Quantitative spin echo R_2 and brain atrophy measurements for subcortical grey matter in patients with multiple sclerosis: A 2-year longitudinal study

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Introduction: In subcortical grey matter (GM), reduced signal intensity on T_2-weighted MRI, suggesting iron accumulation, has been observed in multiple sclerosis (MS) patients [1, 2]. Recent MRI studies on MS have shown iron accumulation in deep GM is associated with disease duration, physical disability, brain lesion load and brain atrophy [2-5]. For longitudinal study, quantitative gradient echo transverse relaxation rate R_2* and brain atrophy measurements have been used [2, 4]. However, gradient echo images are prone to image artifacts and annual brain volume changes are typically very small (1% or less). Spin echo based quantitative R_2 has the potential to offer reliable and reproducible measurements of iron accumulation due to its insensitivity to static, nonlocal background magnetic fields. At high magnetic field, R_2 measurements may be particularly useful because the R_2 value of iron compounds increases linearly with main magnetic field strength [3]. Here, we examine two year changes in spin echo R_2 and brain atrophy in subcortical GM of MS subjects and matched healthy controls.

Methods: Twenty six RRMS patients (age 38±9 years, M/F 19/7, disease duration 5.3±3.4 years, Expanded Disability Status Scale (EDSS) 2.4±0.9) and 26 matched controls (age 38±9, M/F 18/8) were imaged at 4.7 T after obtaining informed consent according to institutional regulations. A 2D multiple-echo spin echo sequence was employed for R_2 mapping: TR 4000 ms, 10 ms echo spacing, 20 echoes, flip angle 90x-180y-180y…, voxel size 1.0 x 1.25 x 4 mm^3, 6 slices and total scan time 13.5 min. For assessing brain volume a whole-brain T_1-weighted 3D Magnetization Prepared Rapid Gradient Echo (MPRAGE) sequence was used (TE 4.5 ms; TR 508 ms; number of slices 84; TI 300 ms; voxel volume 1.5 mm^3; BW 80 kHz; scan time 5 min). Bilateral ROIs were chosen in iron-rich deep grey matter (globus pallidus GP, putamen PUT, caudate nucleus CD, substantia nigra SN, red nucleus RN, pulvinar nucleus PUL, thalamus excluding pulvinar TH) as well as frontal white matter FWM. R_2 values, obtained from ROIs, were averaged over left and right sides of the brain for each subject. R_2 maps were obtained by fitting pixel by pixel using stimulated echo compensation (6). In order to get congruency, R_2 maps were manually translated, rotated and resized using ImageJ to align with 2 year follow-up R_2 maps after skull-stripping using BET (FMRIB's brain extraction tool). For brain atrophy measurement, SIENAX and FSL-FIRST were used [7]. Volumes were then normalized relative to whole head volume for each subject. Statistical analyses were performed using SPSS (V20). MS Severity Score (MSSS) were calculated from EDSS and disease duration [8].

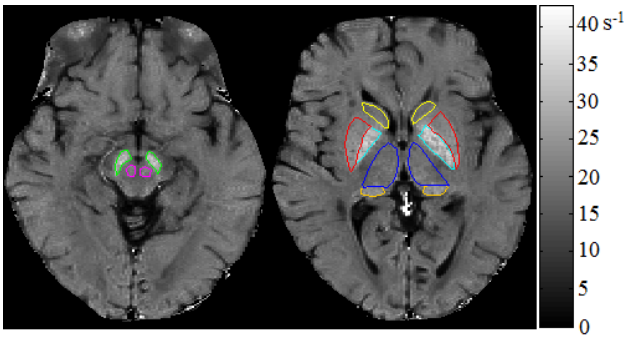

Figure 1: In-vivo R_2 maps at 4.7 T of a 47 year old MS patient. Caudate nucleus (yellow); putamen (red); globus pallidus (cyan); Thalamus (blue); pulvinar nucleus (orange); substantia nigra (green); red nucleus (magenta).

Results: Figure 1 presents R_2 maps from an MS patient showing hyperintense iron rich deep GM. After two year follow-up R_2 values in MS patients increased by ~4% for GP, PUL and SN with p=0.001 (Table 1). While for controls, 2 year increases were no greater than 1.7%. Mean volume of GP, PUT and caudate as well as cortex volume decreased over two years for patients and controls but was not statistically significant. Cortex volume is reduced by less than 1% for patients. Deep GM structures showed group differences between RRMS and controls (Table 1). The correlations between cortex volume and single time point R_2 were significant for GP, PUT, pulvinar and substantia nigra ($p<0.05$) in MS patients while two years difference measurement of R_2 and volume does not correlate significantly. Two year volume changes had a weak, but insignificant correlation to MSSS (r=0.36, p=0.586). However, multiple regression using three deep GM structures as variables, 2 years difference R_2 values indicate high correlation with MSSS (r =0.79, $p<0.001$). Figure 2 shows the plot MSSS at baseline versus predicted MSSS where predicted MSSS were obtained using the Equation: $MSSS = 0.87*\Delta R_{2PUL}+0.76*\Delta R_{2SN}-1.87*\Delta R_{2TH}+3.09$, where ΔR_2 is the difference in R_2 over 2 years for PUL, SN and TH.

Discussion: We have demonstrated 2 year quantitative R_2 changes and related these to volume changes in deep GM areas in patients and age matched control subjects. We found that the disease severity score (MSSS) highly correlates with the R_2 changes over 2 years period but correlation is not statistically significant for volume changes in this short period of time. Spin echo based R_2 mapping is advantageous as it refocuses transverse phase accumulations due to microscopic magnetic field inhomogeneities, leading to fewer image artifacts than gradient echo R_2* methods, especially in areas near air-tissue interface. We obtained significant changes in pulvinar (R_2 increased by 4.42% over 2 years) and in substantia nigra (R_2 increased by 4.75%) with relatively large effect size. We also found decreased R_2 in frontal WM which might be due to demyelination.

Conclusion: Two years difference measurements using R_2 mapping method correlate strongly to disease severity compared to single time point measurements. But single time point measurement correlates negatively with cortex volume for globus pallidus, putamen, and substantia nigra in RRMS patients. This R_2 mapping method can be used as a marker to monitor individuals with MS.

Table 1: Percent (%) changes and p-values over 2 years of patients and controls for R_2 and volume

		R2 MEASUREMENTS			VOLUME		
Region and Group		**R_2 % change (SD) in 2 years**	**p value over time**	**p value between groups**	**Volume % change (SD) in 2 years**	**p value over time**	**p value between groups**
Globus pallidus	patient	3.79 (2.66)	**<0.001**	**<0.001**	-3.80 (5.20)	0.266	0.021
	control	1.73 (2.08)	**0.002**		-2.01 (7.17)	0.833	
Putamen	patient	1.77 (2.06)	**0.011**	0.147	-2.77 (4.47)	0.141	**<0.001**
	control	0.15 (1.96)	0.82		-1.53 (3.58)	0.197	
Caudate	patient	2.14 (2.57)	**0.011**	**0.004**	-1.51 (5.06)	0.326	**<0.001**
	control	0.21 (2.09)	0.767		0.25 (3.76)	0.831	
Thalamus	patient	0.15 (1.94)	0.703	0.283	0.39 (3.96)†	0.758	0.012
	control	0.21 (2.06)	0.779		0.89 (5.85)	0.592	
Pulvinar	patient	4.42 (3.18)	**<0.001**	**0.011**	--	--	--
	control	1.08 (2.65)	0.215		--	--	
Substantia Nigra	patient	4.75 (4.07)	**0.001**	**0.001**	--	--	--
	control	1.72 (2.59)	0.078		--	--	
Red nucleus	patient	3.35 (4.47)	**0.024**	0.409	--	--	--
	control	0.48 (2.24)	0.54		--	--	
Frontal WM	patient	-1.06 (2.34)	0.164	0.126	--	--	--
	control	0.42 (2.25)	0.544		--	--	
Cortex	patient	--	--	--	-0.63 (1.69)	0.334	0.584
	control	--	--		-0.02 (1.72)	0.971	

**p-values were obtained using paired sample t-test. SD, standard deviation; PUL, pulvinar nucleus; TH, thalamus excluding PUL; SN, substantia nigra; RN, red nucleus; FWM, frontal white matter; † TH included PUL.*

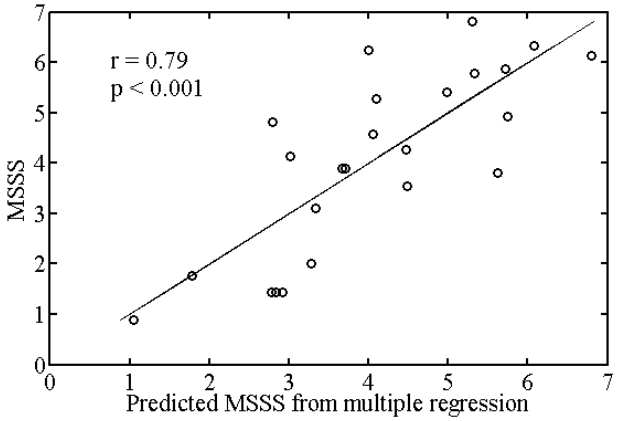

Figure 2: Measured MSSS versus predicted MSSS obtained from multiple regression of 2 years R_2 difference. PUL, TH and SN are included for regression model.

References: [1] Schenck JF, NMR Biomed 17(7) 2004; [2] Khalil M, *Neurology* 77, 2011; [3] Lebel RM, Mult Scler. 18(4) 2012. [4] Walsh AJ, Radiology 270 (1), 2014; [5] Jacobsen C., NNP 85, 2014; [6] Lebel RM, MRM 2010; [7] FSL version 5.0, http://fsl.fmrib.ox.ac.uk/fsl; [8] Roxburgh RH, Neurology 64, 2005.