

Sensitive and Noise-Resistant Identification of Voxel-Wise Changes in Magnetization Transfer Ratio via Cluster Enhancement and M-Estimator-Based Monte Carlo Simulation

M. G. Dwyer¹, N. Bergsland¹, S. Hussein¹, J. Durfee¹, B. Weinstock-Guttman^{1,2}, and R. Zivadinov^{1,2}

¹Buffalo Neuroimaging Analysis Center, State University of New York, Buffalo, NY, United States, ²The Jacobs Neurological Institute, State University of New York, Buffalo, NY, United States

Objective: To develop a sensitive and reliable means for automatic quantification of voxel-wise (VW) changes in magnetization transfer ratio (MTR) in patients with multiple sclerosis (MS)..

Background: Most MTR analysis techniques have been histogram-based approaches looking at measures of mean MTR in a-priori regions of interest (ROIs) such as tissue segmentation maps or hand-drawn anatomical masks. Although these techniques can provide a great deal of information, they rely on a-priori location assumptions, and may therefore be less sensitive to changes that do not occur cleanly within predefined boundaries. Additionally, they are sensitive only to mean change in the area being analyzed rather than the overall level of activity. Competing processes of demyelination and remyelination may cancel each other out and result in a measurement falsely suggesting a lack of disease activity. More recent techniques have used a voxelwise approach to MTR change measurement that addresses the shortcomings of ROI-histogram approaches, but at the cost of greatly reduced sensitivity. With only a single observation per voxel, random noise in the underlying MTR maps results in the need for a very high change threshold, making it easy to miss large areas of subtle change. The recently proposed threshold-free cluster enhancement (TFCE) technique may allow for more sensitive analysis, but it is important to retain statistical rigor to determine what is likely to represent a valid change. To address this, we propose a Monte-Carlo simulation approach based on an M-estimator-based noise estimate taken from the normal-appearing-brain-tissue (NABT).

Methods: 1.5T MRI was performed at baseline and 1 year follow-up for thirty (30) patients with MS (19 relapsing-remitting, 11 secondary-progressive, age 43.1+/-10.8, median EDSS 4.0) and 15 normal controls (NC). Rigid-body co-registration was then performed for each subject to bring both baseline and follow-up images into a common halfway-space, after which MTR maps were generated. MTR map inhomogeneities due to coil and/or pulse effects were corrected via a combination of the N3 algorithm and very conservative high-pass filtering. VW subtraction was then performed to create a subject-specific longitudinal MTR change map. This map was then processed with the TFCE technique, enhancing voxels' signal based on a combination of degree of difference and extent of local neighborhood support. To determine a statistically motivated TFCE threshold, subject-specific Monte Carlo simulation was performed, driven by a robust scale estimate from the non-lesion tissue of the non-enhanced difference map. Random images were generated with a normal distribution and the observed standard deviation, TFCE was performed on each image, and a distribution of TFCE values was recorded. This approach allows for well-defined selection of thresholds using family-wise error correction, false discovery rate correction, or simple voxel-wise correction. For the current study, voxel-level 95th percentile supra-threshold focal areas of decrease (demyelination) or increase (remyelination) were quantified.

Results: Patients showed significantly more MTR decrease ($p<0.001$), but not increase compared to NC. Patients also showed more MTR decrease than increase ($p<0.001$). There was a correlation between MTR decrease and worsening of disability over 1-year.

Conclusion: The proposed VWMTR method provides a sensitive, clinically relevant means for identifying amount of demyelination/remyelination in vivo.



Figure 1. Left: Baseline MTR map. Center: Follow-up MTR map. Right: Color-coded MTR activity classification map, with yellow representing stable tissue, green representing significant increase, and red representing significant decrease.