

# Preparation for Multi-site Myelin Water Relaxation Studies: Inter and Intra-site Reproducibility in Normal Controls

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## Introduction

Quantitative assessment of  $T_1$  and  $T_2$  relaxation in central nervous system tissue can provide information about water environments which may become altered in diseases such as multiple sclerosis.  $T_1$  measures (which are related to water content) and  $T_2$  measures (such as myelin associated water and geometric mean  $T_2$ ) have the potential to be in-vivo markers for pathological changes that result in clinical disability and progression, as well as being used to evaluate treatment efficacy. Implementation of quantitative pulse sequences such as multiple inversion recovery  $T_1$  and multi-echo  $T_2$  in a standardized multi-site clinical trial setting is non-trivial; inter and intra-site reproducibility need to be assessed. The present study aims to examine cross-site reproducibility of quantitative  $T_1$  and  $T_2$  data by determining the differences in mean  $T_1$ , geometric mean  $T_2$  and myelin water fraction measured on the same subjects at multiple sites.

## Methods

**MR Examinations:** Five healthy volunteers (3 female, 2 male; mean age 37 years (range 24-54 years)) were scanned twice within a 24 hour period at 6 different sites. All MRI examinations were performed on Philips 3T Achieva MR scanners. The transverse MR examination was positioned such that the most inferior slice was in line with the base of the genu and splenium of the corpus callosum. MR experiments included a  **$T_1$  inversion recovery** (5 TIs (150 - 3500ms), TR/TE=8.0/4.6ms, SENSE=2, TFE=105, shot interval = 5000ms, FA = 12°, 13 slices) and a **3D  $T_2$  relaxation** (utilizing a 90° excitation pulse followed by 32 slab-selective refocusing pulses flanked by gradient crusher pulses, 7 slices, 32 echoes, TR = 1000ms, 10ms echo spacing)<sup>1</sup>. Slice thickness for both the  $T_1$  and  $T_2$  experiments was 5mm.

**Analysis:** All images were registered to the first scan at Site 1 using FSL. Regions of interest throughout the white matter were drawn.  $T_1$  was calculated using a mono-exponential fit.  $T_2$  distributions were calculated for every voxel in the  $T_2$  relaxation data set using a regularized non-negative least squares (NNLS) algorithm<sup>2</sup>. MWF was the area under the  $T_2$  distribution from 0-40ms divided by the total area. GMT<sub>2</sub> were calculated as the mean on a logarithmic scale from 40ms <  $T_2$  < 200ms.

**Inter-site reproducibility:** To determine the inter-site reproducibility for each MR measure, the following steps were taken: first a mean MR value for each volunteer was determined from all 12 data sets collected across the 6 sites (2 at each site); next the percent difference between the MR measure at each scan and mean MR measure was determined; finally, for each site a mean inter-site percentage difference was determined by averaging across the 5 volunteers.

**Intra-site reproducibility:** Mean intra-site percent differences were calculated for each MR measure from the two repeated scans done within 24 hours for each subject. The mean values for each subject were then averaged to determine each sites average intra reproducibility.

## Results

Figure 1 shows the good qualitative correspondence of myelin water maps from one volunteer scanned at 6 different sites. Inter and intra-site percent differences are shown in Table 1.

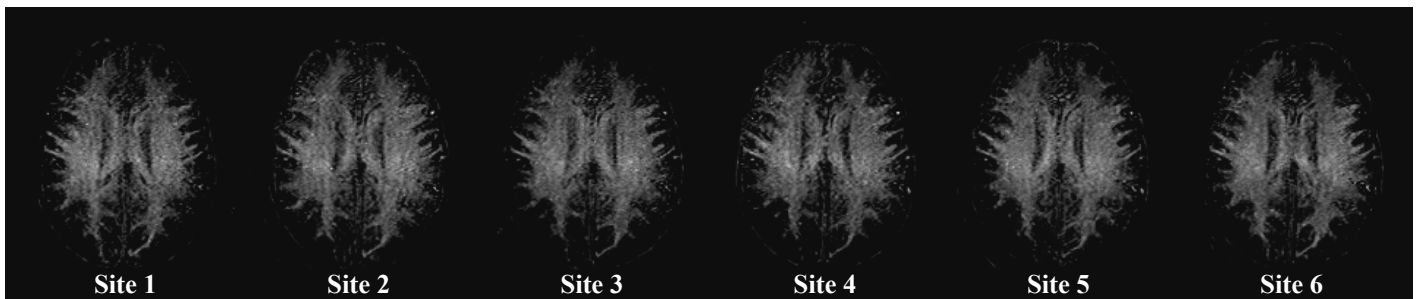


Figure 1 – Myelin water maps from one volunteer at 6 different sites look qualitatively very similar.

Table 1: Inter and Intra-site reproducibility for each MR measure and each site.

Site	Percent Differences of Inter and Intra-site Reproducibility					
	$T_1$		Geometric Mean $T_2$		Myelin Water Fraction	
	Inter	Intra	Inter	Intra	Inter	Intra
1	4.90	0.98	0.38	0.50	5.24	7.58
2	4.09	2.68	0.55	0.54	5.88	3.80
3	1.08	1.22	0.62	0.73	14.15	3.72
4	4.66	2.52	0.47	0.94	6.53	6.27
5	1.40	2.57	0.43	0.61	5.95	7.88
6	2.71	1.13	0.49	0.42	6.93	6.85
Average	3.14	1.85	0.49	0.62	7.45	5.85

## Discussion

This study demonstrates that it may be feasible to carry out multi-centre clinical trials using quantitative  $T_1$  and  $T_2$  relaxation measures. While mean  $T_1$  and GMT<sub>2</sub> have slightly better reproducibility, myelin water fraction provides a specific measure of brain myelin content, which is invaluable for assessing neuroprotective and remyelination therapies. Total white matter segmentation may improve inter and intra-site reproducibility.

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**References:** 1. Mädler B ISMRM 2006 p. 2112 2. Whittall KP JMR 1989;84:134-152