Macromolecular proton fraction as a new clinical biomarker of demyelination in multiple sclerosis

Vasily L. Yarnykh[1], James D. Bowen[2], Alexey A. Samsonov[3], Pavle Repovic[2], Angeli Mayadev[2], Bart P. Keogh[2], Beena Gangadharan[2], Hunter R. Underhill[1], Kenneth R. Maravilla[1], and Lily K. Jung Henson[2]

[1]Radiology, University of Washington, Seattle, WA, United States, [2]Swedish Medical Center, Seattle, WA, United States, [3]Radiology, University of Wisconsin, Madison, WI, United States

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. However, clinical applications of MPF have been hampered due to the absence of methods allowing fast and reliable in vivo measurements of this parameter. A new fast whole-brain 3D MPF mapping technology based on a single off-resonance MT measurement has been recently developed[1]. The purpose of this study was to evaluate the clinical utility of whole-brain fast MPF mapping in multiple sclerosis (MS) by determining pathological changes of MPF caused by the disease and establishing the capability of the method to predict clinical disability.

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.

MRI protocol and image processing: Images were acquired on a 3T (Philips Achieva) whole-body scanner with a quadrature transmit-receive head coil. The protocol for acquisition and reconstruction of MPF maps is outlined in Fig. 1. Additionally, 2D T_2-weighted FLAIR sequence for lesion detection was applied with in-plane resolution 1 mm^2 and slice thickness 4 mm.

Image analysis: Skull-stripped MPF maps were segmented using FAST software included in the FSL package (FSL, Oxford, UK). We found empirically that single-channel automated segmentation of MPF maps allows anatomically consistent definition of four tissue classes (Fig. 2). The defined tissue classes correspond to WM, two types of GM (with high and low myelin content - hGM and lGM, respectively), and a superficial layer of GM subjected to the partial volume averaging with CSF (sGM). Since MS lesions potentially can fall into any tissue class, they were separately segmented from FLAIR images using the region-growing semi-automated algorithm implemented in Jim software (Xinapse Systems, Aldwincle, UK). Example binary segmentation masks are presented in Fig. 2. It is noticeable that subcortical nuclei (except for the caudate nucleus, which partially falls into the lGM class) are consistently classified as hGM. Additional contribution to this class arises from partial volume averaging with WM at the WM-GM junction. The lGM class is almost entirely composed of cortical GM without partial volume contributions from WM or CSF, thus providing a conservative source of MPF estimates in GM. The hGM and lGM tissues were both analyzed separately and merged into the total GM (tGM) mask.

Statistical analysis: Mean MPF values computed within each tissue mask were compared between subject groups using independent two-tailed t-test. Associations between MPF and clinical variables were assessed using Pearson's correlation coefficient (r).

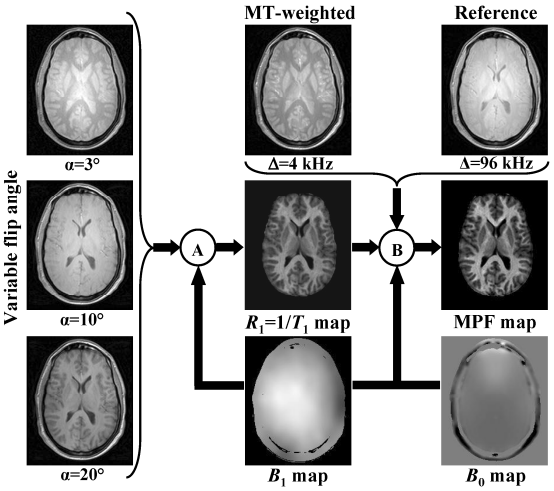

Fig. 1. Image acquisition and processing in the fast 3D MPF mapping method[1]. Source data include 3 spoiled gradient-echo (GRE) images (TR=20 ms, excitation flip angles (FA) α=3, 10, and 20°) for variable flip angle (VFA) T_1 mapping, an MT-weighted GRE image (TR=43 ms, α=10°) with off-resonance saturation pulse (offset Δ=4 kHz, effective FA 950º), a reference GRE image with the same TR and α for normalization of MT data, a dual-echo GRE B_0 map, and an Actual Flip-angle Imaging (AFI) B_1 map. Image processing steps (**A**) and (**B**) correspond to the fit of the Ernst equation to VFA data with B_1 correction to yield R_1 maps (step (**A**)) and iterative solution of the pulsed MT equation by the Gauss-Newton method with B_0 and B_1 correction and appropriate constraints for other model parameters to yield MPF maps (step (**B**)). Acquisition time for the entire 3D protocol with 1.5x1.5x4 mm^3 voxel size and whole-brain coverage (3D FOV=240x180x184 mm^3) is 15 min.

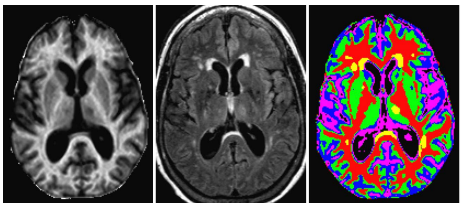

Fig. 2. Segmentation of an MPF map (**Left**) with a lesion mask obtained from a FLAIR image (**Center**). Color-coded tissue masks (**Right**) correspond to WM (red), hGM (green), lGM (blue), sGM (magenta), and lesions (yellow). Data are from an SPMS patient.

Results: *Group comparisons:* Mean MPF values in segmented brain tissues are listed in Table 1. MPF in WM and GM (including lGM and hGM) demonstrated a highly significant reduction in MS compared to controls. MPF in all tissue classes was significantly lower in SPMS compared to RRMS.

Correlations with clinical data: Highly significant correlations were identified between MPF in all tissue classes 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 lGM demonstrated the strongest associations with all clinical data. The weakest correlations with all clinical variables were observed for MPF in lesions. Lesion volume demonstrated consistently weaker associations with clinical data than MPF in both WM and GM (Table 2).

Table 2. Pearson's correlations (r) between MPF, lesion volume (LV), and clinical scales.

	DD	EDSS	MSFC
MPF(WM)	−0.54**	−0.56**	0.72***
MPF(tGM)	−0.64***	−0.70***	0.81***
MPF(hGM)	−0.60***	−0.65***	0.78***
MPF(lGM)	−0.67***	−0.74***	0.81***
MPF(sGM)	−0.42*	−0.64***	0.50**
MPF(Les)	−0.32	−0.42*	0.50**
LV	0.42*	0.42*	−0.57***

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

Table 1. Comparisons between mean MPF (%) in tissue classes.

Tissue	NC	All MS	RRMS	SPMS
WM	13.48±0.37	12.29±0.78***	12.56±0.64***	11.82±0.81***§§
tGM	7.39±0.28	6.70±0.51***	6.95±0.34***	6.26±0.44***§§§
hGM	8.96±0.34	8.09±0.60***	8.37±0.45***	7.61±0.52***§§§
lGM	5.77±0.34	5.18±0.49***	5.44±0.32**	4.73±0.41***§§§
sGM	2.71±0.43	2.54±0.33	2.69±0.28	2.29±0.28*§§§
Lesions	–	8.08±0.99	8.45±0.78	7.44±1.01§§

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

Discussion: We present the first clinical evaluation of a new fast whole-brain MPF mapping technology[1]. We found a highly significant decrease of MPF in brain tissues in MS, more pronounced in SPMS compared to RRMS, and strong correlations between MPF and clinical status. Our observations are in accordance with the expected pathological specificity of MPF to demyelination (as suggested by earlier animal studies[1]), which is a key pathological substrate of neural tissue damage in MS. This study highlights the primary role of MRI-invisible myelin damage in normal appearing WM and GM, where MPF values were much stronger predictors of disability than either the lesion volume or MPF in lesions. The key finding of this study is that MPF in GM demonstrated the strongest correlations with clinical status, thus emphasizing a critical role of GM demyelination for disability progression in MS, which is traditionally considered a WM disease.

Conclusions: This study establishes MPF as a new quantitative imaging biomarker of demyelination in MS, which captures pathological changes in both WM and GM. The described fast and robust MPF mapping methodology can be straightforwardly used in various clinical trials.

References: 1. Yarnykh VL. Fast macromolecular proton fraction mapping from a single off-resonance magnetization transfer measurement. Magn Reson Med 2012;68:166-178.