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 study investigating tract size in MND demonstrated a significant decrease in white matter fibre volume in the genu of the corpus callosum (CC) of MND patients compared to healthy subjects (p<0.03). 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 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/mm², 2.35mm 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 Constraining 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) L₂ norm metric, and trilinear interpolation of SH coefficients (maximum degree L₉ = 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 l₉₈ = 8, which were then averaged to form a group average FOD image (Fig. 1a).

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. 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 CC and 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 to employ higher order information to define image registration for TBM, and to perform group comparisons using group average tractography on a higher order model.