Reliability and Reproducibility of Myelin Water Fraction Analysis: A Comparison of Region of Interest and Pixel by Pixel Methods

S. M. Meyers[1], C. Laule[2], I. M. Vavasour[2], S. H. Kolind[3], B. Maedler[4], R. Tam[2], J. S. Lee[5], A. L. Traboulsee[5], D. K. Li[2], and A. L. MacKay[2,3]

[1]Physics, University of Alberta, Edmonton, AB, Canada, [2]Radiology, University of British Columbia, Vancouver, BC, Canada, [3]Physics & Astronomy, University of British Columbia, Vancouver, BC, Canada, [4]Philips Medical Systems, Vancouver, BC, Canada, [5]Medicine, University of British Columbia, Vancouver, BC, Canada

INTRODUCTION

Water environments in the brain can be probed by measuring T_2 relaxation. Water in healthy human brain can be separated into 3 components with T_2s of ~2s (cerebrospinal fluid), ~80ms (intra/extracellular water) and ~20ms (water trapped between the myelin bilayers, or *myelin water*)[1]. The ratio of myelin water signal (15ms<T_2<40ms) to total signal gives the myelin water fraction (MWF)[2], which correlates with histological staining for myelin[3]. In recent years, a number of groups have embarked on research in the area of T_2 relaxation in brain and spinal cord, with particular interest in studying MWF in healthy controls and diseases such as multiple sclerosis, schizophrenia, phenylketonuria and Alzheimer's disease. While several methods are available to analyse multi-exponential T_2 relaxation decay data, the method most frequently used and described in the literature is the non-negative least squares (NNLS) algorithm[4]. The NNLS approach uses a χ^2 minimization algorithm to fit the decay curve with a T_2 distribution (a plot of amplitude vs. T_2), from which the MWF can be determined as the fractional signal with T_2 between 15 and 40ms[5]. Using NNLS, several methods can be employed to determine MWF for a defined region in an image. A common approach (the *ROI method*) is to outline a region of interest (ROI) on an image and then calculate a single decay curve using the average signal intensity within this ROI for each echo. This average ROI decay curve is then inverted to a T_2 distribution using NNLS. A second approach (the *PBP method*) is to carry out the NNLS inversion on a pixel by pixel (PBP) basis: the MWF is first determined for every pixel in the image in order to create a "myelin map" to which the ROIs are then applied and the mean MWF of individual pixels within the ROI is calculated. If NNLS was a linear inversion technique, MWFs from the ROI and PBP methods would be identical. However, NNLS is a complex algorithm that produces T_2 distributions which are sensitive to noise. Since the two approaches sample the noise differently, we expect the resulting MWFs to differ slightly. **The ultimate goal of this study was to determine the optimal method of MWF analysis using NNLS. Specifically, we wished to determine which of the ROI and PBP analysis techniques had the highest reliability amongst different observers and smallest variability in repeated MWF measurements in brain.**

METHODS

MRI Experiments: 20 healthy volunteers (11F/9M), mean age 30yrs (range: 21-49yrs), were scanned twice in one day. MR examinations were conducted using a phased array head coil on a Philips Achieva 3T MR scanner. After localizers and an inversion recovery (IR) experiment (5 TIs (150-3000ms), TR/TE=6.4/3.1ms, SENSE=2, TFE=120, shot interval=5000ms, FA=10°, 13 slices, 256x256)[6], a 3D 32-echo sequence for T_2 relaxation measurement was acquired (TR=1200ms, echo spacing=10ms, 7 slices, 256x128)[7]. FOV for all scans was 240x205mm and slice thickness was 5mm.

Regions of Interest: 5 grey matter (GM) and 5 white matter (WM) structures were outlined by 4 observers on the baseline IR 150ms MR image on a transverse slice through the base of the genu and splenium of the corpus callosum and mapped onto registered scan 1 and scan 2 of the T_2 experiment using in-house software.

Analysis: MWF was determined using both the ROI method (MWF_{ROI}) and the PBP method (MWF_{PBP}). T_2 decay curves were analyzed with a regularized NNLS method using 120 input relaxation times spaced logarithmically from 15ms to 2s[5]. Both χ^2 and solution roughness were minimized such that χ^2 fell between 1.02 and 1.025 times the minimum χ^2 from the non-regularized least-squares solution. MWF_{ROI} and MWF_{PBP} were compared between the 4 observers and between the 2 time points for each subject. Reliability coefficients (RC) between the different observers were calculated using Cronbach's Alpha[8] for each structure. Intercorrelation matrices (IM) were also determined for the different observers. A measure of signal to noise for the decay curve, SNR_{NNLS}, was calculated as the ratio of the t=0 intercept of the decay curve to the standard deviation of the residuals from the NNLS fit.

RESULTS

Comparison between observers: The RC was very high (>0.9) for all WM structures and most GM structures (Table 1). Therefore, although the mean may differ slightly between observers, the difference in MWF was consistent between all structures and can be treated as an offset. The low reliability coefficients in some GM structures was attributed to the near zero MWF being dominated by noise and therefore not systematic. Reliability coefficients were always higher using the PBP over the ROI method (average RC = 0.79 vs. 0.91) indicating better reliability especially in the GM structures. The IM showed no consistent difference between observers.

Comparisons within a single scan: A strong correlation was observed between MWF_{ROI} and MWF_{PBP} for each subject (mean R=0.97, range:0.95-0.98). T-tests revealed that MWF_{PBP} was significantly higher than MWF_{ROI} for all structures except for the minor forceps and thalamus (Table 1, * indicates p<0.05). SNR_{NNLS} was ~2 times significantly higher for the ROI method than for the PBP method, for all structures except the cingulate gyrus and cortical grey.

Comparisons between scans: Fig. 1 shows the correlations between MWFs on repeated scans for the two analysis methods for all subjects combined. Both approaches gave MWFs that were highly correlated between scan 1 and 2 for each subject (ROI: mean R=0.95 (0.87–0.99), PBP: mean R=0.98 (0.88–1.00)). The mean square difference (MSD) between scan 1 and 2 was 3.84 for MWF_{ROI} and 1.30 for MWF_{PBP}.

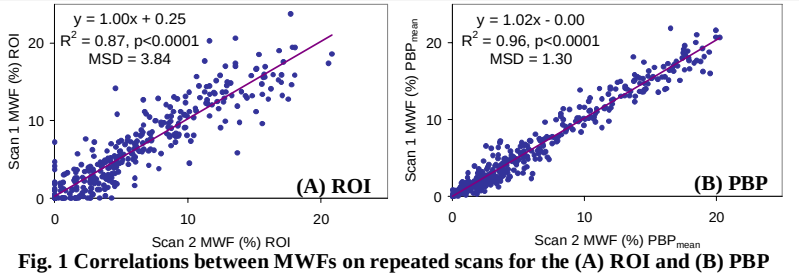

Fig. 1 Correlations between MWFs on repeated scans for the (A) ROI and (B) PBP analysis methods for all subjects combined. Mean square difference (MSD) is shown.

Table 1: RC and MWF for PBP and ROI methods (*p<0.05)

	RC_{ROI}	RC_{PBP}	MWF_{ROI} (%)	MWF_{PBP}(%)
caudate	0.92	0.96	1.5 ± 0.2	2.1 ± 0.1*
cingulate	0.05	0.72	0.00 ± 0.00	0.70 ± 0.09*
cortical grey	0.24	0.59	0.01 ± 0.00	0.60 ± 0.05*
putamen	0.98	0.99	2.9 ± 0.3	4.3 ±0.2*
thalamus	0.9	0.97	3.5 ± 0.2	3.5 ± 0.2
Average GM	**0.62**	**0.85**	**1.6 ± 0.1**	**2.23 ± 0.09***
genu	0.97	0.99	8.6 ± 0.3	10.2 ± 0.2*
p. int. capsules	0.91	0.95	15.4 ± 0.3	17.2 ± 0.2*
major forceps	0.97	0.99	6.9 ± 0.2	7.4 ± 0.2*
minor forceps	0.99	0.99	3.9 ± 0.2	3.7 ± 0.2
splenium	0.95	0.98	12.5 ± 0.3	14.4 ± 0.2*
Average WM	**0.96**	**0.98**	**9.5 ± 0.2**	**10.6 ± 0.3***

CONCLUSION

1. MWF values we obtained were in agreement with other studies at 1.5T and 3.0T[2, 9].
2. MWF was found to be reliable amongst different observers for most structures indicating that the observers were self consistent in the drawing of ROIs and that any differences in the mean are simply a scalar factor. **Reliability coefficients were always higher using the PBP over the ROI method.**
3. **A high correlation was observed between MWF of scan 1 and scan 2 for both ROI and PBP analysis** (although PBP analysis was higher)
4. **The mean square difference for the PBP method was 1/3 that of the ROI method,** suggesting that the PBP method is a more reproducible analysis method.

In summary, ROI and PBP analysis methods were equally robust to slight variations in ROI shape arising from different observers. Although SNR for the ROI method was higher, the PBP technique gave rise to similar MWFs as ROI analysis, was more robust on repeated scans and was equally robust over ROIs drawn by different analysts, we recommend the PBP method over the ROI method for analysing MWF, provided the SNR for an individual pixel is greater than 100.

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