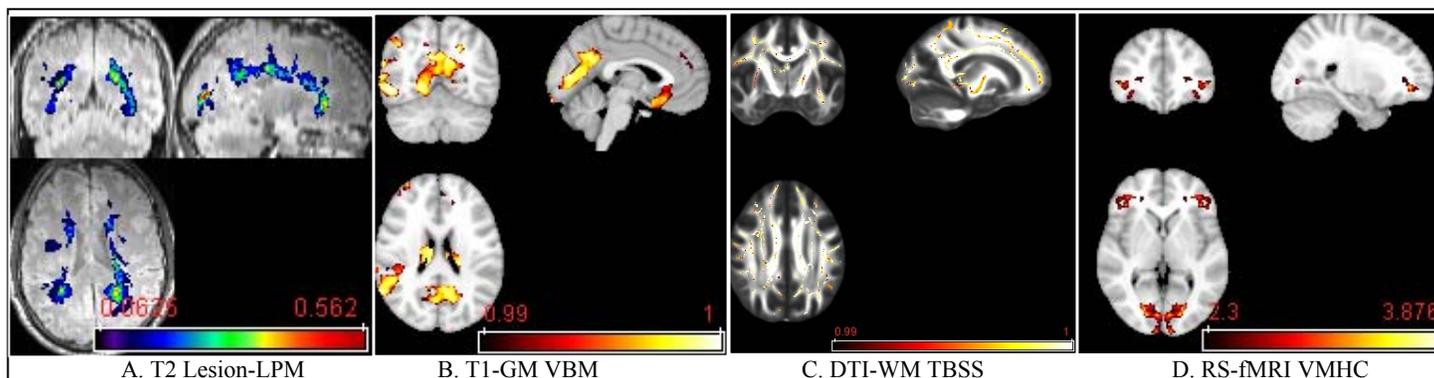


## Voxel-based Structural and Functional MRI Pattern Recognition and Correlation in Multiple Sclerosis (MS)

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**Introduction:** Multiple sclerosis (MS) is a chronic inflammatory demyelinating disease that affects the whole brain. The aim of this study was to assess different pathophysiological changes by investigating MRI distribution patterns of lesion probability, regional atrophy, microstructural integrity, and inter-hemispherical synchronization and their inter-correlation using voxel-based whole brain analyses in patients with MS.

**Methods:** Sixteen patients with clinically definite relapsing-remitting (RR) MS (mean age 43±8.7 years, 11 females, mean EDSS: 2.59±2.3) and 16 health volunteers (mean age 34±7.4 years, 9 females) were studied on Siemens 3T Tim Trio MR. Conventional imaging including axial T2-weighted and FLAIR imaging sequence as well as sagittal MPRAGE were obtained with whole brain coverage. In addition, whole-brain 3D DTI data were acquired with 3 b-values (0, 500, 1000) s/mm<sup>2</sup> and 30 diffuse directions (TR/TE = 6800/85msec, resolution of 2.3x2.3x2.3mm<sup>3</sup>, 55 axial slices). Resting state (RS)-fMRI was performed with subjects stay awake and eyes closed using a gradient echo EPI sequence (TR/TE = 2000/30msec, flip angle = 70°, resolution=3x3x3mm<sup>3</sup>, 0.6mm slice gap, 153 volumes) with 33 slices collected parallel to AC-PC line to cover the entire cerebrum. Lesions were first segmented using a semi-automatic in-house software (Firevoxel)<sup>1</sup> based on FLAIR images to create lesion volume image that was normalized to a common MNI template (2mm) in order to produce lesion probability map (LPM). After removing extracranial tissues with ROBEX<sup>2</sup> based on MPRAGE data, voxel-based morphometry (VBM) package in FSL was used for gray matter (GM), white matter (WM) and CSF segmentation and regional atrophy analysis with lesion paint-in algorithm to correct lesion misclassification on T1-MPRAGE. For evaluation of microstructural changes, voxelwise tract-based spatial statistics (TBSS)<sup>3</sup> was used to analyze DTI fractional anisotropy (FA) data on WM skeleton. In addition, RS-fMRI data were used to produce voxel-mirrored homotopic correlation (VMHC)<sup>4</sup> (scripts adapted from The 1000 Functional Connectomes Project: [http://www.nitrc.org/projects/fcon\\_1000](http://www.nitrc.org/projects/fcon_1000)) to evaluate inter-hemispherical coordination/synchronization. Lastly, support vector machine (SVM) classifier and factor analysis were performed to the global indices of each modality including lesion volume (mL), GM atrophy ratio, WM average FA and global GM VMHC to discriminate MS patients from controls and to investigate the contribution of each measurement. These parameters were fit with a Gaussian linear model (GLM) to patients' EDSS score to see how well they predict EDSS score.



**Figure 1.** Whole brain voxel-based analysis of lesion probability map (A) and regional GM atrophy (B), WM FA reductions (C) and VMHC deficits (D) in patients compared to controls (color indicates statistical probability in A-C and t-score in D).

**Results:** LPM (lesion distribution) was shown in *Figure 1A* with most lesions seen in the periventricular WM regions with a probability >12% in MS patients. Group analyses between patients and controls ( $P < 0.01$ ) showed regional GM atrophy (posterior cingulate, inferior parietal, middle frontal lobe, thalamus, basal forebrain and primary somatosensory cortex) (*Figure 1B*) and FA reduction in WM regions (corpus callosum, periventricular areas, cingulate bundles, optic radiation, etc) (*Figure 1C*). VMHC based RS-fMRI (*Figure 1D*) showed reduced inter-hemispherical homotopic correlation mainly in bilateral dorso-lateral prefrontal regions and primary visual cortex (cluster corrected  $P < 0.05$ ). In WM, the overlap regions of lesions and reduced FA regions by TBSS are primarily seen in the left periventricular WM around the occipital horn. There was a significant negative correlation between lesion volume and average FA of global WM in MS patients ( $r = -0.68$ ,  $P = 0.004$ ). In GM, the overlap regions between regional atrophy and VMHC changes were primarily seen in bilateral primary visual cortex without significant correlation between GM atrophy and global VMHC changes. The anatomical GM-WM abnormality correspondences between GM atrophy and WM FA reduction are identified in posterior cingulate / cingulate bundle, primary visual cortex / optic radiation, thalamus / thalamic radiation, and somatosensory cortex / superior longitudinal fasciculus. There was significantly reduced brain parenchyma fraction in MS patients (mean of 0.79 compared to 0.81 in controls,  $P = 0.03$ ). SVM showed that combining all the four measurements could achieve 88% accuracy of automatic classification of disease with majority of ~80% contribution from global VMHC and average FA. GLM fit showed that EDSS score is mostly influenced by patient's lesion volume, WM average FA and global GM VMHC ( $P < 0.01$ ).

**Conclusion:** Voxel-based whole brain analysis of multi-parameter MRI provides a useful tool to visualize regional abnormalities underlying different pathophysiological processes in MS patients. Our results of different distribution patterns from multispectral MRI with relatively less regional overlap may suggest the structural and functional measures are complementary to each other in understanding the complicated disease processes.

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3. Smith et al. Neuroimage. 2006;31:1487-1505. 4. Zuo et al. J Neuroscience. 2010;30(45):15034-15043.

**Acknowledgement:** This work was supported by the NIH grant R01 NS029029.