Direct comparison between macromolecular proton fraction, R1, magnetization transfer ratio, and lesion volume as predictors of clinical status in multiple sclerosis

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Target audience: Neurologists, Radiologists, MRI Physicists, Pharmaceutical industry.

Purpose: Macromolecular proton fraction (MPF) is a key biophysical parameter determining magnetization transfer (MT) between water and macromolecules in tissues. Over recent years, MPF has attracted significant interest as a potential biomarker of myelin in brain tissues with a particular focus on multiple sclerosis (MS) applications. A new fast whole-brain 3D MPF mapping method based on a single off-resonance MT measurement enables clinical MPF mapping with high accuracy, image quality, and reasonable scan time[1]. An important feature of this method is that more traditional quantitative parameters associated with brain tissue integrity, such as $R_1=1/T_1$ and magnetization transfer ratio (MTR) can be obtained from source images at no additional cost. The purpose of this study was to compare MPF with more established approaches for brain characterization in MS including MTR, R_1, and lesion volume (LV) in their capability to predict clinical disability and discriminate between disease courses.

Methods: *Study design and population:* This is the cross-sectional study involving three groups of subjects (number, age ± standard deviation (SD), male/female ratio): 1) Normal controls (NC) (14, 43.6±10.6, 7/7); 2) Relapsing-remitting MS (RRMS) patients (19, 49.2±11.4, 7/12); and 3) Secondary progressive MS (SPMS) patients (11, 55.0±6.1, 4/7).

Clinical data: MS patients had a neurological examination within two weeks prior to MRI. Neurological status was reported as the Expanded Disability Status Scale (EDSS) and Multiple Sclerosis Functional Composite (MSFC). MS patients had EDSS range 1.0-8.0.

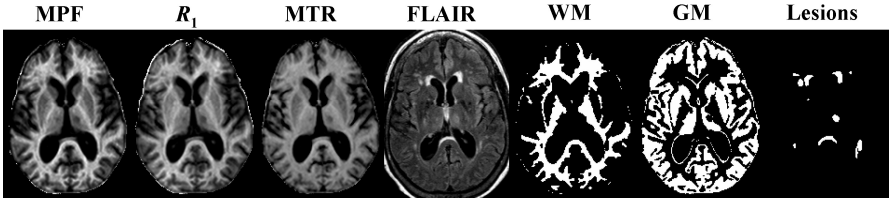

Fig. 1. Example MPF, R_1, and MTR maps, FLAIR image, and segmented normal appearing WM, normal appearing GM, and lesion masks obtained from an SPMS patient.

MRI protocol and image processing: Images were acquired on a 3T (Philips Achieva) whole-body scanner with a quadrature transmit-receive head coil. MPF maps were obtained using the recently published fast single-point method[1]. In brief, this method utilizes a single MT-weighted image with off-resonance saturation, a reference image, and an R_1 map to compute an MPF map based on the pulsed MT model with appropriate constraints for other model parameters[1]. Source data included three spoiled gradient-echo (GRE) images (TR/TE=20/2.3 ms, excitation flip angles (FA) α=3, 10, and 20°) for variable flip angle (VFA) R_1 mapping, an MT-weighted GRE image (TR/TE=43/2.3ms, α=10°) with off-resonance saturation pulse (sinc-gauss shape, offset 4 kHz, effective FA 950º, duration 19 ms), and a reference GRE image with the same parameters and without off-resonance saturation. The last two images also allow calculation of an MTR map. All images were acquired with 1.5x1.5x4 mm^3 voxel size and whole-brain coverage (3D FOV=240x180x184 mm^3). Additionally, a dual-echo GRE B_0 map[2], and an Actual Flip-angle Imaging (AFI) B_1 map[3] were acquired and used for correction of field inhomogeneities as described earlier[1]. Acquisition time for the entire MPF mapping protocol including field mapping sequences was 15 min. For the purpose of lesion segmentation, 2D T_2-weighted FLAIR images were also acquired with in-plane resolution 1 mm^2 and slice thickness 4 mm.

Table 1. Group comparisons between imaging variables in tissues.

	NC	All MS	RRMS	SPMS
MPF(WM), %	13.48±0.37	12.29±0.78***	12.56±0.64***	11.82±0.81***§§
MPF(GM), %	7.39±0.28	6.70±0.51***	6.95±0.34***	6.26±0.44***§§§
MPF(Les), %	–	8.08±0.99	8.45±0.78	7.44±1.01§§
R_1(WM), s^{-1}	0.997±0.019	0.951±0.041***	0.961±0.033**	0.934±0.048***
R_1(GM), s^{-1}	0.705±0.018	0.678±0.025***	0.684±0.025*	0.667±0.023***
R_1(Les), s^{-1}	–	0.748±0.053	0.767±0.047	0.716±0.050§
MTR(WM), %	38.28±1.27	37.88±1.61	38.20±1.20	37.33±2.10
MTR(GM), %	28.95±1.34	28.21±1.64	28.83±1.05	27.16±1.95*§§
MTR (Les), %	–	31.33±2.23	31.98±1.80	30.20±2.51§
LV, ml	–	12.46±13.43	7.42±6.54	21.15±17.74§§

*Comparisons with NC: *P<0.05, **P<0.01, ***P<0.001
§Comparisons with RRMS: §P<0.05, §§P<0.01, §§§P<0.001

Image analysis: MPF maps were used as source images for white matter (WM) and gray matte (GM) segmentation. WM and GM segmentation was carried out using FSL software (FSL, Oxford, UK) with FAST automated single-channel procedure. MS lesions were independently segmented from FLAIR images by the region-growing semi-automated algorithm using Jim software (Xinapse Systems, Aldwincle, UK). Since MS lesions potentially can fall into any tissue class during WM and GM segmentation, lesion masks were excluded from WM and GM masks obtained using FSL, thus providing masks of normal appearing brain tissues. Mean values of quantitative MRI parameters (MPF, MTR, and R_1) were calculated within the same tissue masks. All data are reported separately for normal appearing WM, GM, and lesions. Example parameter maps and binary segmentation masks are presented in Fig. 1.

Statistical analysis: Mean parameter values computed within each tissue mask were compared between subject groups using independent two-tailed t-tests. Associations between imaging and clinical variables were assessed using Pearson's correlation coefficient (r). Stepwise linear regression with EDSS or MSFC as dependent variables and all imaging variables as predictors was used to identify imaging parameters with the best predictive value.

Table 2. Correlations (r) between imaging and clinical variables.

	DD	EDSS	MSFC
MPF(WM)	−0.54**	−0.56**	0.72***
MPF(GM)	−0.64***	−0.70***	0.81***
MPF(Les)	−0.32	−0.42*	0.50**
R_1(WM)	−0.43*	−0.33	0.56**
R_1(GM)	−0.41*	−0.29	0.49**
R_1(Les)	−0.32	−0.28	0.46*
MTR(WM)	−0.34	−0.42*	0.54**
MTR(GM)	−0.46*	−0.56**	0.65***
MTR(Les)	−0.22	−0.38*	0.42*
LV	0.42*	0.42*	−0.57***

*P<0.05, **P<0.01, ***P<0.001

Results: *Group comparisons:* Mean parameter values (±standard deviation) in segmented brain tissues are listed in Table 1. MPF in WM and GM demonstrated a highly significant reduction in MS compared to controls. MPF in all tissues were significantly lower in SPMS compared to RRMS. R_1 in normal appearing tissues were significantly lower in patients compared to controls but did not differ significantly between RRMS and SPMS. Only R_1 in lesions reached significance for the RRMS vs. SPMS comparison. MTR showed a limited capability to distinguish between patients and controls with significant differences only for the SPMS group in GM and lesions.

Correlations with clinical data: Highly significant correlations were identified between MPF and commonly used clinical status scales EDSS and MSFC (Table 2). Stronger associations were generally observed for MSFC due to the continuous nature of this scale. Weaker but significant correlations were also found between MPF and the disease duration (DD in Table 2). Among all tissue classes, MPF in GM demonstrated the strongest associations with all clinical data, while the weakest correlations were observed for MPF in lesions. R_1, MTR, and lesion volume demonstrated consistently weaker (non-significant for R_1 and EDSS) associations than MPF (Table 2). In stepwise linear regression analyses with inclusion of all imaging variables, only MPF in GM has been retained as a significant independent predictor of both EDSS (adjusted r^2=0.48) and MSFC (adjusted r^2=0.64).

Conclusions: This study demonstrates the superiority of MPF in both discrimination of pathologic brain tissue changes and correlations with clinical status in MS compared to MTR, R_1, and lesion load. These parameters do not provide additional clinical information beyond that captured by MPF. MPF in GM appears the strongest independent predictor of disability that emphasizes a critical role of GM demyelination in MS. Based on the fast whole-brain clinically targeted acquisition technology, MPF mapping provides promising biomarkers for studies of new and existing therapies in MS.

References: 1. Yarnykh VL. Magn Reson Med 2012;68:166-178. **2.** Skinner TE, Glover GH. . Magn Reson Med 1997;37:628-630. **3.** Yarnykh VL. Magn Reson Med 2007;57:192-200.