INVESTIGATING LONGITUDINAL CHANGES IN FRACTIONAL ANISOTROPY IN ALZHEIMER'S DISEASE USING DIFFERENT REGISTRATION METHODS

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Purpose: Diffusion tensor imaging (DTI) has the potential to non-invasively detect microstructural changes in white matter before they present clinically, giving it the potential to demonstrate disease progression, as well as track white matter (WM) changes as a result of a particular therapeutic intervention. Changes in normal brain structure associated with a decrease in fractional anisotropy (FA) correlates well with cognitive decline[1]. Few studies exist in the literature that has investigated the longitudinal changes in diffusion metrics such as FA in Alzheimer's disease (AD) and of those studies, FA changes have been reported in the fornix, left cingulum and genu and body of the corpus callosum[2]. Many studies use the freely available Tract-based spatial statistics (TBSS) in FSL[3], which generates a WM skeleton common to all inputted brain images, highlighting changes in FA between populations or time. Recent studies have shown that enhancing TBSS with an altered pipeline, namely improving registrations, can implicate the specificity of results[2, 4]. The aim of this study was to modify the TBSS pipeline using ANTs registrations to investigate how this would affect the spatial distribution of FA change in the core WM tracts for AD patients within six months. Herein, Standard TBSS was compared with TBSS enhanced with ANTs registrations[5], and with a study ANTs-derived specific template.

Methods: This imaging study was part of the Velacor study, which was approved by the Human Research Ethics Committee at Melbourne Health. In total, 9 mild-moderate Alzheimer's disease patients were included in this study. All participants underwent MR imaging on a Siemens 3.0T Tim Trio (Diffusion protocol: TR/TE=8700/92ms, FOV 240x240mm, acquisition matrix 96x96, b=1000s/mm^2, voxel size 2.5x2.5x2.5mm, 30 directions). All 9 participants underwent MR imaging at two time points, upon initial recruitment and 6 months following. FA maps were generated using the Fdt diffusion toolbox in FSL, and three different approaches were used for analysing the FA maps:

1) *Standard TBSS:* The standard TBSS pipeline was executed with the recommended options available on the FSL online user guide (tbss2reg –T, tbss3postreg –S).
2) *TBSS + ANTs:* The original FA images were registered using the ANTs registration suite (1.9.v4), followed by post-registration and pre-statistics methods in TBSS.
3) *Study-specific template:* The baseline FA images were used to create a template using the "build template" function available in ANTs. These original FA images were then registered to the newly created template with both affine and diffeomorphic registrations using a cross-correlation (CC) similarity measure. SyN [0.25] and Guass [3,0] were used for the transformation and regularisation model respectively. This was followed by the post-registration and pre-statistics methods in TBSS.

For all three methods, the threshold-free cluster enhanced (TFCE) permutation-based method "randomise" available in FSL was used, taking care that the options were optimised for our study group i.e. variance smoothing at 5mm (recommended for small study groups), threshold-free cluster enhancement, and 10000 permutations.

Results: The accuracy of registrations were determined visually, and with the Measure Image Similarity algorithm in the ANTs registration suite[5] using the Mutual Information (MI) metric. The best registrations were to the study-specific template (MI=0.8370), however all methods gave similar quality registrations to their respective templates (table 1). The volume (23378±714.76mm^3) and the mean and standard deviation of significant FA change in the WM skeleton were similar (figure 2, table 1) in all three methods. Using the Juelich Histological Atlas available in FSL, the areas of change that were consistently affected were the callosal body and corticospinal tract.

Table 1: Quality of registration fits and FA changes in significant clusters.

	Standard TBSS	TBSS + ANTS	Study-specific template
Avg registration similarity	0.7527	0.8152	0.8370
Volume FA change (mm^3)	22569	23924	23641
FA change	-0.033±0.019	-0.031±0.022	-0.033±0.018

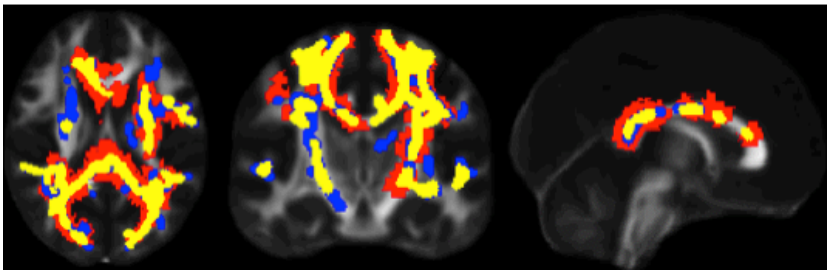

Figure 1: Significant TFCE clusters over 6 months ($p<0.05$) using methods 1 (yellow), 2 (blue) and 3 (red). Note: These regions of change have been thickened using tbss fill in FSL for ease of visualisation. The results from the study-specific template were transformed to MNI152 standard space purely for comparison.

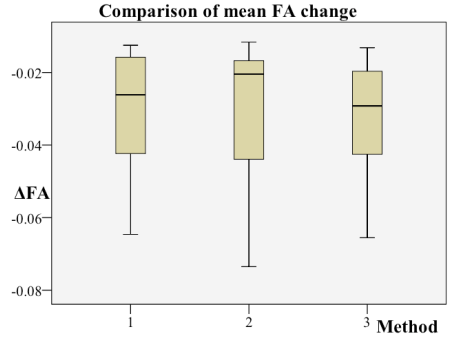

Figure 2: Comparing mean FA change of significant TFCE clusters between methods.

Discussion: Despite improved registrations using ANTs in methods 2 and 3, the areas of significant FA decrease in the WM skeleton using the three registration methods were consistent. The mean FA change over six months was comparable to the literature for yearly change, with the only difference being that in this study the entire WM skeleton was used for the statistical tests, instead of prior defined regions of interest[2]. Small differences in registration between the three methods in producing the 4D FA volumes needed by randomise are likely to explain the areas of FA change that do not overlap. The older brains in this study typically have dilated ventricles, varying degrees and spread of atrophy and anatomical shifts, which can create serious problems for transformation to MNI152 standard space (based on younger healthy brains). It is therefore felt that creating an unbiased, high SNR, study-specific template based on the diffusion data (method 3) is potentially the most promising option and avoids the interpolation artefacts from resampling the diffusion data to MNI152 standard space. Limitations of this study include partial volume effects, the prevalence of crossing fibres, and the small sample size, which may be insufficient to truly delineate the differences between the three methods. Methods that use the complete information in the diffusion tensor rather than just the scalar quantity FA may also help address some of these issues, as well as better incorporating a priori information such as segmented WM distributions for individual patients to guide the registration process. Whether the skeleton-projection method in TBSS which was designed to correct for voxel alignment errors is sufficient to overcome the problems in DTI data with modest to significant amounts of atrophy needs further investigation.

Conclusion: Longitudinal changes in fractional anisotropy in a small cohort of AD patients were investigated using three different registration methods. The consistencies between the standard TBSS, ANTs-modified TBSS, and study-specific template results suggests that running the simple TBSS pipeline may be sufficient for longitudinal analyses in complex pathologies such as Alzheimer's disease, however further studies with greater sample size are required to confirm these findings.

References: [1] Malloy, P., et al., The Clinical Neuropsychologist, 2007. **21**(1): p. 73-109. [2] Keihaninejad, S., et al., NeuroImage, 2013. **72**: p. 153-163. [3] Smith, S.M., et al., NeuroImage, 2006. **31**(4): p. 1487-1505. [4] de Groot, M., et al., NeuroImage, 2013. **76**(1): p. 400-411. [5] Avants, B.B. et al., Insight J, 2009.