Longitudinal VBM of regional progression in human prion disease

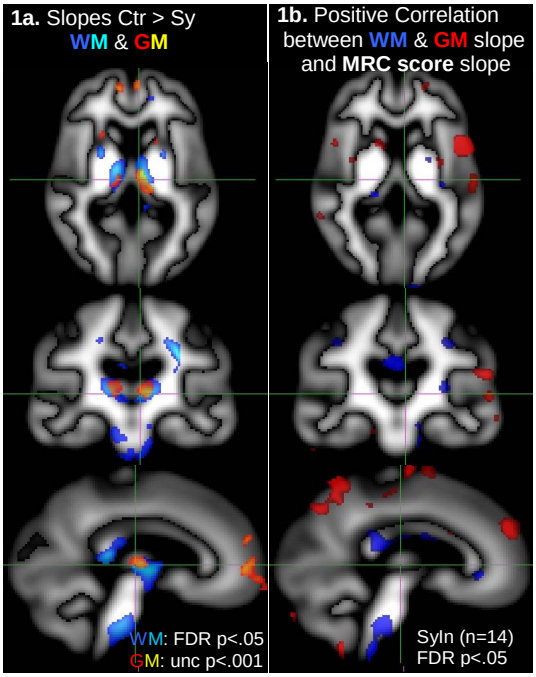
Enrico De Vita[1,2], Harpreet Hyare[3,4], Gerard Ridgway[5], Marie-Claire Porter[3,4], Andrew Thompson[3,4], Chris Carswell[3,4], Ana Lukic[3,4], Rolf Jager[1,2], Diana Caine[3,4], Peter Rudge[3,4], Tarek Yousry[1,2], John Collinge[3,4], Simon Mead[3,4], and John Thornton[1,2]

[1]Lysholm Department of Neuroradiology, National Hospital for Neurology and Neurosurgery, UCLH NHS Foundation Trust, London, United Kingdom, [2]Academic Neuroradiological Unit, Department of Brain Repair and Rehabilitation, UCL Institute of Neurology, London, United Kingdom, [3]MRC Prion Unit, Department of Neurodegenerative Diseases, UCL Institute of Neurology, London, United Kingdom, [4]National Prion Clinic, National Hospital for Neurology and Neurosurgery, UCLH NHS Foundation Trust, London, United Kingdom, [5]Wellcome Department of Cognitive Neurology, UCL Institute of Neurology, London, United Kingdom

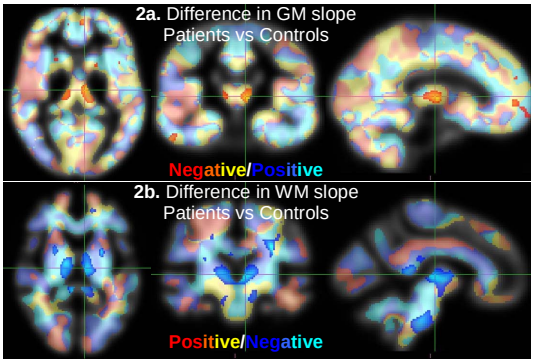
Introduction. Human prion diseases (transmissible spongiform encephalopathies) are progressive neurodegenerative disorders caused by abnormally folded prion protein accumulation that provide a molecular model for neurodegeneration [1]. Voxel based morphometry (VBM) [2] has been used to study prion disease pathology in cross sectional studies [3,4], but only whole-brain summary measures have been employed to assess disease progression longitudinally [5]. Here we followed up a large number of prion disease patients with serial cerebral MRI and applied longitudinal VBM to characterize progressive structural change.

Methods. ***Subjects and MRI.*** 85 subjects were scanned with informed consent at 3T (Siemens Tim TRIO) with a 32-channel head array coil. Data were analysed from 51 subjects in which 2 or more good quality structural scans were obtained (total: 125 datasets): 22 healthy controls (Ctr, median age at 1st scan/range 47/24-69, 49 scans), 10 presymptomatic prion protein gene (PRNP) mutation carriers (As, 44/21-72 years, 29 scans), 19 symptomatic patients (Sy, 50/25-62 years, 55 scans; 15 inherited, 2 sporadic CJD, 1 variant CJD and 1 growth hormone). The structural scan was a 3D T1-weighted MPRAGE with TR 2.2s, TE 2.9ms TI 900ms, echo spacing 6.7ms, α=10º, FoV $(282mm)^2$, matrix 256^2, 208 1.1mm sagittal partitions, 9'23" acquisition.

Data Processing and Analysis. Longitudinal VBM was performed using MATLAB with in-house processing scripts [6] as well as SPM8 [7] tools. In brief: (a) serial datasets from each subject were first segmented using 'unified segmentation' [8] ('New Segment' tool) and images were bias corrected and intensity normalised to have consistent white-matter mean intensity. (b) Images were rigidly aligned then non-rigidly warped to their (iteratively evolving) within-subject average using the high dimensional warping algorithm (HDW) [9]. This spatial processing methodology removes the bias that would be present if simply registering to the 1st or last scan [10]. (c) The within-subject average was then re-segmented, and individual pseudo-time-points were obtained by multiplying the average tissue segment by the Jacobian of the deformation needed to warp the original dataset to the within-subject average. (d) DARTEL [11] was used with the 51 individual subject averages to generate cohort-specific grey and white matter (GM, WM) templates at $(1.5mm)^3$ resolution. (e) Individual subject GM and WM segments from (c) were warped to these templates and smoothed (6mm Gaussian kernel). (f) 'slopes' for the yearly change of GM and WM density were calculated on a voxel-wise basis using all available individual (warped, smoothed) time-points; (g) the 'optimal threshold' method [12] was used to generate GM and WM masks for statistical analysis. (h) Group differences between slopes were evaluated (separately for GM and WM) in SPM8. Effect size maps were also evaluated e.g.: *SlopeGM_Sy – SlopeGM_Ctr*. (i) within the patient group we also selected a subgroup consisting of all the symptomatic PRNP mutation carriers for which the minimum interscan interval was 20 weeks (SyIn, n=14) and for these we assessed the correlation between GM (or WM) slopes and the average yearly change in the recently established *MRC rating scale* prion disease clinical assessment score [13]. SPM-t maps are shown with a voxel-level threshold of p<0.001 (uncp) or corrected for multiple comparisons with false discovery rate (FDR) with p<0.05.



Results. Only a few subjects had more than 2 scans: 5 Ctr (3 scans each), 1 As (3 scans), 11 Sy (8 with 3 scans, 3 with 5 scans) with the 2nd and 3rd scans performed respectively at 0.89±.33 and 1.40±.56 years after baseline. Significantly greater rates of GM and WM decline were seen in Sy *vs* Ctr predominantly in the pons, corpus callosum, thalamus and putamen (Fig.1a, where significant differences are shown for GM (red/yellow, uncp<0.001) and WM (blue/cyan, FDR p<0.05) slopes for Ctr>Sy (Sy slopes were generally more negative than Ctr)). A positive correlation (FDR p<0.05) between tissue segment slopes (GM red, WM blue) and MRC rating scale slopes for the SyIn subgroup was observed in some of the same regions and also in the left precuneus and left superior parietal lobule, left superior temporal gyrus and bilateral superior and middle frontal gyri (Fig. 1b) [superimposed on a background of cohort averaged GM and WM segments -- the dark line indicating the WM/GM boundary]. Fig. 2 shows difference maps for Sy (*vs* Ctr) in GM slope (a, top) and WM slope (b, bottom) with the statistically significant anatomical areas (as displayed in Fig. 1a) overlayed. No significant results were observed for As *vs.* Ctr at uncp<0.001 whilst As *vs* Sy contrasts showed similar (though less spatially extended) results as Ctr *vs* Sy.



Discussion. For healthy subjects, the tissue segment slopes were negative over extended areas (not shown) consistent with normal aging. The patients slopes were more negative indicating brain density decreases faster than for healthy controls. Additionally, for inherited prion patients we observe a correlated reduction in MRC rating scale in specific brain regions known to be associated with frontal executive dysfunction (frontal) and visuospatial problems (parietal) reflected in the scale. With this modality, processing methodology and sample-size, presymptomatic patients cannot be distinguished from healthy subjects in our cohort. Though we used 'low' statistical thresholds (prone to producing false positives), our observations on prion patients are in line with expectations and known neuropathological findings [14].

Conclusions. This first voxel-based analysis of longitudinal parenchymal changes in prion disease reveal the anatomical areas with the most significant structural changes over time and the strongest correlations with functional clinical scores. This information will help monitoring disease progression in future clinical trials.

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