Voxel Based Analysis of Motor Neurone Disease using Apparent Fibre Density

D. Raffelt[1,2], S. Rose[3], J-D. Tournier[4,5], R. Henderson[6], S. Crozier[2], O. Salvado[1], and A. Connelly[4,5]

[1]The Australian E-Health Research Centre, CSIRO, Brisbane, QLD, Australia, [2]Biomedical Engineering, School of ITEE, University of Queensland, Brisbane, QLD, Australia, [3]Centre for Advanced Imaging, University of Queensland, Brisbane, QLD, Australia, [4]Brain Research Institute, Florey Neuroscience Institutes (Austin), Melbourne, VIC, Australia, [5]Department of Medicine, University of Melbourne, Melbourne, VIC, Australia, [6]Department of Neurology, Royal Brisbane and Women's Hospital, Brisbane, QLD, Australia

Introduction: Motor Neurone Disease (MND) (also known as Amyotrophic Lateral Sclerosis) is caused by progressive degeneration of the motor neurons and results in the loss of voluntary muscle activities, such as speaking, walking, breathing and swallowing. Upon diagnosis, MND is typically fatal within 2-5 years and consequently there is a considerable need for imaging biomarkers to aid in both prognosis and pharmaceutical development. Previous studies have detected significant changes in both the diffusion characteristics and the volume of white matter (WM) pathways, in particular the corticospinal tract, and the corpus callosal fibres connecting the left and right primary motor cortices [1].

In this paper we investigate the ability of a recently developed measure called Apparent Fibre Density (AFD) [2] to detect changes in MND patients. AFD uses information provided by Fibre Orientation Distributions (FOD) computed from high angular resolution diffusion-weighted images [3]. Any differences in the FOD amplitude along a given orientation can be attributed to differences in the relative *amount of underlying axons* thought to be aligned with this orientation [2]. The amount of axons for a given orientation is referred to as '*Apparent'* Fibre Density because it is not an absolute measure of density. The motivation behind AFD is its ability to identify differences between populations and localise them in both the spatial *and* orientation domains. Unlike existing measures such as Fractional Anisotropy [4], this enables differences to be attributed to a single fibre population within a voxel containing multiple fibres. In this work we demonstrate the first use of AFD to detect voxel-wise changes in MND patients, and identify the specific pathways involved.

Methods: Data were acquired from 13 MND subjects and 13 age and gender 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 [5], DW bias field correction based on a b=0 image [6], motion correction (mutual information towards a b=0 image with gradient reorientation), and mean DW intensity normalisation across subjects. 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 [8], using the group average response function.

To establish voxel-wise correspondence between subjects we employed a FOD non-linear registration method to normalise images to an unbiased group average template using an iterative averaging approach [10]. This was performed using the FOD spherical harmonic (SH) L_2 norm metric with a maximum SH degree (l_{max}) of 4. During registration, the Jacobian matrix at each point in the displacement field was used to reorient the FODs [10]. Final transformations were applied to normalise FOD images with l_{max}=8. Because the non-linear registration process alters a fibre bundle's total volume and therefore its total AFD, when applying the final transformations the AFD is modulated by an amount proportional to the corresponding change in cross-sectional area (and hence in axonal density) [2]. As in [2], statistical differences in AFD were identified by first smoothing FODs in the spatial domain (4mm FWHM Gaussian kernel) and in the orientation domain (truncation to l_{max}=4), and performing t-tests on the AFD along 100 equally distributed orientations. The resulting t-values were mapped to SH for display.

Results: Fig. 1a-b demonstrates the average spatially normalised, modulated FOD image for all 26 subjects. The mean difference in AFD between the MND and healthy groups was computed by subtracting the SH coefficients of the MND group average image from the healthy group average image. As seen in Fig. 1c, a notable difference is observed that extends the entire length of the corticospinal tract corresponding to its known orientation (note that differences in the CST are more extensive than can be appreciated from the single slice shown). A difference can also be seen in the region of the corpus callosum related to the primary motor cortices (Fig. 1d). Statistically significant differences (p<0.05) were observed along the orientations shown in red (Fig 1e-f). Importantly, in the region crossing through the superior longitudinal fasciculus, significant differences were only observed along corpus callosum orientations (Fig. 1g&h).

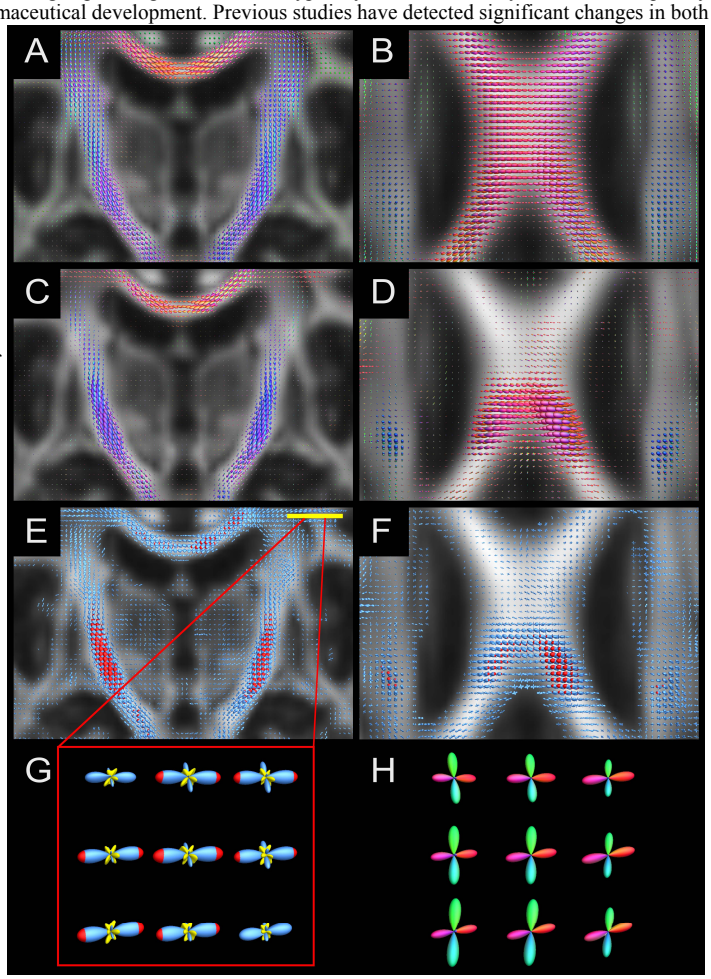

Figure 1. A) Coronal slice of the FOD average image of all 26 spatially normalised subjects. **B)** Axial slice of the FOD average image showing the Corpus Callosum. **C)** The difference between healthy and MND group FOD images. **D)** Axial view of the MND-healthy group difference. **E)** Coronal view of the t-test plots. Blue indicates positive t-values, with red orientations being significant ($p < 0.05$). **F)** Axial t-test plots. **G)** Zoomed t-test plots of an *axial* slice as indicated by the yellow line in E. Negative t-values are shown in yellow. **H)** Average FODs of all 26 subjects corresponding to the region in G, indicating 2 fibre orientations, only one of which shows significant differences.

Discussion: Using a single canonical response function for the spherical deconvolution implies similar diffusion characteristics within the same white matter structure across subjects, an assumption that may not hold in pathology. However, any deviations from this assumed response function will still be detected as a change in AFD. For example, an increased radial diffusivity, often associated with pathology and a loss of 'connectivity', will result in a decrease in the *Apparent* Fibre Density [9]. Hence, whether a decrease in AFD is caused by increased radial diffusivity or a reduction in the amount of underlying axons, in both cases the reduction in AFD appropriately reflects the reduced capacity of the relevant fibre bundle to transfer information.

Although these results have *not* been corrected for multiple comparisons, the spatial and orientation coherence of the differences identified strongly supports their validity. The use of supra-threshold cluster-based permutation testing as a correction for multiple comparisons is currently being investigated.

Conclusion: We have demonstrated the ability of AFD to detect changes in MND *specifically* within WM pathways known to be affected [1]. In addition to corroborating previous findings in MND, this study demonstrates the clear advantage of using this type of analysis in the context of multiple fibre orientations, by identifying not only the location, but also the orientations along which differences exist.

References: [1] Agosta F et al. AJNR ajnr.A2043 (2010). **[2]** Raffelt D et al. Proc ISMRM 18, #575 (2010). **[3]** Tuch D et al. MRM 48:577-82 (2002). **[4]** Basser P. NMR Biomed. 8:333-4 (1995). **[5]** Jenkinson, M. MRM 49:193-7 (2003). **[6]** Salvado O et al. IEEE TMI 25:539-52 (2006). **[7]** Tournier J et al. Neuroimage 35:1459-72 (2007). **[8]** MRtrix. http://www.brain.org.au/software/ **[9]** Dell'Acqua F et al. Proc ISMRM 18, #574 (2010). **[10]** Raffelt D et al. Proc ISMRM 18, #3969 (2010).