Characterizing Normal Appearing and Diseased White Matter in Multiple Sclerosis Using Quantitative MRI

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Introduction: Multiple Sclerosis (MS), a chronic, inflammatory, demyelinating disease of the central nervous system often preceded by an acute clinically isolated syndrome with monofocal or multifocal lesions. MRI is sensitive in detecting white matter abnormalities, but the lack of pathologic specificity is problematic (1). In contrast to normal appearing white matter (NAWM) and focal WM lesions; subtle regions of diffuse signal intensity changes are often seen in T2-weighted images. These regions, which have slightly higher signal intensity than NAWM but lower than lesions, are referred to as *diffusely abnormal white matter* or *dirty-appearing white matter* (DAWM) (2). Using conventional MRI, these regions are difficult to characterize, given their diffuse nature. Recent studies, however, emphasize the importance of these diffuse changes since they may be an important marker for disease progression (3).

Quantitative Magnetic Resonance Imaging (qMRI) is a technique to obtain absolute numeric values of tissue parameters, such as the longitudinal and transversal relaxation times, T1 and T2, and the proton density (PD). These parameters are, in principle, insensitive to MR scanner hardware and MRI acquisition. Therefore, qMRI may be a sensitive technique to assess DAWM.

The aim of this study was to determine if DAWM in MS patients exhibit different qMRI characteristics than NAWM and WM lesions, and compared to normal white matter (NWM) in healthy controls.

Materials and Methods: *In vivo* imaging was performed using a Philips Achieva 1.5 T MR-scanner in 10 patients (3 male, 7 female, age 43.8 ± 7.8, range 31 to 58 years) with clinically definite MS and 10 healthy controls (age and gender matched). The mean disease duration of the MS patients was 12.3 years (range 3 to 25 years) and the mean Expanded Disability Status Scale (EDSS) score (4) was 3.7 (range 1.5 to 8.5). For each subject quantitative MR data was acquired with the QRAPMASTER sequence (5) (*TR=2950ms, TE=5*15ms, 4x1x1mm*^{3}) and conventional FLAIR images were also acquired. The study was approved by the local ethics committee and written informed consent was obtained from all subjects prior to study entry.

In healthy controls; two 3x3mm^2 regions of interest (ROIs) were manually placed in NWM. In each MS patient two 3x3mm^2 ROIs were manually placed in NAWM, DAWM and in WM-lesions. All ROIs were placed by an experienced radiologist in qMRI images on the basis of conventional FLAIR image findings. DAWM was defined as slightly hyperintense regions that could not be attributed to a WM-lesion hyperintensity nor NAWM. For each voxel of all ROIs the T1, T2 and PD quantitative measurements were obtained.

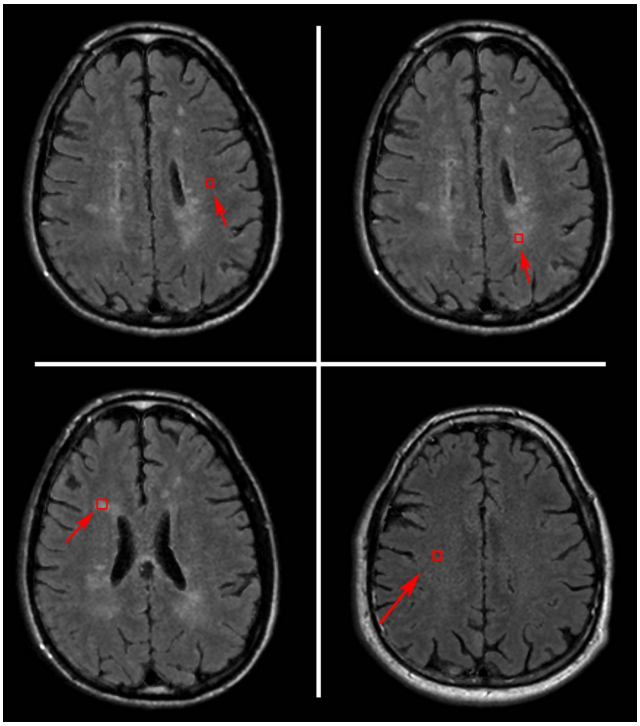

Figure 1: *ROI placement in MS patients: NAWM (top left), DAWM (top right), T2-lesion (bottom left) and ROI placement in NWM of a healthy control (bottom right).*

Descriptive statistics (mean±SD) for the qMRI parameters of each tissue type were calculated. To examine whether the tissue types were significantly different, ANOVA with post-hoc Tukey test was performed before and after rank transformation (to account for non-normal distributions). Statistical analyses were carried out in SPSS Statistics 19 (IBM, 2010).

Results: In total, 20 ROIs were defined for each of the four tissue types. Fig. 1 shows sample ROI placements. Descriptive statistics for the tissue types are given in Table 1. Statistically significant differences were found between NAWM, DAWM and lesions (*p<0.001*, Table 2). The difference between DAWM and NWM was also significant (*p<0.001*), but no statistically significant difference between NAWM and NWM was detected.

Table 1: qMRI t*issue parameters for NWM (in healthy controls), NAWM, DAWM and T2-lesions (in MS patients).*

Tissue	T1 [ms]	T2 [ms]	PD [%]
NWM	627 ± 43	79 ± 6	66 ± 2
NAWM	609 ± 44	81 ± 7	65 ± 2
DAWM	757 ± 104	108 ± 14	73 ± 6
T2-lesion	912 ± 137	118 ± 16	82 ± 7

Table 2: *Results from post-hoc Tukey test showing the mean difference between tissue types. ***p<0.001*

(I) Tissue 1	(J) Tissue 2	T1 [ms] Mean difference	T1 [ms] 95% Confidence Interval	T2 [ms] Mean difference	T2 [ms] 95% Confidence Interval	PD [%] Mean difference	PD [%] 95% Confidence Interval
NWM	NAWM	18	-7 to 43	-1	-4 to 1	1	-1 to 3
	DAWM	-130***	-155 to -105	-28***	-31 to -25	-7***	-8 to -5
	T2-lesion	-285***	-310 to -260	-38***	-41 to -35	-15***	-17 to -14
NAWM	DAWM	-148***	-173 to -123	-27***	-30 to -24	-8***	-9 to -6
	T2-lesion	-303***	-328 to -278	-37***	-40 to -31	-16***	-17 to -14
DAWM	T2-lesion	-155***	-180 to -130	-10***	-13 to -7	-9***	-10 to -7

Discussion and Conclusions: This study showed that qMRI was able to differentiate DAWM from both NAWM and WM-lesions. This suggests that DAWM may be a different pathological process in the development of the disease, an explanation that is also consistent with previous findings using volumetric and magnetization transfer ratio (MTR) measurements (6). In conclusion, qMRI may be used as a marker to differentiate DAWM from other types of tissue. Using the clustering approach to segment tissues described in (7), this result may allow quantitative volume measurements of DAWM.

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