Magnetisation transfer imaging of subpial cortical abnormalities in multiple sclerosis

Rebecca Sara Samson[1], Manuel Jorge Cardoso[2,3], Nils Muhlert[4], Varun Sethi[4], Claudia Angela M Wheeler-Kingshott[4], Maria A Ron[4], Sebastian Ourselin[2,3], David H Miller[4], and Declan T Chard[4]

[1]NMR Research Unit, Queen Square MS Centre, Department of Neuroinflammation, UCL Institute of Neurology, London, England, United Kingdom, [2]Centre for Medical Image Computing, UCL Department of Computer Sciences, London, United Kingdom, [3]Dementia Research Centre, UCL Institute of Neurology, London, United Kingdom, [4]NMR Research Unit, Queen Square MS Centre, Department of Neuroinflammation, UCL Institute of Neurology, London, United Kingdom

Target audience: Clinicians interested in measures of cortical abnormalities in multiple sclerosis (MS) and advanced image analysis methods

Purpose: To develop a method for separation of inner and outer cortical grey matter (GM) bands and investigate associations of clinical status with inner and outer cortex magnetization transfer ratio (MTR) measurements in a large cohort of people with MS and healthy volunteers

Introduction: Cortical demyelination is a common pathological finding in MS. *Post mortem* studies, sampling tissue from people with predominantly long-standing progressive MS, have shown extensive cortical demyelination, in some instances exceeding that observed in the white matter (WM) (1-3). Cortical lesions have also frequently been seen in biopsy material taken from people after a first clinical episode that later developed into MS (4). MRI studies investigating cortical lesions have been hampered by low sensitivity, and subpial lesions (the most common type of cortical lesion observed pathologically) are almost never detected with current clinical scanners (operating at up to 3T). An alternative approach to assess the effect of cortical lesions *in vivo* is to use a quantifiable MRI measure that is sensitive to demyelination; MTR has proven sensitive to myelin content in WM (5-6), and as such has potential to be a biomarker of cortical demyelination *in vivo* in humans. The aim of this study was to investigate the relationship between inner and outer cortical abnormality and clinical course by subdividing the cortex into inner and outer 'bands', measuring the MTR in them, and investigating possible associations with clinical course of MS in a large cohort of MS patients.

Methods: ***Subjects:*** Forty-four relapsing-remitting (RR) (mean age 41.9 years, median Expanded Disability Status Scale (EDSS) 2.0), 25 secondary progressive (SP) (54.1 years, EDSS 6.5) and 19 primary progressive (PP) (53.1 years, EDSS 6.0) MS patients and 35 healthy control (HC) subjects (mean age 39.2 years) were included in this study. Patients were clinically assessed, and their EDSS score and components of the MS Functional Composite (MSFC) (nine hole peg test [9HPT], 25 foot timed walk test [TWT] and Paced Auditory Serial Addition Test [PASAT], expressed as z-scores) were determined using published normative data (7).

MR acquisition: Subjects were scanned using a 3T Philips Achieva system (Philips Healthcare, Best, The Netherlands) with a 32-channel head coil and multi-transmit technology, using the following sequences (both acquired sagittally, with field-of-view (FOV) 256x256x180mm^3; voxel size1x1x1mm^3): i) T_1-weighted (T_1w) volumes using a 3D inversion-prepared (TI=824ms) gradient echo (FFE) sequence (TR/TE=6.9/3.1ms); flip angle (α)=8°; ii) MTR data with a 3D slab selective spoiled gradient echo (FFE) sequence with 2 echoes (TR=6.4ms, TE1/TE2=2.7/4.3ms, α=9°) with and without Sinc-Gaussian shaped MT saturating pulses of nominal α=360º, offset frequency 1kHz, duration 16ms applied prior to the excitation pulse.

Image Analysis: Each subject's lesion-filled (8) T_1-weighted volume was segmented using the 'new segment' tool in SPM8 (Wellcome Trust Centre for Neuroimaging, London, UK), and the resulting tissue probability maps used to generate a brain mask, as a starting point for the LoAd (9) segmentation algorithm, which explicitly models partial volume corrupted intensities. A conservative 90% threshold was applied to the cortical GM probability maps in order to limit potential partial volume effects. The cortex was subdivided into inner (adjoining WM) and outer (subpial, abutting CSF) bands using a Laplace equation based framework. The normalised central curve (10) of the Laplace equation based cortical thickness map was used to bisect the cortex (as in (9-11)), ensuring an equidistant separation of the cortex, when measured along the inner-to-outer boundary trajectory. MTR data for each subject were affine registered to their T_1w volume, and inner and outer cortical masks were then applied to calculated MTR maps to obtain MTR values for each cortical band. These processes are illustrated in figure 1. All statistical analysis was performed using SPSS version 11.0 for Windows (SPSS, Inc., Chicago, IL, USA). Differences compared to control values were tested via one-way ANCOVA tests with post-hoc paired comparisons, with age, gender and cortical band volume included as covariates.

Results: MTR values in the inner and outer cortical bands are given in Table 1. ***Outer cortex:*** Significant correlations of outer cortex MTR with clinical outcome measures were observed when the RR and SPMS subtypes were combined into a relapse-onset group: EDSS (r=-0.50, p<0.001), TWT (r=0.45, p<0.001, 9HPT (r=0.39, p<0.001), PASAT (r=0.37, p<0.01), disease duration (r=-0.43, p<0.001). In the RRMS subgroup, correlations with outer cortex MTR were as follows: EDSS (r=-0.48, p<0.01), TWT (r=-0.53, p<0.001), 9HPT (r=0.41, p<0.01), PASAT (r=0.38, p<0.05), disease duration (r=-0.38, p<0.01). ***Inner cortex:*** In the relapse-onset patient group the following significant correlations were observed with inner cortex MTR: EDSS (r=-0.43, p<0.001), TWT (r=-0.41, p<0.001), 9HPT (r=0.26, p<0.05), PASAT (r=0.39, p<0.001), disease duration (r=-0.29, p<0.05). In RRMS patients, significant correlations with inner cortex MTR were as follows: EDSS (r=-0.45, p<0.01), TWT (r=-0.56, p<0.001), 9HPT (r=0.35, p<0.05), PASAT (r=0.46, p<0.01), disease duration (r=-0.31, p<0.05). No significant correlations of clinical outcome measures or disease duration with inner or outer cortex MTR were observed in the PP or SPMS subgroups.

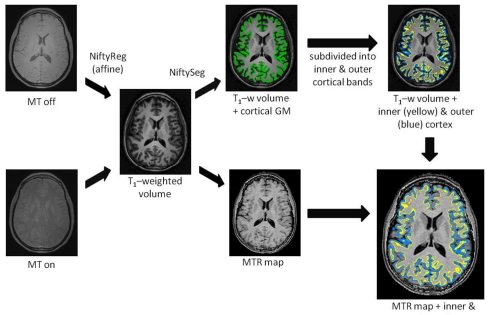

Figure 1: Flowchart illustrating image analysis steps

Table 1: Inner and outer cortex mean MTR values for all subject groups, with mean percentage reductions compared to the mean control value in italics; *= p<0.05, **= p<0.01, ***= p<0.001 compared to the control MTR value

Group	Inner cortex MTR (± SD) (pu), *% reduction*	Outer cortex MTR (± SD) (pu), *% reduction*	Ratio of outer to inner cortex MTR (± SD)
Controls	34.6 (±0.61)	32.2 (± 0.61)	0.93 (± 0.008)
All MS	34.0 (± 0.84)**, *1.7%*	31.2 (± 1.37)**, *3.2%*	0.92 (± 0.026)*
PPMS	34.1 (± 0.78)*, *1.6%*	31.5 (± 1.00), *2.1%*	0.93 (± 0.018)
SPMS	33.7 (± 0.94)***, *2.7%*	30.4 (± 1.56)***, *5.7%*	0.90 (± 0.034)***
RRMS	34.2 (± 0.76)*, *1.2%*	31.5 (± 1.23)*, *2.3%*	0.92 (± 0.021)

Discussion: In all groups, including HC, MTR was lower in the outer compared with the inner cortex, likely due to the increasing myelin density from the outer to inner margins of the cortex, abutting the WM. A significant decrease in outer cortical MTR, which would be consistent with the presence of subpial demyelination (5-6), was observed in RR and SPMS, but not PPMS. The results indicate that subpial cortical pathology begins in the RR phase of MS but becomes more prominent when people develop SPMS. The results also suggest that preferential subpial cortical pathology is not necessarily a feature of progressive MS *per se*, but is more characteristic of SP than PPMS. Set in the context of previous histopathological studies, this implies a potential role for CSF-mediated factors or meningeal inflammation in the pathogenesis of relapse-onset MS, and a less significant role in PPMS, where the inner cortex is abnormal but outer layers are relatively spared. Correlations with clinical measures were seen with inner and outer cortical MTR, but were generally stronger with outer rather than inner cortical MTR, and were confined to the RRMS group. This suggests that outer more so than inner cortical MTR reflects clinically relevant pathology, particularly in the RR phase of MS. Further work is required to determine if early subpial changes in RRMS are of prognostic significance. Studies including larger progressive cohorts in particular would be desirable, and longitudinal observations are necessary to determine the dynamics and ongoing clinical significance of outer cortical MTR abnormalities.

References: [1] Peterson JW *et al.* Ann Neurol. 2001; 50(3):389-400; [2] Bo L *et al.* J Neuropathol Exp Neurol. 2003; 62(7):723-32; [3] Kutzelnigg A *et al.* Brain. 2005; 128(11):2705-12; [4] Luchinetti CF *et al.* N Engl J Med. 2011; 365(23):2188-97; [5] Schmierer K *et al.* Ann Neurol. 2004;56(3):407-15; [6] Schmierer K *et al.* J Magn Reson Imaging. 2007; 26(1):41-51; [7] Fischer JS *et al.* Mult Scler. 1999; 5(4):244-50; [8] Chard DT *et al.* J Magn Reson Imaging. 2010; 32(1):223-8; [9] Cardoso MJ *et al.* NeuroImage. 2011; 56(3):1386-97; [10] Yezzi A, Prince JL. Computer Vision - Eccv 2002, Pt Iv. Berlin: Springer-Verlag Berlin; 2002. p. 575-89; [11] Cardoso MJ *et al.* Inf Proc Med Imag; Kloster Irsee, Germany, 2011. p. 159-70.

Acknowledgements: *The authors would like to thank the MS Society of Great Britain and Northern Ireland, the EPSRC and the Department of Health's NIHR Biomedical Research Centres funding scheme for funding. We would also like to thank all the participants of this study.*