Multiple Sclerosis lesion fingerprint using multicontrast MRI

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Purpose: Conventional magnetic resonance imaging (MRI) measures of multiple sclerosis (MS) patients provide limited information about the nature and the extent of brain damage and repair. Previous studies applied quantitative and semiquantitative MRI techniques to assess either inflammation or demyelination or tissue degeneration in lesion tissue (1); however, MS plaques are complex and various since they show different degree of concomitant inflammatory and degenerative processes. For this reason, we established a clinically compatible protocol including three quantitative MRI techniques (qMRI, T1, T2, T2* relaxometry) and semiquantitative Magnetisation Transfer Imaging (sq MRI, MTI) in order to (i) provide a comprehensive MRI fingerprint (CMF) of lesions that is more adherent to the real underlying pathology and to (ii) assess the CMF contribution to clinical performances in patients.

Methods: Relaxometry and MTI 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 = 1.0×1.0×1.2 mm^3, FoV = 256×240×223.2 mm^3, acquisition time (aT) = 6:27 mn); 3D double inversion recovery (DIR) (TR/TE/TI = 10000/218/3650 ms, voxel size = 1.1×1.0×1.2 mm^3, FoV = 256×240×192 mm^3, aT = 12:52 mn), MPRAGE (TR/TE = 2300/2.98 ms, voxel size = 1×1×1.2 mm^3, FoV = 256×240×160, aT = 5:12 mn), MP2RAGE (TR/TE = 5000/3 ms, inversion time = 700 ms, FA = 4°, voxel size = 1×1×1.2 mm^3, FoV = 256×240×160, aT = 8:22 mn), T2 relaxometry (TR/TE = 5850/9-189 ms, voxel size = 1×1×4 mm^3, FoV = 30×192×160, 21 echoes, aT = 3 mn), T2* relaxometry (TR/TE = 47/1.23 ms, 32 gradient echoes, voxel size = 1.6×1.6×1.6 mm^3, FoV = 217×217×179 mm^3 , aT = 11:16 mn) with and without magnetization transfer (MT) pulse. T2* maps were obtained using a correction method based on an estimated B1 field map (2). MTR were computed from the T2* data. T2 maps were estimated from the multiecho spin-echo data using a model-based reconstruction (3). T1 maps were derived from the MP2RAGE volume (4). The biological substrate of q/sq maps changes is reported in table 1. MPRAGE, T2* echoes and T2 maps were linearly registered to respectively MP2RAGE volumes and T1 maps using ELASTIX (5). In order to assess, T1, T2, T2* and MTR average value in normal tissue we segmented lobar white and gray matter (frontal, parietal, occipital, temporal) from the MPRAGE images using an in-house software based on variational expectation-maximization tissue classification (6). 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 (7). In order to maximize the sensitivity of lesion count and volume, lesion masks from each contrast were merged into a union mask. Z-scores (z) were computed between lesion mean in T1, T2, T2*, MTR maps and corresponding ROI distribution in HC. We classified all lesions according to the parametric z distribution and created 3 *groups*: (i) z very low ($z < -2$), (ii) z very high ($z > 2$) and (iii) z close to the HC distribution ($-2 \leq z \leq 2$). For each subject then, we computed all possible combinations of z for each contrast (e.g. : combination 1 = $z_{T1} > 2$, $z_{T2} > 2$, $z_{T2^*} > 2$, $z_{MTR} < -2$; combination 2 = $z_{T1} > 2$, $z_{T2} > 2$, $-2 < z_{T2^*} < 2$, $z_{MTR} < -2$, etc...) and assessed the total lesion volume per group. Each enrolled subject underwent neurological, cognitive and behavioural examination including: Brief Repeatable Battery of Neuropsychological tests (BRB-N), Hospital Anxiety (HADA) and Depression scale (HADD), Fatigue Scale for Motor and Cognitive function (FSMC) and the Multiple Sclerosis Functional Composite score (MSFC). A generalized linear model (GLM) with stepwise regression was computed to predict cognitive and motor performances in patients using quantitative data, 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: Analysis of the lesions z showed 12 different possible combinations, indicating various degree of tissue alteration (table 2 and figure 1). The greatest lesion volumes were found in groups 1 and 4, indicating lesion types respectively characterized by minor tissue changes and subtle loss of tissue (increased T1, table 2). The smallest lesion volumes were found in groups 3 and 5 representing inflammatory lesions (increased T2 and T2*, table 2). The GLM showed significant correlation between lesion types and clinical scores: Volume of lesion belonging to combinations 10 and 2 with HADA and age predicted the verbal memory (SRT) score (adj-R^2 = 0.43, $p < 0.001$); Volume of lesions of combinations 4, 6, 7 and 11 with gender predicted attention score (SDMT) (adj-R^2 = 0.35, p = 0.002); Volume of lesions of combinations 4, 6, 8, 9, 10 and 11 together with age, gender and HADD predicted general disability (MSFC) score (adj-R^2 = 0.44, p = 0.002); Volume of lesions of combinations 6, 9 and 10 with HADD predicted FSMC cognitive score (adj-R^2 = 0.29,p = 0.005); Volume of lesions of combinations 8, 9, 10, 11 and HADD predicted FSMC motor score (adj-R^2 = 0.40,$p < 0.001$). Combinations 11 and 10, corresponding to very low negative MTR z and very high positive T1 (indicating important demyelination and tissue loss) with either T2 or T2* high positive z, were the most influencing predictors of clinical scores.

Conclusion: Combination of q/sq MRI parameters reveals new insights into nature and severity of tissue alterations in MS lesions, providing an "in vivo" histopathological characterization of MS plaques. Lesions characteristics highly correlated with patients clinical performance and more severe lesions appeared to drive the clinic-radiological correlations. Future work will aim at integrating lesion location as co-predictor of patients outcome and at monitoring lesion evolution during 2 years follow-up.

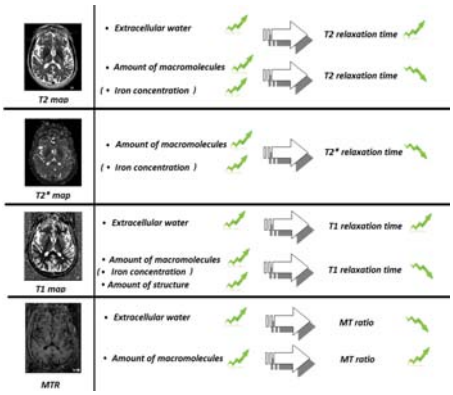

Table 1. *(top) Biophysical basis of MRI*

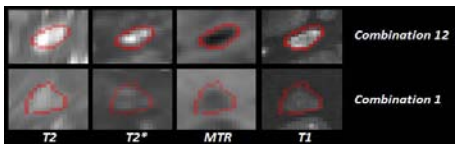

Figure 1. *Representative slice of T2, T2*, MTR and T1 of lesion in combination 12 (most severe) and a lesion in combination 1 (least severe)*

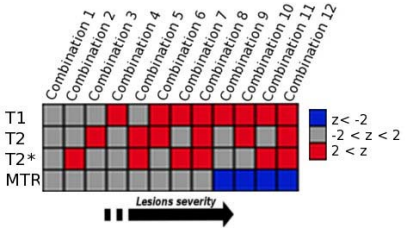

Table 2. *Combinations of MS lesions z-scores for T1, T2, T2* and MTR q/sq MRI from the least (combination 1) to the most (combination 12) severe stage. The presence of irreversible tissue loss was considered a sign of higher severity than inflammation.*

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;*

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