Highly reproducible whole brain myelin water mapping with FAST-T2 in 4 minutes using geometric echo time sampling

Thanh D Nguyen[1], Kofi Deh[1], Sneha Pandya[1], Elizabeth Monohan[1], Ashish Raj[1], Yi Wang[1], and Susan A Gauthier[1]
[1]*Weill Cornell Medical College, New York, NY, United States*

Target Audience Researchers and clinicians interested in multiple sclerosis (MS).

PURPOSE A robust quantitative biomarker of myelin content is essential for disease monitoring and therapeutic assessment in MS. Myelin water fraction (MWF) (1,2) is a clinically relevant measure of myelin (3), which has been validated by histopathology (4,5). Currently, performing longitudinal MWF mapping in MS patients is challenging due to long scan time (>10 min) (6-9) or limited reproducibility when a shorter scan time or voxel based analysis is desired. The purpose of this study is to develop a whole brain MWF mapping method which is both fast (4 min) and highly reproducible. We hypothesize that this goal can be achieved through Fast Acquisition with Spiral Trajectory and T2prep (FAST-T2) sequence (8) with 6 geometric TE sampling and a robust Spatially constrained Nonlinear (SPAN) data fitting algorithm.

METHODS: **FAST-T2 acceleration via geometric TE sampling**. Mathematical analysis (10) indicates that 5 geometrically spaced TEs are more effective in reducing noise amplification than previously used 32 equidistant (7) or 15 non-linear TEs (11). We propose to acquire an additional TE=0 (by turning T2prep off) to improve signal sensitivity to the fast decaying myelin water (T2~10 ms). Compared to existing FAST-T2 implementation (15 TEs), our design reduces scan time by 60% from 10 to 4 min.

SPAN algorithm. Conventional methods solve the multi-exponential signal fitting problem voxel by voxel using a linear least squares (LS) algorithm, which produces noisy MWF maps under low SNR. Here we overcome this problem by applying global spatial constraints as in (12) to jointly solve a three-pool nonlinear LS problem over all voxels:

$$\mathbf{x} = \arg\min_{\mathbf{x}} \|f(\mathbf{x}, \mathbf{TE}) - \mathbf{y}\|_2^2 + \lambda\|\nabla_s \mathbf{x}\|_2^2$$

where $\mathbf{x}$ is a vector of unknown pool fractions and T2s, $\mathbf{y}$ is MR signal, ∇_s is the spatial gradient operator (estimated using central differences), and f denotes a nonlinear multi-exponential function.

Imaging experiments. Seven healthy volunteers were imaged twice on a GE HDxt 3T scanner within 24 hours (subjects were repositioned between scans). Typical FAST-T2 parameters: 192x192x32 matrix, 24 cm FOV, 5 mm slice, spiral TR/TE = 7.8/0.5 ms with 32 spiral leaves, 6 geometric TEs, 4 min scan time. A modified BIR-4 adiabatic pulse was used to provide robust T2 signal weighting at 3T (13). The utility of the developed FAST-T2/SPAN method was further evaluated in three stable MS patients (all RRMS) who were scanned twice within a one year period.

Data analysis. MWF maps were extracted using conventional single-voxel algorithm (using Levenberg-Marquardt solver) and proposed multi-voxel SPAN algorithm (using a memory efficient L-BFGS solver). Images were co-registered using FSL. The reproducibility of both ROI and voxel based analysis was assessed using linear regression and Bland-Altman plots. For ROI analysis, both WM (genu and splenium of corpus callosum, minor forceps, major forceps, internal capsules) and GM (putamen, caudate head) regions were sampled.

RESULTS Figure 1 demonstrates significantly improved MWF map quality obtained with SPAN algorithm on whole brain FAST-T2 data acquired in only 4 min. When mean ROI analysis was used, both algorithms provided excellent reproducibility (Fig.1a). However, on a per voxel basis, the noise introduced by the conventional single-voxel algorithm leads to poor reproducibility. The use of global spatial consistency constraints in SPAN reduces noise while preserving salient features (Fig.1b). Figure 2 shows an example of highly reproducible MWF maps. Over all healthy volunteers (n=7), Bland-Altman plots for all brain voxels shows a negligible MWF bias of about 0.1% for both algorithms, while the 95% limits of agreement of [-4.4%,4.6%] by the conventional algorithm was reduced by half to [-1.9%,2.2%] by the proposed SPAN algorithm. Figure 3 demonstrates excellent lesion detection on two scans obtained from an MS patient.

DISCUSSION Our preliminary data demonstrated the feasibility of a highly reproducible method for whole brain myelin mapping in only 4 min, providing a promising imaging tool for longitudinal study of MS. In agreement with previous reproducibility studies conducted with conventional methods (14,15), mean MWF within major GM and WM structures were highly reproducible. The main advantage of the proposed method is significantly improved reproducibility on a per voxel basis, which may have critical impact on the follow-up of small MS lesions. Future work will focus on multi-platform and multi-site evaluation.

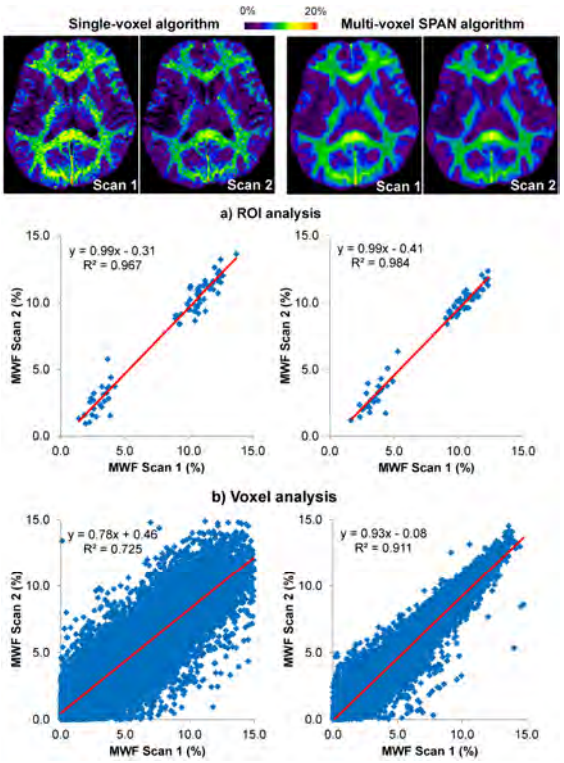

Fig.1. Reproducibility of MWF maps obtained with a 4 min FAST-T2 whole brain acquisition using conventional single-voxel and proposed multi-voxel algorithms. Scatter plots were shown for all 12 ROIs from each of 7 subjects in a, and for all brain voxels from the single slice shown at the top in b. SPAN significantly improves reproducibility for voxel wise analysis.

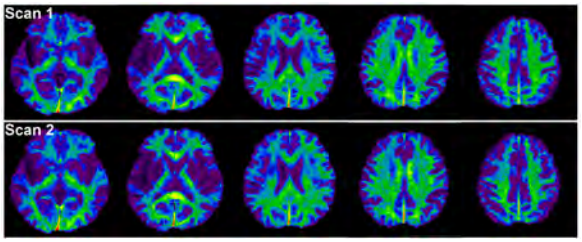

Fig.2. Example of highly reproducible MWF maps obtained with a 4 min FAST-T2 acquisition (only 5 out of 28 slices are shown).

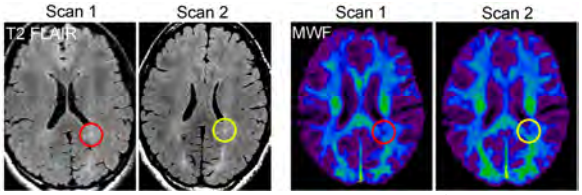

Fig.3. T2 FLAIR images and MWF maps obtained from an MS patient with a one year interval between the two scans, demonstrating excellent detection of small lesions.

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