Voxel-based analysis of high- and standard b-value diffusion weighted imaging and voxel-based morphometry in inherited prion disease

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Introduction. Neuroimaging may provide objective measures of human prion disease activity, vital in up-coming therapeutic trials. Diffusion weighted imaging (DWI) at standard b values (b~1000s/mm²; b1k) is the most sensitive diagnostic MRI sequence in prion disease [1]. Recently high-b value imaging (b>3000s/mm²; b3k) has been shown more sensitive to pathology than b1k in sporadic Creutzfeldt-Jacob disease (sCJD) [2]. Most MRI studies in prion diseases have used region of interest (ROI) analyses, while voxel-based morphometry (VBM) [3] of structural images, and voxel-based analysis (VBA) of DWI data have been rarely used [4]. We aimed 1) to employ operator-independent VBM and DWI-VBA to characterise structural parenchymal changes and 2) to investigate the relative sensitivity of b1k and b3k acquisitions in a specific form of inherited prion disease (iPD).

Methods. Patients. Six iPD patients with 6 Octapeptide repeat insertion mutation (6-OPRI) (median age/range 37/32-43 years; 3 males) and 6 controls (Ctr; median age/range 39/33-54 years; 2 males) recruited as part of the MRC Prion-1 Trial [5] were studied.

MRI. Subjects were examined at 1.5T (GE Signa LX). Structural imaging (T1-volume) used 3D-IR-SPGR (TR/TE 5/35ms, flip angle 35°, 124 1.5mm partitions, field of view (FoV) 24x24cm, matrix 256x128). DWI employed single-shot EPI (TR 10s, FoV 26x26cm², matrix 96x128, 3 directions for b=1000 or 3000 s/mm²); for b1k, TE 101ms, 1 average; for b3k, TE 136ms, 3 averages.

Results. T-maps for Ctr>iPD VBM (GM and WM), b1k and b3k VBA and Sub1-3k are shown for p<0.01 (t-thresholds: 3.7 (GM), 7.3(WM), 3.2 (b1k), 3.5 (3k), 3.9 (Sub1-3k)) in figures 1a-d, overlaid onto selected slices of the smoothed average image from the sum of warped GM and WM*0.3. For Ctr>iPD, no supra-threshold voxels were present even at FDR corrected p<0.05. Over the F-mask <t b1k>=4.84±1.68 vs <t b3k>=4.04±1.49 (mean±standard deviations); the mean percent changes ADCb1k-ADCb3k were 24±9% (b1k) and 16±8% (b3k). The percent residuals (100%2-sqrt(ResidualMeanSquares)/(ADCb1k+ADCb3k)) were 8.5±3.6% (b1k) and 6.9±3.2% (b3k). Cumulative distribution analysis (fractions of voxels within mask below any given p-value) gave a distribution of p-values for b3k consistently below those for b1k. Plotting t-values at corresponding voxels (t b3k VS t b1k) also showed generally higher significance for b1k.

Discussion and Conclusions. The analysis indicates atrophy and increased ADC in iPD, mostly in deep and posterior cortical GM reflecting the clinical presentation of apraxia and consistent with previous ROI ad histogram ADC findings in this patient group [10]. Both b1k and b3k VBA analyses appear more sensitive than VBM in this cohort, in terms of number/extent of supra-threshold voxels at any given significance level. VBM detects atrophy in cerebellar GM, where no significant ADC difference is apparent. In contrast to sCJD [2], b1k appears to show a significant ADC increase in iPD vs Ctr over larger regions than b3k (fig. 1b vs 1c), which does not appear to be related to a decreased SNR (increased residuals) in the b3k dataset. ADCb1k-ADCb3k is significantly higher in iPD than in Ctr (fig. 1d) with ADCb1k increasing more than ADCb3k in iPD patients (vs Ctr). This may be because DWI at b1k is more sensitive to faster diffusion changes associated with the histopathological findings of increased neuronal loss and prion protein deposition in iPD, as compared to spongiform degeneration in sCJD. In conclusion, DWI-VBA appears more sensitive than VBM in iPD, potentially indicating microstructural changes occurring before GM atrophy. These findings support the potential of DWI-VBA as a sensitive objective neuroimaging method for use in therapeutic trials in patients with prion disease.
