Cross-site reproducibility of myelin water estimates

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INTRODUCTION: Central nervous system tissue has been shown to consist of three, MRI separable, water reservoirs: (i) myelin water (short T2 component at ~15 ms), (ii) intra/extra-cellular water (middle T2 component at ~80 ms), and (iii) cerebral spinal fluid (long T2 component > 2 s). Quantitative multi-echo acquisitions are therefore of significant interest in diseases such as multiple sclerosis since estimates of myelin water fraction (MWF) could serve as a specific indicator of myelin tissue content [1,2]. However, to be useful in multi-centre trials the cross-site stability of the T2 based MWF acquisition and analysis technique needs to be established. In this study we collected and analyzed data at two sites and compared T2 distributions and MWF estimates in various white matter (WM) and grey matter (GM) regions of interest (ROIs) in healthy brain.

METHODS: T2 relaxation data was acquired with a single-slice multi-echo CPMG imaging sequence with composite (90°_x-180°_y-90°_x) non-selective refocusing pulses flanked by spoiler gradients with alternating sign and decreasing intensity. A non-negative least squares (NNLS) algorithm was applied to the decay curve to estimate the corresponding T2 distribution which was based on 120 logarithmically spaced values between 10 – 4000 ms. The T2 distribution was regularized by minimizing the energy while allowing χ^2 to increase by 2 - 2.5% of its nominal amount. Two acquisition protocols (1 and 2) and two sites (A and B using a 1.5 T GE Signa and 1.5 T Siemens Sonata, respectively) were involved in the collection of data from the same slice of the same healthy subject (female, aged 25 years). Protocol 1 was developed at Site A extensively [1,2,3,4]. It consists of 32 echoes with an echo spacing of 10 ms, TR = 3 s, slice thickness = 5 mm, an in-plane resolution of 0.86 x 1.72 mm and 4 signal averages with a total scan time of ~26 minutes. Protocol 2 also consisted of 32 echoes with an echo spacing of 10 ms but with TR = 2 s, slice thickness = 7 mm, in-plane resolution of 2 x 2 mm and 1 signal average with a total scan time of ~4 minutes. Protocol 2 was developed at site B with the goal of decreasing scan time at the expense of spatial resolution while maintaining a high SNR [5,6]. Matching ROIs were established and analysis was performed by both sites using local implementations of the same NNLS technique. Protocol 1 was tested at both sites, while protocol 2 was only tested at site B. We then compared: (i) protocol 1 results across sites, and (ii) protocol 1 and 2 results at one site. MWF, defined as the ratio of myelin water to the total water content, is typically calculated using the integral of the signal between 10 – 50 ms divided by the signal from the entire T2 distribution [2,3,4]. To assess the sensitivity of the MWF estimates to the defined T2 range of the myelin water compartment, we also calculated MWF estimates using a fixed myelin water (MW) range of 10 – 40 ms as well as a variable range based on manual peak separation where signal below the main T2 peak is assigned as myelin water.

RESULTS: Comparing the MWFs (see Table 1) calculated by both sites using the 10 – 50 ms MW range on protocol 1, site A and protocol 1, site B data demonstrate that the NNLS fitting implementations are consistent. Figure 1a illustrates how data acquired at different sites using the same protocol have similar distributions but with some variation in the locations of the short and middle T2 peaks and the width of the middle T2 peak. This variation translates into MWF estimates with absolute differences of less than ~2% (Table 1). Protocols 1 and 2 acquired at site B show MWFs with absolute discrepancies as large as ~8% with a 10 - 50 ms MW definition. Defining the MW T2 range to be 10 - 40 ms or using manual peak separation results in large variations in the absolute MWF estimates (as much as ~22%).

DISCUSSION and CONCLUSIONS: Cross-site acquisition and analysis of the same quantitative T2 protocol on the same subject shows that T2 distributions, and therefore MWFs, are in reasonable agreement. However, data from different protocols, with similar SNRs, acquired on the same scanner and subject shows large variations in MWFs. The larger voxels of protocol 2 are more susceptible to partial voluming but our ROI selection should have minimized this effect. Similarly, the potential slight mismatch between the single slices is likely not able to explain the large MWF variations we observed. Since some WM T2 distributions did not contain a clearly defined short T2 peak, the manual peak separation method reports a zero MWF, which is clearly not biologically consistent with healthy WM. From these preliminary results we can conclude that it is essential for multi-site MWF studies to maintain a consistent acquisition protocol and carefully assess cross-site variability in healthy subjects or an appropriate multi-component phantom.

Figure 1. Comparison of the T2 distributions of various ROIs in a normal subject using **(a)** protocol 1 at both sites, and **(b)** protocols 1 and 2 at site B.

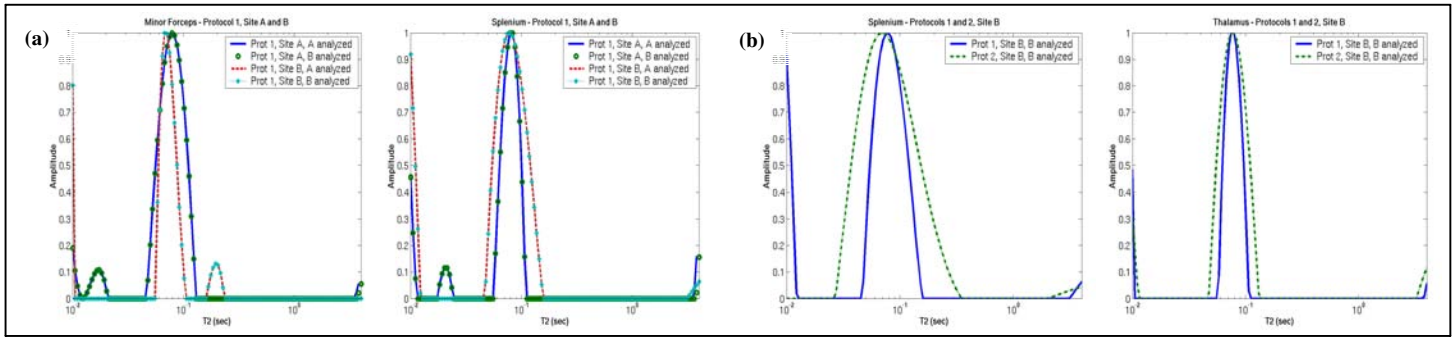

Table 1. Comparison of the myelin water fraction (%) from various white and grey matter regions in a normal subject.

ROIs	Protocol 1, Site A		Protocol 1, Site B		Protocol 2, Site B		
	Site A analyzed	*Site B analyzed*	*Site A analyzed*	*Site B analyzed*	*Site B analyzed*		
	10 – 50 ms	*10 – 50 ms*	*10 – 50 ms*	*10 – 50 ms*	*10 – 40 ms*	*10 – 50 ms*	*Manual peak separation*
Genu of cc	10.35	10.28	10.16	10.18	8.18	17.56	5.36
Splenium of cc	12.93	12.93	14.17	14.05	10.74	21.78	0
Major forcep	10.56	10.67	10.49	10.48	10.22	10.22	10.22
Minor forcep	7.71	7.71	8.97	8.97	6.77	11.52	6.77
Head of caudate	3.05	3.02	4.63	4.65	2.08	2.08	2.08
Thalamus	7.50	7.53	5.58	5.60	3.96	5.53	3.96

References

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