Reproducibility of *in vivo* inner and outer cortical magnetisation transfer ratio measurements

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

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

Target audience: Clinicians and scientists interested in measures of cortical abnormalities and advanced image analysis methods.

Purpose: To investigate the reproducibility of inner and outer cortical grey matter (GM) magnetization transfer ratio (MTR) in healthy volunteers.

Introduction: Cortical grey matter (CGM) pathology is commonly observed in multiple sclerosis (MS). Cortical demyelinating lesions may be present early in the disease course (1) and can be extensive, especially in long-standing progressive MS (2-4). Additional cortical pathological findings include significant neuronal loss, reductions in synapse and neurite/axon density, microglial activation, and damage to the glia limitans (2,5). A high frequency of demyelinating lesions has been reported in the outer, subpial, cortex, especially in secondary progressive MS (3,4), but subpial lesions are almost never detected with current clinical scanners (operating at up to 3T).

In a recent study (6), the relationship between inner and outer cortical abnormality (as measured by the magnetisation transfer ratio (MTR) and clinical course was investigated in a large cohort of MS patients of different clinical subgroups and healthy volunteers. A higher inner than outer cortical MTR was observed in healthy controls, and attributed to the higher myelin content in inner cortical layers. Outer cortical MTR reductions (consistent with subpial demyelination) were demonstrated in patients, with the largest changes observed in secondary progressive MS. The reduced inner and outer cortical MTR in MS patients compared to controls is compatible with the tissue damage reported in neuropathological studies of CGM, especially demyelination and neuroaxonal loss.

To be of broad applicability, however, the measurement method should have high intra-site reproducibility. The aim of this work, therefore, was to establish the reproducibility of inner and outer cortical MTR measurements in healthy controls.

Methods:

Subjects: Eight healthy control subjects (5 male, mean age 37.8 (± 15.0) years) were scanned twice with a mean time between scans of 1.66 (± 0.49) years, and their results were used to assess the test-retest reliability of inner and outer cortical MTR measurements.

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, and duration 16ms applied prior to the excitation pulse.

Image Analysis: Each subject's lesion-filled (7) T_1-weighted volumes were segmented using the 'new segment' tool in SPM8 (Wellcome Trust Centre for Neuroimaging, London, UK), and the resulting tissue probability maps were used to generate a brain mask, which in turn was the starting point for the LoAd (8) segmentation algorithm, which explicitly models partial volume corrupted intensities. A conservative 90% threshold was applied to the cortical GM probability maps obtained from LoAd in order to limit potential partial volume effects (see also reference [6]). The cortex was subdivided into inner (adjoining WM) and outer (subpial, abutting CSF) bands using a Laplace equation based framework. The normalised central curve (9) of the Laplace equation based cortical thickness map was used to bisect the cortex (as in (8-10)), taking into account local curvature and different regional thicknesses. MTR data for each subject were affine registered to their T_1w volume using NiftyReg (11, 12), and inner and outer cortical masks were then applied to calculated MTR maps [$MTR=(MT_{off}-MT_{on})/MT_{off}$], measured in percent units (pu), to obtain MTR values for each cortical band. The same cortical grey matter masks were used to estimate inner and outer cortical band tissue volumes in each subject.

Paired t-tests were performed to test for differences in MTR and volume between the two time points and coefficients of variation (CV) were calculated.

Results: Figure 1 shows a single subject MTR map with inner and outer cortical bands superimposed, at baseline and follow-up (with follow-up data rigid-body aligned to baseline data for illustration). Inner and outer cortical band MTR values and volumes measured at both time points (1 and 2) are given in Table 1.

Table 1: Individual subject inner and outer cortical MTR and volume measurements at two time points 1 and 2

Subject	Inner MTR 1 (pu)	Inner MTR 2 (pu)	Inner Volume 1 (ml)	Inner Volume 2 (ml)	Outer MTR 1 (pu)	Outer MTR 2 (pu)	Outer Volume 1 (ml)	Outer Volume 2 (ml)
1	34.6	34.0	156.5	139.6	32.4	31.8	210.6	185.3
2	34.8	34.6	166.3	166.1	32.5	32.5	204.4	200.1
3	34.3	33.8	213.8	207.9	31.6	31.5	248.0	239.0
4	34.1	34.1	187.9	182.3	31.9	31.7	228.4	208.9
5	34.0	34.6	152.2	158.8	31.9	32.5	187.8	193.5
6	35.4	34.1	194.9	172.0	32.8	32.0	242.0	203.1
7	34.2	33.8	144.5	146.0	31.9	32.3	177.0	173.8
8	34.5	34.6	183.5	163.6	32.6	32.7	238.4	202.2

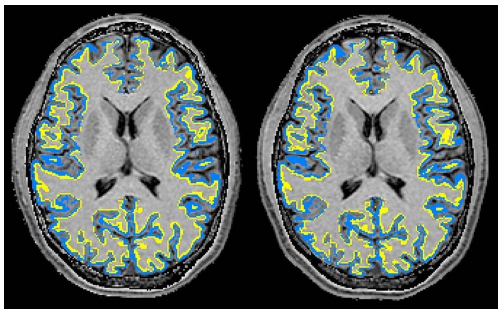

Figure 1: Single subject MTR map with inner and outer cortical bands, at timepoints 1 (left) and 2

No significant difference was observed in inner or outer cortical MTR between the two time points, or inner cortical band volume. However, the mean outer cortical volume was reduced from 217.1ml to 200.7ml ($p<0.05$), which might partially be explained by normal aging. However, the cortical masks used to extract MTR values were substantially smaller than segmentations used for atrophy measures (obtained using SPM8) and reflect the deliberately conservative nature of segmentation designed to exclude partial volume influences on the MTR findings. Examining repeat scans of 8 healthy controls, we found CVs of 1.23% for inner cortical MTR and 0.99% for outer cortical MTR.

Discussion and Conclusions: Our findings demonstrate the high reproducibility of the technique, with very low CVs observed for both inner and outer cortical MTR in healthy subjects over a time-span that is consistent with longitudinal studies of pathology or clinical trials in neurodegenerative diseases. Further work might include investigating the co-registration of data at both time-points to a common 'mid-point' prior to data analysis, in addition to studying a larger group of subjects.

References: [1] Luchinetti CF *et al*. N Engl J Med. 2011; 365(23):2188-97; [2] Peterson JW *et al*. Ann Neurol. 2001; 50(3):389-400; [3] Bo L *et al*. J Neuropathol Exp Neurol. 2003; 62(7):723-32; [4] Kutzelnigg A *et al*. Brain. 2005; 128(11):2705-12; [5] Wegner C *et al*, Neurology. 2006;67(6):960-7; [6] Samson RS *et al*. Proc ISMRM 2013, SLC, USA (0049); [7] Chard DT *et al*. J Magn Reson Imaging. 2010; 32(1):223-8; [8] Cardoso MJ *et al*. NeuroImage. 2011; 56(3):1386-97; [9] Yezzi A, Prince JL. Computer Vision - Eccv 2002, Pt Iv. Berlin: Springer-Verlag Berlin; 2002. p. 575-89; [10] Cardoso MJ *et al*. Inf Proc Med Imag; Kloster Irsee, Germany, 2011. p. 159-70; [11] Modat M *et al*. Comput Methods Programs Biomed. 2010; 98: 278-84; [12] Ourselin S *et al*. Image and Vision Computing. 2001; 19: 25-31.

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.*