Focal cerebellar pathology in early relapsing-remitting multiple sclerosis patients: a MP2RAGE study at 3T and 7T MRI

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Synopsis: In this work, we assessed the sensitivity of MP2RAGE at 7T MRI to detect focal cerebellar pathology, both in grey and white matter. To do this, we compared cerebellar lesion count in 7T and 3T MP2RAGE images in a cohort of MS patients. Lesion detection rate at 7T MRI was higher than the one at 3T, yet the total lesion volume was comparable at different field strengths. Lesion volumes calculated on 7T MP2RAGE images showed higher correlations with clinical scores than the ones at 3T, pointing at a clinical value of 7T MRI for complex regions such as cerebellum.

Introduction: Multiple Sclerosis (MS) is an autoimmune disease characterized by focal and diffuse brain inflammation, degeneration and repair in the central nervous system. Extended demyelination in the cerebellum has been shown *ex vivo* in patients with advanced disease[1], and a number of recent studies evidenced cerebellar grey-matter (GM) and global cerebellar atrophy at various disease stages[2,3]. Nevertheless, while focal white-matter (WM) pathology in the cerebellum has been extensively investigated, there are only few studies focusing on focal cortical cerebellar pathology *in vivo*[4]. Due to the complex structure of the cerebellum, whose folia are made by an inner strip of WM bounded by a thin cortical layer, ultra-high-field MRI might be of benefit to detect cerebellar lesions both in WM and in the cortex. In this work, we studied a cohort of early-stage MS patients and evaluated the impact of focal cerebellar pathology using MP2RAGE[5,6] at ultra-high (7T) and high (3T) field MRI. Next, we assessed the relationship between cerebellar lesion number and volume, as obtained using 3T and 7T images, and clinical scores in patients.

Material and Methods: Nineteen patients (4 males, 15 females, median age 35 years, age range: 21-46 years) with early RRMS (disease duration < 5 years from diagnosis) and mild disability (median Expand Disability Status Scale-EDSS 1.5, range: 1-2) underwent MR examinations on a 3T (MAGNETOM Trio a Tim system, Siemens Healthcare, Germany) and on a research 7T system (Siemens Healthcare, Germany) using a 32-channel head coil. From the MRI acquisition protocol, we used the high-resolution Magnetization-Prepared 2 Rapid Acquisitions Gradient Echo (MP2RAGE)[6] with the following parameters:

- 3T: TR/TI1/TI2=5000/700/2500 ms and voxel size = 1.0x1.0x1.2 mm^3;
- 7T: TR/TI1/TI2=6000/750/2350 ms and voxel size = 0.75x0.75x0.9 mm^3.

Each subject underwent a neurological examination including the following cognitive and behavioral tests: 1) Brief Repeatable Battery of Neuropsychological Tests (BRB-N), which examines verbal and spatial memory, sustained attention, information processing speed, and verbal fluency on semantic cues; 2) Multiple Sclerosis Functional Composite (MSFC) scores to quantify motor and cognitive performance, and 3) EDSS.
Cerebellum segmentation was obtained using the MorphoBox[7,8] prototype. Lesion maps for each patient were obtained manually and automatically. Manual detection was performed by two experts (a neurologist and a radiologist) in the MP2RAGE image at both 3T and 7T. Automated lesion detection was performed by an in-house automated tool[9], only for use in this research study. Total lesion load (TLL), total lesion volume (TLV) and mean lesion volume (MLV) per patient were estimated at 3T and 7T. Correlation between cognitive and behavioral tests with the TLL, TLV and MLV were performed using the Spearman test adjusted for False Discovery Rate (FDR). The performance of the automated segmentation was evaluated for both scenarios using a leave-one-out cross validation. Detection rate (DR, number of detected lesions/total manual segmented lesions) was obtained for each scenario. Finally, statistical difference was computed using the Wilcoxon signed-rank test.

Results: Illustration of original data, manual and automated segmentation is reported in Figure 1. We observed a significantly higher TLL at 7T compared to 3T (average ± SD, 7T: 9 ± 9 lesions, range: 0 – 31; 3T: 5 ± 8 lesions, range: 0 - 29, $P<0.001$, Figure 2). And remarkably, MPRAGE at 7T showed 33% more WM lesions and only 5% more GM lesions. The average TLV per patient at 7T was 0.29 ± 0.54 mL (range: 0 - 2.20 mL) and did not significantly differ from TLV at 3T (0.29 ± 0.61 mL, range: 0 - 2.54 mL, $P=0.231$). However, average MLV in the entire patients cohort was lower at 7T (0.022 ± 0.018 mL) compared to 3T (0.041 ± 0.048 mL, $P<0.05$). No correlation was found between the lesion measures at 3T and 7T and motor performance tests. Yet interestingly, negative correlations with MLV from manual segmentations on 7T with some cognitive tests (SRTR: $\rho=-0.5$, $P=0.0063$; SRTD: $\rho=-0.7$, $P=0.0005$; VIST: $\rho=-0.5$, $P=0.0068$; and VISD: $\rho=-0.5$, $P=0.0069$ after FDR correction, Figure 3) were observed. Automatic detection rates on MP2RAGE images were similar at both field strengths (7T: median DR 72%; 3T median DR 67%, $P=0.534$, Figure 4).

Discussion & Conclusion:
We have previously shown that the MP2RAGE sequence is sensitive to both WM and GM pathology in MS patients[6]. Our current study demonstrates the benefits of using MP2RAGE at ultra-high field to assess the presence and clinical impact of cerebellar lesions at early disease stages. MP2RAGE at 7T evidenced a higher lesion load than MP2RAGE at 3T, probably due to improved spatial resolution, lower partial-volume effects and higher contrast-to-noise. This was significant for manual lesion segmentation but failed to reach significance for automated lesion count using an in-house software. Future efforts will be devoted to improve automated lesion detection in the cerebellum at 7T by combining MP2RAGE with other contrasts like FLAIR[10]. Notably, significant correlations were found between 7T cerebellar lesion volume and verbal and visual memory performances in patients, suggesting that 7T MRI may have an important clinical value in multiple sclerosis for complex brain regions such as cerebellum.

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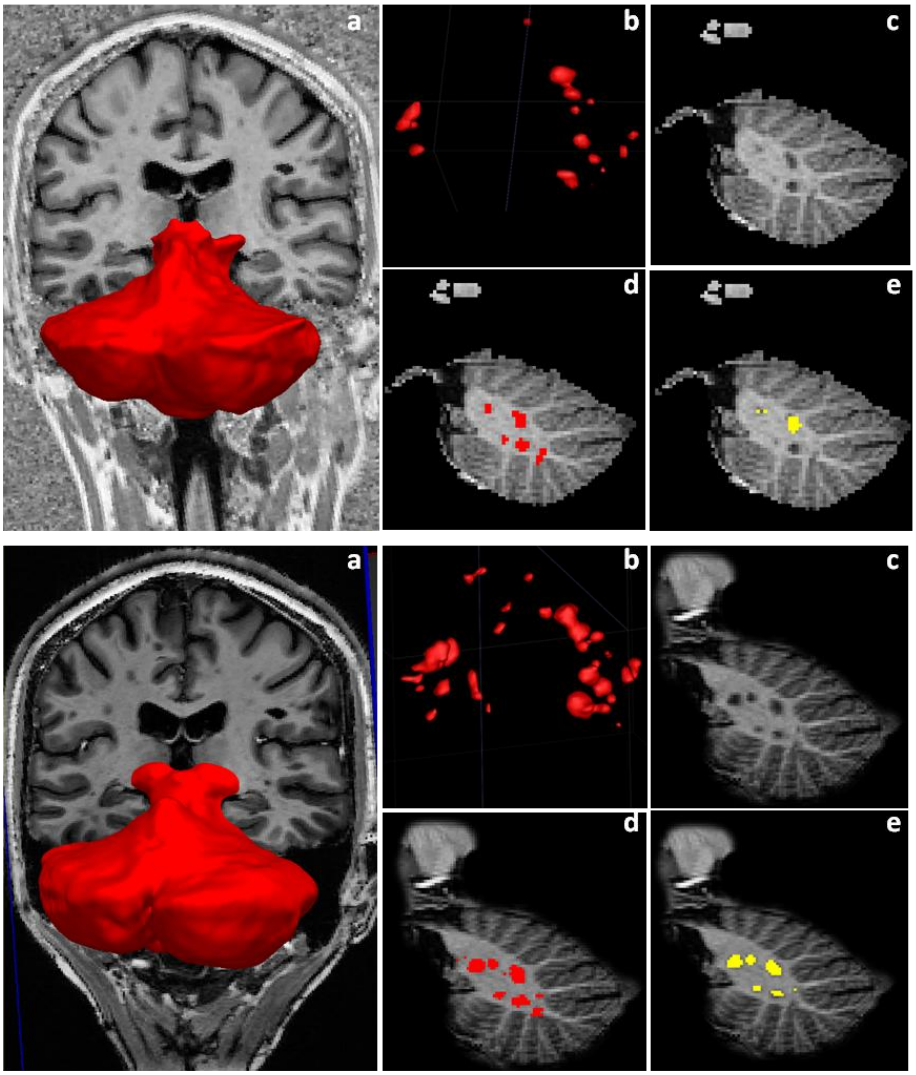

Figure 1 - Example of a MS patient scanned at 3T (top row) and 7T (bottom row): a. Visualization 3D of the infratentorial mask obtained with the MorphoBox prototype; b. 3D rendering of the manual lesion segmentation; c. MP2RAGE image slice (sagittal view) of the cerebellum; d. Manual segmentation of cerebellar lesions; e: results of automated segmentation.

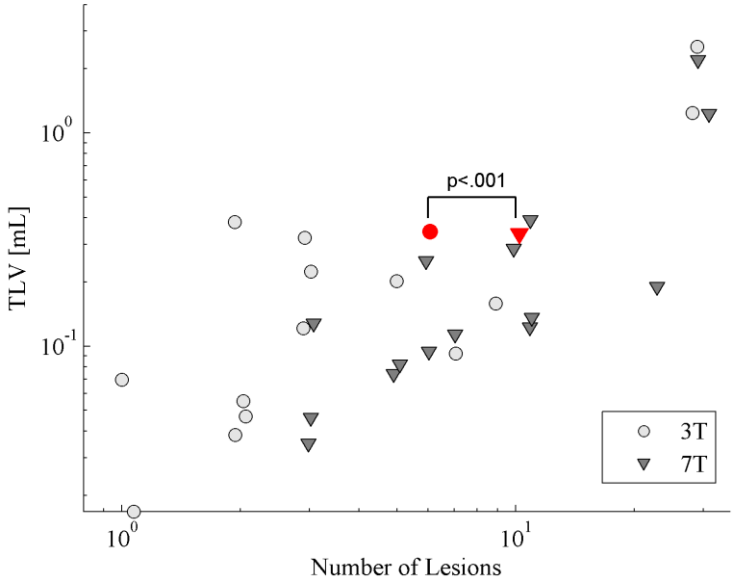

Figure 2 - Log-log plot of manual segmentation results in terms of total lesion volume (TLV) and number of lesions obtained from 3T (circle) and 7T (triangle) data. Grey and red symbols represent the values per patient and average values, respectively.

		3T									7T								
		TLL			TLV			MLV			TLL			TLV			MLV		
		ρ	*P*	*P_FDR*	ρ	*P*	*P_FDR*	ρ	*P*	*P_FDR*	ρ	*P*	*P_FDR*	ρ	*P*	*P_FDR*	ρ	*P*	*P_FDR*
BRB-N	SRTS[1)]	-0.237	0.328	0.407	-0.401	0.089	<0.05	-0.333	0.163	<0.001	**-0.543***	0.016	<0.01	**-0.566***	0.012	<0.001	-0.413	0.079	<0.05
	SRTR[2)]	-0.257	0.289	0.431	**-0.506***	0.027		**-0.473***	0.041		-0.282	0.241		-0.415	0.078		**-0.489***	0.034	
	SRTD[3)]	-0.275	0.254	0.946	**-0.458***	0.048		-0.355	0.135		-0.287	0.234		-0.580*	0.009		**-0.688****	0.001	
	VIST[4)]	-0.030	0.905	0.674	-0.292	0.225		-0.319	0.183		-0.224	0.356		-0.308	0.199		**-0.457***	0.049	
	VISD[5)]	0.003	0.991	0.671	-0.181	0.458		-0.125	0.610		-0.244	0.315		-0.399	0.091		**-0.514***	0.025	
	SDMT[6)]	-0.258	0.285	0.531	-0.430	0.066		-0.366	0.123		-0.189	0.438		-0.172	0.482		-0.286	0.235	
	PASAT[7)]	-0.275	0.254	0.631	-0.330	0.168		**-0.460***	0.047		-0.184	0.452		-0.098	0.691		-0.141	0.563	
	FV[8)]	-0.145	0.553	0.589	-0.183	0.452		-0.262	0.278		0.048	0.845		0.148	0.544		-0.051	0.836	
Motor Performance	Leg-function	-0.114	0.642	1.000	-0.137	0.575		-0.217	0.371		-0.264	0.275		-0.400	0.089		-0.352	0.140	
	Arm-function	0.109	0.656	0.598	-0.085	0.729		-0.168	0.493		-0.388	0.101		-0.400	0.091		-0.071	0.772	
EDSS[9)]		-0.355	0.136	0.543	-0.328	0.170		-0.281	0.243		-0.155	0.525		-0.025	0.920		-0.196	0.422	

1) SRTS – Selective Reminding Test-Long Term Storage; **2) SRTR** – Selective Reminding Test-Consistent Long Term Storage; **3) SRTD** – Selective Reminding Test-Delayed; **4) VIST** – Visual Memory Test; **5) VISD** – Visual Memory Test Delayed; **6) SDMT** – Symbol Digit Modalities Test; **7) PASAT** – Paced Auditory Serial Addition Test; **8) VF** – Verbal Fluency; **9) EDSS** – Expand Disability Status Scale.

Figure 3 - Correlation analyses using Spearman's rho between cognitive/behavioral tests and Total Lesion Load (TLL), Total Lesion Volume (TLV), and Mean Lesion Volume (MLV) using data sets acquired at 3 and 7T. *P*-values were adjusted using False Discovery Rate (FDR). Significant correlation at uncorrected *P*-value are identified by *(*P*<0.05) and **(*P*<0.001).

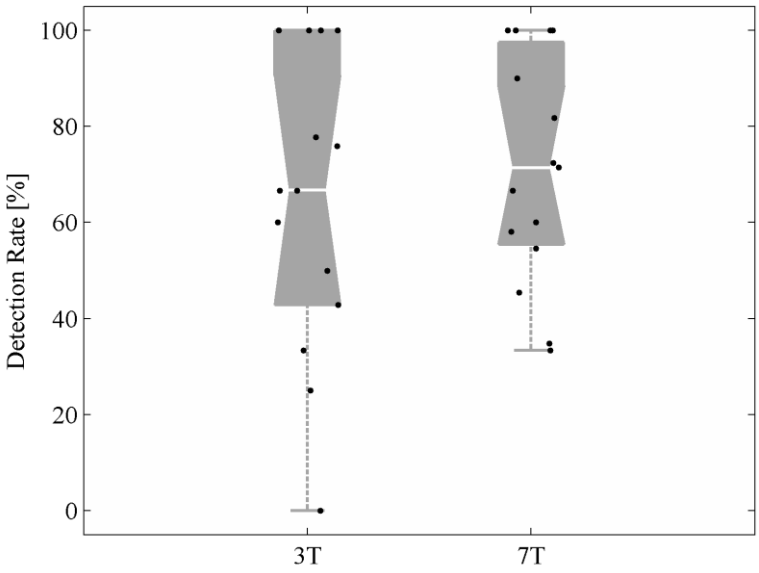

Figure 4 - Boxplots of detection rate (DR) from all patients at 3 and 7T. The dots in the plot represent the values of DR per each patient.