Tensor Based Morphometry of White Matter Tracts using Fibre Orientation Distributions

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Introduction: Tensor based morphometry (TBM) exploits information obtained during spatial normalisation to investigate differences in brain anatomical structure across populations and time. At each point in the non-linear warp the local affine transformation is defined by the spatial derivative (Jacobian matrix). A popular approach to TBM involves voxel based analysis of the Jacobian determinant, which describes the local volumetric changes. When investigating tissue such as grey matter, differences in the Jacobian determinant imply a difference in the number of neuronal cells if a constant density is assumed. However when employing TBM to investigate white matter, the direction of the expansion or contraction is important due to the orientation dependent nature of the underlying cellular structure. Expansion or contraction parallel to the orientation of a fibre bundle implies a difference in axon length. However, a change to the cross sectional area in the perpendicular plane implies a difference in the number of axons and is potentially more relevant when investigating pathology.

A previous method [1] to perform TBM on white matter utilised the diffusion tensor (DT) [2] to infer fibre bundle orientation which was used to compute two intuitive indices from the Jacobian matrix. One index describes volume changes parallel to the assumed orientation of the fibre, and the other describes changes to the area in the perpendicular plane. A limitation of this work is the ability of the diffusion tensor to correctly characterise voxels with crossing fibres. Recent work suggests that up to 90% of white matter voxels contain more than one fibre population [3] and therefore fibre orientation estimates in these voxels based on the DT principal eigenvector are likely to be inaccurate. Other white matter morphometry studies have investigated changes to individual tract size or shape indentified using fibre tractography [4,5,6]. In these studies tract properties were projected onto tubular [4,5] or sheet like [6] skeletons where subsequent comparisons were made. Although dimensionality reduction has the advantage of increasing statistical power, it is often difficult to properly characterise known fibre bundle shapes with such simplistic models. For example, in [6] 2D manifolds were used to represent major white matter structures such as the corpus callosum (CC) and cortico-spinal tract (CST), as identified using DTI tractography. However these fibre pathways are known to contain lateral projections (and are therefore not sheet like) that are only identified when tractography using higher order models are used (see e.g.Fig 1b & c).

In this work we describe a novel TBM method to investigate changes in white matter cross sectional area using probabilistic tractography performed on group average fibre orientation distributions (FOD) [7].

Methods: We demonstrated the proposed method using a cohort of 13 motor neurone disease (MND) patients and 16 age matched healthy volunteers (3T Siemens Trio, 64 DW directions, b=3000 s/mm^2, 2.3mm in-plane resolution, 2.5mm slice thickness). Pre-processing involved EPI distortion correction [8], DW bias field correction based on the b=0 signal [9], and motion correction (mutual information towards a b=0 image with gradient reorientation). The DW image resolution was up-sampled by a factor of 2 using cubic b-spline interpolation, since in our experience this improves image alignment during the registration process. FODs were computed by Constrained Spherical Deconvolution [7] using MRtrix [10]. To gain voxel-wise correspondence we used a symmetric diffeomorphic FOD registration method [11] to normalise images to an unbiased group average template using an iterative averaging approach [11]. Registration was performed using the FOD spherical harmonic (SH) L_2 norm metric, and tri-linear interpolation of SH coefficients (maximum degree l_{max} = 4). During registration we used the Jacobian matrix at each point in the displacement field to reorient the FODs [11]. Final transformations were applied to FOD images represented with l_{max}= 8, which were then averaged to form a group average FOD image (Fig. 1a).

Changes to white matter in MND patients have been previously reported in the CC and CST [12]. To identify these structures we performed probabilistic tractography on the group average FOD image using MRtrix [10] (Fig 1b & c). Seed points were placed in the brain stem, and mid sagittal plane for the CST and CC respectively. The fibre orientation in each voxel was computed as the mean tract tangent (Fig. d & e), and subsequently used to compute the change to cross sectional area, c, for all subjects. This was performed by $c = \|\mathbf{Jv}\| / \det(\mathbf{J})$, where $\mathbf{J}$ is the Jacobian matrix, and $\mathbf{v}$ is the Cartesian vector defining the fibre orientation. Note that in a similar manner to the method proposed in [1], we compute the change in cross sectional area with respect to each subject's local frame of reference using $\mathbf{J}$ computed in the template space. However, our approach is not limited to a single fibre orientation and therefore can be used where tracts overlap in regions with crossing fibres. To investigate group differences in the cross sectional area for both the CC and CST, we first smoothed the data (4mm Gaussian kernel), then determined statistically significant voxels using Randomise [13] with 5000 permutations and cluster forming threshold of t > 2.

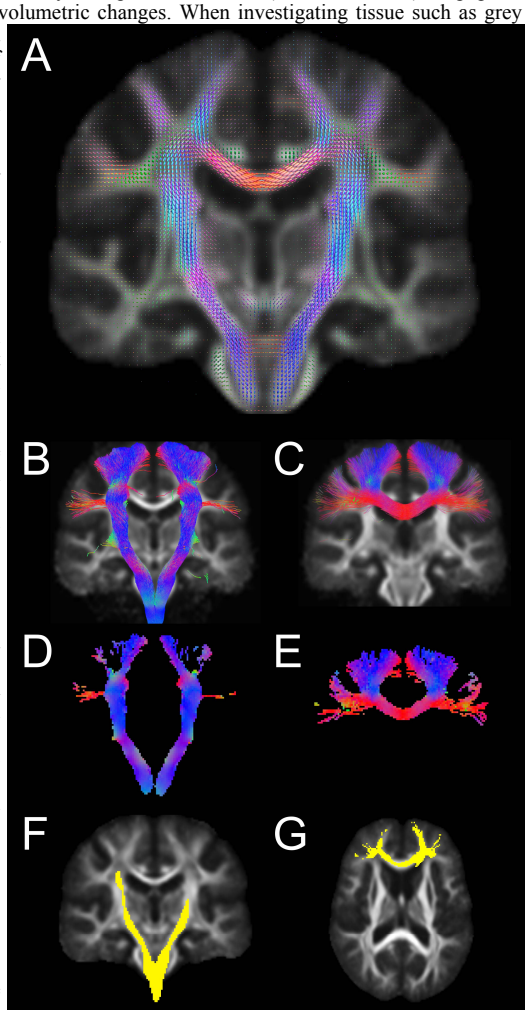

Figure 1. A) Average FOD image of all spatially normalised 29 subjects, overlaid on the group average FA image. **B)** 20mm slab of corticospinal tracts identified using probabilistic tractography on data in A. **C)** 20mm slab of corpus callosum tracts identified using probabilistic tractography on data in A . **D)** Colour coded image defining the mean fibre orientation from tracts in B. **E)** Colour coded image defining the mean fibre orientation from tracts in C. **F)** Voxels with a statistically significant decrease in cross sectional area in MND. To visualise all voxels in this cluster we computed a maximum intensity projection along the A-P axis and overlaid on the coronal FA image shown. **G)** Voxels with a statistically significant *increase* in cross sectional area in MND.

Results: As seen in Fig. 1f, a significant reduction in cross sectional area was found in the CST of MND patients compared to healthy subjects ($p<0.04$). Interestingly, as shown in Fig. 1g, we observed a significant *increase* in cross sectional area in the CC of MND compared to healthy subjects ($p<0.03$).

Discussion: Our findings in the CST of MND patients corroborate previous research [12]; however to the best of our knowledge we are the first to report an increase in white matter fibre volume in the genu of the CC. Future work to investigate regional volume differences using T1W images may help to confirm the observed result. Note that in this study we performed fibre tractography using manually placed seeds to identify tracks previously known to be affected in MND, however clustering of whole brain fibre tractography results could be used to perform an analysis of all major fibre pathways.

Conclusion: We have presented a novel method that exploits fibre orientations computed using group average tractography to investigate morphological differences in fibre bundle cross sectional area. To the best of our knowledge this is the first study to employ higher order information to drive registration for TBM, and to perform group comparisons using group average tractography on a higher order model.

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