM_DTI_81_FA which was developed by Mori et al. (2008) was used as the target image to transform FA images from different subjects to a standard space.

2) The mean of all aligned FA images was created and then fed into the FA skeletonisation program to create a skeletonized mean FA image. The FA value threshold was set at 0.2 to suppress areas of low mean FA and/or high intersubject variability.

3) Each participant's (aligned) FA image was projected onto the skeleton.

4) We carried out voxel-wise statistics between patients with stroke and healthy controls on the FA data in skeleton space.

The threshold was set at $p<0.005$ (uncorrected), thus we achieved the statistical result, as in Figure 2. According to the result image which represented the significantly reduction of FA value, a whole brain mask could be created by setting the intensity of active voxels intensity to 1, other areas to 0.

### *C. Measures for DTI Fingerprinting*

Since quantitative measurement of DTI fingerprints relied on accurate evaluation standard, a method of unsupervised learning was proposed to process image signals based on abnormal brain areas. To distinguish the severity of stroke, clustering recognition was applied on the nineteen subjects. By selecting the ratio values from manual ROIs and TBSS mask as clustering features, the feature dimensionality was determined according to the PCA (Principal Component Analysis) method. PCA used an orthogonal transformation to convert a set of ratio values into linearly uncorrelated principal components. In current study, 3 dimensionalities were reduced from 21 (20 gradient directions and 1 B0 image) by over 95 percent weighting of the total variance. The hierarchical merging algorithm was applied to get the final clustering results by use of an appropriate metric and a linkage criterion. We set Euclidean Distance and Cosine Distance as the measure of distance between pairs of fingerprints and single-linkage criterion which specified the dissimilarity of sets. The Euclidean distance was calculated as follows:

$$D_E = \sqrt{(\boldsymbol{x}_s - \boldsymbol{x}_t)(\boldsymbol{x}_s - \boldsymbol{x}_t)'} \quad (1)$$

where $\boldsymbol{x}_s$ and $\boldsymbol{x}_t$ are feature vectors of two subjects. The Cosine distance was calculated as follows:

$$D_C = 1 - \frac{x_s x_t'}{\sqrt{(x_s x_s')(x_t x_t')}} \quad (2)$$

The single-linkage criterion is defined as follows:

$$\min\{D(x_s, x_t) : x_s \in A, x_t \in B\} \quad (3)$$

where $x_s$ and $x_t$ are feature vectors from two clusters $A$ and $B$. $D$ is the metric of distance.

## III. Results

The results obtained from the 19 subjects were shown in Table 1. For each subject, the classification or final clustering pattern labels with different methods were presented in each column. The classification of clinical diagnosis was set as a reference in the first column. For the clinical reference, 1 represents the normal control; 2 represents the group with acute stroke lesion and 3 represents the group with stroke sequela. For manual ROI method, different numbers are different clustering labels. All the subjects in the normal control were clustered into one group. In addition, no subjects diagnosed with stroke were clustered into normal group. On the other hand, one normal participant (Subject 4) was clustered falsely to the stroke group for TBSS mask. Moreover, with Cosine Distance, 3 instances of stroke patients were grouped falsely (79% accuracy), and the accuracy with Euclidean Distance dropped to 63%.

TABLE I. CLUSTERING RESULT AND EVALUATION

| | C.R | Manual ROI | | TBSS mask | |
|---|---|---|---|---|---|
| | | *E.D* | *C.D* | *E.D* | *C.D* |
| Subject 1 | 1 | 1 | 1 | 1 | 1 |
| Subject 2 | 1 | 1 | 1 | 1 | 1 |
| Subject 3 | 1 | 1 | 1 | 1 | 1 |
| Subject 4 | 1 | 1 | 1 | 2 | 2 |
| Subject 5 | 1 | 1 | 1 | 1 | 1 |
| Subject 6 | 1 | 1 | 1 | 1 | 1 |
| Subject 7 | 1 | 1 | 1 | 1 | 1 |
| Subject 8 | 1 | 1 | 1 | 1 | 1 |
| Subject 9 | 2 | 2 | 2 | 3 | 2 |
| Subject10 | 2 | 2 | 2 | 4 | 2 |
| Subject11 | 2 | 2 | 2 | 5 | 3 |
| Subject12 | 3 | 3 | 3 | 4 | 4 |
| Subject13 | 2 | 4 | 2 | 4 | 2 |
| Subject14 | 2 | 2 | 2 | 6 | 3 |
| Subject15 | 2 | 2 | 2 | 4 | 2 |
| Subject16 | 3 | 3 | 3 | 6 | 2 |
| Subject17 | 2 | 2 | 2 | 1 | 1 |
| Subject18 | 2 | 2 | 2 | 4 | 2 |
| Subject19 | 3 | 3 | 3 | 7 | 4 |
| F value | | 0.97 | 1 | 0.71 | 0.78 |

C.R: Clinical Reference; E.D: Euclidean Distance; C.D: Cosine Distance.

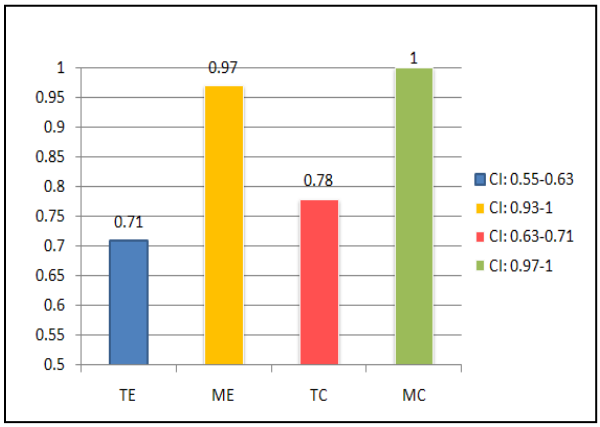


Figure 3. F score with two distances under Manual ROI and TBSS mask. TE: Euclidean distance using TBSS mask; ME: Euclidean Distance using manual ROI; TC: Cosine distance using TBSS mask; MC: Cosine Distance using manual ROI; CI: 95% confidence interval.

As for evaluation of the clustering results, F score was a common measurement to estimate how close the clustering was to the predetermined benchmark classes. It can be interpreted as a weighted average of the precision and recall, where F score reaches its best value at 1 and worst score at 0. Figure 3 demonstrated F score calculated under different situations. Comparing with the manual ROI method, the F scores with the TBSS method were over 20 percent lower. Besides, the F scores with Cosine Distance were 3 and 7 percent higher than those with Euclidean Distance for both manual ROI and TBSS mask, respectively.

## IV. Discussion

Current study proposed a DTI Fingerprinting technology to detect DWI pattern features, which is the first trial to search the inherent relation between DTI data and the brain features. Since DTI method allows an exploration of fiber tract integrity and orientation in the human brain [12-15], researchers generally focused on spatial detection of abnormal brain tissue using DTI [16-19]. In this study, the DTI Fingerprinting is proposed to measure diffusion weighting signal features quantitatively more than hyperintense area observation around brain lesion.

The result in the proposed study shows that such technology is promising in detecting brain diseases like stroke. By comparison with the clinical reference in Table 1, a perfect manual ROI/reference match for Cosine Distance is observed in all subjects (F score=1), validating DTI fingerprints for stroke lesion. In other words, the clustering of DTI fingerprints will coincide with the clinical reference when the acquisition of ROI is accurate. Most of all, the present study provides a possible identity of the brain abnormalities since the clustering result for manual ROI could identify the stroke sequelae out of the general stroke patients.

The advantage of the method using TBSS mask is automatically calculating the fingerprint areas quantitatively by statistical analysis [20, 21]. Although the F scores for TBSS mask are lower than those in manual ROI situation, the

clustering result is close to diagnosed classification, especially for Cosine Distance. Moreover, the clustering result with Cosine Distance is higher than that with Euclidean Distance, which coincides with the fact that Cosine Distance reflects more signal pattern information, while the Euclidean Distance contains more signal intensity information. Thus DTI Fingerprinting is able to provide a new angel for detection of brain abnormalities.

Although it is optimistic that DTI Fingerprinting with manual ROI acquisition performs well, the accuracy of clustering based on TBSS mask drops more than 20 percent than that of clinical reference. This result may be on account of FA misuse in TBSS. FA maps representing the orientation and anisotropy of the fiber tract in white matter, may not reflect the signal evolving features of brain lesions. Therefore, the TBSS mask based on FA probably fails to locate total area of the disturbed tissue. Future work should concentrate on developing mask generation in an automatic statistic method. Another factor that possibly limits the accuracy of clustering is the unpaired ages between the normal control and the patient group. The result will be more objective when avoiding interference from subjects. In conclusion, this preliminary study indicates the potential of DTI Fingerprinting to classify brain abnormalities, and provides a more comprehensive measure of DTI data.

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## REFERENCES

[1] Basser P J, Mattiello J, LeBihan D. "MR diffusion tensor spectroscopy and imaging," Biophysical journal, vol. 66, pp. 259-267, 1994.

[2] C. B. Grandin, T. P. Duprez, Anne M. Smith, et al. "Usefulness of Magnetic Resonance–Derived Quantitative Measurements of Cerebral Blood Flow and Volume in Prediction of Infarct Growth in Hyperacute Stroke," Stroke, vol. 32, pp. 1147-1153, 2001.

[3] Rosalia D.A., Manuel G, Marina F. A., et al. "Structural Integrity of the Contralesional Hemisphere Predicts Cognitive Impairment in Ischemic Stroke at Three Months," PLOS ONE, vol. 9, 2014.

[4] Ming Yang, Ya-ru Yang, Hui-jun Li, et al. "Fully Automated Detection of Corticospinal Tract Damage in Chronic Stroke Patients," Computational and Mathematical Methods in Medicine, Article ID 370849, 2014.

[5] Basser P J. "Inferring microstructural features and the physiological state of tissues from diffusion‐weighted images," NMR in Biomedicine, vol. 8: pp. 333-344, 1995.

[6] Tonya White, A. T. K. Kendi, et al. "Disruption of hippocampal connectivity in children and adolescents with schizophrenia — A voxel-based diffusion tensor imaging study," Schizophrenia Research, vol. 90, pp. 302–307, 2007.

[7] Dan Ma, V. Gulani, N. Seiberlich, K. Liu, J. L. Duerk and M. A. Griswold. "Magnetic Resonance Fingerprinting," Nature 495, 187192, 2013.

[8] D. Yin, X. Yan, M. Fan, et al. "Secondary Degeneration Detected by Combining VBM and TBSS in Subcortical Strokes with Different Outcomes in Hand Function," Published as 10.3174/ajnr.A3410, Feb. 2013.

[9] Giuliani NR, Calhoun VD, Pearlson GD, et al. "Voxel-based morphometry versus region of interest: a comparison of two methods for analyzing gray matter differences in schizophrenia," Schizophrenia Research, vol. 74, pp. 135–47, May 2005.

[10] Smith SM, Jenkinson M, Johansen-Berg H, et al. "Tract-based spatial statistics: voxelwise analysis of multi-subject diffusion data," NeuroImage, vol. 31, pp. 1487–1505, 2006

[11] Hangyi Jiang, Peter C.M., Jinsuh Kim, et al. "DtiStudio: Resource program for diffusion tensor computation and fiber bundle tracking," Computer Methods and Programs in Biomedicine, vol. 81, pp. 106–116, 2006.

[12] Yaniv Assaf, Ofer Pasternak, "Diffusion Tensor Imaging (DTI)-based White Matter Mapping in Brain Research: A Review," Journal of Molecular Neuroscience, vol. 34, pp.51–61, Jan. 2008.

[13] Hao Huang, Jiangyang Zhang, Peter C.M. van Zijl and Susumu Mori, "Analysis of noise effects on DTI-based tractography using the brute-force and multi-ROI approach," Magnetic Resonance in Medicine, vol. 52, pp. 559–565, Sept. 2004.

[14] M Møller, J Frandsen, G Andersen, et al. "Dynamic changes in corticospinal tracts after stroke detected by fibretracking," J Neurol Neurosurg Psychiatry, vol. 78, pp. 587–592, 2007.

[15] Quan Jiang, Zheng Gang Zhang, Guang Liang Ding, et al. "MRI detects white matter reorganization after neural progenitor cell treatment of stroke," NeuroImage, vol. 32, pp. 1080–1089, Sept. 2006.

[16] K. Brockmann, J. Finsterbusch, U. Schara, et al. "Stroke-like pattern in DTI and MRS of childhood mitochondrial leukoencephalopathy," Neuroradiology, vol. 46, pp. 267–271, April 2004.

[17] David J Werring, A. T Toosy, C. A Clark, et al. "Diffusion tensor imaging can detect and quantify corticospinal tract degeneration after stroke," Journal of Neurol Neurosurg Psychiatry, vol. 69, pp. 269–272, 2000.

[18] M. Urbanski, M. T. Schotten, S. Rodrigo, et al. "DTI-MR tractography of white matter damage in stroke patients with neglect," Experimental Brain Research, vol. 208, pp. 491–505, Feb. 2011.

[19] T. Wessels, C. Wessels, A. Ellsiepen, et al. "Contribution of Diffusion-Weighted Imaging in Determination of Stroke Etiology," AJNR, vol. 27, pp. 35–39, Jan. 2006.

[20] Sung Ho Jang, Sang-Hyun Cho, Yun-Hee Kim, et al. "Diffusion anisotrophy in the early stages of stroke can predict motor outcome," Restorative Neurology and Neuroscience, vol. 23, pp. 11–17, 2005.

[21] Qing Yang, Brian M. Tress, P. Alan Barber, et al. "Serial Study of Apparent Diffusion Coefficient and Anisotropy in Patients with Acute Stroke," Stroke, vol. 30, pp. 2382–2390, 1999.