Evidence of Subcortical Grey Matter Atrophy and Surface Morphology Differences in Primary Progressive Multiple Sclerosis

R. Gelineau-Kattner[1,2], T. Arun[1], D. Jenkins[1], M. Hough[1], J. Palace[3], and M. Jenkinson[1]
[1]FMRIB Centre, University of Oxford, Oxford, United Kingdom, [2]Baylor College of Medicine, Houston, Texas, United States, [3]Clinical Neurology, Oxford University and Oxford Radcliffe Hospitals NHS Trust, United Kingdom

Introduction: While Multiple Sclerosis (MS) is traditionally considered a demyelinating disease of the white matter, grey matter involvement is increasingly recognized (1). Therefore, evaluating subcortical grey matter damage is important in MS. Primary Progressive Multiple Sclerosis (PPMS) is a useful model to investigate the evolution of grey matter damage as the potential confounding factors of inflammation and edema play a lesser role than other MS subtypes (2). Previous imaging measures of subcortical structures (3) have been difficult to obtain due to a lack of reliable segmentation techniques. In this study we use a fully automated technique specifically tailored for segmentation of subcortical structures to investigate the distribution of subcortical atrophy in PPMS patients and healthy volunteers, looking both at baseline volume difference between groups and longitudinal changes over one year. We also examine the change in surface morphology of subcortical structures in patients with PPMS at baseline and at one year.

Methods: Patients: Scans from 22 PPMS patients and 7 healthy volunteers were analysed. The mean age was 48 years (range 36-55 years) in patients and 49.3 years (range 45-53 years) in controls. MS patients had a mean disease duration of 7.8 years (range 3-23 years) and median EDSS score of 3.8 (range 0-6.5). Acquisition: High-resolution 3D-T1-weighted images (MPRAGE) were obtained on a 1.5 T scanner (Siemens Sonata). Each patient and control was scanned four times, at baseline (t=0) and at 2, 50 and 52 weeks after the first scan. Image Analysis: Post-processing was done using an automated tool FreeSurfer (http://surfer.nmr.mgh.harvard.edu/) to measure cross-sectional volume of the subcortical structures at baseline. Surface morphology changes were analysed at baseline and one year using the vertex analysis feature of the FSL software, FIRST (http://www.fmrib.ox.ac.uk/fsl/first/index.html) and were corrected for multiple comparisons. To measure longitudinal changes in structure volume, scan-rescan variability was calculated between the first two scans (baseline and two weeks) and the second two scans (50 and 52 weeks). Structural volumes at baseline and two weeks, and 50 and 52 weeks were averaged, and the longitudinal percent difference was calculated.

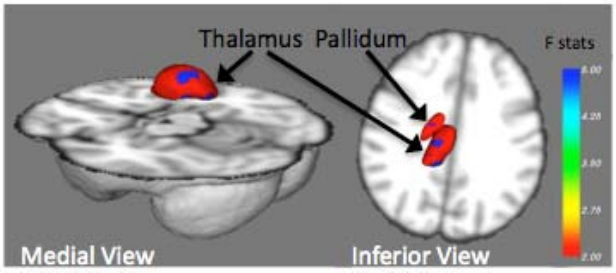

Figure 1: Vertex analysis of patients versus controls at baseline. Significant differences in structural morphology between patients and controls are indicated by the blue areas on the right thalamus and right pallidum.

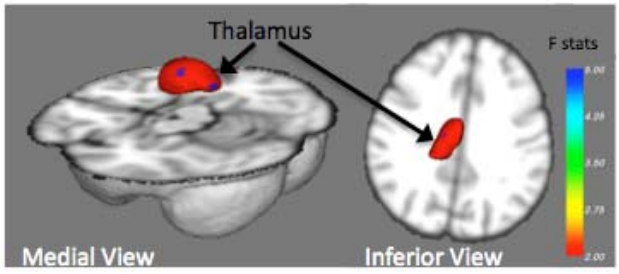

Figure 2: Vertex analysis of patients versus controls at 52 weeks. Significant differences in structural morphology between patients and controls are indicated by the blue areas on the right thalamus.

Results: Changes at baseline: PPMS patients had significantly reduced volumes when compared to healthy controls in the putamen (11.1%, $p < 0.01$), pallidum (16.2%, $p < 0.01$) and amygdala (13.1%, $p=0.02$) but not in the thalamus, caudate, or hippocampus. Significant correlations between subcortical structures were found in patients between the thalamus and putamen ($r=0.569$, $p=0.01$), thalamus and pallidum ($r=0.576$, $p=0.01$), thalamus and hippocampus ($r=0.522$ $p=0.02$), caudate and putamen ($r=0.580$, $p < 0.01$), caudate and pallidum (0.716, $p<0.01$), putamen and pallidum ($r=0.887$ $p=< 0.01$) and hippocampus and putamen ($r=0.586$, $p < 0.01$). Significant correlations with brain volume were found in the putamen ($r=0.735$, $p<0.01$), pallidum ($r=0.700$, $p<0.01$), hippocampus ($r=0.863$, $p<0.01$) and amygdala ($r=0.794$, $p<0.01$). There were no significant structural correlations between controls, although brain volume was correlated with the thalamus ($r=0.868$, $p=0.01$) and pallidum ($r=0.887$, $p<0.01$). Analysis of cross-sectional between-group changes in surface morphology of structures at baseline revealed differences in the right thalamus and right pallidum (**Fig 1**). The same analysis performed at week 52 showed surface morphology differences in similar regions of the right thalamus compared to baseline scans (**Fig 2**). Scan-Rescan variability: In patients, the average scan-rescan variability in structure volumes was 4.4% between baseline and two weeks and 4.4% between the 50 and 52 week scans. Longitudinal change over one year: Patients showed reductions in all structure volumes over one year, with 1.99% average decrease in thalamic volume, 1.49% in the caudate, 0.61% in the putamen, 6.56% in the pallidum, and 1.65% in the hippocampus. Controls showed reductions in volume of 0.38% in the thalamus and 0.29% in the caudate, with an average increase in volume of 0.56% in the putamen, 0.09% in the pallidum, and 0.36% in the hippocampus. Relationship to demographics: Cross-sectional correlation in patients of baseline structure volumes with EDSS revealed significant relationships in the putamen ($r=-0.560$, $p=0.016$), pallidum ($r=-0.482$, $p=0.043$), hippocampus ($r=-0.582$, $p=0.011$), and amygdala ($r=-0.538$, $p=0.021$). Disease duration was significantly correlated to structure volumes in the caudate ($r=-0.533$, $p=0.023$), putamen (-0.570. $p=0.014$), and pallidum ($r=-0.521$, $p=0.027$).

Discussion and Conclusion: Our results confirm the findings previously reported in imaging and pathological studies that atrophy of the deep grey matter structures plays a role in the pathology of PPMS (4,5). Furthermore, longitudinal comparisons of structural volumes demonstrate the progressive atrophy in deep grey matter structures over one year. To our knowledge this is the first study which has used a specifically optimized tool to examine changes in the structural morphology of deep grey matter structures. The finding that similar locations of morphological differences are found between groups at baseline and after one year suggests that specific deep grey matter areas may be targeted throughout the disease course. Future studies could elaborate on these findings by examining the connectivity to surrounding white matter tracts, cortex, or even other deep grey matter structures in order to elucidate whether the subcortical grey matter atrophy and morphological changes are isolated events or are driven by their extensive connections with other damaged areas.

References: [1] De Stefano N et al. Neurology 2003; 60: 1157-1162. [2] Thompson AJ et al. Ann Neurol 1991; 29: 53-62. [3] Fischl B et al. Neuron 2002; 33:341-355. [4] Pagani E et al. Am J Neuroradiol 2005; 26(2): 341-346. [5] Sepulcre J et al. Arch Neurol 2006; 63(8): 1175-1180.