Putamen radial diffusivity is an independent predictor of prion disease severity

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Target Audience: Scientists and clinicians working in the field of brain microstructural changes in neurodegeneration.

Purpose: Human prion diseases remain a major public health concern with focus in the development of treatments[1]. Diffusion Tensor Imaging (DTI) allows assessment of alterations in tissue microstructure in specific brain regions and can be used to examine the integrity of specific anatomical structures and white matter pathways. We hypothesized that DTI metrics could reveal brain abnormalities that correlate with disease severity measures for potential use as secondary end points in future therapeutic clinical trials in human prion diseases. To test this hypothesis, we performed voxel-based analysis of DTI (VBA-DTI) and TBSS in a large cohort of patients with a range of different forms of prion diseases.

Methods: *Patients:* 95 subjects comprising: 24 at risk individuals (As) (13 male, mean age 41.3); 37 symptomatic patients with prion disease (Sy) (20 male, mean age 50.7) and 34 healthy controls (Co) (15 male, mean age 48.7) were recruited as part of the National Prion Monitoring Cohort. 63 of these subjects underwent serial scanning (16 at risk individuals, 23 symptomatic subjects and 24 controls) up to 4 years. All patients underwent neurological assessment with the newly devised MRC scale that measures neurological, cognitive and functional features and gives a measure of disease severity[2]. *MRI:* Imaging was performed at 3T (Siemens Tim Trio) with structural (T1) data obtained by 3D-MPRAGE (repetition (TR)/echo time (TE)/inversion time 2200/2.9/900ms, flip angle 10°, 208 1.1mm partitions, field of view (FoV) 28.2x28.2cm^2, matrix 256x256). For DTI imaging, 75 slices of thickness 2.0mm with b value = 1000s/mm^2 in 64 non-colinear directions were collected (TR/TE 9500/93ms, FoV (19.2cm)^2, matrix 96x96, 1 average) with 8 images with b value = 0s/mm^2. *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[3] (SPM 8[4]) to obtain cohort-specific GM, WM templates at 1.5mm isotropic resolution; (iii) Warping (with 'modulation') of individual GM and WM segments to this template; (iv) 6mm smoothing (Gaussian kernel); (v) mask generation using the 'optimal threshold' method[7]. DTI data was first unwarped based on the acquired B0 field maps using the SPM Fieldmap toolbox[5]. The FDT tool in FSL[6] was used to process the data: motion/eddy current correction and generation of mean diffusivity (MD), radial diffusivity (RD), axial diffusivity (AxD) and fractional anisotropy (FA) maps. DTI-VBA involved: (i) affine registration of DTI data to T1 datasets (with transformations estimated using b0 images); (ii) warping (without 'modulation') of individual MD, RD, AxD, FA maps to the VBM template; (iii) 6mm smoothing; (iv) mask generation by summing GM and WM masks. A group level random effect model ANCOVA consisting of diagnostic grouping (As, Sy, Co) with individual age and total intracranial volume as covariates, was performed. For multiple comparison correction we used voxel-wise false discovery rate (FDR) with p <0.05. Results were confirmed by performing TBSS[7]. In the symptomatic patients, we also assessed the correlation between MRC scale and GM, WM, MD, FA, RD and AxD separately, by performing voxel-wise linear regression models with individual age and total intracranial volume as covariates. Finally, for longitudinal analysis the individual DTI metrics were extracted in key anatomical regions of interest (ROI): caudate, putamen and thalamus and a correlation of change in each outcome measure in each ROI with change in MRC scale was performed in the symptomatic subjects. A linear regression analysis was performed to find the outcome measure that was the best predictor of decline in MRC scale, adjusted for age and disease duration.

Results: *Cross sectional analysis:* Symptomatic patients showed grey matter loss in perisylvian cortex and thalamus. DTI-VBA showed decreased fractional anisotropy (FA) in the corpus callosum, frontal white matter and posterior limb of the internal capsule. Significantly increased MD and RD but not AxD was seen in the perisylvian cortex and TBSS confirmed that the increases were in radial but not axial diffusivity. No significant differences were seen for presymptomatic patients for VBM or VBA-DTI. Voxel-wise correlation with MRC scale revealed a significant decrease in MD, RD and AxD in the putamen bilaterally with decline in MRC scale (Figures A and B). No significant correlations were seen for FA, GM or WM.
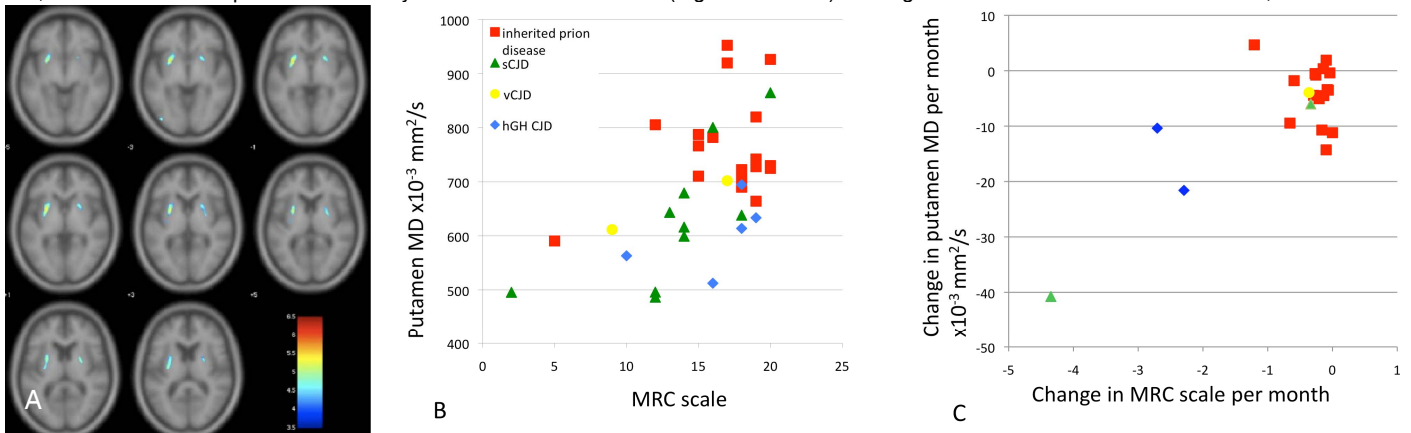
Longitudinal analysis: Significant decrease in putamen MD, AxD and RD observed for symptomatic patients compared to controls (p=0.01) and a significant correlation for decrease in putamen MD (Figure C), AxD and RD with decline in MRC scale (p<0.001). No significant correlation was observed for caudate and thalamus ROIs. Step-wise linear regression analysis, with dependent variable decline in MRC scale and co-variates age, sex and disease duration, showed decline in putamen RD was the strongest predictor of decline in MRC scale (p<0.001).

Discussion: The putamen comprises part of the basal ganglia, integral to motor control, cognition and learning and involvement is well-established in sporadic CJD[8]. We detected diffusivity changes in the putamen that correlated with disease severity at baseline and over time. Severe spongiform change restricting the extracellular space has been advocated as a potential cause of decreased MD in the putamen[9]. Given the spheric dendritic arborization of neurons on the putamen, decreased diffusivity in all directions could be affected so it is interesting that putamen RD was the strongest predictor of disease severity. The putamen is a region with abundant blood supply and disease associated prion deposition in vessel walls may contribute to the changes in putamen RD[10].

Conclusion: Putamen radial diifusivity has potential as a secondary outcome measure in future therapeutic trials in human prion diseases.

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