A Voxel-Wise Random Field Theory-Based Magnetization Transfer Approach for Detecting Focal Demyelination and Remyelination in Multiple Sclerosis

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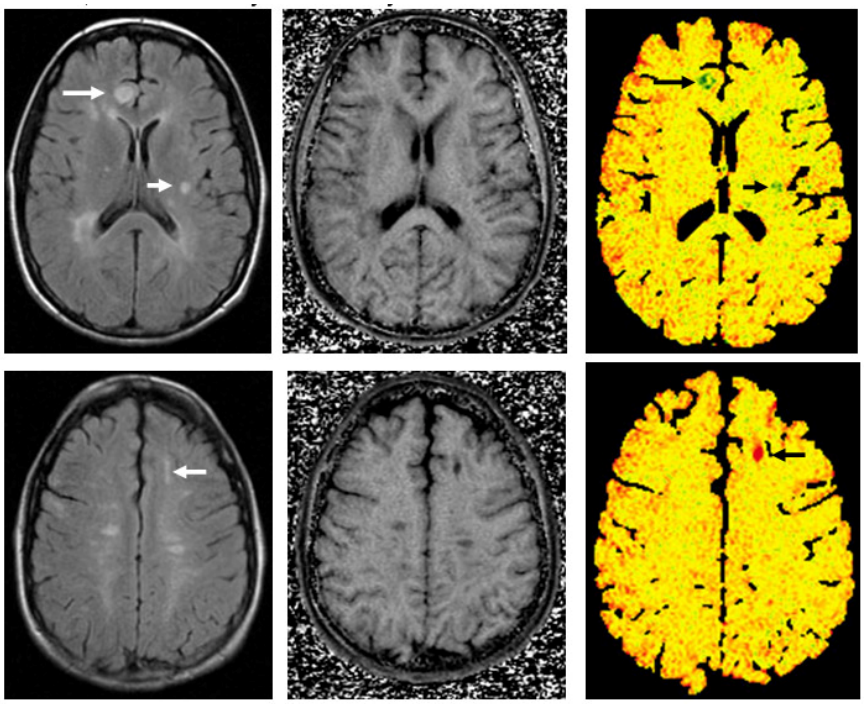
Objectives: To create and validate a sensitive MRI-based method for detecting subject-specific active demyelination and remyelination in-vivo in patients with multiple sclerosis (MS).

Background: Compared to conventional MRI imaging techniques, magnetization transfer ratio (MTR) mapping has demonstrated increased sensitivity and specificity for detecting myelin changes. However, most approaches (cross-sectional or longitudinal) for investigating MTR abnormalities have been limited to either global or region-of-interest measures. Spatially-specific approaches (i.e. voxel-wise) have recently been histopathologically validated, but have been limited in their sensitivity by the need for very conservative change thresholds due to the large multiple-comparisons problem. Random field theory (RFT) has been used extensively for functional MRI and for voxel-based morphometry (VBM), and provides a means of evaluating probabilities for clusters of voxels instead of for individual voxels, and therefore allows for less conservative but equally statistically rigorous change thresholds.

Methods: We performed one-year serial magnetization transfer imaging (MTI) on 15 patients with MS and 10 normal controls (NC). MTI images were processed to create baseline and follow-up MTR maps, which were then co-registered into the baseline space via a fully automated rigid-body registration algorithm. Follow-up and baseline maps were then bias-corrected to remove positioning and time-related differences in field and MT pulse effects. Both images were then smoothed with a 3mm (FWHM) window to diminish noise according to the matched filter theorem and to better facilitate subsequent RFT analysis. Voxel-wise subtraction was then performed on the smoothed maps to create a voxel-wise change map. A robust intensity normalization procedure was then applied to the change map to yield voxel-wise change Z-scores. The final Z-score map was then evaluated with an RFT-based clustering algorithm, retaining only clusters with an overall p-value of 0.05.

Results: NC showed 2.3 ml of decreased MTR and 6.5 ml of increased MTR, while MS patients presented 139.9 ml of decreased and 32.6 ml of increased MTR. The differences were highly significant between the groups.

Conclusions: The RFT voxel-wise MTR approach provides an opportunity to measure focal demyelination and remyelination in-vivo in patients with MS. Clinical relevance of this method is under investigation.



RFT MTR difference map approach. From left to right are displayed baseline and follow-up MTR maps and dynamic MTR change maps. The MTR change map shows areas of MTR stability (yellow) decrease in MTR (red) and increase in MTR (green) associated with lesions and normal appearing brain tissue in a patient with multiple sclerosis over one year. Upper row: Note the two T2 lesions (arrows) corresponding to the green areas (increase of MTR) on the MTR change map (arrows) over the follow-up - possibly reflecting remyelination. Lower row: Note the T2 lesion (arrow) corresponding to the red area (decrease of MTR) on the MTR change map (arrow) over the follow-up possibly reflecting demyelination. Upper and lower rows: Note the high number of red and green areas widespread in the brain reflecting possible demyelinating and remyelinating processes.