Voxel-based analysis of magnetisation transfer ratio as a potential biomarker in prion diseases.

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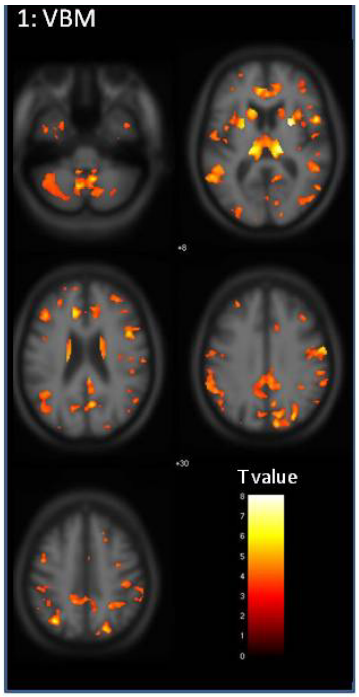
Introduction: Inherited Prion Diseases (IPD) are progressive neurodegenerative disorders caused by mutations within the prion protein (PRNP) gene[1]. As treatments are developed, there is a need for objective non-invasive neuroimaging biomarkers that could be used to monitor therapeutic efficacy in clinical trials. Magnetisation Transfer (MT) MR has been shown to be a sensitive marker of pathological change in conditions such as multiple sclerosis[2], prior to development of signal abnormalities on conventional MR. We have shown that *in vivo* whole brain MT ratio (MTR) histogram measures are lower in patients with human prion disease and correlate with disease severity at baseline[3]. The purpose of this study was to characterise neuroanatomical differences in patients with IPD compared to controls using voxel-based morphometry (VBM) and voxel-based analysis (VBA) of MTR data, investigating their potential as neuroimaging biomarkers.

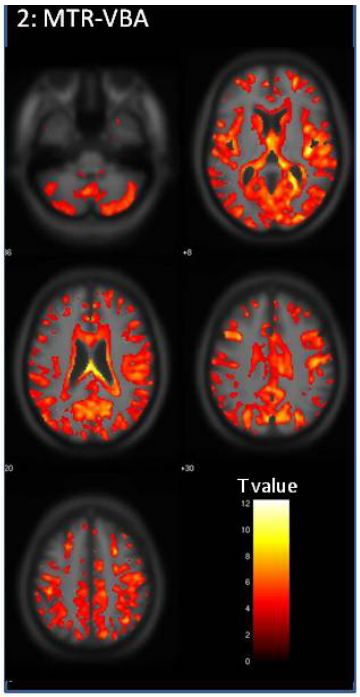
Methods: *Patients:* 17 symptomatic (IS) patients IPD (median age 42 years; range 32-65; 8 males), 6 asymptomatic (AS) mutation carriers (median age 40 years; range 32-59; 4 males) and 13 controls (Co) (median age 54 years; range 41-63; 5 males) recruited as part of the MRC Prion-1 Trial[4] were included.

MRI: Imaging was performed at 1.5T (GE Medical Systems, Milwaukee, WI) with structural (T1) data obtained by 3D-ISPGR (repetition (TR)/echo time (TE) 5/35ms, flip angle 35deg, 124 1.5m partitions, field of view (FoV) 24x24cm^2, matrix 256x128). For MT imaging, 30 slices of thickness 5mm and separation 1.5mm were collected; matrix 256x192; FoV 24x18cm^2, NEX 0.75, TE 15.4 ms, TR 1500 ms and flip angle 70° with total acquisition time 12 mins. The presaturation pulse (for Msat) was a Gaussian pulse with a duration of 12.8 ms and a peak amplitude of 23.2 μT giving a nominal bandwidth of 125 Hz, applied 2 kHz off water resonance. MTR maps were generated from M0 and Msat data as MTR=1-Msat/M0.

Data Processing and Statistical Analysis: Spatial processing for VBM involved: (i) 'unified segmentation', generating grey, white matter and cerebrospinal fluid (GM, WM, CSF) segments; (ii) DARTEL[5] (SPM 8[6]) to obtain cohort-specific GM, WM templates at 1.5mm isotropic resolution; (iii) Warping (with 'modulation') of individual GM and WM segments; (iv) 4mm smoothing (Gaussian kernel); (v) mask generation using the 'optimal threshold' method[7]. MTR-VBA involved: (i) estimation of affine transformations between the MTR images and the corresponding T1 datasets; (ii) warping (without 'modulation') of individual MTR maps to the cohort T1-template generated for VBM; (iii) 4mm smoothing; (iv) mask generation by summing GM and WM masks from VBM. The images were submitted to a group level random effect model ANCOVA consisting of diagnostic grouping (Co, IS, AS) with individual age and total intracranial volume (estimated as sum of GM, WM and cerebrospinal fluid (CSF) segments) as covariates. For multiple comparison correction we used voxel-wise false discovery rate (FDR); and corrected p-values<0.005 and <0.001. Voxels surviving the threshold are overlaid onto the averaged warped T1 for visualization.

Results: For VBM, we found a significant difference in GM voxels between IS and Co in the basal ganglia, posterior cortical areas and cerebellum (T maps for Co>IS GM-VBM and MTR-VBA are shown in Figure 1 and 2; p<0.001). No significant differences were found at this threshold or p<0.005 for Co vs AS or AS vs IS in GM, or for any comparison in the WM-VBM analysis. However, for the VBA-MTR at the same threshold, more extensive reductions in MTR were observed in IS compared to Co, including WM voxels (Figure 2) but no significant differences beween AS and Co.





Conclusions: Although volume loss in prion diseases has previously been reported[9], this analysis demonstrates the regional specificity of the atrophy in deep and posterior cortical GM regions. In terms of supra-threshold voxels at any given significance value, the MTR-VBA analysis appear more sensitive than VBM, demonstrating WM changes and more diffuse GM changes. Our results suggest the MTR may be more sensitive to microstructural changes than atrophy measures in this disease and offers potential as a neuroimaging biomarker.

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