

Surface-based techniques reveal regions of reduced cortical magnetization transfer ratio in patients with MS

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Introduction: Evidence from pathological studies continues to underscore the significant involvement of cortical grey matter (GM) in multiple sclerosis (MS) [Stadelmann, C., et al., *Curr Opin Neurol*, 2008. 21(3):229-34]. Although some of this cortical pathology is now detectable as a result of advances in sequence development (e.g., double inversion recovery), contiguous areas of subpial demyelination, which are the most common subtype of cortical lesions sampled at autopsy, remain largely undetectable with conventional methods [Geurts JJ, et al., *AJNR*, 2005 26(3):572-7]. Magnetization transfer imaging has already been shown to be sensitive to changes in myelin content in white matter [Pike, G B, et al., *Radiology*, 2000. 215(3):824-30; Schmierer, K., et al., *Ann Neurol*, 2004. 56(3): 407-15]. We used a novel surface-based method to quantify the extent of subpial decreases in magnetization transfer ratio (MTR) in order to identify regions of cortical demyelination. Our method was applied to group data from MS patients and normal controls, as well as to data from individuals to identify areas that differed from the control group.

Methods: MR scans of patients recruited from the MS Clinic of the Montreal Neurological Institute and Hospital for a previous study were analyzed in this retrospective analysis. Twelve patients with secondary progressive MS [SP: 8 females, 4 males; Age: mean (range) = 47 yrs (30-62); Symptom Duration: 14 yrs (3-26); Kurtzke's Expanded Disability Status Scale (EDSS): 5.7 (3.5-8.0)] who had baseline scans that passed our quality-control standard were selected. Twelve normal controls [NC, 8 females, 4 males; Age: 44 yrs (28-60)] and 12 patients with relapsing remitting MS [RR, 8 females, 4 males; Age: 45 yrs (30-59), Symptom Duration: 13 yrs (1-33), EDSS: 2.5 (1.0-4.0)] were also selected from all baseline scans such that all groups were matched for sex and mean age. Subjects were scanned on a 1.5T Philips ACS II scanner (Philips Medical Systems, Best, the Netherlands). Oblique axial T1-weighted images were acquired parallel to the antero-posterior commissural line using a spoiled gradient-recalled echo sequence (TR = 35 ms, TE = 10 ms, 256x256 matrix, 250 mm field-of-view, 60 slices, 3 mm thickness, 1 signal average). Images were acquired without and with a 1.2 ms on-resonance, bipolar (1-2⁻¹) magnetization transfer pulse (20 μ T RF field strength) placed just before each slice-selective excitation. To calculate the MTR for each patient, the MT image volume acquired with the saturation pulse (Sat) was first linearly registered (mrirtself, McConnell Brain Imaging Centre) to the volume without the saturation pulse (NoSat), and the MTR image volume then calculated as: $100 * (\text{NoSat} - \text{Sat})/\text{NoSat}$.

Cortical reconstruction was performed using the NoSat T1w image volume as input to the Freesurfer image analysis suite (v4.0.5), which is documented and freely available online (<http://surfer.nmr.mgh.harvard.edu/>). Intermediary surfaces were then created from the generated pial and white matter surfaces. The information from the MTR image volume was computed for every vertex on each surface and blurred along the surface with a 10 mm FWHM kernel. To facilitate group comparisons, the cortical models were registered to a spherical atlas that utilizes individual cortical folding patterns to match cortical geometry across subjects, after which *t*-statistics for the MTR differences at each vertex were computed and then thresholded for significance using a false discovery rate of 0.05. This was done for each group (SP vs. NC, RR vs. NC) and for each patient compared to the NC group.

Simulations were performed to estimate the sensitivity of our technique at detecting areas of decreased MTR. MTR values at each vertex along a surface were uniformly decreased to be from 1 to 6 MTR percentage units (pu) below the average MTR value of the 12 NC. Each of the seven simulation datasets were then run through the method described above, where each vertex of these lowered MTR surfaces was compared to the group of 12 NC. The resulting thresholded maps show the areas where we are sensitive to detecting a significant difference, given a decrease in MTR greater than or equal to the simulated level.

Results and Discussion: When the SP and NC groups were compared, large significant decreases in MTR values were detected along multiple surfaces. Conversely, no significant areas of decreased MTR were found for the RR group compared to the NC group. The highlighted areas that were detected between groups map the spatial distribution of decreases in cortical MTR within a particular disease subset. When individual subjects were compared to the NC group, no significant differences were detected in 14 of 24 patients (4 SP, 10 RR); however, the remaining 10 of 24 (8 SP, 2 RR) patients showed large areas of contiguous decreased MTR, with spatial distributions similar to subpial GM lesions described pathologically [Bø L, et al., *J Neuropathol Exp Neurol*, 2003 62(7):723-32]. The increased frequency of patients with a detectable difference in the SP group compared to the RR group, as well as the general increased extent of the differences seen, are consistent with the expected increase in cortical pathology in the later stages of MS. Simulation results indicated that, once a deviation of 4 pu from the mean is achieved, we can reliably detect changes in many areas of the brain; they also indicated that our sensitivity is nearly global once the MTR values deviate by 6 pu from the mean of the normal controls.

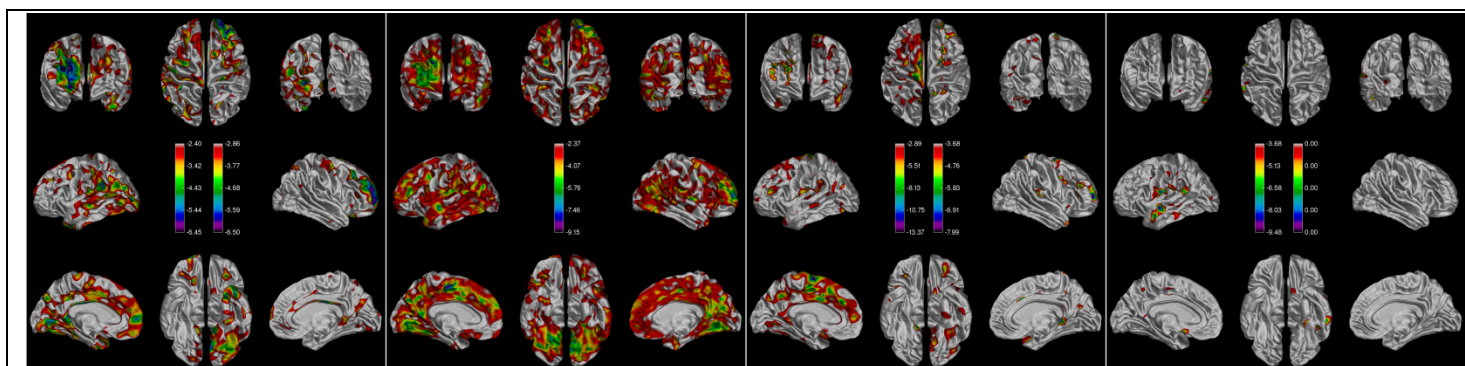


Figure 1 - Colored areas indicate thresholded *t*-statistics for regions of significantly low MTR. Two color bars are used where the threshold was different for the left and right hemispheres. From left to right: (i) SP group compared to NC group (RR group compared to NC showed no difference); (ii) simulation results for a decrease of 4 pu (highlighted areas show the regions in which we are able to detect a significant difference given a brain that was 4 pu below our NC MTR values); (iii) individual results for the median SP patient in terms of extent of decreased MTR; (iv) individual results for the median RR patient in terms of extent of decreased MTR. (Note the decreased extent of coverage in the median RR patient compared to the median SP patient.)