A methodological study on DTI indices: from preprocessing to analysis with application to multiple sclerosis

Catarina Freitas[1], Varun Sethi[1], Nils Muhlert[1], Olga Ciccarelli[2], Mara Cercignani[3], Declan Chard[2], Hui Zhang[4], and Claudia Wheeler-Kingshott[1]

[1]Department of Neuroinflammation, UCL Institute of Neurology, London, United Kingdom, [2]Department of Brain Repair and Rehabilitation, UCL Institute of Neurology, London, United Kingdom, [3]Department of Neuroscience, University of Sussex, Brighton, United Kingdom, [4]Department of Computer Science & Centre for Medical Image Computing, University College London, London, United Kingdom

Target audience – Researchers who use diffusion tensor imaging (DTI) data to quantitatively assess white matter (WM) pathology in the brain.

Purpose – When DTI is applied to study the WM of the brain, the tensor's principal direction is typically assumed to be aligned with the direction of the axonal fibres. However, in the voxels where pathology is present, this assumption may not hold, leading to potential misinterpretation of DTI indices in comparative studies. In order to overcome this problem, a new DTI data analysis methodology was suggested by Wheeler-Kingshott et al.[1] – the projected approach – which was applied to individual patients with multiple sclerosis (MS). The idea behind this approach is to build a reference DTI dataset from healthy controls (HCs) to use as a reference for the principal fibre direction. Individual subject's tensors can therefore be projected along this reference tensor eigenvectors and the resulting diffusivities used to calculate the projected indices. The current work aimed to test this new approach in a group comparison of HCs and patients with MS to investigate whether the projected diffusivities approach offers higher sensitivity to WM changes in MS subjects. We additionally investigated to what degree the type of registration employed in the pre-processing can influence the results by using two different registration methods: DT-based and fractional anisotropy (FA)-based.

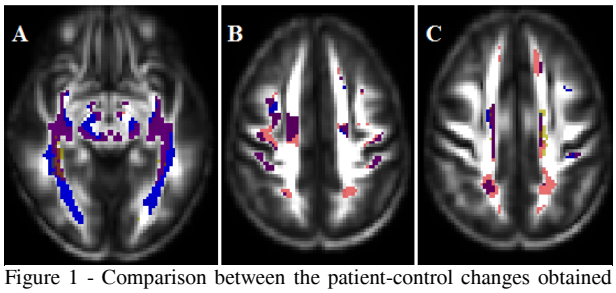

Figure 1 - Comparison between the patient-control changes obtained with FA-based (pink) and DT-based registration (blue). A - Increase of AD; B - Increase of RD; C - Decrease of FA. Purple represents the overlay of pink and blue, and yellow the LPM thresholded at 10%.

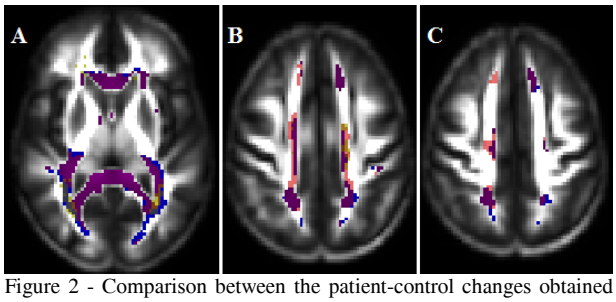

Figure 2 - Comparison between the patient-control changes obtained with FA-based registration using standard (blue) or projected (pink) indices. A - Increase of AD and PAD; B and C - Decrease of FA and PFA. Purple represents the overlay of pink and blue, and yellow the LPM thresholded at 10%.

Methods – Subjects - 76 MS patients (EDSS=4.73±2.24, 27 relapsing-remitting (RR), 29 secondary-progressive (SP), 20 primary-progressive (PP)) and 48 healthy controls (HC) took part on this study. MRI Protocol – Diffusion-Weighted (DW) data was acquired using a Phillips Achieva 3T system with a 32-channel head-coil and a DW-SE-EPI sequence. T2-weighted scans were acquired with a dual-echo sequence. Image processing - The diffusion tensor (DT) images were calculated with Camino. The DTI data was normalized using two different registration methods: (1) a DT-based registration with DTI-TK[2,3]; and (2) a FA-based registration using NiftyReg[4]. The target template for the registration was representative of the population as it was created from 20 HC and 20 MS patients using DTI-TK. DTI indices – For each registration method, the standard indices, i.e. the axial and radial diffusivities (AD, RD) and FA, and the projected indices were calculated. For the latter, a reference DT dataset was created as the mean DT of the HCs in template space, in order to estimate the most likely fibre direction in each voxel. Then, the individual subject's DTs were projected along the eigenvectors of this reference DT. Finally, the projected diffusivities were used to calculate the projected parameters PAD, PRD and PFA; Statistical Analysis – For each parameter, the HCs and the MS patients differences were analyzed at a group level using SPM8: after smoothing the data with a 8mm FWHM Gaussian kernel, a voxel based analysis (VBA) in the reference DT space was performed, using a two-sample t-test with age and sex as covariates, FWE correction thresholded at 0.05 level, and an analysis mask correspondent to all reference DT template voxels with FA≥0.3. The results were compared between analogous projected and standard indices, and between corresponding indices calculated with different registration methods. Angle Analysis – It was also studied how the orientation of the tensors differed between the average of controls and the average of the patients. The patients from each registration pipeline were averaged to create a mean MS DT dataset. For each normalization method, the angle between corresponding tensors of the two mean datasets (mean HCs DT and mean MS DT) was calculated: $\alpha = Arccos\left(\frac{|v_{1,HC} \cdot v_{1,MS}|}{|v_{1,HC}||v_{1,MS}|}\right)$, where $v_{1,HC}$ and $v_{1,MS}$ correspond to the principal eigenvector of each controls and patients mean DT-dataset. From normalized histograms of the magnitude of these angles maps, the percentage of angles above 5 degrees was calculated for WM voxels (FA≥0.3). Lesion Probability Map (LPM) – A LPM was created from T2 hyperintense MS lesion masks drawn by an experienced neurologist (VS).

	DT-based	FA-based	Module of difference
AD (Figure 1.A)	11400	8038	3362
RD (Figure 1.B)	14364	14381	17
FA (Figure 1.C)	10829	11107	278

Table 1 – Overall number of voxels showing a significant difference in patient-control VBA for each registration pipeline.

Results – The two registration methods originated significantly different results (Figure 1). Changes detected with the projected parameters mostly overlapped with the ones detected with the standard parameters, with the exception of some voxels or small areas where PAD increases were less extensive than the areas with increased AD, and areas with increase of PRD and decreased PFA were more extensive than the areas with increased RD and decreased FA, respectively (Figure 2). The results from the FA-based registration presented more differences between the two types of parameters than the DT-based registration. These differences are quantified by voxels number in Table 1. The deviation in the principal direction of corresponding tensors was mostly below 5 degrees, however the percentage of voxels that exceeded 5 degrees was more than two times higher for the FA-based registration (29%) than for the DT-based registration (13%).

Discussion – The difference in the results obtained from the two registration pipelines supports the importance of understanding the implications of the registration method in a VBA of DT-MRI data. Higher dispersion across the DT-datasets registered with the FA-based pipeline justifies why differences in the projected-vs-standard approaches were more noticeable. Moreover, in this group study, information given by the projected parameters might have been averaged out at a group level; however the results suggest a higher sensitivity of PRD and PFA to pathological changes.

Conclusion – Investigating the projected DT indices may help to reveal subtle changes when no advanced (non-Gaussian) microstructural imaging methods are applicable to analyze the data. The pathological substrate of the projected and standard indices should be investigated with *post mortem* studies in order to determine which one better represents MS pathology. It is also important to investigate how FA-based and DT-based registration methods affect the DT information regarding the pathological microstructural changes and to assess which pipeline is more appropriate when conducting comparative studies between controls and patients. Computer simulations and correlation studies with clinical scores should be conducted to help answer these questions.

References – 1. Wheeler-Kingshott et al Func. Neur., 17(1027), 2012; 2. H. Zhang et al. IEEE Trans. Med. Imag., 26(11):1585-1597, 2007; 3. H. Zhang et al., Med. Imag. Analysis, 10(5):764-785, 2006; 4. D. Rueckert et al. IEEE Trans. Med. Imag., 18:712–721, 1999.

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