ORIGINAL COMMUNICATION

MP2RAGE provides new clinically-compatible correlates of mild cognitive deficits in relapsing-remitting multiple sclerosis

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Abstract Despite that cognitive impairment is a known early feature present in multiple sclerosis (MS) patients, the biological substrate of cognitive deficits in MS remains elusive. In this study, we assessed whether T1 relaxometry, as obtained in clinically acceptable scan times by the recent Magnetization Prepared 2 Rapid Acquisition Gradient Echoes (MP2RAGE) sequence, may help identifying the structural correlate of cognitive deficits in relapsing-remitting MS patients (RRMS). Twenty-nine healthy controls (HC) and forty-nine RRMS patients underwent high-resolution 3T magnetic resonance imaging to obtain optimal cortical lesion (CL) and white matter lesion (WML) count/volume and T1 relaxation times. T1 z scores were then obtained between T1 relaxation times in lesion and the corresponding HC tissue. Patient cognitive performance was tested using the Brief Repeatable Battery of Neuro-psychological Tests. Multivariate analysis was applied to assess the contribution of MRI variables (T1 z scores, lesion count/volume) to cognition in patients and Bonferroni correction was applied for multiple comparison. T1 z scores were higher in WML ($p < 0.001$) and CL-I ($p < 0.01$) than in the corresponding normal-appearing tissue in patients, indicating relative microstructural loss. (1) T1 z scores in CL-I ($p = 0.01$) and the number of CL-II ($p = 0.04$) were predictors of long-term memory; (2) T1 z scores in CL-I ($\beta = 0.3$; $p = 0.03$) were independent determinants of long-term memory storage, and (3) lesion volume did not significantly influenced cognitive performances in patients. Our study supports evidence that T1 relaxometry from MP2RAGE provides information about microstructural properties in CL and WML and improves correlation with cognition in RRMS patients, compared to conventional measures of disease burden.

Keywords High field MRI · T1 relaxation time · Multiple sclerosis · Cognitive impairment · Cortical pathology

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Introduction

Cognitive impairment affects approximately 40–70 % of the multiple sclerosis (MS) patients [1, 2]. Frequently affected functions include attention, information processing speed, executive functioning, and long-term memory

[3]. Among these, information processing speed appears to be one the most common cognitive deficits in early MS [4].

Conventional magnetic resonance imaging (MRI) has been extensively exploited to investigate cognitive dysfunction in MS [3, 5, 6]. Nevertheless, correlations between the extent of white matter (WM) abnormalities detected on conventional brain MRI and cognitive impairment are generally low [7–11]. Likewise, measures of whole-brain atrophy showed only moderate correlations with cognitive dysfunction [3, 6]. Recently, the number of cortical lesions (CLs), detected with Double Inversion Recovery [DIR] sequence [12], has shown higher correlations with cognitive impairment than the number of WM plaques [8, 13, 14]. Cortical atrophy has also been reported to have a higher impact than whole-brain atrophy on cognitive impairment [15], and recent ultra-high-field MRI investigations provided evidence that a specific subtype of cortical lesions (mixed white matter-grey matter, type I) are major determinants of neuropsychological performance in MS patients [16].

Nevertheless, most of the cited studies applied techniques that are not compatible with clinical practice due to important artefacts (DIR) [12], long measurement times or magnetic fields that are not homologated for clinical routine (7T). In addition, most published studies focused on patients with late RRMS or on secondary progressive MS patients with moderate to severe cognitive dysfunction.

T1 quantitative measures provide more direct measures of the microstructural lesions and are paraclinical used as markers of subtle microstructural damage. T1 relaxation times help distinguish lesions from normal-appearing (NA) tissue in patients and healthy tissue in controls [17–19]. Long T1 values suggest loss of tissue structure or water accumulation and short T1 values correspond to pathological processes such as accumulation of methemoglobin, proteinaceous material, lipids, free radicals, paramagnetic metals (non-heme iron) and remyelination [20]. Therefore, T1 measurements might provide information to increase correlation between MRI measures of disease states and cognitive deficits. Whole-brain T1 relaxometry can be obtained in clinically acceptable scan-times using the MP2RAGE sequence [21], which has been recently shown to be nearly as sensitive as DIR for cortical lesion detection and more sensitive than 3D FLAIR for WM lesion detection [22].

In this study, we aimed at assessing the clinical value of MP2RAGE T1 relaxometry at early stages of MS. Specifically, we investigated whether quantitative T1 measures of tissue lesion alterations improve correlations with subtle cognitive symptoms in a cohort of RRMS patients with less than 6 years of disease duration.

Methods

Subject population

Forty-nine patients (14 males and 35 females) with early (disease duration <6 years) RRMS according to the McDonald criteria [23, 24] were enrolled in the study (age 34.2 ± 8.8 years, mean $\pm$ standard deviation; educational level 15.2 ± 2.9 years; disease duration 2.9 ± 1.9 years; expanded disability status scale EDSS 1.6 ± 0.3). Patients with a diagnosis of major depression or other psychiatric disorders according to the DSM-IV criteria were not considered.

The healthy control (HC) group consisted of twenty-nine healthy volunteers (8 males and 21 females; mean age: 32.3 ± 8.3 years; mean educational level 16.7 ± 3.2 years) with no history of alcohol or drug abuse, major psychiatric disorders (major depression, psychosis, untreated bipolar disorders), head trauma, other neurological disorders or systemic illness.

All participants underwent a neuropsychological examination and brain MRI. The study was approved by the local Ethics Committee and all subjects gave informed consent for their participation.

Neuropsychological assessment

All participants underwent the Brief Repeatable Battery of Neuropsychological Tests (BRB-N) [25]. In short, the BRB-N is composed of the following tests:

1. The Selective Reminding Test (SRT) measures verbal learning and delayed recall through presentation of a list of 12 words and six consecutive learning trials. The SRT allows distinguishing between retrieval from short-term and long-term memory and also examines the consistency of retrieval from long-term memory. This study used three indices: the long-term storage (LTS) defined as any word recalled on two consecutive trials, the consistent long-term retrieval (CLTR) defined as any word in LTS consistently recalled on all subsequent trials and the Delayed recall (SRTD) representing the total number of words recalled after a 20-min delay.
2. The 10/36 spatial recall test (SPART) assesses visuospatial learning and recall by recreating the pattern of 10 checkers on a 6×6 checkerboard viewed for 10 s.
3. The symbol digit modalities test (SDMT) measures sustained attention and processing speed by requiring the subject to associate symbols with numbers and quickly orally generating the number when shown the symbol during 90 s.

4. The paced auditory serial addition task (PASAT) evaluates sustained attention, auditory information processing speed and working memory and is measured by asking the patient to add each number to the preceding number with additional numbers presented every 3 s;

5. The word list generation (WLG) measures semantic verbal fluency, evaluating the spontaneous production of words from a specific semantic category for 60 s. The complete set of neuropsychological tests is presented in Table 1.

Mood symptoms and fatigue were quantified using the Hospital Anxiety and Depression scale (HAD) [26] and the Fatigue Scale for Motor and Cognitive functions (FSMC) [27], respectively.

MRI data acquisition

Within 2 weeks from neuropsychological assessment, participants underwent brain MRI at 3T (Magnetom Trio a Tim System, Siemens Healthcare, Germany) using a commercial 32-channel head coil. The acquisition protocol was optimized to maximise lesion detection in WM and GM as well as in the cerebrum and the cerebellum.

The imaging protocol included the magnetization-prepared rapid gradient echo (MPRAGE), the double-inversion recovery (DIR) [12], the two inversion-contrast magnetization-prepared rapid gradient echo (MP2RAGE) [21] and the 3-dimensional fluid attenuated inversion recovery (3D FLAIR) sequences [28]. For sequence parameter details see Table 2.

Table 1 Neuropsychological tests

BRB-N	Tested cognitive functions
SRT-CLTR	Verbal learning and memory: consistency of retrieval from long-term memory component
SRT-D	Verbal learning and memory: delayed recall component
SRT-LTS	Verbal learning and memory: long-term storage component
SDMT	Processing speed and working memory
PASAT	Sustained attention and information processing speed
SPART	Visuospatial learning and recall
SPART-D	Visuospatial learning and delayed recall
WLG	Semantic verbal fuency test

BRB-N brief repeatable battery of neuropsychological tests, SRT-CLTR selective reminding test-consistent long-term retrieval, SRT-D selective reminding test-delayed recall, SRT-LTS selective reminding test-long-term storage, SDMT symbol digit modalities test, PASAT paced auditory serial addition test at 3 s, SPART 10/36 spatial recall test, SPART-D 10/36 spatial recall test-delayed, WLG word list generation

Table 2 MRI sequences parameters

	3D FLAIR	MP-RAGE	MP2RAGE	DIR
Sequence parameters				
Acquisition	3D	3D	3D	3D
Resolution	$1 \times 1 \times 1.2$ mm^3	$1 \times 1 \times 1.2$ mm^3	$1 \times 1 \times 1.2$ mm^3	$1.1 \times 1 \times 1.2$ mm^3
Orientation/readout	Sagittal/A $\gg$ P			
Matrix size	240×256	256×256	240×256	240×256
Slice/partitions	176	160	176	160
Acquisition time	6 min 27 s	5 min 12	8 min 22 s	12 min 52 s
No patients/controls scans	49/29	49/29	49/29	49/29
Acceleration factor	2	2	3	2
TE (ms)	394	2.98	2.89	218
Inversion time(s) (ms)	1,800	900	700/2,500	3,650
Flip angle(s) (°)	VFL[a]	9	4	VFL[a]
Echo/readout train length (ms)	835	1,162	1,162	640
TR (ms)	5,000	2,300	5,000	10,000
Bandwidth (Hz/pixels)	781	240	240	651

Parameters of all employed imaging sequences. All 3D contrasts were acquired with the same spatial resolution

3DFLAIR 3-dimensional fluid attenuated inversion recovery, MP2RAGE two inversion-contrast magnetization-prepared rapid gradient echo, DIR double-inversion recover, TE echo time, TR repetition time

[a] Optimized variable flip angle (VFL) pattern over the readout train

Post-processing

In order to maximize lesion detection (number and volume), a certified neurologist and a certified neuroradiologist identified brain lesions by consensus in DIR, MP2RAGE uniform and 3DFLAIR images separately, as previously reported [22]. Subsequently, the lesions were manually contoured and assigned to one of the following classes: GM (cortical lesion type II, CL-II), mixed cerebral GM/WM (cortical lesion type I, CL-I) and WM (white matter). The resulting masks were confirmed a second time and, if necessary, corrected by a study physician.

The imaging volume and lesion masks were patient-wise co-registered to a common image space using an in-house registration software. Subsequently, a single-set union-mask was created per patient containing all lesions from all contrasts with their maximum spatial extent [22]. The union mask was applied to the T1-maps from the MP2RAGE. Lesion volumes were obtained using an in-house software [29]. Cortical and WM lesion number, volume and T1 relaxation times were evaluated for each of the union mask sets.

For each patient, T1 z scores of mean relaxation times were calculated for each cortical and WM lesion as follows:

$$z = \frac{x - \mu}{\sigma},$$

where x is the T1 mean relaxation time for each patient lesion, μ is the T1 mean relaxation time for each HC in the corresponding tissue (cortical GM and WM) and σ is the standard deviation of the T1 relaxation time in HC within the same tissue region. Cortical GM and WM regions of interest in the HC were derived from the MPRAGE image using in-house software based on variational expectation–maximization tissue classification [30].

T1 z score measures of T1 relaxation times were preferred to T1 relaxation times in order to be able to perform correlation analysis in the whole cohort of patients, including subjects lacking lesions in a specific location (i.e. CL-I and CL-II).

Statistical analysis

Kruskal–Wallis test was used to compare demographic, clinical and behavioural findings between patients and controls. A Box–Cox transformation was applied to all demographic, clinical and MRI variables (lesion number and volume) to obtain data normalization prior to analysis.

The same test was also applied to compare T1 z scores in lesions and corresponding normal-appearing tissue.

A general linear model regression was applied to evaluate the correlation between cognitive scores and MRI scores (T1 z scores, lesion number and volume) as well as covariates

(age, gender and education) and behavioural score (HAD) as predictors. Backward stepwise analyses were conducted with the Wald criterion using $p = 0.05$ for entry level and $p = 0.10$ for removal. Bonferroni correction was applied for multiple comparison. The significant variables were identified with p value <0.05. All statistical analysis was performed using MATLAB R2013a Statistical Toolbox.

Results

Clinical and neuropsychological results

Patients did not differ from HCs for gender ($p = 0.9$) and age ($p = 0.12$). However, RRMS patients had slightly lower education than controls ($p = 0.02$, mean education level of patients = 15.2 years and controls = 16.7 years).

Results of cognitive tests are reported in Table 3. Patients showed on average significantly lower scores on measures of sustained attention and working memory (PASAT, p value = 0.01).

On the behavioural questionnaires, RRMS patients and controls had comparable scores on the HAD anxiety scale ($p = 0.19$) but significantly different scores on the HAD depression scale ($p = 0.006$). Moreover, patients showed higher scores of fatigue on the total FSMC score ($p < 0.001$), both on the physical dimension of the scale ($p = 0.001$) and on its cognitive dimension ($p < 0.001$).

Cortical and subcortical lesion counts and T1 relaxation times/z scores

Lesion counts in patients and in HCs are presented in Table 4. All early RRMS patients showed cortical lesions

Table 3 Cognitive test results in RRMS patients and HCs

Cognitive tests	RRMS patients ($n = 49$)	HC ($n = 29$)	p value
SRT-LTS	62.5 ± 6.82	64.5 ± 6.5	0.08
SRT-CLTR	56.6 ± 11.1	59.9 ± 9.7	0.22
SRT-D	11.2 ± 1.14	11.5 ± 0.9	0.08
SPART	23.4 ± 4.3	23.3 ± 4.6	0.96
SPART-D	8.6 ± 2.05	8.6 ± 1.8	0.66
SDMT	56.9 ± 9.56	59.6 ± 11.4	0.23
PASAT	46.8 ± 10.8	51.9 ± 10.5	**0.01**
WLG	27.7 ± 5.3	28.7 ± 6.9	0.18

Bold value corresponds to p value <0.05

SRT-LTS selective reminding test-long-term storage, *SRT-CLTR* selective reminding test-consistent long-term retrieval, *SRT-D* selective reminding test-delayed recall, *SDMT* symbol digit modalities test, *PASAT* paced auditory serial addition test at 3 s, *SPART* 10/36 spatial recall test, *SPART-D* 10/36 spatial recall test-delayed, *np* number of patients, *nc* number of controls, *WLG* word list generation

(CLs), whereas no CLs were observed in HCs. The majority of CL in patients consisted of type I lesions (Table 4). The rest of the CLs were type II (intra-cortical lesions). No type III/IV lesions were detected.

Lesion z scores are reported in Table 4. Except for the pure cortical (CL-II) lesions, T1 z scores were consistently higher in lesions compared to the corresponding normal-appearing tissue in patients (WM lesions: $p < 0.001$, CL-I: $p < 0.01$ Fig. 1).

Table 4 Number of lesions, volume and T1 z scores in HCs and in RRMS patients

Lesion type	Lesions in RRMS patients (no.)			Lesion volume in RRMS patients (mm^3)			T1 z scores in RRMS patients		
	Median	Max	Min	Median	Max	Min	Median	Max	Min
WMLs	32	140	3	2,449	12,367	58	11.14	20.49	−0.42
CLs II	0	6	0	0	278.4	0	0.00	15.04	−7.58
CLs I	3	31.5	0	174	2,707.2	0	2.31	15.92	−7.82

Lesion type	Lesions in HC (no.)			Lesion volume in HC (mm^3)					
	Median	Max	Min	Median	Max	Min			
WMLs	1	11	0	11.4	387.6	0			
CLs II	0	0	0	0	0	0			
CLs I	0	1	0	0	38.4	0			

Median median value, *Max* maximum value, *Min* minimum value, *WMLs* white matter lesions, *CLs I* mixed cortical lesions, *CLs II* grey matter cortical lesions, *HC* healthy controls
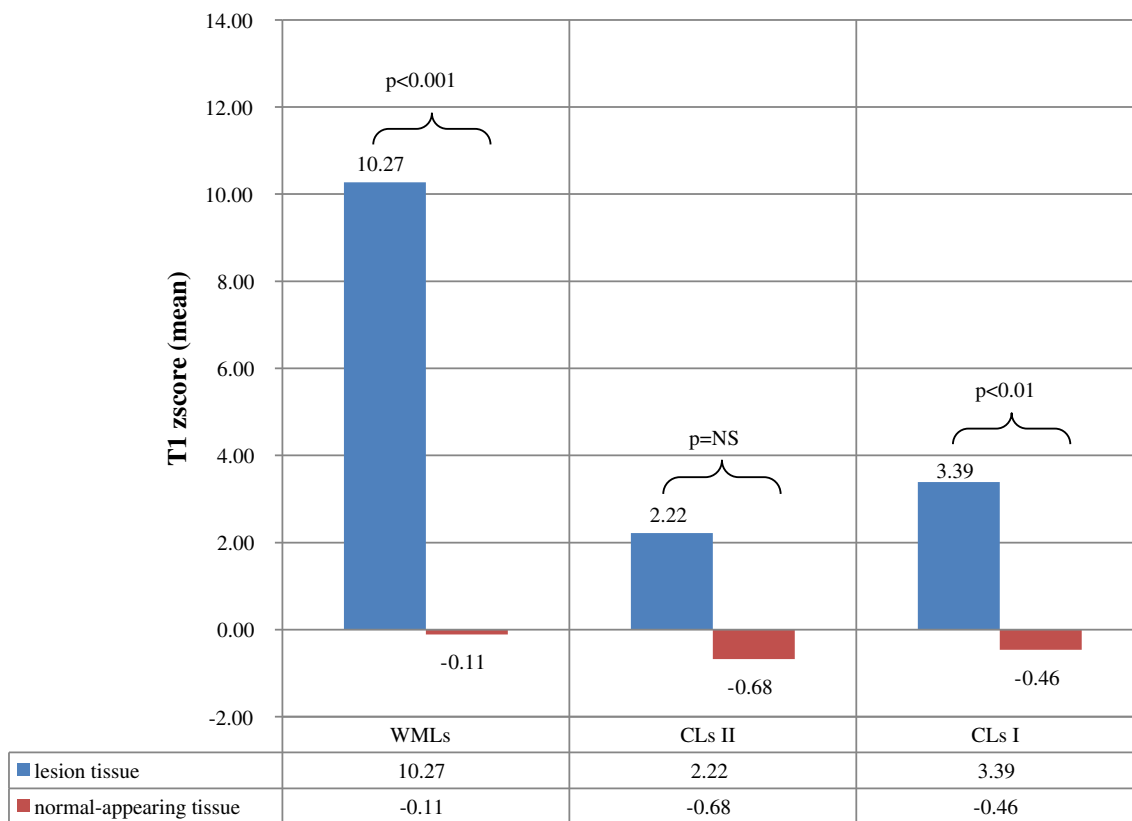

Fig. 1 T1 z scores (mean) in lesions and normal appearing tissue in RRMS patients. *WMLs* white matter lesions, *CLs II* grey matter cortical lesions, *CLs I* mixed cortical lesions, *NS* not significant. WM and CLI lesions show significantly higher T1 z scores compared to corresponding normal appearing brain tissue in patients. T1 z scores in pure cortical lesions (CLs II) did not significantly differ from normal-appearing tissue in patients

Table 5 Multiple linear regression

BRB-N tests	Multiple linear regression													R^2	F	p value
	Age	Gender	Education (years)	HAD	WMLs T1z	WMLs N	WMLs V	CLs II T1z	CLs II N	CLs II V	CLs I T1z	CLs I N	CLs I V			
SRT-CLTR	NS	$\beta = 0.28$ $p = 0.03$	NS	NS	NS	NS	NS	NS	$\beta = -0.26$ $p = 0.04$	NS	$\beta = 0.35$ $p = 0.01$	NS	NS	0.3	4.2	0.02
SRT-D	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	–	–	–
SRT-LTS	NS	NS	$\beta = 0.31$ $p = 0.02$	$\beta = -0.31$ $p = 0.03$	NS	NS	NS	NS	NS	NS	$\beta = 0.32$ $p = 0.03$	NS	NS	0.3	4.1	0.04
SDMT	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	–	–	–
PASAT	NS	NS	$\beta = 0.49$ $p = 0.0005$	$\beta = -0.25$ $p = 0.02$	$\beta = -0.29$ $p = 0.06$	NS	NS	NS	NS	NS	NS	NS	NS	0.2	7.0	0.004
SPART	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	–	–	–
SPART-D	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	–	–	–
WLG	NS	$\beta = 0.41$ $p = 0.003$	$\beta = 0.05$ $p = 0.007$	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	0.3	7.8	0.01

Bold values correspond to p value <0.05

BRB-N tests brief repeatable battery of neuropsychological tests, *WMLs* white matter lesions, *CLs I* mixed cortical lesions, *CLs II* grey matter cortical lesions, *N* number, *V* volume, *T1z* T1 z scores, *SRT-CLTR* selective reminding test-consistent long-term retrieval, *SRT-D* selective reminding test-delayed recall, *SRT-LTS* selective reminding test-long-term storage, *SDMT* symbol digit modalities test, *PASAT* paced auditory serial addition test at 3 s, *SPART* 10/36 spatial recall test, *SPART-D* 10/36 spatial recall test-delayed, *WLG* word list generation, *HADS* hospital anxiety and depression scale, *NS* non significant, *p value* p value after Bonferroni correction

Multiple regression analysis

The results of multiple regression analysis are reported in Table 5.

Consistent long-term memory retrieval in SRT was significantly dependent on gender ($\beta = 0.3$; $p = 0.03$), T1 z scores in CL-I ($\beta = 0.4$; $p = 0.01$) and CL-II lesions number ($\beta = -0.3$; $p = 0.04$) ($r^2 = 0.3$; $F = 4.2$; $p = 0.02$ corrected). Education ($\beta = 0.3$; $p = 0.02$), HAD ($\beta = -0.3$; $p = 0.03$) and T1 z scores in CL-I ($\beta = 0.3$; $p = 0.03$) were found to be independent predictors of Long-Term Storage component in SRT ($r^2 = 0.3$; $F = 4.1$; $p = 0.04$ corrected).

Education ($\beta = 0.5$; $p = 0.0005$) and HAD ($\beta = -0.3$; $p = 0.02$) appeared to be independent predictors of sustained attention and working memory (PASAT), whereas T1 z scores ($\beta = -0.3$; $p = 0.06$) in WM lesions failed to reach significance ($\beta = -0.3$; $p = 0.06$) ($r^2 = 0.3$; $F = 7.0$; $p = 0.004$ corrected). Gender ($\beta = 0.41$; $p = 0.003$) and education ($\beta = 0.007$; $p < 0.01$) were independent predictors of semantic verbal fluency ($r^2 = 0.3$; $F = 7.8$; $p = 0.01$ corrected).

Discussion

In this study, we show that T1-based microstructural characteristics of cortical lesions, as measured by MP2RAGE, improve clinical–radiological correlations with cognitive performances in early MS, compared to conventional measures (lesion number and volume).

MP2RAGE is a self-bias-corrected sequence that supports with T1-weighted images of high anatomical quality as well as high-resolution T1 relaxometry in a clinically compatible scan-time [21]. Recently, we showed that MP2RAGE uniform images provide higher sensitivity to lesion count than standard MPRAGE and FLAIR sequences and are nearly as sensitive as DIR for cortical lesion detection [22].

T1 relaxometry measurements, as provided by MP2RAGE, are globally influenced by pathological changes of different severity, such as demyelination, gliosis, inflammation, axonal injury and axonal loss [31–33]. In acute MS lesions, there is first a T1 prolongation due to acute oedema, rapidly followed by T1 shortening; in chronic plaques, T1 relaxation times are variable, indicating pathological heterogeneity [15]. T1 relaxometry has been exploited to assess the degree of tissue alteration in different MS subtypes [18, 34–36] and our group previously reported that, in early RRMS, MP2RAGE T1 relaxation times are longer in CL-I and WM lesions compared to healthy control tissue [22]. Moreover, quantitative T1 measurements were shown to moderately correlate with

global disability (i.e. EDSS) [18, 37] and MS Functional composite (MSFC) scores [38].

In this work, we aimed at assessing whether the information provided by MP2RAGE relaxometry improves the correlation between MRI markers of early MS disease and cognition.

We studied a cohort of RRMS patients with less than 6 years of disease duration, who benefitted from a complete neurocognitive examination. Patients exhibited mild cognitive deficits in sustained attention and working memory (PASAT), which is in line with previous studies at early MS stages [2–4, 9, 39–41].

In order to assess the contribution of T1-based measures of tissue integrity to cognitive performances in patients, we computed T1 relaxation times z scores between lesions/NA tissue in patients and corresponding healthy control tissue. T1 z scores in CL-I and WM lesions were significantly higher than corresponding T1 z scores in patients NA tissue, indicating relative tissue loss. Furthermore, T1 z scores in CL-I lesions were major determinants of both long-term memory retrieval and storage (SRT-CLTR and SRT-LTS), whereas the number of CL-II contributed only to memory retrieval.

Lower verbal memory performances were related to higher T1 z scores in CL-I lesions (positive correlation coefficient between SRT-CLRT and CL-I T1 z scores), suggesting that the higher the focal tissue loss the more important the deficits. On the other hand, the number of CL-II was a negative predictor of the SRT-CLRT, signifying that a higher number of pure cortical lesions is concomitant with less important memory retrieval deficits. This finding, at a first glance counterintuitive, might suggests that a certain threshold of GM damage is necessary to activate compensatory mechanisms for retrieval memory like it was previously observed in the motor cortex [40] and in the working memory system [9].

Our results confirm a recent 7T MRI study reporting that the number of CL-I was a predictor of cognitive performance in advanced MS [16] and extend it to early disease stages.

In addition, our work provides evidence that the degree of cortical and juxta-cortical damage is closely related to the presence of memory deficits and suggests potential pathophysiological mechanisms leading to cognitive dysfunction in early MS.

In summary, we show that T1 relaxation times obtained from MP2RAGE provide new biomarkers of cognitive impairment in early MS. Further studies should assess the prognostic value and sensitivity to therapy of these measurements.

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