# Postmortem Magnetisation Transfer Ratio in Human Prion Diseases at 1.5T and Histopathological Correlation at 9.4T

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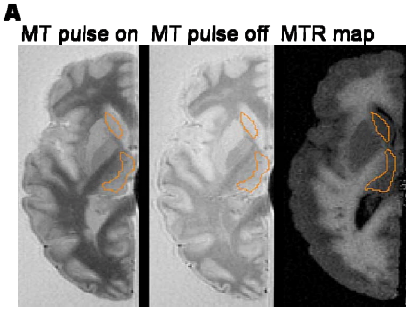
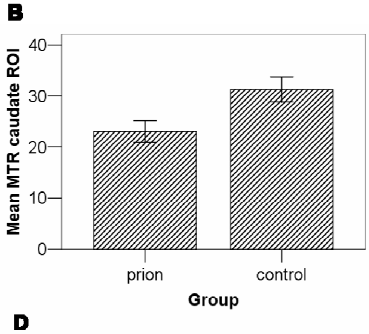
**Introduction:** Human prion diseases are rapidly progressive, uniformly fatal and rare degenerative disorders, with an incidence of 1 person per million in the worldwide population[1], classified etiologically into sporadic, inherited and acquired forms (including variant Creutzfeldt-Jakob disease (vCJD)). Magnetisation Transfer Ratio (MTR) has been shown to be a sensitive marker of cerebral pathology in conditions such as multiple sclerosis, *in vivo*[2] as well as post-mortem[3]. We have shown that *in vivo* whole brain MTR measures in patients with human prion disease decrease with disease severity at baseline[4]. The purpose of this study was firstly to determine *ex vivo* MTRs across intact cerebral and cerebellar hemispheres in a group of subjects with human prion diseases and to compare these with values obtained in a control group. Secondly, using smaller specimens obtained from a vCJD subgroup we utilised the higher spatial resolution and SNR available at 9.4T to correlate frontal cortex MTRs with histopathological measures.

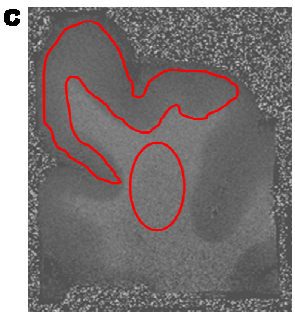
**Methods:** Institutional Ethical approval was obtained and all acquisitions performed with the prior consent of patients or their families. *Ex vivo* magnetisation transfer imaging (interleaved 2D gradient-echo sequence, TE7, TR1500, MT offset frequency 2kHz) of formalin-fixed cerebral and cerebellar hemispheres from 17 patients (11 male, 6 female, mean age 52.5, range 19 - 68) with the 3 forms of human prion disease (4 variant, 7 sporadic, 6 inherited), and 6 controls (1 male, 5 female, mean age 68.6, range 47 – 86) was performed at 1.5 T (GE Healthcare, Milwaukee, WI). MTR maps were generated and mean MTR calculated in 6 regions of interest (ROIs): cerebellar, frontal and occipital cortices, caudate nucleus, thalamus and frontal white matter using DispImage software [5] (see Figure A for caudate and thalamic ROIs). In the 6 vCJD cases, a block from the frontal cortex was excised and high-resolution MTR imaging (TE5, TR186, 16 averages, MT offset frequency 6 kHz) was performed at 9.4T (Varian Inc., Palo Alto, CA). MTR maps were calculated and ROIs defined in the frontal grey and white matter (Fig C). Following MRI, routine histological processing including immunohistochemistry was performed and the degree of gliosis, spongiosis and prion protein deposition in the frontal white and grey matter were scored from 0-3 (3 most severe). The Mann-Whitney U test was used to assess differences between the combined patient group and controls and Spearman rank correlation to assess relationships between MTR and histological measures.

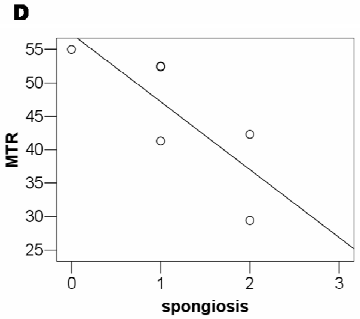
**Results:** Mean ROI MTR at 1.5T was significantly lower in patients with human prion diseases as compared to controls in cerebellar (p=0.003), frontal (p=0.004) occipital cortex (p=0.03), caudate nucleus (p=0.001) (see Fig B) and thalamic (p=0.001) ROIs, but not in the frontal white matter (p=0.35)). The high-resolution 9.4T measurements revealed a significant negative correlation between cortical MTR and spongiosis (r=-0.686, p=0.020, Fig D). No significant correlations between MTR and white matter histopathology scores were observed.

**Conclusions:** We have shown for the first time that, *ex vivo*, MTR is lower in cortical and deep grey matter, but not white matter, in patients with human prion disease compared to controls, presumably reflecting an increase in the fraction of free-to-bound water within these tissues. In targeted high-resolution MTR measurements we have also shown that cortical MTR correlated negatively with increasing spongiosis, a histopathological feature unique to prion disease[6]. The major advantage of post mortem quantitative MRI is the possibility of direct comparison with histology; our results suggest that MTR may provide a useful *in vivo* surrogate marker for pathology in human prion disease.

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