Outer and inner cortical MTR abnormalities observed in clinically isolated syndromes

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PURPOSE:
To investigate inner and outer cortical magnetisation transfer ratio (MTR) changes in people with a clinically-isolated syndrome (CIS) and compare MTR abnormalities in those who remained CIS and those who went on to develop multiple sclerosis (MS) after 15 years.

BACKGROUND: Cortical grey matter (CGM) pathology is common in MS (1-3). Histopathological studies have shown that demyelinating lesions preferentially form in the outer (subpial) CGM (4,5), in some people with secondary progressive (SP) MS neuroaxonal loss is also greater adjacent to the outer surface of the brain, and it has been suggested that these abnormalities may be associated with meningeal inflammation (6). While most marked in SPMS, a recent biopsy study has shown evidence of CGM pathology in clinically early MS (1). CGM abnormalities are difficult to detect using MRI. A recent study used MTR to investigate inner and outer cortical abnormalities in relapse-onset MS (7), and consistent with histopathological findings, found greater disease effects on outer when compared with inner cortical MTR (cMTR) in people with relapsing-remitting and SPMS. We wanted to investigate whether inner and outer cMTR abnormalities are present in patients with CIS, which is often the first clinical manifestation of relapse-onset MS.

METHODS:
Subjects: Seventy-two people with clinically-isolated optic neuritis (ON) underwent MRI scanning within 6 months of onset (mean age 33.4 years, 51 female) and were followed up 15 years later. MS was diagnosed using the McDonald 2010 criteria (8). Thirty-six healthy controls (mean age 34.0, 24 female) were also scanned.

MRI acquisition: Imaging was performed using a 1.5 T GE Signa scanner (GE, Milwaukee, WI). The following data were acquired (sequence details are given in Figure 1):

(i) Dual-echo proton-density (PD)/T_2-weighted images
(ii) 3D fast spoiled gradient recalled (FSPGR) images
(iii) MTR data using a dual-echo, spin-echo sequence

Image Analysis: White matter lesions were outlined on PD/T2-weighted images using Jim v6.0 (Xinapse systems, Aldwincle, UK) by one investigator (WJB). Lesion masks were registered to corresponding 3D-FSPGR (T_1-weighted) images via pseudo-T_1-weighted images (9). Transformations were computed using NiftyReg (10,11) and applied to lesion masks to enable lesion filling (12, 13). Segmentation of lesion filled T_1-weighted images was performed using SPM12 (Wellcome Trust Centre for Neuroimaging, London, UK)). Maximum likelihood classification of all voxels was performed, and resulting tissue probability maps were binarised using a ≥90% probability threshold (7). Brain parenchymal fractions (BPF) were calculated for use as a covariate in the statistical models, and T_1-weighted lesion filled brain extracted volumes were also generated, as required by the NiftySeg software (14).

Following cortical segmentation (14) sub-division of CGM into inner and outer cortical bands was performed using methods described previously (7, 15, 16) (a conservative 99% threshold was applied to CGM probability maps to limit potential partial volume effects). T_1-weighted data were affine registered to each subject's MTR data, via the pseudo-T_1-weighted images (10, 11), and MTR maps were calculated (using the short echo data because of its higher signal-to-noise ratio (SNR) than the longer echo data).

Statistical Analysis: All statistical analyses were performed using SPSS (IBM SPSS version 22 for Windows (SPSS, Inc., Chicago, IL, USA)). Between-group differences in inner and outer mean cMTR were examined using one-way analysis of covariance (ANCOVA) tests (with post-hoc paired comparisons), adjusted for age, gender and BPF.

RESULTS:

At baseline the ON group had significantly lower outer ($p<0.001$) and inner cMTR ($p<0.001$) compared with controls. The outer-to inner cMTR ratio was significantly lower in ON than controls ($p<0.001$) (values reported in Figure 2).

In the ON group, inner and outer cMTR were lower in both those who developed MS after 15 years ($n=56$, $p<0.001$) and in those that remained CIS ($n=16$, $p<0.05$) compared with controls. The outer-to-inner cMTR ratio was also significantly lower in patients who developed MS ($p<0.001$) compared with controls. There was no difference in the outer-to-inner cMTR ratio between those who remained CIS and controls.

Example healthy control single slice images with inner and outer cortical bands superimposed are shown in Figure 3.

DISCUSSION AND CONCLUSIONS:

Soon after a clinically isolated ON we found reductions in the outer and inner cMTR similar to previous findings in established relapse-onset MS (7). When compared with controls, a significant reduction in outer-to-inner cMTR ratio was observed in those who developed MS within the next 15 years, but not those who remained CIS. These findings suggest that the pathological changes underlying abnormal outer-to-inner cMTR ratios start early in the course of relapse-onset MS, and greater outer cortical changes may be relevant to the development of MS in patients with CIS.

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Sequence	Imaging plane	TR (ms)	TE (ms)	TI (ms)	Slices	Slice thickness	FOV	Acquisition matrix	MT pulse details
Dual echo PD/T_2-weighted	Axial	3200	15/90		46	3mm	240x180mm^2	256x256	
3D-FSPGR (T_1-weighted)	Coronal	16	4.2	450	124	1.5mm	300x225mm^2	256x160	
MTR	Axial	1720	30/80		28	5mm	240x240mm^2	256x128	Hamming apodized 3-lobe sinc pulse, duration 64ms, flip angle 1430°, peak amplitude 14.6 μT giving a normal bandwidth of 62.5 Hz, applied 1kHz off resonance

Figure 1: Sequence acquisition parameters

	Healthy Controls (n=36)	Patients		All patients (n=72)
		CIS (n=16)	MS (n=56)	
Outer cMTR (± SD) (pu)	31.4 (±0.71)	30.9 (±0.77)*	30.8 (±0.57)***	30.8 (±0.62)***
Inner cMTR (± SD) (pu)	34.5 (±0.48)	34.2 (±0.51)*	34.1 (±0.47)***	34.2 (±0.47)***
Outer-to-inner cMTR ratio	0.908 (±0.0105)	0.904 (±0.0102)	**0.901 (±0.0078)*****	0.901 (±0.0084)

*p<0.05, **p<0.01, ***p<0.001 compared to controls

Figure 2: Inner and outer cortical MTR (cMTR) values and outer-to-inner cMTR ratio values for different subgroups scanned in the study.

Figure 3: Example healthy control subject single slice T_1-weighted image (left, in MTR space) and corresponding MTR map (right), with inner (yellow) and outer (blue) cortical bands superimposed