Early putamen hypertrophy and ongoing hippocampus atrophy predict cognitive performance in the first ten years of relapsing-remitting multiple sclerosis

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Abstract

Background The first years of relapsing-remitting multiple sclerosis (RRMS) constitute the most vulnerable phase for the progression of cognitive impairment (CImp), due to a gradual decrease of compensatory mechanisms. In the first 10 years of RRMS, the temporal volumetric changes of deep gray matter structures must be clarified, since they could constitute reliable cognitive biomarkers for diagnostic, prognostic, and therapeutic purposes.

Methods Forty-five cognitively asymptomatic patients with RRMS lasting ≤ 10 years, and with a brain MRI performed in a year from the neuropsychological evaluation (Te-MRI), were included. They performed the Brief International Cognitive Assessment battery for MS. Thirty-one brain MRIs performed in the year of diagnosis (Td-MRI) and 13 brain MRIs of age- and sex-matched healthy controls (HCs) were also included in the study. The relationships between clinical features, cognitive performances, and Te- and Td-MRI volumes were statistically analyzed.

Results Cognitively preserved (CP) patients had significantly increased Td-L-putamen ($P = 0.035$) and Td-R-putamen volume ($P = 0.027$) with respect to cognitively impaired (CI) ones. CI patients had significantly reduced Te-L-hippocampus ($P = 0.019$) and Te-R-hippocampus volume ($P = 0.042$) compared, respectively, with Td-L-hippocampus and Td-R-hippocampus volume. Td-L-putamen volume ($P = 0.011$) and Te-L-hippocampus volume ($P = 0.023$) were independent predictors of the Symbol Digit Modalities Test score in all patients (r2 = 0.31, $F = 6.175$, $P = 0.001$).

Conclusion In the first years of RRMS, putamen hypertrophy and hippocampus atrophy could represent promising indices of cognitive performance and reserve, and become potentially useful tools for diagnostic, prognostic, and therapeutic purposes.

Keywords Atrophy · Cognitive impairment · Hippocampus · Hypertrophy · Putamen

Introduction

Cognitive impairment (CImp) is present in mostly 40–70% of patients with multiple sclerosis (PwMS), according to the stage of the disease [1], and it negatively affects overall quality of life [2]. Subjective cognitive difficulties have no direct link with objective cognitive deterioration [3–5], probably because they bear closer relationships with other symptoms, such as depression, fatigue, and anxiety [3–6]. The first years of the disease constitute the most vulnerable phase for the onset and progression of CImp in MS [7], since a gradual decrease of compensatory mechanisms occurs with the progression of disease [8]; nevertheless, these years probably represent the most suitable window for cognitive rehabilitation. The *core* cognitive functions which are compromised in MS are short-term visuospatial memory (ST-VSM), short-term verbal memory (ST-VM), information processing speed (IPS), working memory, sustained and divided attention, and executive functions [1]. Subcortical gray matter (scGM) structures provide points of convergence across multiple functional circuits in the brain

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and are involved in procedural and working memory, attention, and executive functions [9–12]. Hippocampus and deep GM nuclei could be involved in the development of CImp before more advanced global brain damage is manifested, and they could be potential reliable markers of it. In patients with relapsing-remitting (RR) MS, some cross-sectional studies have found that CImp could be predicted by magnetic resonance imaging (MRI) cortical lesions, cortical GM, hippocampus, putamen, and thalamus volume [13–16]. Only one longitudinal retrospective study [17], which investigated patients with progressive and RRMS, showed that lower gray matter volume (GMV) predicted worse cognitive performance. In the first 10 years of RRMS, the temporal changes in volume of brain structures in asymptomatic cognitively impaired (CI) patients must be clarified. To this purpose, the relationships between clinical features, cognitive performances, and MRI brain volumes of the year of neuropsychological evaluation (Te-MRI) and of the year of diagnosis (Td-MRI) were statistically analyzed.

Methods

Subjects and clinical assessment

Forty-five PwMS were included with the following inclusion criteria: age > 18 years, diagnosis of RRMS (revised McDonald criteria, 2010), disease duration ≤ 10 years, absence of any self-reported cognitive symptoms in the previous neurological visits or neuropsychological evaluation (NPE), and a brain 2D-MRI scan performed in the year of the NPE (Te-MRI). Exclusion criteria were as follows: diagnosis of progressive MS, a relapse or steroid treatment within the previous 30 days before the NPE or MRI scan, history or signs of other neurological disorders (e.g., head injury, cerebrovascular disease, brain surgery, tumor, and major psychiatric diagnoses), and use of medications that could interfere with the NPE. A brain 2D-MRI performed in the year of diagnosis (Td-MRI), with the same scanner and protocol used for Te-MRI, was retrospectively collected in 31 out of the 45 patients included in the study. Brain 2D-MRIs from 13 healthy controls (HCs), performed with the same scanner and protocol used for Te/Td-MRI, were also included for comparisons with brain Te- and Td-MRI volumes of patients. HCs were age- and sex-matched to cognitively preserved (CP) and CI subgroups of patients (mean age (SD), 38 (10); F/M, 7/6)), both at the time of NPE and at the time of diagnosis. Clinical variables (i.e., sex, age at diagnosis, Expanded Disability Status Scale (EDSS) at diagnosis, total number of clinical relapses, disease duration (years in the time span comprising the diagnosis and the NPE, corresponding to the inter-scan interval between Td- and Te-MRI), age at NPE, EDSS at NPE, and ongoing line of disease-modifying treatment (DMTs) (none; first line interferons, glatiramer acetate, dimethyl fumarate, teriflunomide; second line fingolimod, natalizumab, alemtuzumab) were collected for each patient involved in the study.

Neuropsychological evaluation

Patients included in the study were screened for CImp using the Brief International Cognitive Assessment for MS (BICAMS). It is an international neuropsychological battery [18], also validated in the Italian population [19], which permit a rapid, feasible, and cost-effective assessment of the cognitive functions most typically compromised in MS patients. The BICAMS battery was administrated by an experienced neuropsychologist, lasts 15 min, and includes the following three tests: the Symbol Digit Modalities Test (SDMT), a visual IPS test; the California Verbal Learning Test (CVLT)-II, a ST-VM test; and the Brief Visuospatial Memory Test-Revised (BVMT-R), a ST-VSM test. For the CVLT-II, a list of 16 words in the Italian language, known in the Italian culture and belonging to four semantic categories (animals, landscapes, instruments, and fruits), was drawn up by an experienced Italian translator and interpreter. For the normative data of BICAMS, we used the corrected values for sex, age, and education provided by Goretti et al. (2014) [19]. Patients were classified as CI when they failed in at least one of the three tests (T score < 35) [19]. To evaluate the impact of psychological variables (i.e., anxiety, depression and fatigue) on the cognitive performances of patients, a psychological assessment by means of the standardized scales State Trait Anxiety Inventory-State/Trait (STAI-S/T), Beck Depression Inventory (BDI), and Modified Fatigue Impact Scale (MFIS) was also performed by each patient after the execution of the BICAMS.

Image acquisition and pre-processing

2D-MRI scans of patients and HCs were routinely performed on a 1.5 T unit (Philips MRI System Achieva 1.5T release 2.1.3.4, Master, Best, The Netherlands) and included a T1-weighted spin echo sequence of 25 contiguous axial slices parallel to the inferior borders of the corpus callosum and covering the whole brain (no gap; TR/TE, 530 ms/8.9 ms; voxel size, $0.9 \times 0.9 \times 5$ mm^3; echo time, 8.9 ms; flip angle, 90°; matrix size, 320×256), which was used for volumetric analyses.

Image post-processing and analysis

All original DICOM images were converted to the NIfTI format. T1-weighted sequences of patients were carefully evaluated for the presence of white matter (WM) hypointense lesions to be refilled [20]. Then, volumes of brain tissues (total

brain volume (TBV), GMV, WM volume (WMV), and cortical GMV (cGMV)) of patients and HCs were calculated by SIENAX, part of the FSL software package [21], according to the validation paper [22]. SIENAX performs a tissue-type segmentation and calculates volumes of brain tissues, normalized for the head size of each subject by the volumetric scaling factor (vSF). Bilateral volumes of scGM structures (thalamus, caudate, putamen, pallidum, hippocampus, and amygdala) of patients and HCs were measured by FIRST [23], also part of FSL [21]. T1-weighted sequences were firstly brain-extracted, so that the brain-extracted MNI template was used in the analysis performed by FIRST, since the spatial head coverage of brain MRIs of subjects had a partial inclusion of scalp and medulla oblongata (Fig. 1). Then, each scGM volume was normalized for the head size of the subject by multiplying it to the vSF generated from SIENAX. Two studies [24, 25] have demonstrated that the majority of scGM structures could be reliably measured from 3 mm-T1-weighted 2D-MRI sequences. Since scGM volumes were quantified from 5 mm-T1-weighted 2D-MRI images, any error during the registrations and subsequent segmentations performed by the FIRST software was checked. In fact, for any image, the "cat *.logs/*.e*" command was used and no error outputs were found. Moreover, both Te- and Td-MRI volumes of brain tissues (TBV, WMV, GMV, and cGMV) and scGM structures of patients were compared with MRI brain volumes of age- and sex-matched HCs.

Statistical analysis

The normality of continuous variables was assessed using the Kolmogorov–Smirnov test. Descriptive statistics for normally distributed continuous variables have been expressed with the analysis of means and standard deviation. Skewed continuous variables were summarized using median and range between minimum and maximum values. Categorical variables have been summarized by frequency and percentages. According to the normality test, comparisons between CI and CP patients with respect to clinical (education, age at diagnosis, EDSS at diagnosis, total number of relapses, disease duration, age at the NPE, EDSS at the NPE), cognitive (SDMT, CVLT-II, and BVMT-R), and psychological (STAI, BDI, and MFIS) variables were performed by parametric tests (independent sample *t* test) or by non-parametric test (Mann–Whitney U test). Comparisons between categorical variables (i.e., sex, category of treatment) were made by chi-square test. Multiple comparisons of Td- and Te-MRI volumetric variables between HCs, CP, and CI patients were performed using a one-way analysis of variance (ANOVA) corrected by post-hoc Fisher's least significant difference (LSD) test [26–28]. We also evaluated the differences between Td- and Te-MRI volumetric measures within CP and CI patients, sequentially, using a paired sample *t* test. To investigate relationships between clinical, neuropsychological, and MRI volumetric variables, Pearson or Spearman correlation coefficient tests were performed**.** Based on significant correlations, we tested how the SDMT scores were related (1) to age at diagnosis, disease duration, and Te-L-hippocampus volume, and (2) to disease duration and Td-L-putamen volume by stepwise multiple linear regression models (inclusion and exclusion probability levels for the stepwise procedure at ≤ 0.05 and ≥ 0.1). Multicollinearity was computed by means of the variance inflation factor (VIF) in order to estimate linear dependence between predictors. All tests were 2-tailed and the value of α was 0.05. Statistical analyses were performed with IBM© SPSS Statistics software version 22 (Armonk, NY, USA). Graphic representation of statistically relevant analyses was made by means of MS Office Excel for Figs. 2 and 3, and of IBM© SPSS Statistics software version 22 for Fig. 4.

Results

Clinical and demographic assessment (Table 1)

None of clinical or demographic variables (sex, education, age at diagnosis, EDSS at diagnosis, total number of relapses, disease duration, age at the NPE, EDSS at the NPE, time interval between Td- and Te-MRI scan, and line of DMT)

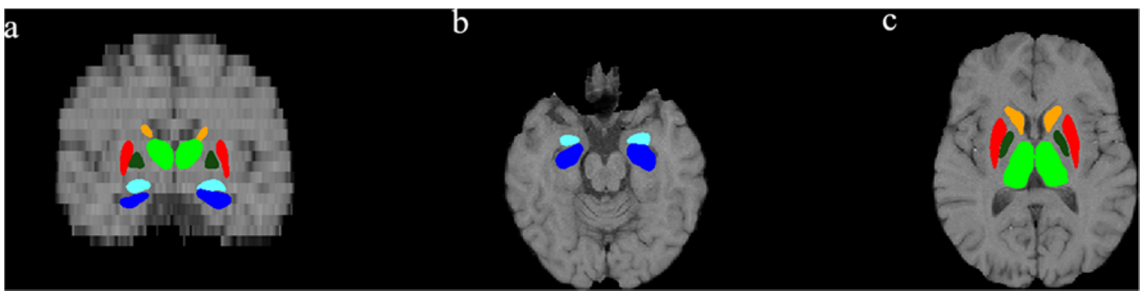

Fig. 1 Subcortical gray matter (scGM) structures automatically segmented by FIRST software from 5 mm-T1-weighted magnetic resonance imaging sequences. Examples of coronal visualization of scGM (**a**), axial visualization of bilateral hippocampus and amygdala (**b**) and of deep gray matter nuclei (**c**). Color legend: thalamus (light green), caudate (orange), putamen (red), pallidum (green), hippocampus (blue), and amygdala (light blue)

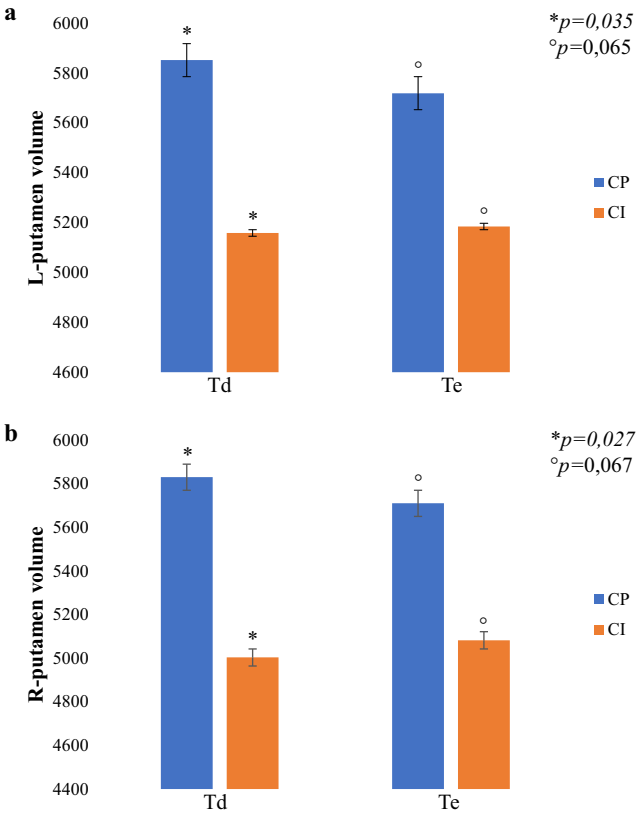

Fig. 2 Histograms presenting mean putamen volume with error bars of cognitively preserved (CP) and cognitively impaired (CI) patients, for the left side (**a**) and right side (**b**), and statistical differences, expressed with *P* value, between patients groups at the time of diagnosis (Td) and at the time of neuropsychological evaluation (Te). CP patients had a significantly larger Td-L-putamen ($P = 0.035$) and Td-R-putamen ($P = 0.027$) volume with respect to CI ones. CP patients had also a tendency, even not statistically significant, to increased Te-L-putamen ($P = 0.065$) and Te-R-putamen ($P = 0.067$) volume with respect to CI ones. Putamen volumes are expressed in cubic millimeters.

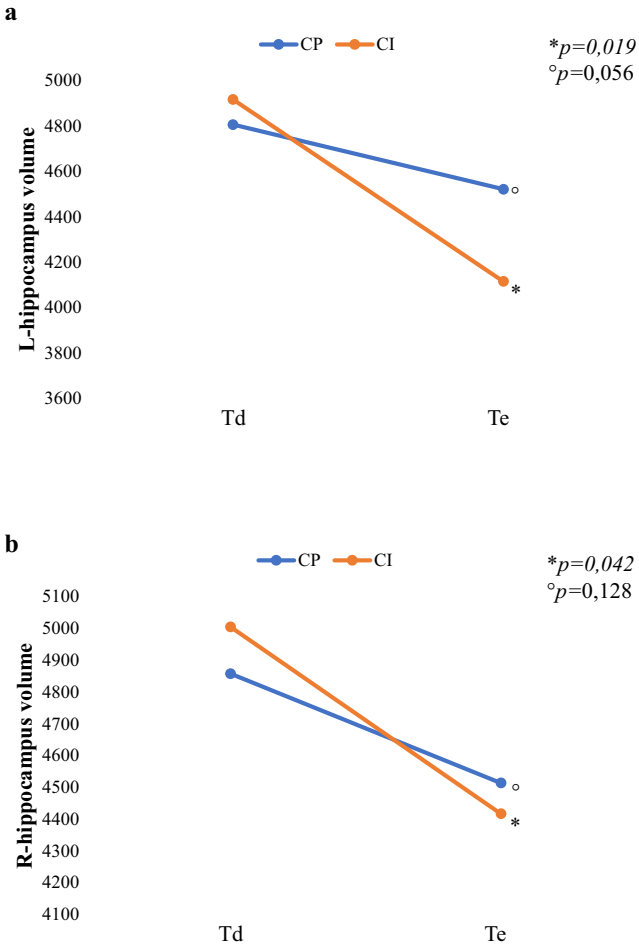

Fig. 3 Graphic lines presenting change from the time of diagnosis (Td) to the time of neuropsychological evaluation (Te), expressed with *P* value, of mean hippocampus volume of cognitively preserved (CP) and cognitively impaired (CI) patients , for the left side (**a**) and right side (**b**). CI patients demonstrated a significant reduction of Te-L-hippocampus ($P = 0.019$) and Te-R-hippocampus ($P = 0.042$) volume compared, respectively, with Td-L-hippocampus and Td-R-hippocampus volume. Instead, CP patients had a not statistically significant tendency to reduced Te-L-hippocampus volume ($P = 0.056$) compared to Td-L-hippocampus volume. Hippocampus volumes are expressed in cubic millimeters

showed statistically significant difference between CP and CI patients.

Cognitive and psychological findings (Table 2)

CImp was found in 33% (15/45) of our cohort of patients. ST-VSM was affected in 73% (11/15), IPS was affected in 20% (3/15), and ST-VM was affected in 7% (1/15) of them. However, all tests showed significantly different scores between CP and CI patients. No significant difference was found in the STAI, BDI, and MFIS scores between the two groups. The SDMT score was positively correlated to the age at diagnosis ($r = 0.294$, $P = 0.049$) and disease duration ($r = 0.307$, $P = 0.040$); consequently, these clinical variables were included in the multiple linear regression model. BVMT-R and CVLT-II were not significantly correlated with clinical and volumetric variables.

MRI volumetric comparisons

Multiple comparisons of Td-MRI brain volumes between HCs, CP, and CI patients (Table 3) evidenced that CP patients had a significantly larger L-putamen ($P = 0.035$) and R-putamen volume ($P = 0.027$) with respect to CI ones (Fig. 2a, b), and a tendency, even not statistically significant, to larger L-putamen volume ($P = 0.067$) with respect to HCs. Multiple comparisons of Te-MRI brain volumes between HCs, CP, and CI patients (Table 3) evidenced that both CP and CI patients had a significantly lower GMV (CP, $P < .001$; CI, $P = 0.002$), cGMV (CP, $P < .001$; CI, $P = 0.002$), L-thalamus (CP, $P = 0.005$; CI, $P = 0.020$), and R-thalamus ($P = 0.001$; CI, $P = 0.012$) with respect to HCs; CP patients

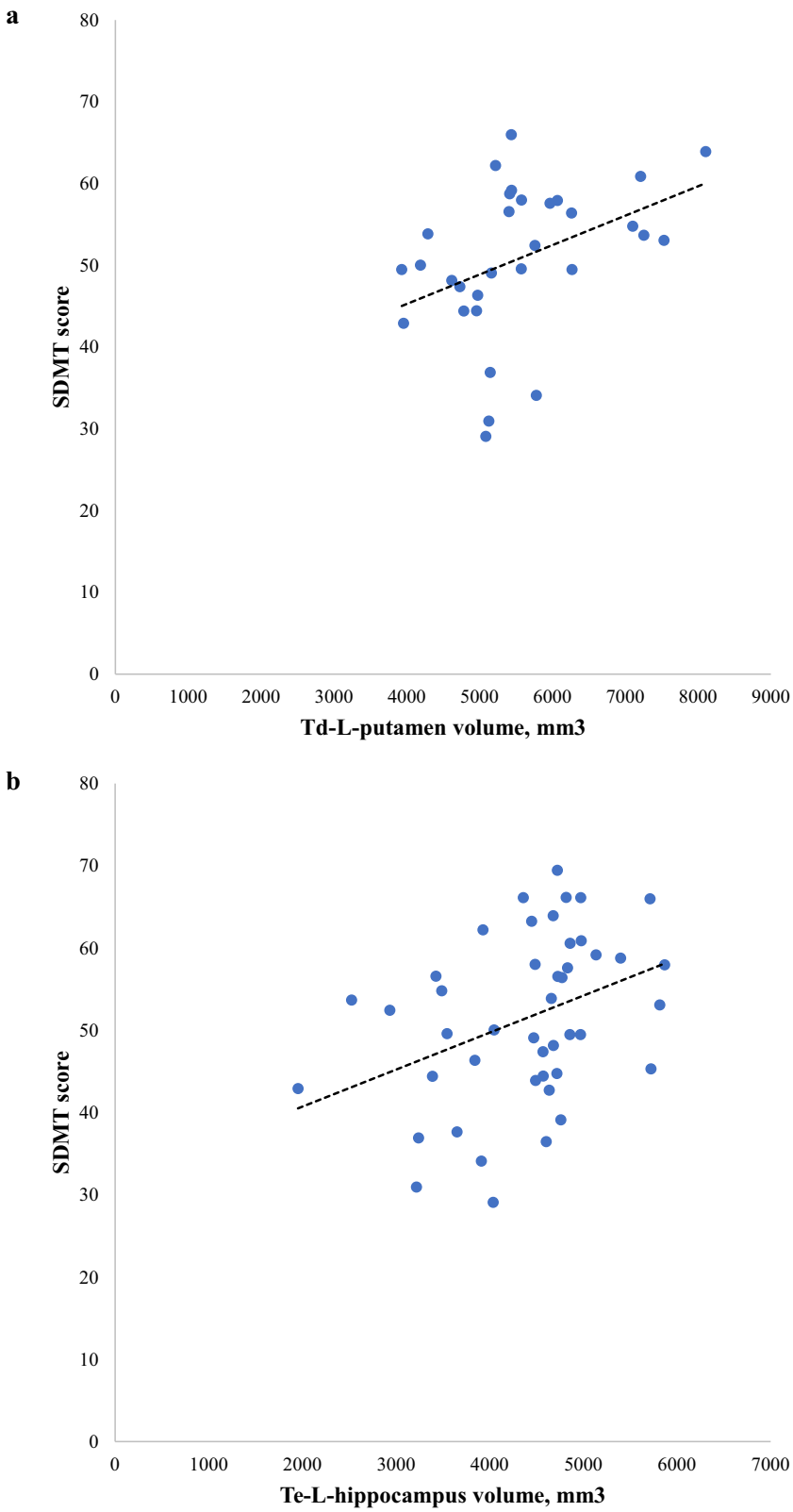

Fig. 4 Scatterplots of the correlations between Symbol Digit Modalities Test (SDMT) score and left putamen volume at the time of diagnosis (Td-L-putamen volume) ($r = 0{,}41$; $P = 0{,}023$) (**a**), and between the SDMT score and L-hippocampus volume at the time of neuropsychological evaluation (Te-L-hippocampus volume) ($r = 0{,}31$; $P = 0{,}035$) (**b**). mm3 = cubic millimeter

had a significantly lower TBV ($P = 0.029$) with respect to HCs; CI patients had a tendency, even not statistically significant, to smaller L-hippocampus volume ($P = 0.071$) with respect to HCs; CP patients had a tendency, even not statistically significant, to larger L-putamen ($P = 0.065$) and R-putamen ($P = 0.067$) volume with respect to CI ones

Table 1 Clinical and demographic characteristics of the patients who underwent the neuropsychological evaluation; comparisons between cognitively preserved and cognitively impaired patients

	CP ($n = 30$)	CI ($n = 15$)	P value
Sex			
F (%)	20 (66.7%)	7 (46.7%)	0.20
M (%)	10 (33.3%)	8 (53.3%)	
Education, median [y] (range)	13 (8–21)	13 (8–21)	0.58
Age of diagnosis, median [y] (range)	33.5 (16–47)	28 (17–49)	0.40
EDSS at diagnosis, median (range)	1 (0–3)	1 (1–2)	0.16
N relapses, median (range)	2 (1–6)	2 (1–8)	0.91
Disease duration, median [y] (range)	4 (0–10)	3 (0–10)	0.74
Age at the NPE, median [y] (range)	40 (19–54)	37 (19–49)	0.30
EDSS at the NPE, median (range)	1 (0–3)	1 (0–2.5)	0.69
Time interval between Td- and Te-MRI scan, median [y] (range)	4 (0–10)	3 (0–10)	0.74
Treatment			
None (%)	6 (20.0%)	0 (0.0%)	0.20
First line (%)	19 (63.3%)	12 (80.0%)	
Second line (%)	5 (16.7%)	3 (20.0%)	

CI = cognitively impaired; *CP* = cognitively preserved; *EDSS* = Expanded Disability Status Scale; *F* = female; *M* = male; *N* = number; *NPE* = neuropsychological evaluation; *Td* = time of diagnosis; *Te* = time of neuropsychological evaluation; *y* = years

(Fig. 2a, b). Comparisons between Td- and Te-MRI volumes in CP and CI patients, sequentially (Table 4), showed, both in CP and CI patients, a significant reduction of GMV (CP, $P = 0.036$; CI, $P = 0.030$) and cGMV (CP, $P = 0.015$; CI, $P = 0.019$); in CP patients, there is a significant reduction of TBV ($P = 0.020$) and a tendency, even not statistically significant, to a smaller L-hippocampus volume ($P = 0.056$); in CI patients, there is a significant reduction of L-hippocampus ($P = 0.019$), R-hippocampus ($P = 0.042$) (Fig. 3a, b), and L-pallidum volume ($P = 0.018$). The SDMT score was significantly correlated with Td-L-putamen ($r = 0.406$, $P = 0.023$; Fig. 4a), Td-L-caudate ($r = 0.395$, $P = 0.028$), and Te-L hippocampus volumes ($r = 0.315$, $P = 0.035$; Fig. 4b).

Table 2 Comparison of the T score (mean ± SD) of the three tests administered with the Brief International Cognitive Assessment in Multiple Sclerosis and of the standardized scores (median; range) of the State Trait Anxiety Inventory-State/Trait, Beck Depression Inventory, and Modified Fatigue Impact Scale in cognitively preserved and cognitively impaired patients with relapsing-remitting multiple sclerosis

	CP ($n = 30$)	CI ($n = 15$)	P value
BICAMS			
SDMT	55.08 ± 8.80	44.21 ± 9.02	0.000**
CVLT-II	66.12 ± 7.36	59.61 ± 13.42	0.041*
BVMT-R	74.18 ± 27.77	31.42 ± 23.07	0.000**
STAI-S	43; 34–92	48; 39–75	0.151
STAI-T	46.5; 33–99	52; 43–60	0.294
BDI	3.5; 0–39	5; 1–19	0.468
MFIS	16.5; 0–68	21; 3–55	0.621

BDI = Beck Depression Inventory; *BICAMS* = Brief International Cognitive Assessment in Multiple Sclerosis; *BVMT-R* = Brief Visual Memory Test-revised; *CI* = cognitively impaired; *CP* = cognitively preserved; *CVLT-II* = California Verbal Learning Test-version II; *MFIS* = Modified Fatigue Impact Scale; *SDMT* = Single Digit Memory Test; *STAI-S/T* = State Trait Anxiety Inventory-State/Trait

*=$P < 0.05$; **$P < 0.001$

Contribution of brain structures in predicting IPS

Stepwise multiple linear regression models revealed significant contributions of Td-L-putamen volume ($P = 0.011$) and disease duration ($P = 0.005$) ($r^2 = 0.376$, $F = 8.434$, $P = 0.001$; Table S1), and of Te-L-hippocampus volume ($P = 0.023$), disease duration ($P = 0.006$), and age at diagnosis ($P = 0.017$) as independent predictors of the SDMT score taking into account all patients ($r^2 = 0.31$, $F = 6.175$, $P = 0.001$; Table S2).

Discussion

The main findings of this study are the following: (1) CP patients with RRMS show a significantly increased Td-MRI bilateral putamen volume with respect to CI ones, and L-putamen volume at this stage predicts better future cognitive performances (i.e., IPS) in all patients; (2) putamen volume does not undergo significant reductions of volume over time in all patients, and, at Te, in CP patients, it tends to maintain a significantly larger volume compared with that of CI patients;

Table 3 Multiple comparison of MRI brain volumes between healthy controls, cognitively preserved patients, and cognitively impaired patients, at the time of diagnosis and at the time of evaluation. Mean volumes (SD) are reported in cubic millimeters

	MRI brain volume	*HCs (n = 13)*	*CP patients (n = 18)*	*CI patients (n = 13)*	*HCs* vs *CP patients*	*HCs* vs *CI patients*	*CP* vs *CI patients*
Td	TBV	1,583,572 (65060)	1,542,852 (73210)	1,572,085 (52369)	0.098	0.673	0.253
	WMV	855,020 (33269)	863,321 (40716)	875,946 (24091)	0.516	0.150	0.349
	GMV	728,551 (40770)	691,675 (58789)	709,487 (71786)	0.087	0.426	0.425
	cGMV	588,085 (35918)	559,370 (39226)	567,257 (30337)	0.055	0.167	0.571
	L-thalamus	7693 (619)	7308 (1734)	6929 (1063)	0.420	0.142	0.428
	R-thalamus	7584 (771)	6873 (1680)	6647 (994)	0.134	0.069	0.630
	L-caudate	3939 (477)	3889 (366)	3953 (503)	0.760	0.933	0.691
	R-caudate	4377 (557)	4110 (443)	4311 (650)	0.185	0.758	0.317
	L-putamen	5252 (469)	5852 (1216)	5158 (550)	*0.067*	0.785	*0.035
	R-putamen	5184 (606)	5830 (1236)	5003 (893)	0.080	0.643	*0.027
	L-pallidum	2261 (313)	2320 (435)	2419 (305)	0.659	0.278	0.463
	R-pallidum	2263 (209)	2226 (362)	2331 (320)	0.746	0.581	0.360
	L-hippocampus	4650 (442)	4807 (911)	4918 (958)	0.602	0.409	0.712
	R-hippocampus	4754 (586)	4857 (841)	5005 (900)	0.722	0.425	0.613
	L-amygdala	1584 (312)	1689 (359)	1556 (293)	0.381	0.829	0.269
	R-amygdala	1526 (482)	1448 (373)	1367 (303)	0.587	0.306	0.572
	MRI brain volume	*HCs (n = 13)*	*CP patients (n = 30)*	*CI patients (n = 15)*	*HCs* vs *CP patients*	*HCs* vs *CI patients*	*CP* vs *CI patients*
Te	TBV	1,583,572 (65060)	1,526,511 (80944)	1,536,697 (75154)	*0.029	0.123	0.690
	WMV	855,020 (33269)	860,960 (38846)	873,438 (27648)	0.616	0.189	0.294
	GMV	728,551 (40770)	665,551 (50334)	663,258 (56714)	**0.000	*0.002	0.891
	cGMV	588,085 (35918)	533,592 (40574)	533,588 (50255)	**0.000	*0.002	1,000
	L-thalamus	7693 (619)	6715 (1074)	6733 (1152)	*0.005	*0.020	0.956
	R-thalamus	7584 (771)	6348 (1046)	6563 (1206)	*0.001	*0.012	0.517
	L-caudate	3939 (477)	3872 (418)	3938 (650)	0.692	0.998	0.680
	R-caudate	4377 (557)	4034 (537)	3997 (607)	0.064	0.079	0.835
	L-putamen	5252 (469)	5719 (1017)	5184 (914)	0.123	0.842	*0.065*
	R-putamen	5184 (606)	5710 (1183)	5082 (1103)	0.142	0.800	*0.067*
	L-pallidum	2261 (313)	2273 (397)	2239 (314)	0.920	0.871	0.765
	R-pallidum	2263 (209)	2214 (361)	2240 (311)	0.648	0.855	0.794
	L-hippocampus	4650 (442)	4522 (889)	4116 (700)	0.615	*0.071*	0.099
	R-hippocampus	4754 (586)	4513 (676)	4416 (841)	0.309	0.211	0.665
	L-amygdala	1584 (312)	1696 (412)	1744 (522)	0.430	0.323	0.720
	R-amygdala	1526 (482)	1475 (330)	1508 (422)	0.696	0.905	0.790

cGMV = cortical gray matter volume; *CI* = cognitively impaired; *CP* = cognitively preserved; *GMV* = gray matter volume; *HCs* = healthy controls; *L* = left; *R* = right; *TBV* = total brain volume; *Td* = time of diagnosis; *Te* = time of neuropsychological evaluation; *WMV* = white matter volume

*=$P < .05$; **=$P < .001$

(3) from Td to Te, in CI patients with RRMS of a maximum duration of 10 years, there is more significant accumulation of damage to the bilateral hippocampus over time than in CP ones, so that Te-MRI L-hippocampus volume predicts current worse cognitive performance (e.g., IPS) in all patients.

An unanticipated and very interesting finding of the current study was the presence of bilateral putamen hypertrophy in CP patients, which is more evident at Td. Some works have reported the presence of putamen hypertrophy both in neurological and psychiatric pathologies, correlating it not only with better cognitive performances but also with a better prognosis for the disease. Patients with good-outcome schizophrenia had larger relative mean putamen size than poor-outcome patients or normal controls, suggesting the possibility that the expansion of putamen size at disease onset may be a predictor of good outcome [29]. Children with recent onset benign epilepsy with centrotemporal spikes demonstrated significantly hypertrophied putamen, which was selective among the subcortical regions examined, suggesting that the structural brain anomalies occurred prior to the diagnosis of epilepsy [30].

Table 4 Paired comparisons of MRI brain volumes between the time of diagnosis and of the time of neuropsychological evaluation in cognitively preserved and cognitively impaired patients, sequentially. Mean volumes (SD) are reported in milliliters

CP patients (n = 18)			
MRI brain volume	*Td*	*Te*	*P value*
TBV	1542.85 (73.21)	1513.75 (84.49)	0.020*
WMV	863.32 (40.72)	857.24 (39.21)	0.381
GMV	691.67 (58.79)	656.51 (52.52)	0.036*
cGMV	559.37 (39.23)	528.20 (44.55)	0.015*
L-thalamus	7.31 (1.73)	6.47 (1.10)	0.067
R-thalamus	6.87 (1.68)	6.11 (0.96)	0.055
L-hippocampus	4.81 (0.91)	4.41 (1.08)	*0.056*
R-hippocampus	4.86 (0.84)	4.43 (0.77)	0.128
L-caudate	3.89 (0.37)	3.87 (0.42)	0.880
R-caudate	4.11 (0.44)	4.04 (0.47)	0.303
L-putamen	5.85 (1.22)	5.69 (0.93)	0.551
R-putamen	5.83 (1.24)	5.68 (1.19)	0.577
L-pallidum	2.32 (0.43)	2.25 (0.43)	0.554
R-pallidum	2.23 (0.36)	2.26 (0.39)	0.766
L-amygdala	1.69 (0.36)	1.84 (0.37)	0.061
R-amygdala	1.45 (0.37)	1.53 (0.35)	0.386
CI patients (n = 13)			
MRI brain volume	*Td*	*Te*	*P value*
TBV	1572.08 (52.37)	1545.93 (78.14)	0.151
WMV	875.95 (24.09)	879.48 (22.31)	0.489
GMV	709.49 (71.79)	666.46 (61.35)	0.030*
cGMV	567.26 (30.34)	535.57 (54.13)	0.019*
L-thalamus	6.93 (1.06)	6.80 (1.13)	0.655
R-thalamus	6.65 (0.99)	6.77 (1.15)	0.722
L-hippocampus	4.92 (0.96)	4.04 (0.72)	0.019*
R-hippocampus	5.00 (0.90)	4.37 (0.88)	0.042*
L-caudate	3.95 (0.50)	3.99 (0.63)	0.806
R-caudate	4.31 (0.65)	4.03 (0.63)	0.076
L-putamen	5.16 (0.55)	5.27 (0.93)	0.739
R-putamen	5.00 (0.89)	5.14 (1.14)	0.752
L-pallidum	2.42 (0.30)	2.22 (0.33)	0.018*
R-pallidum	2.33 (0.32)	2.21 (0.32)	0.261
L-amygdala	1.56 (0.29)	1.76 (0.54)	0.162
R-amygdala	1.37 (0.30)	1.50 (0.43)	0.278

cGMV = cortical gray matter volume; *CI* = cognitively impaired; *CP* = cognitively preserved; *GMV* = gray matter volume; *L* = left; *R* = right; *TBV* = total brain volume; *Td* = time of diagnosis; *Te* = time of neuropsychological evaluation; *WMV* = white matter volume

*=$P < .05$

Moreover, in these epileptic young patients, larger putamen volumes were linked to better cognitive performances on two complementary executive function tests [31]. Thus, the findings of the current study suggest that putamen hypertrophy in CP patients with RRMS might be cognitively adaptive, as enlargement is associated with improved cognitive performances [30]. In fact, larger putamen volumes are linked to better performances on visual IPS measured by the SDMT test. However, it remains to be determined if such adaptive responses are due to nature or environment. On the one hand, the human brain has considerable neuroplasticity and appears to be amendable to environmental influences (i.e., cognitive reserve), on the other hand, human brain shape and size are largely determined prenatally (i.e., brain reserve). In MS, higher levels of education, higher occupational status, and higher general intelligence may serve as protective mechanisms to both cognitive function and striatal atrophy during the period closest to disease onset, when cognition is known to decline at a more rapid rate. Higher cognitive reserve has been significantly associated with slower rate of volume loss in caudate and putamen for patients estimated to be closest to motor onset of Huntington's disease (HD) [32]. Moreover, research in rodents has suggested that environmental enrichment is associated with increased levels of brain-derived neurotrophic factor (BDNF) and improved motor and cognitive performance in models of HD [33], suggesting a possible protective effect of BDNF on symptom progression. The striatum (caudate and putamen) receives inputs from several regions of the frontal cortex, participating in motor, oculomotor, cognitive, and limbic circuits [34]. The frontal eye field circuitry passes through the striatum (primarily the putamen), and it is involved in the performance of planning tasks with a component of visual searching [35]. Working memory processes recruit large areas of deep GM nuclei, primarily centered over the anterior putamen, and they could be L-dominant [10]. These data could explain the role of the L-putamen in predicting better visual IPS in all patients. A functional MRI (fMRI) study of patients with clinically isolated syndrome (CIS) showed that load-related abnormalities were present in the recruitment of putamen during attentional process, suggesting that a saturation of the cognitive role of this deep GM nucleus can occur early in the disease course [36]. Moreover, Cavallari et al. (2014) found an association between increased fractional anisotropy in the putamen and impaired performance on ST-VSM and ST-VM [37]. Interestingly, in patients with RRMS, it was shown that putamen atrophy had a decreasing progression after the onset of the disease, since its cumulative atrophy was stronger in the first rather than later stages of the disease [38]. This previous evidence could explain the finding of a lack of a significant reduction of putamen volume over time in all patients.

Our findings also showed that, during the first 10 years from diagnosis of RRMS, CI patients suffer from a significant progression of hippocampal atrophy in comparison with CP ones, and that L hippocampal volume could represent a marker of ongoing cognitive decline. In the earliest stages of the disease, the hippocampus could present a regional (rather than

global) vulnerability to damage, which could contribute to the appearance of cognitive deficits. In fact, hippocampal atrophy spreads from the CA4/dentate gyrus subfield, in the CIS stage, within the CA1 subfield after 1 year of the disease [39]. These data could explain our finding of a progressive hippocampal atrophy during the first 10 years of RRMS in CI patients with respect to CP ones, instead of a lack of a significant difference in global hippocampal volume between CI and CP patients both at Td and at Te. Moreover, a previous fMRI study [40] showed that, despite the lack of a significant difference in the global volume of the hippocampus between CP and CI patients with MS, the functional activation of the hippocampal network during episodic memory tasks was increased in CP patients and reduced in CI ones, particularly at the level of the L hippocampus. It is therefore possible that the ability to adapt to the progression of hippocampal damage, that prevents the appearance of cognitive deficits, is sufficient in CP patients and exhausted in CI ones [41]. In fact, hippocampal volume has been related to measures of cognitive reserve [42], and its quantification might also help to develop targeted rehabilitative interventions against cognitive decline. The predictive value of hippocampal volume for IPS after the time of diagnosis could reflect the growing relationship between progressive hippocampal atrophy in its different subfields [39] and the global cognitive decline in MS. In fact, an impairment of IPS is very sensitive to global CImp [43]. Moreover, a structural connectivity analysis of the hippocampal-related episodic memory network has been showed to be impaired at several levels in MS and to be related to a decreased efficiency of IPS [44]. This previous finding could account for the role of the hippocampus in predicting the SDMT score. An intrinsic greater vulnerability to the damage of the L hippocampus compared with the R ones has been demonstrated in other pathologies, such as post-traumatic stress disorder, epilepsy, and schizophrenia [45–47]. The higher relationship between hippocampal atrophy and IPS in younger patients may be due to an increased vulnerability of some neural subpopulations or by an increased cerebral growth factor dysregulation [48]. Furthermore, several studies reported a major prevalence of CImp in pediatric or juvenile MS [49].

In this study, 33% of cognitively asymptomatic patients with RRMS of a maximum duration of 10 years, assessed through the BICAMS battery, were found to suffer from an initial CImp, with ST-VSM and IPS resulting, respectively, the first and second most commonly affected cognitive domain in these patients. Other studies reported that IPS is the mainly affected cognitive domain in MS [50, 51], and that the SDMT is the most sensitive tool for cognitive monitoring in PwMS [16]. However, deficits in one cognitive domain (e.g., memory) can contribute to dysfunction in other domains (e.g., processing speed) [52], in fact slow IPS has been associated to poor learning abilities in MS [1]. Notably, SDMT is a test of "visual" IPS, and its good psychometric properties are probably due to the involvement of multiple functions affected in MS, such as visual scanning and attention, processing speed, and short-term memory [51]. Thus, based on our findings, during the first ten years of RRMS, ST-VSM could be affected before visual IPS in cognitively asymptomatic patients, and this last cognitive ability could be significantly reduced even if it is found in normal ranges of values.

From Td to Te, significant reductions of GMV, cGMV, and bilateral thalamus of both CI and CP patients with respect to HCs were present, thus possibly suggesting that loss of GMV, cGMV, and thalamic volume may not be a specific marker of CImp in the first years of the disease. A progressive atrophy of L-pallidum from Td to Te was found only in CI patients, which could be consequent to a trans-synaptic anterograde degeneration, primarily caused by putamen degeneration. In fact, the pallidum is the major output of the fronto-striatal-thalamic loops, and it is involved in a range of cognitive, emotional, motor, and oculomotor functions [53]. It has been reported that an anterograde infarction of the pallidum may occur some days after a primitive stroke of the ipsilateral striatum (caudate and putamen) [54]. Although previous evidence reported that TBV predicts the occurrence of CImp [55], a lower TBV vs HCs and a progressive loss of it was found only in CP patients. This result could have been determined by the fact that in our cohort, CP patients tended to be older and to have lower TBV, GMV, and cGMV compared with CI patients. Consequently, a cumulative effect of the physiological loss of brain volume with advancing age and the pathological MS-related neurodegeneration could have been present in these patients. Moreover, also in the study by Bishop et al. (2017) [56], overall brain volumes were significantly higher in early-onset compared with late-onset patients, who were matched for disease duration and other clinical variables.

This research presents limitations, such us the retrospective design of part of the analyses and the lack of a NPE at the time of diagnosis. We focused on the study of normal-appearing GM (i.e., brain tissues and scGM structures), since multiple studies have already investigated the association between cognitive function and WM lesions and damage in PwMS [50], reporting various degrees of correlation. These findings have thus suggested that WM damage is not the sole feature influencing cognitive performance in MS and pointed to more likely involved mechanisms, such as GM atrophy, which has proven to correlate better with the patient's clinical and cognitive disabilities with respect to WM atrophy or lesion count/volume [57], and whose evaluation is less time-consuming and cheaper with respect to WM lesion count and volume detection.

Conclusions

Instead of measures of advanced brain damage, putamen and hippocampus volume could represent promising indices of cognitive performance, as well as of neuroprotection and cognitive reserve, in the first years of MS, and become potentially useful tools for diagnostic, prognostic and therapeutic purposes. This work provides a proof of how complementary cognitive systems cooperate to determine a reserve that could limit the onset and progression of CImp in PwMS. Further research is now needed to confirm these data on a prospective longitudinal setting, as well as in the progressive forms of the disease, and to study the influences of different DMTs and rehabilitative approaches on these structures and clinical manifestations.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval The protocol and procedures employed in this study were approved by the Local Ethical Committee. An informed consent was signed by all participants prior to assessment, according to the Declaration of Helsinski (October 2013 version).

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