

Multicontrasts MRI improved the clinico-radiological correlation in early multiple sclerosis patients with minor deficits

Guillaume Bonnier^{1,2}, Alexis Roche^{1,3}, David Romanasco⁴, Samanta Simioni², Djalel-Eddine Meskaldji⁴, David Rotzinger³, Ying-Chia Lin⁵, Gloria Menegaz⁵, Myriam Schluep², Renaud Du Pasquier², Tilman Johannes Sumpf⁶, Jens Frahm⁶, Jean-Philippe Thiran⁴, Gunnar Krueger^{1,7}, and Cristina Granziera^{1,2}

¹Advanced Clinical Imaging technology group, Siemens-CIBM, EPFL, Lausanne, Vaud, Switzerland, ²Department of Clinical Neurosciences, Centre Hospitalier Universitaire Vaudois and University of Lausanne, Lausanne, Vaud, Switzerland, ³Department of Radiology, Centre Hospitalier Universitaire Vaudois and University of Lausanne, Vaud, Switzerland, ⁴STI / IEL / LTS5, EPFL, Lausanne, Vaud, Switzerland, ⁵Dept. of Computer Science, University of Verona, Italy, ⁶Biomedizinische NMR Forschungs GmbH, Max Planck Institute for Biophysical Chemistry, Göttingen, Germany, ⁷Healthcare Sector IM&WS S, Siemens Schweiz AG, Suisse, Switzerland

Target audience : Clinicians interested in multiple sclerosis, quantitative mapping and multiparametric analysis

Purpose: Conventional magnetic resonance imaging (MRI) of patients with multiple sclerosis (MS) provides only limited insights into the nature of brain tissue damage with modest clinical-radiological correlations. In this context, quantitative (q) and semi-quantitative (sq) brain MRI might help us to specify brain tissue alteration processes and provide new biomarkers of disease impact. In fact, changes in quantitative measures of proton relaxation times (T1, T2, T2*) as well as in semi-quantitative parameters such as magnetisation transfer ratio (MTR) reflect pathological processes such as demyelination, edema, tissue loss or iron accumulation. In this study, qMRI and sq-MRI techniques (T1, T2, T2*, MTR) were applied to study the potential of the MRI-accessible microstructural information to predict cognitive and motor scores in patients.

Methods: T1, T2, T2* relaxometry and magnetisation transfer MRI were performed at 3T in 36 relapsing remitting MS patients and 18 healthy controls (HC). All subjects were scanned on a 3 Tesla scanner 32-head channel coil (Magnetom Trio a Tim system, Siemens Healthcare, Erlangen, Germany). The protocol included : high-resolution 3D fluid attenuated inversion recovery (FLAIR) (TR/TE/TI = 5000/394/1800 ms, voxel size = 1.0x1.0x1.2 mm³, FoV = 256x240x223.2 mm³); 3D double inversion recovery (DIR) (TR/TE/TI = 10000/218/3650 ms, voxel size = 1.1x1.0x1.2 mm³, FoV = 256x240x192 mm³), MP2RAGE (TR/TE = 2300/2.98 ms, voxel size = 1x1x1.2 mm³, FoV = 256x240x160), MP2RAGE (TR/TE = 5000/3 ms, inversion time = 700 ms, FA = 4°, voxel size = 1x1x1.2 mm³, FoV = 256x240x160), T2 relaxometry (TR/TE = 5850/9-189 ms, voxel size = 1x1x4 mm³, FoV = 30x192x160, 21 echoes), T2* relaxometry (TR/TE = 47/1.23 ms, 32 gradient echoes, voxel size = 1.6x1.6x1.6 mm³, FoV = 217x217x179 mm³) with and without magnetization transfer (MT) pulse. T2* maps were obtained using a correction method based on an estimated B1 field map (1). MTR were computed from the T2* data. T2 maps were estimated from the multiecho spin-echo data using a model-based reconstruction (2). T1 maps were derived from the MP2RAGE volume (3). MP2RAGE, T2* echoes and T2 maps were linearly registered to respectively MP2RAGE volumes and T1 maps using ELASTIX (4). Regions of interest (ROIs) were then automatically extracted from the MP2RAGE images using an in-house software based on variational expectation-maximization tissue classification (5). The following ROIs were obtained: global white and cortical gray matter, thalamus and basal ganglia, cerebellar WM and GM. In addition, we computed lobar WM and GM (temporal, occipital, frontal, parietal). An experienced neurologist (CG) and a radiologist (DR) manually counted and contoured MS lesions by consensus in 3D FLAIR, 3D DIR and MP2RAGE images for all MS subjects and HC (6). We then computed z-score between lesion and corresponding ROI distribution in HC. Each enrolled subject underwent neurological, cognitive and behavioural examination including: Brief Repeatable Battery of Neuropsychological tests (BRB-N), Hospital Anxiety and Depression scale (HAD), Fatigue Scale for Motor and Cognitive function (FSMC) and the Multiple Sclerosis Functional Composite score (MSFC). Multiparametric analysis was performed for normal-appearing (NA) tissue and MS lesions. A generalized linear model (GLM) with stepwise regression was computed to predict cognitive and motor performances in patients using multiparametric MRI data, conventional MRI measures (lesion count and volumes) as well as age, gender, education and behavioural data as covariates. Leave-one-out (LOO) cross validation was applied to assess the prediction quality and robustness.

Results: Multivariate analysis showed significant T2 and T2* differences between RRMS patients and HC in the temporal NAWM, indicating subtle micro-edema (p < 0.05 and p < 0.005), figure 2. Lesion z-scores showed that T1 and MTR were more sensitive contrasts than T2 and T2* to describe local brain tissue alterations in plaques, figure 3. The GLM analysis showed significant correlation between q/sqMRI and clinical scores : T2* in NAWM temporal and age predicted the verbal memory (SRT) score (adj-R² = 0.13, p < 0.05); T1, T2 and MTR in temporal NAWM, cortical lesions count together with volume, gender and HADD score predicted the FSMC motor score (adj-R² = 0.27, p < 0.005); T2 in temporal NAWM and lesions, subcortical lesion count and age predicted the visual memory score (adj-R² = 0.18, p < 0.01); T1 and MTR in lesions, together with age and gender, predicted the WLG (executive function) score (adj-R² = 0.31, p < 0.0005); T2 and MTR in temporal NAWM in conjunction with T1 and T2 in lesions as well as cortical and subcortical lesion volume and educational years predicted the SDMT (attention function) score (adj-R² = 0.22, p < 0.05); MTR in temporal NAWM, subcortical lesion volume, educational years, gender and HADD scores predicted the MSFC (general disability) score (adj-R² = 0.32, p < 0.0005), T1 and T2 in temporal NAWM and HADD score predicted the FSMC cognitive score (adj-R² = 0.34, p < 0.0005).

Conclusion: We applied a multiparametric analysis of whole brain abnormalities in a homogeneous cohort of early MS patients and showed that MRI measures of microstructural alterations lead to significant improvement in clinical-radiological correlations even in the presence of minor functional deficits (EDSS 1.7 ± 0.6). In fact, a variable combination of relaxometry and MTR values in NA tissue and lesions, together with traditional measures of disease burden (lesion count and volume) and patient covariates (age, gender, educational years and HADD scores) allowed us to significantly predict not only cognitive performances (verbal and visual memory, attention and executive function) and fatigue (motor and cognitive), but also general disability (MSFC score). Future studies should extend these findings to patients at later disease stages and assess the potential of this method to monitor longitudinal disease evolution and therapy effects.

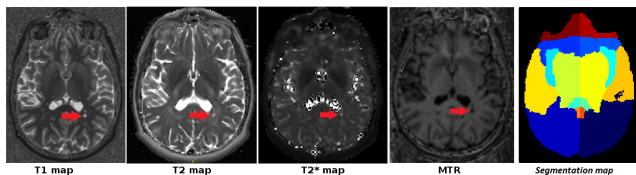


Figure1. Representative Slice of T1, T2, T2*, MTR, and segmentation map of a RRMS patient

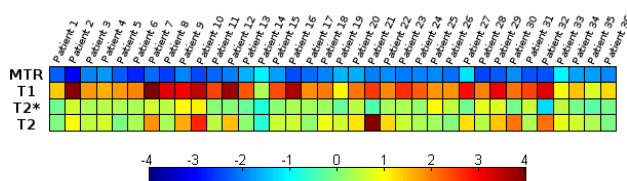


Figure 3. Mean z-scores of MS patients lesions

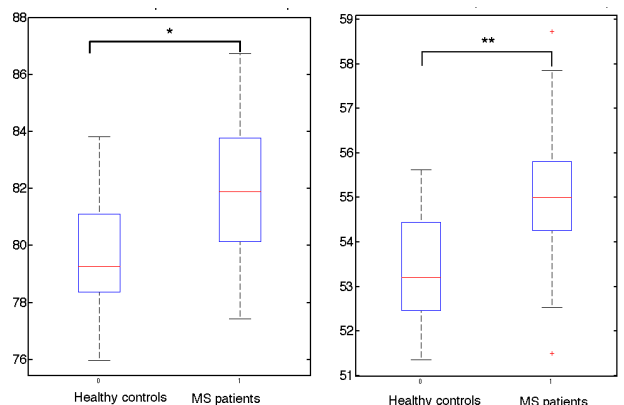


Figure 2. Boxplot of temporal NAWM of T2 (left) and T2* (right) maps

References: 1. Fatnassi C. et al. ISMRM B 2013; 2. Sumpf et al Magn Reson Imaging 2011, 34(2):420-428; 3. Marques JP et al. NeuroImage 2010, 49:1271-1281; 4. Klein et al. IEEE 2010, 29:196-205; 5. Roche A et al Medical Image analysis 2011, 15:830-839; 6. Kober T et al. Investigative radiology 2012, 47:346-352;

Acknowledgment : This study is supported by the CIBM of the UNIL, UNIGE, HUG, CHUV, EPFL and the Leenaards and Jeantet Foundations.