Automated Pipeline for Brain ROI Analysis with Results Comparable to Previous Freehand Measures in Clinical Settings

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Abstract—**Diffusion tensor imaging (DTI) has become a relatively common MR imaging technique in only 10 years. DTI can provide important information of brain microstructure *in vivo*. Many quantitative DTI analysis methods utilize either region of interest (ROI) or voxel-wise whole-brain methods. ROI methods do not require potentially bias-inducing image data altering, e.g., resampling and smoothing, and are the preferred method in clinical settings. We present an automated pipeline for quantitative ROI analysis of brain DTI data. The pipeline includes pre-processing, registrations, and calculation of mean (and SD) DTI scalar values from the automated ROIs. In addition to atlas regions, the pipeline accepts freehand ROIs, as long as the frame of reference is also provided. By the uniquely designed pipeline, we ensure that the results can be retrospectively compared to previously conducted manual freehand ROI measurement results, if desired. We validated the feasibility of the pipeline by comparing manual freehand ROI measurement results from 40 subjects against the results obtained from automated ROIs. A single set of freehand ROIs (drawn similarly to the original freehand manual ROIs in the population) was input to the pipeline, and the resulting scalar values from the automated ROIs were compared to the manual freehand ROIs' data. Adopting a limit for goodness of fit of z = ± 1.6 resulted in 94 % success rate for the pipeline's automated ROI registrations in the whole population. The pipeline can reduce the time taken in clinical ROI measurements.**

Keywords— **DTI, image analysis, pipeline, atlas, ROI**

I. Introduction

The amount of research focusing on the use of diffusion tensor imaging (DTI) has rapidly increased since the beginning of the 21st century. DTI has the potential to noninvasively quantify water diffusion in microscopic structures, essentially providing a method for observing changes in the neural network [1]. A potentially unlimited set of scalars can be calculated from the obtained diffusion tensor data, but currently the most used diffusion scalars are fractional anisotropy (FA) and mean diffusivity (MD), with the more recent addition of axial diffusivity (AD) and radial diffusivity (RD). These scalars can be more or less linked to certain pathologies (e.g. demyelination or axonal degeneration), but especially the interpretation of AD and RD is still slightly debatable [1, 2].

Most common methods used in quantitative analysis of diffusion images are region of interest (ROI), tractography, and voxel-wise whole-brain analysis [3]. Each method has its flaws; ROI method is susceptible to intra- and inter-observer variability, tractography is slightly unreliable and hard to delineate, whereas whole-brain methods rely on image registration and smoothing, a potential source of bias [4, 5].

Various procedures have been suggested to overcome these problems, such as atlas-based ROI analyses, and tract-based spatial statistics for whole-brain approach. Atlas-based image analysis has been successfully applied as an alternative to manual ROI studies [6–8], but the results of these analyses are not comparable to previously conducted manual ROI studies due to the shape differences of the ROIs themselves. Additionally, registration to a standard template may introduce a bias to the atlas-based ROI analyses.

The purpose of this study is to create an automated ROI analysis pipeline, which can produce quantitative ROI data comparable to previously conducted manual freehand ROI measurements. In addition, the pipeline is capable to utilize atlas-based ROIs, which can be of clinical use after a solid normal value database has been established for the atlas regions.

Additionally, we aim to validate the compatibility of the method with manual freehand ROI measurement results by comparing quantitative DTI metric values between the manual freehand and automated ROIs.

II. Materials and Methods

A. Pipeline

The pipeline created for the analysis can be fully automated from the pre-processing step to the extraction of quantitative diffusion metrics. Only minimal user involvement is required in the process, and the most important measure is to visually inspect the accuracy of the automated ROIs. The statistical analysis process can be altered, and a multitude of

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analyses can be performed based on the extracted quantitative image data. The pipeline uses tools included in FSL [9, 10] for pre-processing, registration, and the extraction of quantitative metrics from the ROIs.

We executed the automated ROI analysis by using a single set of manual freehand ROIs. The manual ROIs and the FA map (frame of reference) were fed to the pipeline. We used the control subject pool (n = 40) as the data to be analyzed, and no patient subject was chosen in the analysis for the validation process.

Pre-processing: First the control subject image data were corrected for eddy currents and minor head movements, and a brain mask was created to remove any non-brain tissue from the data. After brain masking, the scalar diffusion data was calculated from the tensor data. After the pre-processing steps, the diffusion metric data (FA, MD, AD and RD maps) is ready for the analysis.

Regions of Interest: The set of ROIs used in our research were manually drawn on the JHU-DTI-SS "Eve" atlas [8] FA map, which was first resampled to the spatial resolution of the acquired control DTI data to simulate the original manual freehand ROI drawing process. The drawn manual freehand ROIs were converted back to the original space of the high resolution JHU FA map by inverse transformation. The ROIs used in the validation were: the genu of the corpus callosum (CC_g), the splenium of the corpus callosum (CC_s), the cerebral peduncle (CP), the posterior limb of internal capsule (PLIC), the corona radiata (CR), the centrum semiovale (CS), the uncinate fasciculus (UF), the forceps minor (FM), and the thalamus. Examples of the ROIs are shown in Fig. 1. Due to image slice orientations, identical ROI regions are not visible on subject 1 and the JHU FA map. Also, the atlas ROIs differ substantially from the freehand based automated ROIs.

All of the manual ROIs were drawn by the same person (U.H.) in order to minimize ROI variability.

Registration: In order to extract values from each individual subject, the manual freehand ROI set was transferred to each subject's native space. First, the frame of reference was linearly registered (FLIRT [11]) to each subject, followed by a nonlinear transformation (FNIRT [12]). The affine registration matrices and the nonlinear registration warp fields were saved for each subject, which were then applied to the ROIs. This effectively placed the ROIs in the desired locations for each individual subject.

In order to improve the ROI accuracy, trilinear interpolation was used in the transformations (instead of nearest-neighbour interpolation often used in ROI registrations). The registered ROIs were then transformed back into binary masks by thresholding them at > 0.15, which produced good results based on visual evaluation (i.e. good accuracy, no overlapping, or too small ROIs). The threshold may differ depending on the used ROIs.

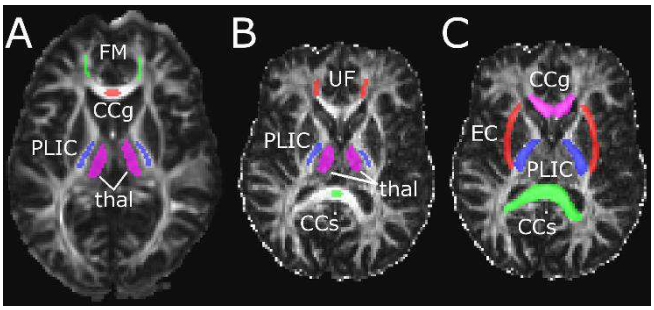

Fig. 1 A: Manual freehand ROIs drawn by U.H. on the JHU-DTI-SS FA map: FM (green), CC_g (red), PLIC (blue), thalamus (magenta). B: Corresponding slice of subject 1 with automated ROIs: UF (red), PLIC (blue), thalamus (magenta), CC_s (green). C: Same slice of subject 1 with automated atlas ROIs: CC_g (magenta), external capsule (red, EC), PLIC (blue), CC_s (green).

Quantitative Analysis: Once the ROIs were transferred to the subjects' space, quantitative DTI metrics were derived from the automated ROIs. Mean FA, MD, RD, and AD values along with standard deviations were calculated for each ROI, for each subject.

The extracted quantitative data can be fed to a statistical software of choice. For research and method validation purposes we collected FA data in a table to compare it with the freehand ROI data collected by U.H.

B. Validation

In order to validate the feasibility of the automated registration step, we compared the automated ROI data obtained through our pipeline to that of the manual freehand ROI measurements. The ROIs' congruency was validated by comparing the manual freehand ROI mean FA values against the pipeline's automated ROI mean FA values. In addition, we tested the difference between the automated ROIs and the manual freehand ROIs by z-scores and a two-tailed t-test. Assuming the ROI voxel values are normally distributed is debatable, but due to the representation of the results, a Mann-Whitney U test could not be performed. The resulting p-value from the t-test is thus only an approximate indication of the possible statistically significant difference.

C. Imaging Data

The DTI data used in the validation of our pipeline consisted of 40 control subjects imaged in the Tampere University Hospital. The subjects were originally gathered as a control group for the Tampere Traumatic Head and Brain Injury Study between August 2010 and July 2012.

Head MRI was done with a 3 Tesla MRI scanner, using a 12-channel head matrix coil. The DTI data were collected by a single-shot, spin echo-based and diffusion-weighted echo

planar imaging sequence. The parameters for the DTI sequence were TR 5144 ms, TE 92 ms, field of view 230 mm, matrix 128 × 128, 3 averages, slice/gap 3.0/0.9 mm, voxel dimension of 1.8 × 1.8 × 3.0 mm, and two b-factors: 0 and 1000 s/mm2 with 20 diffusion gradient orientations.

Conventional MRI findings of the control subjects were interpreted as normal.

III. Results

The described pipeline was applied to the control subject pool, and the utilization value of the pipeline was evaluated with respect to automated ROI compatibility with manual freehand ROI measurements. Additionally, the pipeline was executed with atlas ROIs, but the obtained quantitative data could not be plausibly validated.

A. Freehand ROI

The manual freehand ROIs drawn by U.H. to the low resolution JHU-DTI-SS FA map were transformed to the native resolution of the atlas, and the FA map and the ROIs were then used to run the described pipeline.

We visually inspected the automated ROIs and altered the pipeline parameters iteratively in order to gain adequate registration results for the current dataset. Mean and SD values were then extracted from the ROIs and saved to a table for comparison. Due to the large amount of data, we chose four example subjects to be reported in the paper. The registration validation data for FA of the four subjects is shown in Table 1.

We compared the subjects' automated ROIs' mean FA values, and used z-scores and a statistical t-test to evaluate the accuracy of the pipeline. The SD values used in the calculations were taken from the manual freehand ROIs. We adapted a z-score of 1.6 as a limit for significant difference. Z-values over 1.6 are highlighted with an asterisk in the table, along with p-values less than 0.05, but the significance of the t-test is slightly questionable. The ROIs with best correspondence were the PLIC (mean absolute difference in the population 2.9 %) and CC_s (mean absolute difference in the population 3.9 %). The ROIs with the poorest correspondence were the CP (mean absolute difference in the population 9.5 %) and the CR (mean absolute difference in the population 9.2 %). Of all the ROIs (n=360), a total of 338 had FA values within the limit of $-1.6 < z < 1.6$, which can be considered as a 94 % success rate of the registration. The mean absolute difference in FA across all ROIs and subjects was 6.6 %, and the mean absolute z-value was 0.581.

Table 1 Manual freehand ROI vs. pipeline's automated ROI comparison for FA values. Manual freehand ROI values are considered as reference.

	Subject 1	Subject 2	Subject 3	Subject 4
Age	32	56	22	39
CC genu				
Difference (rel, %)	-5,0	-2,9	-1,1	1,8
Z-value	-0,793	-0,336	-0,218	0,165
P-value	0,020*	0,544	0,534	0,513
CC splenium				
Difference (rel, %)	-2.6	2,4	-8,1	2,7
Z-value	-0,338	0,325	-1,154	0,694
P-value	0,363	0,334	0,001*	0,152
Cerebral peduncle				
Difference (rel, %)	-0,4	-11,2	-0,7	-5,1
Z-value	-0,040	-1,740*	-0,095	-0,415
P-value	0,883	0,001*	0,808	0,160
Corona radiata				
Difference (rel, %)	28,6	3,9	23,9	7,4
Z-value	1,975*	0,261	1,764*	0,387
P-value	< 0,001*	0,092	< 0,001*	0,016*
Centrum semiovale				
Difference (rel, %)	0,3	-4,8	0,1	0,5
Z-value	0,019	-0,276	0,004	0,028
P-value	0,868	0,058	0,974	0,826
Forceps minor				
Difference (rel, %)	-1,5	4,7	-20,6	6,2
Z-value	-0,081	0,233	-1,508	0,276
P-value	0,787	0,546	< 0,001*	0,331
PLIC				
Difference (rel, %)	7,6	-1,7	2,4	4,0
Z-value	0,607	-0,162	0,173	0,364
P-value	0,001*	0,375	0,320	0,053
Thalamus				
Difference (rel, %)	-1,3	-2,4	-6,0	-2,5
Z-value	-0,046	-0,089	-0,238	-0,109
P-value	0,677	0,447	0,046*	0,405
Uncinate fasciculus				
Difference (rel, %)	-14,2	6,1	2,4	-0,2
Z-value	-1,054	0,335	0,122	-0,013
P-value	< 0,001*	0,214	0,574	0,957

*) Significant difference.

B. Atlas Based

In addition to the freehand ROIs, we ran the pipeline using the ICBM-DTI-81 white matter atlas regions. While it is not possible to straightforwardly validate the registration and

DTI metric accuracy of the atlas regions, we visually verified the registration accuracy, and reviewed the standard deviation of each atlas region ROI. We compared the atlas ROIs' deviation against the manual freehand ROIs' SD. The mean SD for all the automated atlas FA ROIs was 28.1 %, whereas the automated freehand ROIs had a mean SD of 13.8 %.

IV. Discussion

Though the pipeline is configured for both manual freehand ROI and atlas usage, further validation and mirroring to previous measurements needs to be done prior to clinical use in both cases. An alternative clinical application could be use of the registration step to speed up freehand ROI drawing. Due to the accuracy of the automated ROIs with respect to the manual freehand ROIs, the registration step alone could save a considerable amount of time in clinical ROI measurements.

While the registration seems reasonably accurate, alternative methods should be studied in the future. Especially in pathologic cases, the lowered FA values may confound the registration. Tensor based registration (DTI-TK) might improve the accuracy of the pipeline with DTI data [13]. The registration accuracy should also be validated through the ROIs themselves in the future, e.g., by overlap percentage or other segmentation comparison metrics.

The high SD obtained from the atlas ROIs could indicate either low SNR, or inclusion of grey matter inside caused by bad registration. This may imply that the use of freehand ROIs in the pipeline would be more robust. Although, due to the notably larger size of the atlas ROIs, the difference in SD cannot be so straightforwardly interpreted.

In the future, we aim to create a standard value library based on a normal population. The standard values would first be collected based on the clinic specific manual freehand ROIs, but also on the ICBM-DTI-81 atlas later on. The automated freehand ROIs can be validated through previous ROI measurement results, and the possible future studies utilizing our pipeline will be comparable to previously conducted clinical ROI studies. Use of the pipeline in clinical settings at Tampere University Hospital will be researched.

V. Conclusions

We have presented and validated the accuracy of an automated pipeline for quantitative ROI analysis. What makes the pipeline unique is its compatibility to previous manual ROI analysis results within a clinic.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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