Relating clinical disability to brain volume and myelin water measurements in primary progressive multiple sclerosis

Anna Combes[1], Gareth J Barker[1], Arshia Seddigh[2], Naomi Sibtain[2], Anthony Traboulsee[3], Steven C.R. Williams[1], Peter A Brex[2], and Shannon Kolind[3]

[1]Department of Neuroimaging, King's College London, London, United Kingdom, [2]King's College Hospital, London, United Kingdom, [3]Medicine, University of British Columbia, Vancouver, BC, Canada

Purpose. Primary progressive multiple sclerosis (PPMS) is an autoimmune disorder characterised by focal and diffuse cerebral and spinal cord damage that lead to the accumulation of neurological symptoms and disability. Cerebral atrophy, a gross measure of tissue destruction, has been investigated as a promising surrogate marker of disease progression, and may reflect clinical status[1]. Myelin damage may also be linked to clinical disability, and can be investigated by using multi-component relaxation imaging[2] to measure the myelin water fraction (MWF). This study aimed to assess regional brain atrophy and MWF in PPMS patients compared with controls. It was hypothesized that PPMS patients would have smaller normalised volumes and lower MWF than controls, and that these decreases would correlate with clinical measures of disability.

Methods. *Subjects*:15 PPMS patients (11M, aged 41-67y) and 11 matched healthy controls (9M, aged 37-64y) were studied. *MRI*: 2D FLAIR and PD/T2-weighted scans were acquired for lesion assessment. Whole brain multi-component relaxation data was acquired using mcDESPOT[3] (1.7mm isotropic voxel size; SPGR: TE/TR = 1.9/5ms, α=3,4,5,6,7,9,13,18°; SSFP: TE/TR=1.8ms/3.6ms, α=12,16,22,28,34,41,53,70°, phase-cycling pattern = 0° and 180° (for correction of off-resonance effects[4])).

Clinical assessment: the Multiple Sclerosis Functional Composite (MSFC) score[5], which includes measures of cognitive processing (Paced Auditory Serial Addition Test; PASAT), manual dexterity (9-Hole Peg Test; 9HPT) and ambulatory function (Timed 25-Foot Walk; T25FW) was assessed for patients.

Atrophy measurements: Whole-brain, peripheral and total grey matter (GM), white matter (WM), and ventricular (vCSF) volumes were calculated using the cross-sectional FSL tool Structural Image Evaluation, using Normalisation, of Atrophy (SIENAX)[6] on a 3D T1-weighted SPGR image from the mcDESPOT data set (flip angle=18°). To ensure that lesioned tissue was not misclassified, lesion masks were applied prior to segmentation. Masks were traced on the PD-weighted scans and resampled into SPGR space using FLIRT[7], resulting in slightly dilated masks. These over-inclusive masks were used for GM volume estimation, to minimise the influence of lesions. As the masks also impinged on the ventricular space, however, they were then thresholded (0.4) to counteract this dilation, and the thresholded masks were used for whole-brain, WM and vCSF volumes, since those rely on accurate ventricular delineation.

MWF measurements: Voxelwise MWF maps were derived using standard mcDESPOT processing[3], and a WM tract skeleton was created from the MWF maps using tract-based spatial statistics[8, 9]. *Statistics*: non-parametric statistics were used; p-values < 0.05 were considered significant after correction for multiple comparisons.
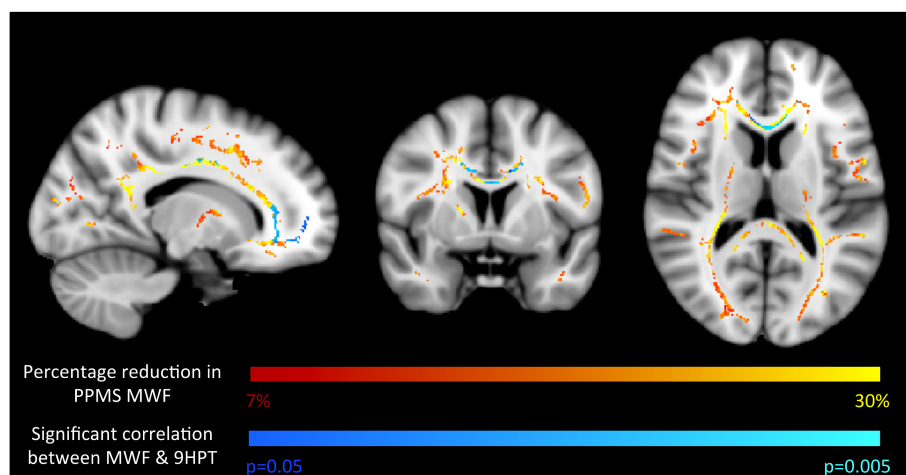

Figure 1: In Red-Yellow, percentage reduction in MWF for PPMS patients compared to controls in areas of significant difference. In Blue, significance level of correlation between reduced MWF and increased time to complete the 9HPT in PPMS.

Results. *Group comparisons*: PPMS patients had smaller whole-brain (on average 4.4%, $p = 0.02$), peripheral (on average 5.5%, $p = 0.02$) and total GM (on average 7.0%, $p = 0.006$) volume than controls, and greater vCSF volume (on average 62%, $p = 0.001$). The difference in WM volumes only neared significance (on average 3.2%, $p = 0.07$). MWF was significantly lower in PPMS throughout much of the WM compared to controls as seen in red-yellow in figure 1 (on average 10% lower across the whole skeleton, 15% lower in areas of significance).

Clinical correlations: vCSF volume was negatively associated with scores on the 9HPT ($R = -0.67$, $p = 0.003$) and PASAT ($R = -0.65$, $p = 0.004$). Decreased MWF was associated with longer 9HPT times in the corpus callosum ($R = 0.67$, $p = 0.008$), as seen in blue in figure 1. No other relationships survived correction for multiple comparisons.

Discussion. The lack of an observable decrease in PPMS WM volumes compared to controls, particularly in light of the significant difference in MWF, may be due to a lack of statistical power. It is also known that tissue-type segmentation in the presence of WM lesions may give rise to inaccuracies in volume estimation not limited to the affected voxels' class. The contribution of lesion load to overall error in measurement may hinder the detection of atrophy in relation to the severity of pathology.

vCSF volume was negatively correlated with two MSFC subtests, suggesting an association between ventricular enlargement, manual dexterity and cognitive processing in this group. This relationship was also apparent with MWF in the corpus callosum, but only for the 9HPT and not the PASAT. This result could reflect the relative sensitivity of the MRI measurements and analysis techniques, or imply that the PASAT score is more closely associated with decreases in whole brain volume than WM myelin content while the 9HPT may be a broader task encompassing more aspects of brain function.

References. [1] Klein et al. AJNR Am J Neuroradiol 2011;32:1138. [2] MacKay et al. MRM 1994;31:673. [3] Deoni et al. MRM 2008;60:1372. [4] Deoni et al. Med 2011;65:1021. [5] Rudick et al. Mult Scler 2002;8:359. [6] Smith et al. Neuroimage 2002;17:479. [7] Jenkinson et al. Neuroimage 2002;17:825. [8] Smith et al. Neuroimage 2006;31:1487. [9] Kolind et al. Neuroimage 2012;60:263.