Multi-parametric Quantitative Magnetic Resonance Imaging of the Normal Appearing Brain in Multiple Sclerosis

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Introduction. Quantitative Magnetic Resonance Imaging aims at the absolute measurement of physical parameters such as the R_1 and R_2 relaxation rates and proton density PD. These parameters are independent of MR scanner settings and hardware imperfections and hence directly reflect the intrinsic tissue characteristics. QMRI was applied to a group of patients diagnosed with Clinically Definite Multiple Sclerosis (CDMS) to measure the differences of the normal appearing brain compared to the normal, healthy brain.

Methods. A group of 16 healthy subjects and 16 patients diagnosed with CDMS were age and gender matched with 4 male and 12 female subjects (median age 48 years, range 27-62 and 48 years, range 29-63 respectively). The patient group consisted of 8 relapsing–remitting and 8 secondary progressive MS patients with a mean disease duration of 16±10 years, a mean Expanded Disability Status Scale (EDSS) of 4.0±2.3 and a mean Multiple Sclerosis Severity Score (MSSS) of 4.6±2.8.

For MR quantification the QRAPMASTER sequence [Warntjes *et al*, MRM 2008] was applied with 4 saturation delays and 5 echoes with a TR of 2950 ms. The resolution was 1x1 mm^2, 30 axial slices of 4 mm thickness were collected in a scan time of 8:21 minutes. The scanner was an Achieva 1.5 T (Philips Healthcare, Best, The Netherlands).

The raw image data was analyzed with the SyMRI Brain Studio software (SyntheticMR AB, Sweden) to retrieve the R_1, R_2 and PD maps. Based on these maps synthetic T2-weighted images were reconstructed for visual guidance. Regions of interest of 3x3 mm were selected in the images at various positions in the brain. The ROIs were placed by a neuro-radiologist in normal appearing tissue, carefully avoiding visible MS lesions and diffuse hyper-intensities in the white matter for the patient group.

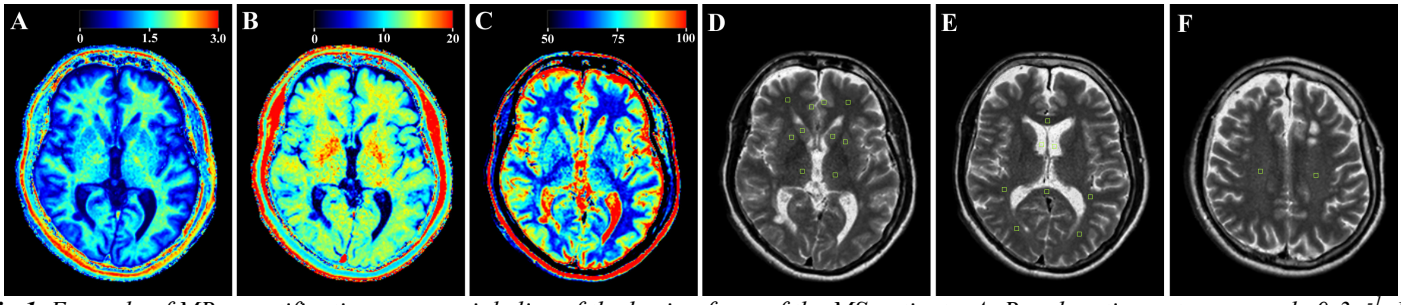

***Fig.1**. Example of MR quantification on an axial slice of the brain of one of the MS patients. A: R_1 relaxation rate on a scale 0-3 s^{-1}, B: R_2 relaxation rate on a scale 0-20 s^{-1} and C: proton density on a scale 50-100% water. In D-F synthetic T2-weighted images are shown were the 18 separate ROIs of the study are displayed.*

Results. Observed values for R_1, R_2 and PD of cerebrospinal fluid (CSF), parasagittal frontal cortex (FCX), head of the caudate nucleus (HCN), putamen (PT), thalamus (TH), centrum semiovale (CS), occipital white matter (OWM), peritrigonal white matter (PWM), frontal white matter (FWM), genu of the corpus callosum (GCC) and splenium of the corpus callosum (SCC). Displayed are the mean value and standard deviation (>6% in bold face). In the last column the mean difference is shown with the significance. Although the variation for all the values increases for the patient group it is only significantly different for R_1. The most prominent difference is the peritrigonial white matter, for most tissues, however, there is no significant difference between healthy subjects and patients.

	Healthy subjects (n = 16)			MS patients (n = 16)			Mean difference		
	R_1 (s^{-1})	R_2 (s^{-1})	PD (%)	R_1 (s^{-1})	R_2 (s^{-1})	PD (%)	ΔR_1 (s^{-1})	ΔR_2 (s^{-1})	ΔPD (%)
CSF	0.25±0.01	0.82±**0.13**	102±2.8	0.26±**0.03**	0.85±**0.17**	100±3.3	0.01(0.2)	0.03(0.6)	-1.0(0.4)
FCX	0.91±0.05	10.3±0.3	84.7±2.5	0.93±**0.06**	10.3±0.4	82.8±1.5	0.03(0.2)	0.05(0.7)	-1.9(**0.01**)
HCN	1.09±0.05	11.8±0.3	80.7±1.9	1.13±**0.08**	12.1±**0.8**	81.0±2.1	0.05(0.7)	0.39(0.07)	0.3(0.7)
PT	1.14±0.06	12.8±0.5	79.9±2.1	1.18±**0.11**	13.0±**0.9**	79.2±3.1	0.04(0.2)	0.17(0.5)	-0.6(0.5)
TH	1.28±**0.10**	12.4±0.5	74.6±2.8	1.31±**0.10**	12.5±0.7	74.1±2.4	0.03(0.4)	0.11(0.6)	-0.5(0.6)
CS	1.56±0.06	12.2±0.4	67.2±1.5	1.56±0.07	12.0±0.7	66.4±2.1	0.00(0.9)	-0.24(0.2)	-0.8(0.2)
OWM	1.69±0.08	12.2±0.4	63.5±1.9	1.65±**0.13**	12.3±0.7	65.1±2.4	-0.05(0.2)	0.14(0.5)	1.7(**0.04**)
SCC	1.76±0.11	13.0±0.8	62.7±2.1	1.64±**0.20**	12.2±**1.2**	64.0±3.3	-0.11(0.06)	-0.78(**0.04**)	1.3(0.2)
PWM	1.80±0.09	12.7±0.7	60.7±2.5	1.66±0.10	12.0±0.5	64.2±2.7	-0.14(**<0.001**)	-0.69(**0.004**)	3.5(**<0.001**)
FWM	1.81±0.10	13.4±0.6	62.4±1.8	1.75±**0.12**	13.6±**0.9**	64.3±2.3	-0.07(0.1)	0.15(0.6)	1.9(**0.01**)
GCC	1.99±0.12	14.0±0.7	59.0±2.0	1.86±**0.20**	13.8±**1.2**	62.1±3.9	-0.13(**0.04**)	-0.23(0.5)	3.1(**0.009**)

Discussion and conclusion. The normal appearing brain of MS patients shows a larger variation in R_1, R_2 and PD characteristics but for most tissues the mean difference compared to healthy subjects is not significant. These findings suggest that MS has little effect on the complete brain but is mainly restricted to the lesions and diffuse hyper-intense (dirty-appearing) white matter.