Cross Sectional and Longitudinal Magnetisation transfer Ratio in Prion disease at 3 Tesla

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Introduction. Human prion diseases are progressive and uniformly fatal neurodegenerative disorders caused by abnormally folded prion protein accumulation [1] and present in inherited, sporadic, iatrogenic and variant CJD forms. In a previous 1.5T study in the inherited prion disease form, whole-brain Magnetisation Transfer (MT) ratio (MTR) histogram metrics predicted clinical severity [2], and voxel-based analysis in a specific mutation [3] suggested MTR is more sensitive to structural changes than conventional imaging. Here, we aimed to exploit the increased sensitivity and spatial resolution available at 3T to elucidate in more detail the association between regional cerebral MTR and disease progression in a cohort including different forms of prion disease patients.

Methods. *Subjects:* 91, comprising: 29 asymptomatic participants (*As*: 26 prion-gene mutation carriers, 3 at risk secondary to contaminated blood product exposure; median age [range] 43 [21-78] years); 36 symptomatic patients with prion disease (*Sy*: 20 inherited, 11 sCJD, 4 growth hormone, 1 variant CJD; median age 53 [36-77] years); 26 healthy controls (*Ctr*; median age 48 [24-68] years). All participants expressed their informed consent. *Longitudinal Analysis:* 20 *As* (median age 44 [21-73]), 20 *Sy* (median age 50, [37-63]), 20 *Ctr* (median age 48, [23-70]) with 2 or more scans of acceptable quality. Median inter-scan intervals were 413/242/406 days respectively for *As*/*Sy*/*Ctr* groups. *Clinical Assessment:* cognitive and neurological examinations at each time point included the MRC prion disease rating scale, assessing domains of cognition, speech, feeding, personal care and mobility [4]. *MRI:* Siemens 3T Tim Trio, 32-channel head coil. Structural imaging: 3D-MPRAGE, repetition time (TR) 2200ms, echo time (TE) 2.9ms, inversion time 900ms, flip angle (α) 10°, 208 1.1mm partitions, $(1.1\text{mm})^2$ in-plane resolution, $(28.2\text{cm})^3$ field of view (FoV). MT measurement: 3D-FLASH with/without presaturation pulse (10ms Gaussian, 1200Hz offset, α 500°), yielding M_{sat} (partially saturated) and M_0 (equilibrium) images; TR 42ms, TE 3ms, α 5°, 60 3mm partitions, $(0.9\text{mm})^2$ in-plane resolution, $(22.2\text{cm})^2$ FoV. *Data Processing and Statistical Analysis:* MTR maps were calculated as $100*(1- M_{sat}/M_0)$ in percent units (p.u.) after rigid registration of M_0 to M_{sat}. Regions of interest (ROIs) were extracted by: *a.* Calculating partial volume (PV) probabilities for GM, WM, CSF on structural images with SPM8. *b.* Further segmenting each image through propagation of anatomical labels from a set of 35 expertly annotated T_1-weighted images [5] *c.* Registering the set of labelled images to each subject image using Niftyreg [6]. *d.* Estimating the final labelled areas by majority voting of the registered labels [7] -**Fig. A**. Combined cortical ROIs, caudate, putamen, pallidum, thalamus, hippocampus and amygdala binary masks were transferred to MTR maps in MT space (**Fig. B**) using affine transforms calculated with FSL FLIRT. Given the lower resolution of the MT space, to reduce contamination from CSF and neighboring tissues, all ROIs were refined by: thresholding them at 0.8; for deep GM ROIs, eliminating voxels with $PV_{CSF}\geq0.01$; for cortex removing voxels with $PV_{CSF}\geq0.03$ or $PV_{WM}\geq0.5$. ROI means were obtained for all ROIs (left and right averaged for deep GM); normalised WM and cortex histograms were generated, and histogram metrics calculated. ANCOVA was used to assess regional and MTR group differences cross-sectionally, controlling for age and gender. Partial correlation between MTR values and MRC score was assessed. Longitudinal data were analysed for ROIs that showed significant group differences at baseline, by computing monthly changes in ROI MTR values and monthly change in MRC score. Multiple linear regressions determined the best predictor of rate of decline of MRC score. Results were considered significant for p<0.05.

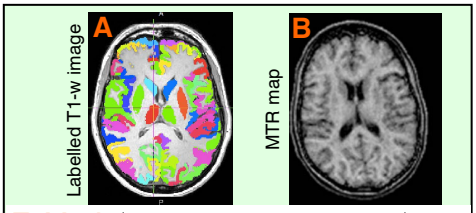
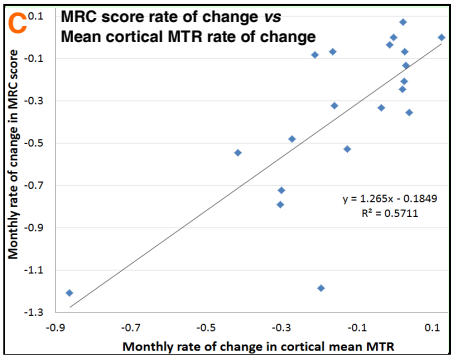


Table 1

MTR (p.u.)	Ctr (n=26) mean (SD)	As (n=29) mean (SD)	Sy (n=36) mean (SD)	p-value
Caudate	30.2 (1.5)	30.2 (1.4)	28.6 (2.0)	**<0.0001**
Hippocampus	31.3 (1.4)	31.1 (1.1)	29.7 (2.2)	**0.0003**
Putamen	31.5 (1.3)	31.7 (1.2)	30.7 (1.2)	**0.003**
Amygdala	32.0 (1.7)	32.4 (1.4)	31.7 (1.4)	0.16
Pallidum	32.9 (1.6)	33.2 (1.1)	32.9 (1.5)	0.53
Thalamus	35.7 (1.2)	35.8 (1.2)	35.4 (1.1)	0.37
Cortex	30.0 (1.4)	29.9 (1.0)	28.0 (2.1)	**<0.0001**
White Matter	36.4 (1.1)	36.6 (1.0)	36.2 (0.9)	0.29

Results. *Cross-sectional analysis:* median *Sy* MRC score was 17.5 (range 8-20). Group ROI MTR means are shown in **Table 1**. In all analyses the *As* group did not significantly differ from the *Ctr* group. *Sy* MTR was lower than *Ctr* in the caudate, hippocampus, putamen, and cortex. *Sy* cortical histograms had significantly lower peak position, median, height, 25th percentile, and skewness than *Ctr*. *Sy* WM histograms had significantly lower peak position, 25th percentile and skewness vs *Ctr*. There were significant partial correlations with MRC score for caudate MTR and cortical histogram 25th percentile, but not median (p=0.06). *Longitudinal analysis:* Only the *Sy* group showed significant differences in MTR and clinical measures *vs.* baseline and *vs. As* and *Ctr* groups. *Sy* MRC score decreased on average by .36 (.38) per month; cortical MTR decreased by .13 (.22) p.u. per month. Rates of hippocampal and caudate MTR decrease did not reach significance. Cortical, but not WM, MTR histogram metrics decreased significantly. There was significant correlation between monthly rate of decline in cortical MTR parameters and monthly decline in MRC score. The rate of decline of mean cortical MTR was the best predictor of rate of decline of MRC score (p<.001; explaining 55% of the variance; **Fig. C**).

Discussion: In this first 3T cerebral MTR study in Prion patients cross-sectionally MTR was decreased in *Sy* vs *Ctr*, in caudate, hippocampus and putamen, presumably secondary to hallmark pathological changes such as prion protein aggregation and spongiosis, and consistent with previous studies in inherited prion disease patients only [4,5]. WM involvement was reflected mostly in a change of the WM MTR histogram shape towards lower values. Cortical MTR distribution was perturbed more comprehensively, with significant changes in most histogram metrics. Longitudinal analysis consistently suggested decline in MTR in the same deep GM regions, although not significantly. While ROI means can well capture the smaller deep GM nuclei changes, histogram analysis was investigated as a tool to characterise the larger cortical and WM ROIs MTR distribution changes. Histogram descriptors were particularly sensitive to subtle WM MTR changes. However, while similar significance (and predictive value) was obtained for most of the cortical histogram summary metrics, the simple cortical ROI mean proved a similarly effective measure. Correlations between brain MTR and MRC score at baseline, and between their longitudinal rates of change support the validity of cerebral MTR as an objective marker of underlying micropathological changes related to clinical deterioration and cognitive decline.



Acknowledgments. Department of Health's NIHR Biomedical Research Centres; Medical Research Council UK. ***References:*** *1: Nicoll, Disord Drug Targets 2009; 9:48. 2: Siddique, Brain 2010; 133(10):3058. 3: De Vita, AJNR 2013; 34(9):1723; 4: Thompson, Brain 2014; 136(Pt 4):1116. 5: Neuromorphometrics inc., Somerville, MA, USA. 6: Modat, Comput Methods Programs Biomed. 2010; 98(3):278. 7: Heckemann, NeuroImage 2006; 33(1): 115.*