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A comparison of DTI pre-processing tools on a dataset of chronic subcortical stroke rehabilitation patients

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***Abstract*— In this paper, we compared the performance of a number of Diffusion Tensor Imaging (DTI) pre-processing tools on a dataset of chronic subcortical stroke patients during rehabilitation exercise. In the comparison, acquired Diffusion-Weighted Images (DWI) are pre-processed by different pipelines, which compose of different DTI pre-processing tools, independently. And a DTI measure, FA (fractional anisotropy), is derived from each processed image. Then, a group-based DTI tractography analysis tool, Tract-Based Spatial Statistics (TBSS), is used to localize brain changes in white matter that correlate to the behavior changes during stroke rehabilitation. Although the ground-truth of the dataset is unavailable, it can be observed that there exist significant variations in the obtained hot spot maps that come with different DTI pre-processing pipelines. It suggests that the imaging technicians and scientists should choose the tools carefully according to the acquisition methods and parameters.**

I. INTRODUCTION

During last two decades, Diffusion Tensor Imaging (DTI) technique has been widely used to understand and track brain recovery after stroke [1], [2] as it provides an unique capability of detecting adaptive changes of structural connectivity in brain. Especially, micro-architectural changes of the white matter and neuronal fiber bundles that relate to motor system is the major focus in the studies. However, DTI images are always suffering from eddy current induced distortion and subject movement during image acquisition process. Removing or at least reducing the impact of the distortions to an acceptable level, is vital to the reliability of the analysis results, so many techniques have been developed [3], [4], [5].

Recently, a new type of distortion, CSF-contamination, has drawn attention from researchers [6], [7], [8]. In previous DTI distortion correction techniques, the diffusion displacement profile in each voxel has been approximately described by a Gaussian function. However, the approximation may bring mismatches between non-gradient and gradient volumes in CSF-grey matter boundary regions, especially in high b-value (bval $> 1000 s \cdot mm^{-2}$) DTI images. An extrapolation-based correction technique has been proposed by Nilsson *et al* [8] to remove the impact of the distortion. Instead of registering each gradient volumes to the non-gradient reference image like most conventional techniques doing, in the technique the correction is performed by registering each gradient volume to a middle image that are extrapolated from the non-gradient reference image. In [8], Nilsson *et al* also compared their technique with a conventional one [9] on a dataset of DTI images acquired using high b-value imaging protocol (up to bval = $2750 s \cdot mm^{-2}$) on a number of PDD patents. It showed that using extrapolation-based correction technique it generated quite different DTI measures compare to the conventional ones, which are FSL's eddy_correct [10] and eddy [11]. However, as ground truth is almost impossible to obtain for real-world clinical data, it is difficult to make a solid judgment in the comparison on which technique has a better performance.

In this paper, we further investigate the performance of extrapolation-based distortion correction technique on a dataset of chronic subcortical stroke patients during rehabilitation exercise. The MRI images were acquired using quite commonly used protocols. Two widely used techniques, FSL's eddy_correct [10] and the DTI pre-processing pipeline of VISTASOFT's MrDiffusion [12], are used in the comparison as counterparts. In this paper they are denoted by EC and MD, respectively. As Nilsson's extrapolation-based distortion correction technique can be used together with other DTI distortion correction algorithms, it is combined with the DTI pre-processing pipeline of VISTASOFT's MrDiffusion in this work. The motion artifacts, eddy-current and EPI distortion can be firstly processed by MrDiffusion's pipeline, then extrapolation-based distortion correction technique is used to further remove motion artifacts by introducing CSF-contamination distortion correction. The third pipeline is denoted as MD+EB.

In the comparison, the DTI images are first pre-processed by the three pipelines independently. Then, the distortion-corrected images are converted into DTI measures by FSL's dtifit tool [10], including Fractional Anisotropy (FA), Mean Diffusivity (MD), etc. After that, FSL's Tract-Based Spatial Statistics (TBSS) group analysis tool [13] is applied on the FA images of each pre-processed dataset to localise the brain changes related to the changes of the patients' behaviours scores, Fugl-Meyer Assessment (FMA) [14], during stroke rehabilitation.

II. MATERIALS AND METHODS

A. Subjects

The study was approved by the Domain Specific Review Board (DSRB) of the National Healthcare Group, Singapore (Clinical Trial Registration-URL: http://www.clinicaltrials.gov. Unique identifier: NCT01897025). Eighteen subjects (54.1±10.8 years old, 5

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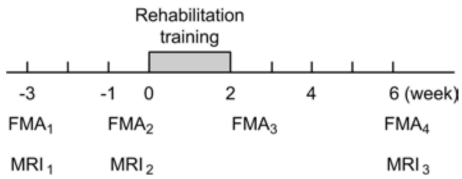

Fig. 1. Timeline of motor function assessments and MRI scanning.

female), who had their first ever subcortical stroke more than 9 months ago, that led to unilateral impairment of upper extremity, were recruited with written informed consent. They went through motor function and corticospinal excitability assessments, study interventions and MRI scanning following the timeline shown in Fig. 1. Among the eighteen subjects, one subject failed his/her first MRI scan, so totally 53 DTI scans and the correspondent FMA scores were used in the comparison. In addition, 11 healthy subjects (57.2±5.0 years old, 5 female) were recruited as control. Two MRI scans (3 weeks apart) were conducted in the healthy control group.

B. *Motor function assessment*

For stroke subjects, motor function of the affected arm was evaluated by the upper extremity component of the FMA at the initial screening, 1 week prior to, immediately after and 4 weeks after the training (Fig. 1).

C. *MRI acquisition*

MRI scanning was conducted on a 3T scanner (Siemens, Germany) with a 32 channel head array coil. DTI data were acquired with spin-echo EPI of 61 diffusion sensitizing directions and 7 non-diffusion (B0) volumes, bval=1000$s \cdot mm^{-2}$, TR=8000ms, TE=87ms, and 2.3mm isotropic resolution. This is a quite commonly used DTI imaging protocol that is not fall in "high b-value" region. T1-weighted images were acquired with a magnetization prepared rapid gradient-echo (MPRAGE) sequence in the sagittal view with TI=900ms, TR=1900ms, TE=2.5ms, and voxel size=1mm isotropic. T2-weighted images were acquired with fluid-attenuated inversion recovery (FLAIR) sequence in the coronal view with TR=9320ms, TE=82ms, and voxel size=0.9x0.9x3mm^3. Stroke lesion masks were manually labelled based on T2-FLAIR images by a radiological expert.

D. *MRI image processing*

The brain extraction for DTI, T1-weighted and T2-weighted images were conducted by FSL's bet tool [10] with manual adjustment. For each patient subject, the lesion masks were casted from T2-FLAIR image into T1-weighted image by FSL's linear registration tool (FLIRT), then into DTI non-gradient reference image by ANTS' non-linear registration tool [15] to reduce the impact of EPI distortion in DTI images. In EC pipeline, the reference image is the first B0 volume, and in MD and MD+EB pipelines, it is the "average" of all 7 B0 volumes. The lesion masks on DTI images were used in TBSS analysis to exclude the impact of lesion when registering with the target image and the displaying of final analysis results. For subjects with lesion on the left hemisphere, images were flipped along the midline so that the lesion appeared on the right hemisphere for all subjects.

E. *DTI pre-processing*

Default parameter settings and linear interpolation were used in EC and MD pre-processing pipelines, as well as the MD part of MD+EB pipeline. In EB part of MD+EB pipeline, FSL's FLIRT tool was used to match each gradient image with its correspondent extrapolated reference image with default parameter settings and linear interpolation. Then the B-matrix is rotated by the linear registration result. It worth pointing out that only DWI images are used as input in EC pipeline, while MD and MD+EB pipelines use both DWI and T1-weighted images as input, and alignment was conduct between them. The functionalities of the three pipelines are summarized in Table I.

TABLE I
FUNCTIONALITIES OF THE DTI PRE-PROCESSING PIPELINES.

	EC	MD	MD+EB
Motion distortion correction	yes	yes	yes
Eddy current distortion correction	yes	yes	yes
B-matrix rotation	no	yes	yes
CSF-contamination correction	no	no	yes

F. *DTI TBSS analysis*

FSL's TBSS pipeline was modified as shown in Fig. 2. In order to remove the impact of stroke lesion in registration, the target FA image was extracted from healthy control group. When conducting registration from subjects's (stroke rehabilitation patients) FA image to the target, subjects' lesion regions were excluded in the registration mask. Visual inspection of each subject's registered FA image in all three pipelines revealed no noticeable misalignment.

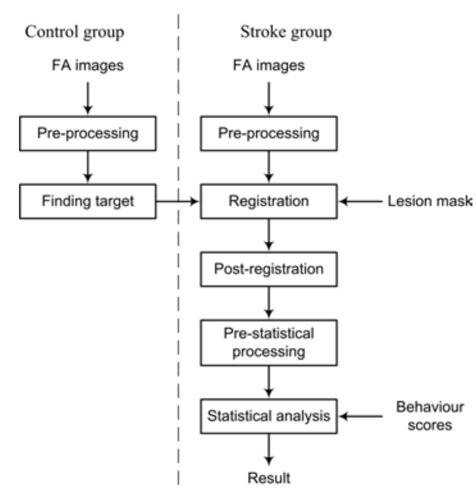

Fig. 2. Flowchart of the modified TBSS analysis.

FSL's "randomise" tool [16] with demeaning option was used to find the correlation between the DTI FA images and the FMA scores. Both Threshold-Free Cluster Enhancement (TFCE) correction [10] and False Discovery Rate (FDR) theory [17] are applied to correct the statistical analysis results. TFCE correction is conducted together with "randomise" permutation interference. Then, FSL's FDR tool is applied to further adjust the TFCE-corrected results. Default parameter settings and linear interpolation were used in dtifit and TBSS pipelines, except a new threshold value of 0.15 instead of the default 0.2 is used in "tbss_4_prestats" when conducting the projection of all subjects' FA data onto the mean FA skeleton. This is to include more micro-structure details of FA image in the analysis. And it worth to emphasis that exactly same TBSS pipeline and parameters are used to analyze the three datasets that pre-processed by EC, MD and MD+EB pipelines, respectively.

III. Results

Figure 3 shows some TBSS statistical analysis results ($p < 0.05$) on the same dataset but pre-processed by different pipelines. The whole 3D t-test statistics image overlapped with mean FA can be found in the supplementary for better observation. The images were generated using FSL's visualization tools, and the regions that falling into lesion areas were removed. The foreground color voxels are the estimated regions that have high correlation with subjects' behaviour scores. Yellow color indicates higher correlation and red is comparatively lower. The background gray scale image is the mean FA images of all patient subjects.

First of all, it can be observed that the mean FA image are quite different among them. Because of the variation exist in the DTI images that pre-processed by different pipelines, different target FA image were obtained from healthy control group in TBSS. And the variation are amplified during registration process. Among the three mean FA images, EC image contains more sparks. And comparing MD with MD+EB, the mean FA image of MD+EB is sharper, which indirectly suggests MD+EB has a better performance.

Second, the estimated behaviour-score-correlated regions are very different, although some similar regions can be found on some major tracts, such as forceps minor and contralesional corticospinal tract. This suggests patients tend to use the contralesional motor cortex to fulfill movement functions and it is not desired for stroke rehabilitation process. However, a strong correlation in ipsilesional corticospinal tract, which lead to ipsilesional primary motor cortex can be seen in EC, but no such observation can be found in MD and MD+EB (Fig. 3(d)). In frontal lobe, activated regions lead to somatosensory cortex can be found in EC result on both hemispheres. While in MD and MD+ED longer activated regions can be found in ipsilesional hemisphere. In contralesional hemisphere, a small activated region can be seen in MD result, but no such activation can be observed in MD+EB (Fig. 3(a)(b)). Moreover, a large high-correlated region can be found in MD in ipsilesional middle front gyrus, but cannot be seen in EC and MD+EB (Fig. 3(c)). In Parietal lobe, EC result shows hot spots lead to visual cortex in both hemispheres, but no strong correlation can be found in MD and MD+EB results. Obviously, quite different conclusions can be drawn from these statistical analysis results, which are based on same dataset with different pre-processing pipelines. This brings confusion to the stroke rehabilitation experts.

IV. Conclusions

In this paper, we investigate the performance of extrapolation-based distortion correction technique on a dataset of chronic subcortical stroke patients during rehabilitation exercise. The extrapolation-based distortion correction technique is combined with VISTASOFT's MrDiffusion pipeline, and compared with FSL's eddy tool and VISTASOFT's MrDiffusion pipeline. It shows that the combined pipeline shows better pre-processing result. Further statistical analysis of the pre-processed data using FSL TBSS tool displays very different results. This shows how important the pre-processing pipeline is. It suggests that the imaging technicians and scientists should choose the pre-processing tools carefully according to the acquisition methods and parameters.

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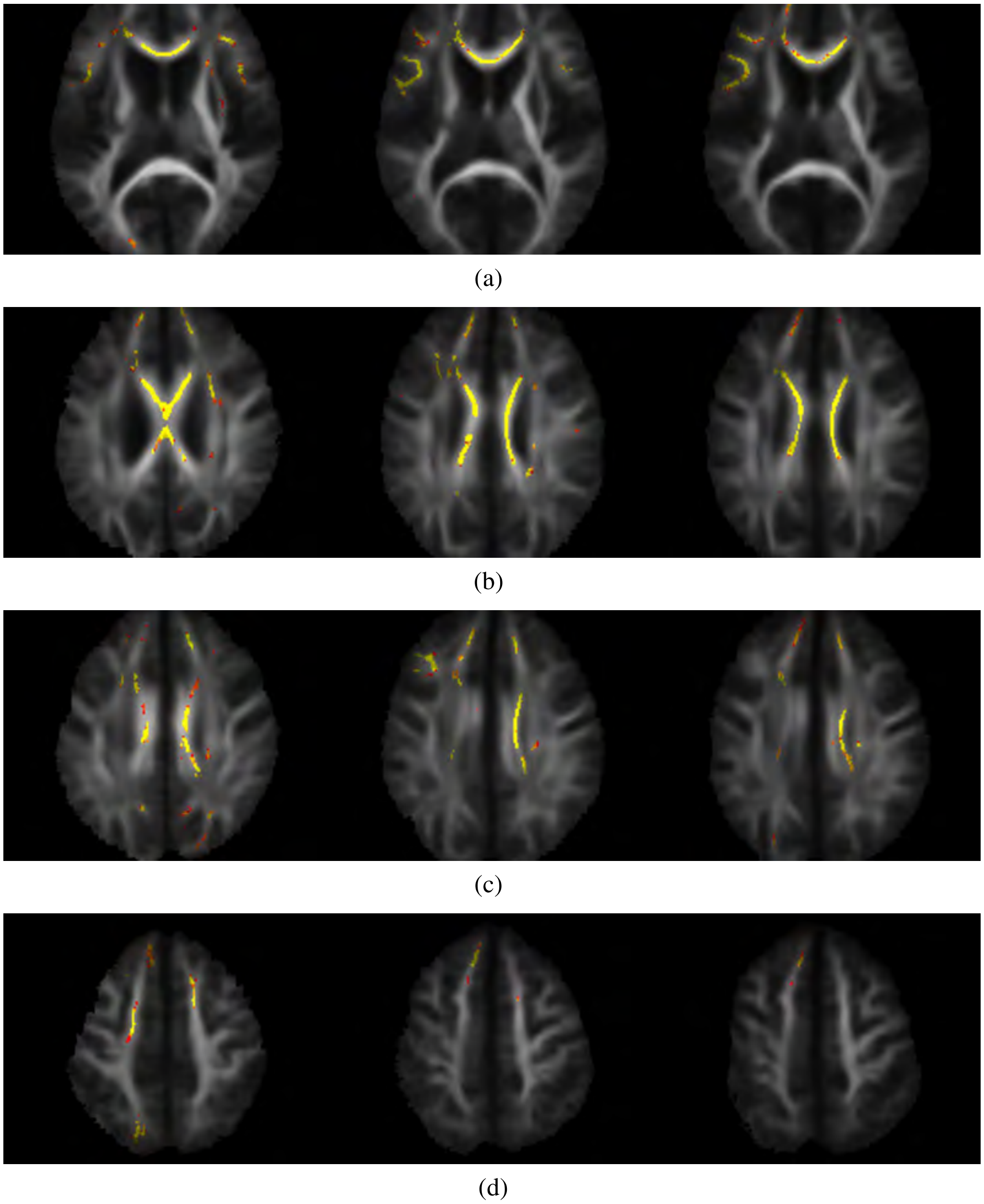

Fig. 3. Detailed TBSS analysis results using different pre-processing pipelines: From left to right are EC, MD, and MD+EB.

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