Subcortical atrophy and cognition

Sex effects in multiple sclerosis

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ABSTRACT

Objectives: Gray matter (GM) atrophy is common in multiple sclerosis (MS), as is cognitive dysfunction. Understanding the exact relationship between atrophy and cognition requires further investigation. The aim of this study was to investigate the relationship between subcortical GM atrophy and cognition in early relapsing onset MS.

Methods: Structural MRI and neuropsychological evaluations were performed in 120 patients (80 women) and 50 controls (30 women), part of an early inception cohort, 6 years postdiagnosis. Deep GM volumes were segmented automatically. Cognition was assessed in 7 domains. Stepwise linear regression was used to predict average cognition in the patient group.

Results: Most deep GM volumes were reduced in patients, with larger effects on average in men (−11%) than in women (−6.3%). Only the bilateral hippocampus, amygdala, and right nucleus accumbens in men, and right hippocampus and nucleus accumbens, bilateral amygdala, and putamen in women, showed no atrophy compared to controls. All cognitive domains except visuospatial memory were affected in men; none were significantly affected in women. In the MS group, average cognition was best predicted by thalamic volume, sex, and education (adjusted R^2 = 0.31), while lesion volume was not a significant predictor in the model.

Conclusions: Six years postdiagnosis, almost all subcortical structures were affected by MS, especially in men. Cognition was most severely affected in male patients. Thalamic volume, sex, and education best predicted average cognition. These results underline the relevance of specific subcortical structures to cognition, as well as the relevance of (sex-specific) atrophy in MS. ***Neurology*® 2012;79:1754–1761**

GLOSSARY

BRB-N = Brief Repeatable Battery for Neurological disease; **DGM** = deep gray matter; **DMT** = disease-modifying therapy; **EDSS** = Expanded Disability Status Scale; **GLM** = general linear model; **GM** = gray matter; **MS** = multiple sclerosis; **NBV** = normalized whole brain volume; **NCGMV** = normalized cortical gray matter volume; **NDGMV** = normalized deep gray matter volume; **NGMV** = normalized total gray matter volume; **NWMV** = normalized total white matter volume; **RRMS** = relapsing-remitting multiple sclerosis; **WM** = white matter.

Atrophy of the gray matter (GM) and white matter (WM) is frequently found in multiple sclerosis (MS),[1,2] and can be reliably measured with MRI.[3] Although already present in early stages, GM atrophy becomes much more dominant in the progressive phase of the disease.[4] As the clinical relevance and the specific histopathologic substrate of GM atrophy in MS is not well known, it is the subject of many recent studies.[5,6]

While the relationship between brain atrophy and clinical measures has been investigated extensively in the past,[7] how atrophy relates to cognition is only recently becoming clearer.[8–11] As cognitive dysfunction is common and present in all stages of the disease,[12–15] exploring the relationship between atrophy and cognition could provide valuable new information.

As most studies that focus on the relationship between atrophy and cognition have applied methods of whole-brain or central atrophy that lack regional specificity, the effect of localized

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Supplemental Data

From the Departments of Radiology (M.M.S., V.P., O.T.W., H.V., F.B.), Anatomy & Neuroscience (M.M.S., J.J.G.G.), Physics and Medical Technology (H.V.), and Neurology (L.D., C.H.P.), VU University Medical Center, Amsterdam, the Netherlands; and Department of Radiology (F.C.R.L.), Federal University of Rio de Janeiro, Brazil.

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atrophy on cognition is at present insufficiently clear. Recent methodologic advances have led to reliable volume estimation of (sub) cortical structures.[16–18] Apart from an effect on information processing speed,[19] the effect of deep gray matter (DGM) atrophy on other cognitive domains remains unclear. In addition, while cognitive dysfunction differs between sexes,[13,20] whether potential sex differences in MS-inflicted DGM atrophy affect cognition has not been studied before.

The aim of this study was therefore to investigate the possibly sex-specific relationship between DGM atrophy and cognitive domains in a large homogenous cohort of patients with early relapsing-remitting MS (RRMS).

METHODS

Participants. A total of 170 subjects were included, of which 50 were healthy controls (30 women) and 120 had RRMS[21] (80 women). All patients were part of the 6-year follow-up of an early inception cohort, in which patients were included at (or closely before) diagnosis and subsequently followed annually. All groups were comparable with respect to age and education level. Physical disability was measured using the Expanded Disability Status Scale (EDSS)[22] and was relatively mild (median EDSS 2.0, range 0.0–6.0). Patients were relapse-free and without steroid treatment for at least 2 months. Controls were recruited from the Amsterdam area using existing databases.

Sixty-nine patients (56.5% of all patients, 42 female) had taken disease-modifying therapies (DMT) in the past or at present. Treatment dose, onset, duration, and sequence varied between patients, but treatment duration of those patients who received DMT was equal between the sexes (women: 62.9 ± 27.3 months and men: 61.2 ± 30.0 months, $Z = -0.50$, $p = 0.61$). Forty-eight patients (30 women) used some form of DMT during the study period, namely β-interferon (30 patients, 20 women), natalizumab (10 patients, 5 women), glatiramer acetate (7 patients, 4 women), and immunosuppressive therapy (1 female patient).

Standard protocol approvals, registrations, and patient consents. The study was approved by the institutional ethics review board and all subjects gave written informed consent prior to participation.

MRI. Subjects received structural 3T MRI scans (GE Signa-HDXT), using 3D-T1 gradient-echo, 2D dual-echo T2, and 2D spin-echo T1 sequences (see e-Methods on the *Neurology*® Web site at www.neurology.org for more details). Subjects for whom MRI data were unavailable (4 of the 120 patients) were only included in cognitive evaluations.

Neuropsychological evaluation. Subjects underwent a comprehensive set of neuropsychological tests comprised of the Brief Repeatable Battery for Neurological disease (BRB-N),[15] as well as the concept shifting test, the Stroop color-word test, and the memory comparison test. This resulted in an evaluation of 7 cognitive domains: executive functioning, verbal memory, information processing speed, visuospatial memory, working memory, attention, and psychomotor speed (see e-Methods). An "average cognition" Z score was calculated by averaging Z scores of all separate domains.

Patients who scored at least 1.5 SDs (i.e., $Z \leq 1.5$) below the average of controls in 2 or more domains were defined as "cognitively impaired."

Brain and lesion volumes. T2-hyperintense and T1-hypointense lesions were marked by an experienced rater and volumes were measured using a local thresholding technique. Brain volumes were analyzed on the 3D-T1 sequence. Excess neck tissue was removed by a registration of a Montreal Neurological Institute standard brain image to each individual scan to identify the lower border of the brain. Normalized total GM (NGMV), total WM (NWMV), and whole brain volume (NBV), corrected for head size, were measured using SIENAX[23] version 2.5 (part of FSL4.1, http://www.fmrib.ox.ac.uk/fsl). SIENAX was run using standardized parameters for brain extraction, including automatic estimation of the center of the head. DGM volumes were measured using FIRST[19] (also part of FSL), providing left and right volumes for the thalamus, caudate, globus pallidus, putamen, hippocampus, amygdala, and nucleus accumbens in a 2-step process (see e-Methods). Afterwards, normalized DGM volumes were pooled to form a total normalized deep GM volume (NDGMV). In addition, to allow exploration of the separate effect of cortical atrophy on cognition, we estimated normalized cortical GM volume (NCGMV) by removing individual FIRST regions of interest from the SIENAX-based NGMV images (figure e-1). Both NDGMV and NCGMV were included in the statistical analyses (details given below). We excluded from those analyses total NGMV and NWMV, because of known SIENAX segmentation problems in regions of deep GM, and WM lesion misclassification.

Statistical analysis. Variables were checked for normality using Kolmogorov-Smirnov and histogram inspection. T1 and T2 lesion volumes were log-transformed. All analyses used age and education level as covariates (where applicable) and were Bonferroni-corrected for multiple comparisons.

General linear models. Cognitive and volumetric variables were separately analyzed using multivariate general linear model (GLM) analyses, using group as a fixed factor, with 4 levels: female patient, male patient, female control, male control. Post hoc Bonferroni analyses included 4 comparisons, namely male patients vs male controls, female patients vs female controls, male controls vs female controls, and male patients vs female patients. Sex was investigated as such to further subdivide the large homogeneous group of patients to further explore possible effects. To investigate effect sizes of atrophic changes, Cohen d (dividing the mean difference by a pooled SD) and percentage volume change were calculated.

Relation of atrophy with cognition. NGMV, NDGMV, NCGMV, and lesion volumes were correlated with average cognition using Pearson correlation coefficient. To investigate independent contributions of individual DGM structures, stepwise linear regression was used to predict average cognition Z scores of all 107 patients (71 women) who received both MRI and cognitive evaluations. Control data were not included in the regression model. To limit the number of variables, only significantly atrophic DGM structures were used as predictors in the regression model. These were entered in the analysis together with sex, EDSS (dichotomized by a median split), disease duration (since first symptom), T1 and T2 lesion volumes, age, and education (also dichotomized). As there is a large overlap between GM volumes calculated by SIENAX and by FIRST, with

Table 1 Descriptive variables for controls and patients and Mann-Whitney *Z* and *p* values, comparing male and female patient groups

	Female controls (n = 30), mean ± SD	Male controls (n = 20), mean ± SD	Female patients (n = 80), mean ± SD or median (range)	Male patients (n = 40), mean ± SD or median (range)	*Z*	*p*
Age, y	40.9 ± 11.0	39.6 ± 11.6	39.6 ± 8.3	40.4 ± 9.0	−0.52	0.61
Education (range 1–7)	5.5 ± 1.5	5.7 ± 1.6	4.9 ± 1.5	5.0 ± 1.5	−0.14	0.89
EDSS (range 1–10)			2.0 (0–6)	2.0 (0–5)	−0.77	0.44
Disease duration, y			7.5 ± 2.3	7.6 ± 1.9	−1.02	0.31
T1 lesion volume, mL			1.7 ± 2.5	2.1 ± 2.5	−0.83	0.41
T2 lesion volume, mL			3.5 ± 3.9	4.7 ± 4.9	−1.18	0.24
T1/T2 volume ratio			0.43 ± 0.20	0.41 ± 0.20	−0.52	0.61

Abbreviation: EDSS = Expanded Disability Status Scale.

the latter being much more sensitive to DGM volume changes, only individual FIRST-based volumes were entered in the regression models.

RESULTS **Subjects.** There were no differences between male and female patients regarding EDSS, T1 or T2 lesion volumes, or disease duration (table 1).

Cognition. Multivariate GLM analyses showed a main effect of group for all cognitive domains except visuospatial memory, which was further excluded (table 2). Post hoc Bonferroni pairwise comparisons revealed all remaining cognitive *Z* scores to be significantly lower in male patients compared to male controls and all except working memory compared to female patients. Female patients did not score significantly lower than female controls in any cognitive domain. The 2 cognitive domains that showed the lowest *Z* score in the entire patient group were working memory ($Z = -0.78$) and information processing speed ($Z = -0.60$). Thirty-four patients (28%) were classified as cognitively impaired, specifically 20 female patients (25%, average cognition $Z = -1.0$) vs 14 male patients (35%, average cognition $Z = -1.7$). Male and female controls did not differ significantly from each other in any of the cognitive domains. Average cognition correlated with EDSS (rho = −0.37, $p < 0.001$).

Brain volume. Multivariate GLM analyses showed a main effect of group for all brain volumes except for the amygdalae bilaterally, which were further excluded (table 2). Post hoc comparisons revealed a reduction in NWMV for both sexes, while NGMV and NBV were only reduced in men (table e-1). All DGM volumes were reduced in male patients compared to male controls except for the hippocampus bilaterally and the right nucleus accumbens (table e-1, NDGMV reduction of 7.2 mL [11.0% volume loss], Cohen $d = -1.25$). In female patients, all DGM volumes were reduced compared to female controls except for the putamen bilaterally, as well as right hippocampus and right nucleus accumbens (table e-1, NDGMV reduction of 4.1 mL [6.3% volume loss], Cohen $d = -0.85$). Male patients, compared to female patients, showed significantly smaller volumes in the left and right caudate nucleus, as well as the right putamen (table e-1). All significant volume reductions were more pronounced in male patients. See figure 1 for an example of matched male and female patients.

DGM atrophy was strongest in the left caudate nucleus for male patients (16%), and the left pallidum for female patients (9%). Very strong reductions in NDGMV, defined as at least 2 standard deviations below sex-matched controls, were found in 23 patients (20%), specifically 13 women (16%, of which 4 were cognitively impaired) vs 10 men (28%, of which 5 were cognitively impaired). In the control group, no volumes significantly differed between the sexes.

Relating atrophy and lesion volumes to cognition. In the patient group, significant correlations were found between average cognition and NGMV ($r = 0.21$, $p = 0.03$), NCGMV ($r = 0.29$, $p = 0.002$), and NDGMV ($r = 0.38$, $p < 0.0001$). Significance in all correlations was driven by male patients ($r = 0.34$, $p = 0.04$ for NGMV; $r = 0.37$, $p = 0.03$ for NCGMV; $r = 0.60$, $p < 0.0001$ for NDGMV) as no correlation with average cognition was significant for female patients. In the entire patient group, only T2 lesion volumes correlated with NGMV ($r = -0.22$, $p = 0.02$). T1 and T2 lesion volumes correlated with NDGMV ($r = -0.37$ and $r = -0.43$, respectively, $p < 0.0001$ for both) but not with NCGMV. Interestingly, this correlation was stronger in male patients (T1: $r = -0.45$, $p = 0.007$; T2: $r = -0.51$, $p = 0.002$) than in female patients (T1: $r = -0.33$, $p = 0.004$; T2: $r = -0.36$, $p = 0.001$), while lesion volumes were equal between both sexes (T1: Mann-Whitney $Z = -0.90$, $p = 0.37$; T2: $Z = -1.31$, $p = 0.19$). A direct correlation between lesion

Table 2 Cognitive and volumetric variables for controls and patients[a]

	Controls, mean ± SD		Patients, mean ± SD		GLM main effect	
	Female (n = 30)	Male (n = 20)	Female (n = 80)	Male (n = 40)	*F*	*p*
Cognitive *Z* scores						
Executive functioning	0.02 ± 0.68	−0.02 ± 0.62	−0.29 ± 0.86	−0.83 ± 1.32	5.72	0.0010
Verbal memory	−0.03 ± 0.94	0.06 ± 0.89	−0.16 ± 0.91	−1.03 ± 0.92	10.14	<0.0001
Processing speed	0.03 ± 1.09	−0.04 ± 0.86	−0.39 ± 1.08	−0.99 ± 1.16	5.48	0.0013
Visuospatial memory	−0.15 ± 1.15	0.24 ± 0.67	−0.51 ± 1.24	−0.15 ± 0.94	2.16	0.0955
Working memory	−0.06 ± 0.86	0.09 ± 0.92	−0.63 ± 1.40	−1.09 ± 1.25	4.08	0.0081
Attention	−0.01 ± 0.65	0.02 ± 0.56	−0.31 ± 0.69	−0.89 ± 1.09	7.64	0.0001
Psychomotor speed	0.00 ± 0.87	0.00 ± 0.65	−0.38 ± 0.94	−0.97 ± 1.23	6.57	0.0003
Average cognition	−0.03 ± 0.63	0.05 ± 0.46	−0.39 ± 0.67	−0.85 ± 0.85	9.39	<0.0001
Whole brain volumes, mL						
NGMV	839.87 ± 44.47	842.36 ± 57.88	828.60 ± 42.92	808.62 ± 47.85	4.40	0.0053
NWMV	679.52 ± 29.03	701.91 ± 36.02	660.80 ± 33.68	665.54 ± 36.06	9.80	<0.0001
NBV	1,519.40 ± 62.59	1,544.27 ± 84.83	1,489.41 ± 64.04	1,474.16 ± 66.53	7.60	0.0001
NCGMV	791.48 ± 51.86	792.01 ± 61.98	777.14 ± 48.67	740.51 ± 52.77	8.98	<0.0001
NDGMV	65.15 ± 3.92	64.81 ± 3.90	61.02 ± 5.20	57.65 ± 6.68	14.96	<0.0001
Deep GM volumes, mL						
Thalamus L	10.70 ± 0.71	10.69 ± 0.82	9.92 ± 0.94	9.41 ± 1.26	14.00	<0.0001
Thalamus R	10.39 ± 0.71	10.52 ± 0.63	9.73 ± 0.85	9.36 ± 1.40	10.21	<0.0001
Caudate L	4.87 ± 0.47	4.95 ± 0.36	4.55 ± 0.61	4.17 ± 0.65	12.00	<0.0001
Caudate R	5.07 ± 0.46	5.05 ± 0.56	4.76 ± 0.62	4.37 ± 0.57	10.48	<0.0001
Putamen L	6.60 ± 0.81	6.74 ± 0.75	6.28 ± 0.68	6.01 ± 0.97	6.01	0.0007
Putamen R	6.68 ± 0.78	6.62 ± 0.58	6.41 ± 0.68	6.02 ± 0.72	6.56	0.0003
Pallidum L	2.40 ± 0.26	2.40 ± 0.15	2.22 ± 0.24	2.08 ± 0.38	11.67	<0.0001
Pallidum R	2.45 ± 0.21	2.44 ± 0.18	2.28 ± 0.26	2.17 ± 0.28	9.81	<0.0001
Hippocampus L	5.37 ± 0.58	5.13 ± 0.62	4.97 ± 0.66	4.67 ± 0.66	6.46	0.0004
Hippocampus R	5.48 ± 0.50	5.22 ± 0.57	5.14 ± 0.62	4.82 ± 0.68	6.25	0.0005
Amygdala L	1.82 ± 0.27	1.83 ± 0.28	1.70 ± 0.31	1.68 ± 0.33	2.21	0.0886
Amygdala R	1.91 ± 0.31	1.84 ± 0.38	1.80 ± 0.27	1.73 ± 0.32	1.69	0.1704
Nucleus accumbens L	0.80 ± 0.12	0.79 ± 0.10	0.70 ± 0.13	0.64 ± 0.13	9.72	<0.0001
Nucleus accumbens R	0.62 ± 0.14	0.60 ± 0.09	0.56 ± 0.11	0.52 ± 0.17	3.69	0.0132

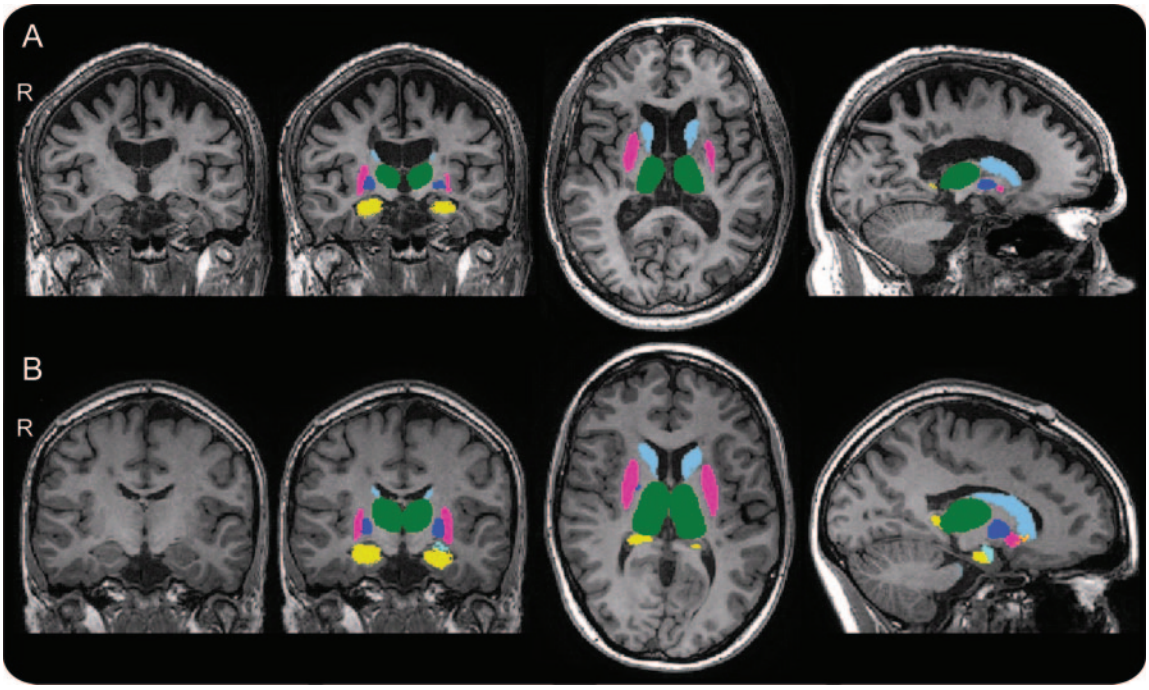
Abbreviations: GLM = general linear model; GM = gray matter; NBV = normalized whole brain volume; NCGMV = normalized cortical gray matter volume; NDGMV = normalized deep gray matter volume; NGMV = normalized total gray matter volume; NWMV = normalized total white matter volume.
[a] All volumes have been corrected for head size. See table e-1 for post hoc GLM *p* values comparing patients to controls.

volumes and average cognition was only found for T1 lesion volumes in male patients ($r = -0.33$, $p = 0.05$).

Linear regression of cognition. Right thalamic volume, sex, and education were the only significant predictors of average cognition, indicating poorer cognitive performance to be related with lower thalamic volumes and male sex, together with lower education. Right thalamic volume correlated directly with average cognition in the entire patient group ($r = 0.37$, $p < 0.0001$), as did left thalamic volume ($r = 0.34$, $p = 0.0002$). Both correlations were driven by male patients ($r = 0.60$, $p = 0.0001$ and $r = 0.57$, $p = 0.0003$, respectively); none were significant in women (figure 2).

Across cognitive domains, performance was to some extent predicted by DGM atrophy. Psychomotor speed and verbal memory were best explained by the regression model. Sex was a significant predictor in all domains except information processing speed and working memory. The most prevalent structure was the thalamus, which was a predictor of all domains except verbal and working memory, where the caudate appeared to be more important. See table 3 for more details and statistics.

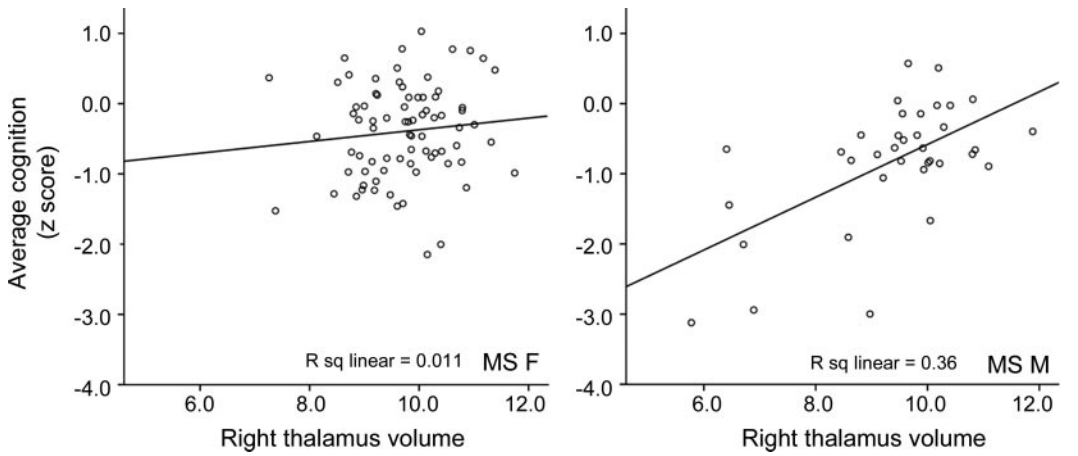
Figure 1 Three-dimensional T1 scans and FIRST volumes for a matched male and female patient



(A) Male patient, 47 years old, education level 6, average cognition $Z = -3.1$, deep gray matter volume 44% below male controls. (B) Female patient, 45 years old, education level 5, average cognition $Z = -0.1$, deep gray matter volume 5% below female controls.

DISCUSSION In this study, we investigated the relationship between DGM atrophy and cognition in MS using a well-characterized inception cohort, 6 years after diagnosis. In this cohort of patients with RRMS with relatively mild disability and low lesion volumes (table 1), DGM structures show extensive atrophy, and the degree of atrophy correlates strongly with cognitive dysfunction. Cognitive impairment was found in 28% of all patients with MS. Cognitive dysfunction was most prominent in the domains of working memory and information processing speed, which confirms previous results.[12] Although visuospatial memory was previously found to be impaired in MS,[12] patients in this study did not score abnormally on SPART, the visuospatial memory test of the BRB-N battery administered to all participants, possibly due to the relatively low sensitivity of SPART.[24] Cognitive abnormalities were more severe in male patients. Strikingly, none of the domains were abnormal in the female patient group. Male patients were more frequently cognitively impaired, and their impairment was also more severe, which is

Figure 2 Cognitive correlations of thalamic volume



The relationship between right thalamus volume and average cognition in female (MS F) and male (MS M) patients. MS = multiple sclerosis.

Table 3 Linear stepwise regression of cognition

	Model			Predictor		
	Adjusted R^2	F	p	Standardized β	t	p
Executive function	0.29	9.91	<0.0001			
Thalamus R				0.53	5.24	<0.0001
Education				0.30	3.76	0.0003
T2 volume				0.24	2.72	0.0077
Sex				−0.19	−2.26	0.0256
Nucleus accumbens L				−0.19	−2.00	0.0485
Verbal memory	0.31	11.06	<0.0001			
Sex				−0.30	−3.70	0.0003
Education				0.23	2.93	0.0041
Hippocampus L				0.21	2.43	0.0169
Disease duration				0.19	2.36	0.0202
Caudate L				0.17	1.97	0.0511
Processing speed	0.27	21.85	<0.0001			
Education				0.38	4.72	<0.0001
Thalamus R				0.38	4.66	<0.0001
Working memory	0.15	7.60	0.0001			
Caudate L				0.37	3.70	0.0003
Nucleus accumbens L				−0.29	−2.98	0.0036
Education				0.21	2.39	0.0187
Attention	0.22	8.26	<0.0001			
Education				0.31	3.58	0.0005
Sex				−0.29	−3.29	0.0014
Thalamus R				0.29	2.91	0.0045
Hippocampus L				−0.24	−2.38	0.0189
Psychomotor speed	0.31	17.79	<0.0001			
Education				0.37	4.72	<0.0001
Thalamus R				0.37	4.69	<0.0001
Sex				−0.17	−2.17	0.0322
Average cognition	0.31	18.04	<0.0001			
Education				0.39	4.96	<0.0001
Thalamus R				0.34	4.33	<0.0001
Sex				−0.20	−2.52	0.0133

in line with previous studies showing male sex to be a significant predictor of cognitive impairment in larger groups of patients.[13,20]

DGM atrophy was most pronounced in the caudate, pallidum, and thalamus, although all DGM structures were found to be atrophic, except bilateral amygdala and the right hippocampus and nucleus accumbens. Volume reductions were generally larger in male patients (table e-1). This sex effect on atrophy has not been shown in such detail before. Studies that have investigated sex effects on brain volumes have mainly been restricted to overall atrophy measures like NGMV.[25] Here, we show that DGM atrophy exhibits larger effect sizes than NGMV (table e-1).

The relationship between brain volume and cognition was stronger for subcortical GM volume than it was for cortical GM volume. Zooming in on subcortical structures, specific MRI predictors of cognition varied per cognitive domain. The most commonly affected structure was the thalamus, which was the sole MRI predictor of average cognitive performance. It was also a significant predictor of executive functioning, information processing speed, attention, and psychomotor speed domains. The predictive value of the thalamus for cognition is in line with earlier research.[26] Using similar methods, a recent study showed the importance of the thalamus for information processing speed,[19] which is confirmed by our results. Additionally, this study also found the putamen to be important for this domain. In our regression analysis, the putamen was not significant as a predictor, but did correlate with information processing speed in male patients only ($r = 0.49$, $p = 0.002$). Sex-specific relations were seen in most cognitive domains involving the thalamus except for information processing speed, where sex was not a significant predictor. Atrophy of the thalamus was present in both male and female patients, but only correlated with average cognition in male patients. Female patients did have thalamic atrophy, but showed little cognitive dysfunction. This might be explained by a relative lack of atrophy in other DGM structures in female patients compared to male patients (table e-1).

The 2 memory-based domains, verbal memory and working memory, were influenced by caudate atrophy, with verbal memory also being influenced by hippocampal volume and sex. A previous fMRI study has highlighted the importance of the caudate nucleus for cognition, although only in primary progressive MS,[27] showing hyperactivation in cognitively preserved compared to cognitively impaired patients. This process of hyperactivation of normally involved regions of the brain and/or recruiting additional regions is often termed functional reorganization.[27] A recent study has also shown the hippocampus to be involved in functional reorganization in MS.[28]

Lesion volumes did not display a direct correlation with average cognitive performance, apart from T1 lesion volumes in male patients. In the regression models, T2 lesion volumes partly predicted executive function. Although the direct relationship between lesion volumes and cognition appeared to be weak, there was a significant correlation between lesion volumes and DGM atrophy. Although lesion volumes were equal between male and female patients, their relationship with atrophy was stronger in men. This

could possibly indicate that the male brain is more sensitive to neurodegeneration secondary to lesional damage in MS, although this is speculation. In our analyses, we did not consider the anatomic locations of lesions; this may be another factor influencing the effect of lesions on clinical and cognitive functioning, as previously shown.[29]

Sex seems to be an important factor that influences MS evolution. For example, in the chronic phase of MS, GM atrophy becomes more dominant[4] and male patients reach this stage of the disease earlier.[30] Although male patients appear to have more atrophy in general,[25] studies using larger sample sizes and appropriate controls are lacking.[31] Notably, several studies found no differences between male and female patients, but did not directly address sex-specific disease-inflicted atrophy by comparing to sex-matched healthy controls.[31] Neuroanatomic sex differences are widespread in healthy controls, however. For example, men have larger overall brain volumes as well as larger relative WM volumes, while women have larger relative GM volumes.[32] Recent studies on network properties also indicate a larger efficiency in female structural networks,[33,34] as well as differences in how functional network properties relate to cognition.[35] Interestingly, the thalamus exhibits extensive sex effects in WM fractional anisotropy, along with many other regions of the brain.[36] Therefore, in our large study, we compared both male and female patients directly with sex-matched controls. This showed that both DGM atrophy and cognitive dysfunction were worse in males, although it is insufficiently clear why. Possibly estrogen may serve as a protective factor in MS, as suggested by animal models,[37–39] but this awaits confirmation in human studies.

Although the present study displays clear effects and relationships, the results are based on cross-sectional data, focused on DGM volume. Future studies will have to investigate cortical atrophy in more detail, as the methodology used in this study was mainly limited to DGM structures. The strength of this study is the large cohort of patients with closely matched disease duration. Nevertheless, our findings should be confirmed in other MS cohorts. Future studies should also investigate the progression of atrophy within individual patients and possible changes in the relationship between atrophy and cognitive dysfunction along the disease course. This is especially relevant when designing new treatment strategies, which could thus differ between male and female patients.

These results show a clear relationship between cognitive dysfunction and subcortical atrophy in MS in a cohort of patients with RRMS 6 years postdiagnosis. This relationship was mostly driven by the thalamus, which was strongly predictive of most cognitive domains. Male sex was also found to be an important predictor of a worse cognitive performance and of higher regional atrophy. Future studies will have to shed more light onto the causes of these distinct sex differences, and will as such hopefully effectuate a more evolved understanding of neurodegenerative processes and cognitive impairment in MS.

AUTHOR CONTRIBUTIONS

Drafting/revising the manuscript: all authors. Study concept or design: M.M.S., V.P., H.V., J.J.G., F.B. Analysis or interpretation of the data: M.M.S., V.P., F.C.R.L., O.T.W., H.V., J.J.G., F.B. Acquisition of data: M.M.S. Statistical analysis: M.M.S., J.J.G. Study supervision or coordination: J.J.G., F.B. Obtaining funding: C.H.P., J.J.G., H.V., F.B.

DISCLOSURE

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