Imaging myelin water fraction to reveal novel aspects of cerebral pathology in motor neuron disease

S. Kolind[1,2], S. Deoni[2,3], R. Sharma[1,4], M. E. Lord[4], S. Knight[5], K. Talbot[4], H. Johansen-Berg[1], and M. R. Turner[1,4]
[1]FMRIB Centre, University of Oxford, Oxford, United Kingdom, [2]Department of Neuroimaging, Institute of Psychiatry, King's College London, London, United Kingdom, [3]Division of Engineering, Brown University, Providence, Rhode Island, United States, [4]Oxford University Nuffield Department of Clinical Neurosciences, John Radcliffe Hospital, Oxford, United Kingdom, [5]OCMR, University of Oxford, Oxford, United Kingdom

BACKGROUND: Motor neuron disease (MND) is an adult-onset neurodegenerative disorder characterised by progressive weakness with variable muscle wasting. The term MND encompasses a broad phenotypic range with variable clinical involvement of the corticospinal tract (CST). There is currently no diagnostic test for MND, resulting in lengthy delays between symptom onset and clinical diagnosis. The commonest phenotype, amyotrophic lateral sclerosis (ALS), is characterized by involvement of both upper (CST) and lower motor neurons (LMNs) of the brainstem and spinal anterior horns. Although the median survival is 2-3 years from symptom onset, there is substantial clinical heterogeneity. Evidence suggests there may be independent processes affecting both the CST and LMNs[1], and a well-characterised wider extra-motor cerebral pathology is now understood in the context of clinicopathological overlap between MND and some types of frontotemporal dementia. In less than 5% of MND cases there is isolated involvement of the CST, termed primary lateral sclerosis (PLS), with a notably prolonged disease course of 10-20 years. However confident diagnosis of PLS cannot currently be made until 4 years after symptom onset.

OBJECTIVES: Neuropathology studies confirm that there is variable demyelination of white matter tracts in MND[2,3]. Though presumed secondary to axonal damage, its occurrence has not been systematically studied. There is also evidence for a widespread active inflammatory process in ALS[4]. Given the clinical heterogeneity, there is a strong desire to better understand the role and time-course of these demyelinative and inflammatory processes. Multi-component relaxometry allows interrogation of the myelin water fraction (MWF)[5], a measure related to myelin content[6], and provides estimates of the myelin and intra/extra-cellular (IE) water T1 and T2, which may be altered by disease processes. In particular, IE-water T2 is expected to increase with inflammation[7]. Multi-component Driven Equilibrium Single Pulse Observation of T1 and T2 (mcDESPOT)[8] is a new high-resolution whole-brain multi-component relaxometry technique that affords us the opportunity to study diffuse myelin changes throughout the brain in a clinical setting. In this work, we applied mcDESPOT imaging to cases of both ALS and PLS in comparison with healthy controls as a novel marker of white matter tract demyelination and potential surrogate for inflammatory activity with the aims of furthering understanding of pathology and phenotype variability.

METHODS: mcDESPOT data were acquired on a Siemens Tim Trio MRI scanner. Nine ALS patients of variable clinical upper motor neuron (UMN) involvement (6 male; mean age 63.8±8.2(SD) years; mean disease duration 57±20 months; mean UMN score 8; range 1-15); 4 PLS patients (0 male; mean age 65.5±15.2 years; mean disease duration 122±55 months); and 5 healthy controls (2 male; mean age 51.2±14.8 years) were included in the study. Acquisition parameters were: FOV=22x22x16cm, 1.7mm isotropic resolution; SPGR: TE/TR = 2.5ms/5.6ms, α={3,4,5,6,7,9,13,18}°, BW=±24kHz; SSFP: TE/TR=2.2ms/4.4ms, α={10,13.3,16.6,20,23.3,30,43.2,60}°, BW=±36kHz, phase-cycling patterns = 0º and 180º (for correction of off-resonance effects[9]). A reduced resolution IR-SPGR image was also acquired with TE/TR/TI/α = 2.5ms/5.6ms/450ms/5° to correct for flip angle inhomogeneity[10]. Total acquisition time was 14 minutes. mcDESPOT processing[8] was performed to derive voxel-wise MWF and IE-water T2 maps for each participant. A white matter skeleton was created from the MWF maps using tract-based spatial statistics (TBSS)[11]. Voxel-wise non-parametric testing was performed on the skeletonised MWF and IE-water T2 data using Randomise (www.fmrib.ox.ac.uk/fsl) to determine areas of group (ALS-Control; PLS-control) difference. Voxels with $p < 0.05$ (corrected for multiple comparisons) were considered significantly different.

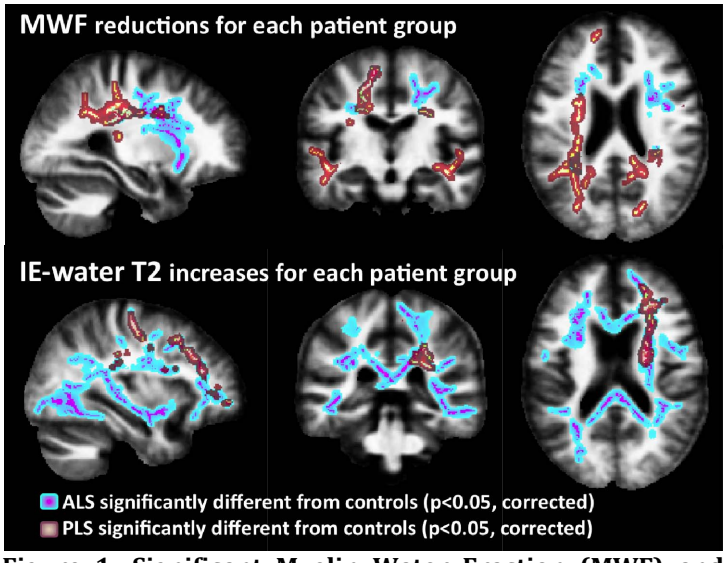

Figure 1: Significant Myelin Water Fraction (MWF) and Intra/Extra-cellular (IE) water T2 differences between motor neuron disease patients and healthy controls

RESULTS: There was reduced MWF and increased IE-water T2 in both ALS and PLS groups compared with healthy controls (see figure 1). In the ALS group, regions of decreased MWF (average 3.5% decrease) were limited to pre-frontal regions, with more widespread increased IE-water T2 (average 11% increase). In the PLS group, regions of decreased MWF (average 6.4% decrease) were noted in the rostral part of the CSTs, parietal and temporal lobes, with more limited areas of increased IE-water T2 (average 15% increase) within pre-motor and frontal lobe projections.

CONCLUSIONS: mcDESPOT has the potential to non-invasively reveal *in vivo* pathology in MND. In this pilot study, there was a distinct pattern of involvement between ALS and PLS. Specifically, these results support the presence of widespread inflammation in ALS (in keeping with previous observations using PET[4]), and greater emphasis on focal regions of demyelination in PLS. These findings may relate to the marked difference in prognosis between ALS and PLS. Longitudinal studies, and investigations of patients soon after symptom onset, may further delineate the contribution of demyelination and inflammation to pathogenesis, and provide diagnostic as well as therapeutic response biomarkers.

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