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Brain atrophy and lesion load in a large population of patients with multiple sclerosis

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Abstract—*Objective:* To measure white matter (WM) and gray matter (GM) atrophy and lesion load in a large population of patients with multiple sclerosis (MS) using a fully automated, operator-independent, multiparametric segmentation method. *Methods:* The study population consisted of 597 patients with MS and 104 control subjects. The MRI parameters were abnormal WM fraction (AWM-f), global WM-f (gWM-f), and GM fraction (GM-f). *Results:* Significant differences between patients with MS and control subjects included higher AWM-f and reduced gWM-f and GM-f. MRI data showed significant differences between patients with relapsing–remitting and secondary progressive forms of MS. Significant correlations between MRI parameters and between MRI and clinical data were found. *Conclusions:* Patients with multiple sclerosis have significant atrophy of both white matter (WM) and gray matter (GM); secondary progressive patients have significantly more atrophy of both WM and GM than do relapsing–remitting patients and a significantly higher lesion load (abnormal WM fraction); lesion load is related to both WM and even more to GM atrophy; lesion load and WM and GM atrophy are significantly related to Expanded Disability Status Scale score and age at onset (suggesting that the younger the age at disease onset, the worse the lesion load and brain atrophy); and GM atrophy is the most significant MRI variable in determining the final disability.

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The histopathologic features of multiple sclerosis (MS) include multiple foci of inflammation and demyelination as well as potentially substantial destructive or degenerative changes in both white matter (WM) and gray matter (GM).[1-4] Recently, advanced MRI techniques have demonstrated that even early in the course of the disease, there is neuronal and axonal damage in the lesions and beyond, thus leading to the concept of the so-called normal-appearing WM (NAWM).[5,6] Furthermore, MRI data have led to the hypothesis that progression of the disease, up to a stage of no return, is dependent on the cumulative effect of axonal damage,[7] which may ultimately result in MRI-visible brain atrophy.[8]

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There has been an active search for sensitive MRI methods to measure brain atrophy and other objective parameters of tissue damage. Up to now, various approaches have been developed to measure brain atrophy. In an effort to obtain reliable, reproducible, and objective measurements of brain atrophy, MRI methods have evolved from semiautomated, operator-dependent segmentation techniques to automated, operator-independent ones.[8,9] A few studies have assessed volume changes in both WM and GM using a largely automated approach,[10-14] but none has been conducted measuring both WM and GM atrophy as well as lesion load on large numbers of patients with MS. Although previous studies[10-14] provided consistent evidence that brain atrophy is a relevant feature of MS, the differential involvement of WM and GM in patients with different disease courses as well as the intercorrelations between WM

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and GM atrophy and lesion load and the correlations between WM and GM atrophy and clinical features have been only partially defined.

We sought to measure WM and GM atrophy and lesion load in a large population of patients with MS using a fully automated, operator-independent, multiparametric segmentation method and to investigate the intercorrelations between WM and GM atrophy and lesion load and the correlations between clinical and MRI data. This was accomplished by organizing a multicenter study, in which an MRI machine housed in a truck traveled to different locations to perform the same MRI protocol in all patients.

Methods. The study design was cross-sectional. During a predefined 6-month time window, all consecutive patients with MS, on the basis of a prescheduled visit, and all consecutive 20- to 50-year-old sex-matched healthy volunteers were included. Patients with definite MS[15] were recruited from the MS outpatient clinics of seven university hospitals (Second University of Naples, University "Federico II" of Naples, and Universities of Bari, Catanzaro, Messina, Catania, and Palermo) and the regional hospital of Potenza. Because these centers supply interferons (IFNs) and other immunomodulators to patients with MS, and considering the high frequency of treatment in Italian patients with MS, it is likely that the patients of our sample are representative of the general MS population. Another selection bias may be due to the number of patients who disagreed to participate to the study. Indeed, the percentage of refusals was very low (<5%).

All enrolled subjects were examined on the same day as the MRI session. Criteria for excluding patients were ongoing clinical relapse, other major medical illnesses, history of substance abuse, and corticosteroid treatment within 12 weeks of the start of the study. Criteria for excluding volunteers were neurologic disorders, major medical illnesses, history of substance abuse, and current drug treatment.

Seven hundred thirty-three subjects took part in the study: 629 patients with MS and 104 control subjects. Thirty-two patients with MS were not included in the final analysis because they did not complete the MRI exam or because of motion artifacts, so the study results are based on 597 patients with MS and 104 control subjects. The protocol was approved by local ethics committees. All participants gave written informed consent.

MRI studies. The same MRI protocol was performed in all subjects using the same MRI machine (1.0 T Genesys Signa; GE Medical Systems, Milwaukee, WI). For each study, two interleaved sets of 15 slices (4 mm thick) covering the entire brain were acquired, using for each set two conventional spin echo sequences (repetition time/echo time [TR/TE] 600/15 milliseconds), two averages; TR/TE 2,300/15 milliseconds, 90-millisecond dual-echo sequence, one average; both with 90° flip angle and 256 × 192 matrix. All the studies were segmented using a multispectral fully automated method, based on relaxometric characterization of brain tissues.[16,17] The program furnishes complete sets of multifeature images (R1 [=1/T1], R2 [= 1/T2], proton density [N(H)-based]) and segmented images and calculates the volumes of the following intracranial tissues: CSF, GM, NAWM, abnormal WM (AWM), and global WM (gWM; calculated as the sum of NAWM and AWM). To normalize for head size variability, the volumes of intracranial tissues were expressed as fractions (f) of the intracranial volume, which were calculated for each subject as the sum of all intracranial tissues. AWM-f is a measure of lesion load as determined by the R1, R2, and N(H) information and morphologic characteristics, the reduction of gWM-f indicates WM atrophy, and the reduction of GM-f indicates GM atrophy. Figure 1 shows a transverse slice of a patient with MS and depicts the major steps of the multiparametric method that, starting with a proton density-weighted image and a T2-weighted image, produces the corresponding multiparametric image and the resulting segmented image. In the latter image, the WM is represented by white, the GM by gray, the CSF by blue, and the lesions by yellow.

For each study, a couple of interactive interslice movies of both multifeature and segmented images were produced, and two neuroimaging experts reviewed them (for a maximum of 2 minutes) to detect motion artifacts and segmentation errors due to the imperfect separation of nasal mucosa and vitreous humor from brain tissue. In 111 studies (15.8%) in which nasal mucosa or vitreous humor was erroneously classified as GM or CSF, manual cuts of thin connections between intra- and extracerebral tissues in the multifeature image set were performed, allowing the program to outcome correct segmentation and volumetry.

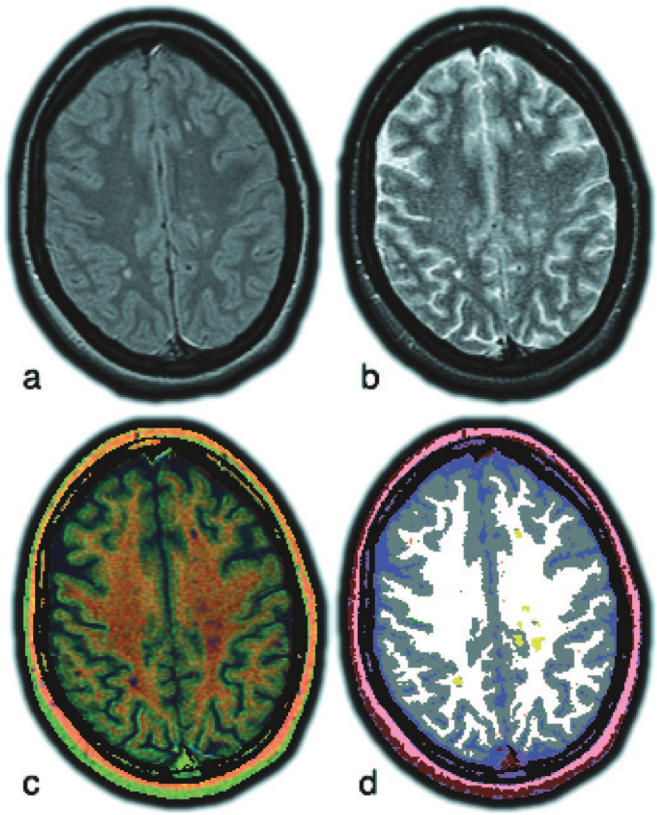

Figure 1. Transverse slice of patient with multiple sclerosis. (A) Proton density-weighted image; (B) T2-weighted image; (C) corresponding multiparametric image; (D) resulting segmented image. In the segmented image, the white matter is represented by white, the gray matter by gray, the CSF by blue, and the lesions by yellow.

Two improvements have been made to the previously published descriptions of the segmentation method: Thanks to better radiofrequency homogeneity of the head coil used, no R1 correction along the *z* axis was performed and, a multi-Gaussian fitting of R1 voxel distribution was introduced to eliminate the previously observed slight underestimation of GM-f in the presence of high AWM-f.

Statistics. MRI volume data were presented as means and 95% CI. The mean MRI parameters of all subjects were adjusted by age, gender, and education using a linear regression model. Before regression analysis, individual variables were checked for skewness and the presence of outliers. Post-hoc comparisons between patient and control groups were conducted with Bonferroni test. The univariate relationships between MRI volume fractions were estimated using Pearson correlation coefficients.

To evaluate the relevance of demographic, clinical, and therapeutic variables on each brain volume fraction, several multivariate analyses were performed. These analyses were performed using a general regression model with a forward stepwise procedure to evaluate the effect of categorical predictors (gender: male vs female; MS course: relapsing–remitting [RR] vs secondary progressive [SP] vs primary progressive [PP]; type of MS onset: monosymptomatic vs polysymptomatic; type of therapy: IFN β vs other therapy vs withdrawal from IFNβ vs never treated) and continuous predictors (age, years of school attended, age at disease onset, disease duration, Expanded Disability Status Scale [EDSS] score,

Table 1 *Comparisons between control subjects and patients with MS for adjusted* MR volumes (as % of whole-brain volume)*

	Mean (95% CI)		
	Patients with MS, n = 597	Controls, n = 104	*p* Value
AWM-f	1.4 (1.3–1.5)	0.1 (0.0–0.4)	<0.001
gWM-f	33.8 (33.5–34.1)	35.1 (34.4–35.7)	<0.001
GM-f	51.0 (50.7–51.2)	53.1 (52.5–53.7)	<0.001

* Adjusted for age, sex, and education.

MS = multiple sclerosis; AWM-f = abnormal white matter fraction; gWM-f = global white matter fraction; GM-f = gray matter fraction.

relapse rate) on a continuous dependent variable (i.e., each MRI volume fraction). Regression models were set with the categorical and continuous predictors previously indicated, and the forward stepwise procedure was applied. Thus, after the first step, the regression equation was composed of those predictors reaching specific thresholds of F and *p* values (for predictor inclusion: $F \geq 1$ and $p \leq 0.05$; for exclusion: $F < 1$ and $p > 0.05$). After several iterations, the final equation was composed only by those variables responding to the entry/removal criteria. The *B* value in the final regression equation expresses the percentage variation of the brain fraction volume on the whole volume for a unit variation of the predictor. The β values are standardized coefficients that provide a comparable weight of each predictor with each other included in the regression equation.

Finally, to evaluate the relative contribution of clinical, sociodemographic, and MRI-related variables to MS outcomes, further multivariate analyses were performed. These general regression models identified the predictors of both disability (as expressed by the EDSS score) and relapse rate, including the following predictors: gender, years of school attended, age at disease onset, disease duration, MS course, MS onset, therapy, and brain volume fractions. Analogously to previous models, these regressions were also set applying the forward stepwise procedure.

Results are presented as the *b* value (SE) and the β coefficient and its 95% CI. All statistical analyses were performed using Statistica version 6.0 (Statsoft s.r.l., Italy) and Confidence Interval Analysis for Windows.[18] *p* values of <0.05 were considered significant.

Results. The study population of patients with MS consisted of 383 women and 214 men (women/men ratio = 1.8) ages 16 to 68 years (mean ± SD 38.1 ± 10.3 years). Their age at disease onset was 10 to 61 years (28.4 ± 9.1 years), and their EDSS scores[19] were 0 to 8.5 points (2.99 ± 1.7 points). Disease duration was 9.73 ± 7.26 years, and number of relapses in the previous 2 years was 1.04 ± 1.3. The clinical course was RR in 427 (71.5%), SP in 140 (23.5%), and PP in 30 (5.0%). EDSS score was ≤3.5 in 452 patients (88.3% RR, 7.5% SP, 4.2% PP), between 4 and 6 in 110 patients (22.7% RR, 60.9% SP, 16.4% PP), and ≥6.5 in 35 patients (57.1% SP, 42.9% PP).

Measurements of segmented MRI volumes in the patients with MS and controls are presented in table 1. In patients with MS, the mean value of AWM-f was 1.4% (95% CI 1.3 to 1.5), which corresponds to a lesion load of about 17 cm^3 in an average brain of 1,200 cm^3. gWM-f was ($p < 0.001$) reduced in patients with MS by 1.3% (95% CI 0.5 to 2.1), which corresponds to a volume loss of about 15.6 cm^3 in an average brain of 1,200 cm^3.

GM-f was reduced ($p < 0.001$) in patients with MS by 2.1% (95% CI 1.4 to 2.8), which corresponds to a volume loss of about 25 cm^3 in an average brain of 1,200 cm^3.

Table 2 shows the comparisons of segmented MRI volumes in patients with MS with different disease courses. Between-group comparisons evidenced significant differences of MRI parameters only in RR patients with respect to SP patients. Both gWM-f and GM-f were significantly lower in the SP group than in the RR group. The magnitude of the gWM-f reduction was similar to that of GM-f, being 1.4% (95% CI 0.8 to 2.0) for both. Furthermore, AWM-f was significantly higher in the SP group than in the RR group [0.7%; 95% CI 0.3 to 1.1).

The intercorrelations between segmented MRI fractions are presented in table E-1 on the *Neurology* Web site at www.neurology.org. Lesion load (AWM-f) was inversely correlated with all other MRI fractions; however, a stronger relationship was found with GM-f ($r = -0.58$) than with gWM-f ($r = -0.35$) ($p < 0.001$, for Pearson *r* coefficient comparison).

The multivariate correlations of MRI fractions with clinical features are reported in table E-2. Three significant predictors of lesion load (AWM-f) were obtained: EDSS, age at disease onset, and drug treatment (IFNβ vs never treated). The strongest predictor was disability: A 1-point increase in the EDSS score corresponded to about a 0.24% increase of AWM-f (2.9 cm^3 for an average brain of 1,200 cm^3). Furthermore, a 0.15% increase of AWM-f was found for each 5 years earlier that the MS had its onset. IFNβ-treated patients had a higher lesion load (adjusted mean of 1.6%; 95% CI 1.4 to 1.7) than did patients who had never been treated (1.2%; 95% CI 1.0 to 1.5, $p = 0.008$).

With regard to WM atrophy (gWM-f), the strongest predictor was age at onset followed by disability: A 0.45% decrease of gWM-f was found for each 5 years earlier of MS onset. Furthermore, a 1-point increase in the EDSS score corresponded to about a 0.41% decrease of gWM-f (about 5 cm^3 for an average brain of 1,200 cm^3).

Table 2 *Comparisons of adjusted* MRI volumes (as % of whole-brain volume) for different MS courses*

	Mean (95% CI)					
	RR, n = 427	SP, n = 140	PP, n = 30	RR vs Sp	RR vs SP	SP vs PP
AWM-f	1.2 (1.0–1.4)	1.9 (1.6–2.2)	1.8 (1.2–2.5)	<0.001	NS	NS
gWM-f	34.2 (33.9–34.5)	32.8 (32.3–33.4)	33.1 (31.9–34.2)	<0.001	NS	NS
GM-f	51.4 (51.1–51.7)	50.0 (49.4–50.5)	50.7 (49.4–50.5)	<0.001	NS	NS

* Adjusted for age, sex, and education.

MS = multiple sclerosis; RR = relapsingremitting; SP = secondary progressive; PP = primary progressive; AWM-f = abnormal white matter fraction; gWM-f = global white matter fraction; GM-f = gray matter fraction.

Table 3 *Predictors of disability (as expressed by EDSS score) by a forward stepwise regression model**

Predictors	*B* (SE)	β Value	(95% CI of)	*p* Value
Intercept	6.7 (0.82)			
MS course, vs PP	−1.45 (0.09)			
RR	0.52 (0.10)	−0.49	(−0.55, −0.43)	<0.001
SP	0.05 (<0.01)	0.16	(0.10, 0.21)	<0.001
Disease duration, y	0.02 (<0.01)	0.22	(0.16, 0.28)	<0.001
Age at disease onset, y	−0.07 (0.02)	0.12	(0.06, 0.18)	<0.001
GM-f, %	−0.05 (0.01)	−0.12	(−0.18, −0.07)	<0.001
Years of school attendance		−0.10	(−0.16, −0.05)	<0.001
Drug treatment,† vs never treated	−0.03 (0.08)			
IFN	0.11 (0.12)	−0.01	(−0.09, 0.07)	0.728
Other treatment	0.21 (0.14)	0.04	(−0.05, 0.12)	0.369
IFN withdrawn	−1.45 (0.09)	0.07	(−0.02, 0.16)	0.129

* After seven steps, the multiple $R2$ of the model was 0.56 (F[9, 587] = 84, $p < 0.001$).
† One hundred seventy-five (29.3%) patients had never been treated, 316 (52.9%) were on IFN, 44 (7.4%) had withdrawn from IFN, and 62 (10.4%) were receiving other therapies (including glatiramer acetate, mitoxantrone, cyclophosphamide, and methotrexate).

EDSS = Expanded Disability Status Scale; MS = multiple sclerosis; SP = secondary progressive; RR = relapsingremitting; PP = primary progressive; GM-f = gray matter fraction; IFN = interferon.

Significant predictors of GM atrophy (GM-f) were again EDSS score and age at disease onset. The relationship between EDSS score and GM atrophy was as strong as that between EDSS score and NAWM atrophy (a 1-point increase in the EDSS score corresponded to a 0.54% decrease of GM-f; i.e., 6.5 cm^3 for an average brain of 1,200 cm^3). On the other hand, although significant, age at disease onset had both a low weight in predicting GM-f and the lowest β coefficient, as a 0.15% decrease of GM-f was found for each 5 years earlier of MS onset.

Table 3 shows the predictors of disability (as expressed by the EDSS score), considering demographic, clinical, and all MRI-related variables (which explain 56% of the variance of EDSS values in our MS cohort). MS disease course was the strongest predictor of disability, followed by disease duration, age at disease onset, number of years of schooling, and drug treatment. GM-f was the only MRI-related variable significantly predicting level of disability. None of the demographic, clinical, or MRI-related variables predicted relapse rate over the previous 2 years (full model: F[15, 581] < 1.0, $p = 0.458$).

Figure 2 shows the adjusted mean value of each brain volume fraction according to both EDSS and age at onset. With regard to AWM-f, a lower lesion load (lower fraction volume) was present among patients with EDSS of <3.5 compared with an EDSS score between 4.0 and 6.0 ($p = 0.007$). Patients with an age at disease onset before 20 years had the highest lesion load (highest AWM-f) with respect to patients who were older at disease onset ($p = 0.007$ vs category 20 to 30 years; and $p < 0.001$ vs category >30 years). With regard to GM-f, patients with EDSS score of <3.5 displayed the lowest GM atrophy (highest GM-f) compared with patients with higher EDSS score ($p < 0.001$ vs category 4.0 to 6.0 points; and $p = 0.006$ vs category >6.5 points). With regard to gWM-f, an inverse pattern between EDSS and age at onset was found. In

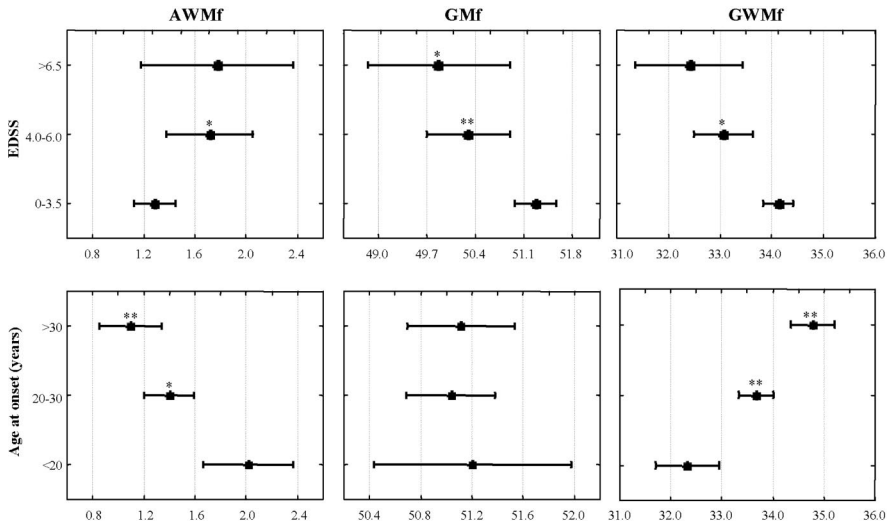

*Figure 2. Adjusted mean value (and 95% CI) of brain volume fractions according to both Expanded Disability Status Scale and age at onset (years). AWM-f = abnormal white matter fraction; GM-f = gray matter fraction; gWM-f = global white matter fraction.*p < 0.01, **p < 0.001 comparison vs the lower category.*

more detail, patients with an EDSS score of <3.5 showed the lowest gWM atrophy (highest gWM-f) with respect to patients with higher EDSS score ($p = 0.003$ vs 4.0 to 6.0 category). Remarkably, a decreasing level of gWM atrophy was present passing from cases with age at onset of <20 years to cases with a disease onset over 30 years ($p < 0.001$ for both comparisons).

Discussion. In this study, a fully automated MRI technique was used in a large MS population to assess both WM and GM atrophy and lesion load as well as to investigate the intercorrelations between MRI measurements of atrophy and lesion load and the correlations between clinical and MRI data.

Some methodologic considerations need to be addressed. The method used provides AWM-f as a measure of lesion load based on the multiparametric and fully automated approach, and it offers the advantage of simultaneously measuring both lesion load and WM and GM atrophy. We can therefore expect that it would be highly sensitive at simultaneously measuring lesion load and WM and GM atrophy. On the other hand, we chose not to take into account the possible contribution of additional important variables such as cervical spinal atrophy and postcontrast brain MRI, as neither would have been easily quantifiable and both would have lengthened the MRI examination and reading time.

Overall, compared with controls, patients with MS had more atrophy of both WM (−1.3%) and GM (−2.1%), and the burden of MS on brain volume, with respect to an average brain of 1,200 cm^3, can be summarized by the appearance of 17 cm^3 of AWM-f and by the lack of about 16 cm^3 of gWM-f and 25 cm^3 and of GM-f. In more detail, patients with MS lost 17 cm^3 of WM because of MRI-identifiable lesions (AWM-f) and 16 cm^3 because of volumetric measurable atrophy (gWM-f). Our results are in agreement with previously published data,[11] which described, in 26 patients with MS, a significant reduction of both WM (approximately −4.9%) and GM fractions (approximately −2.8%). The slight differences in the amount of WM and GM atrophy may be due to a large difference in the number of patients studied, although a difference in the segmentation methods cannot be ruled out. In a small group of RR patients, the loss of parenchymal volume in RR MS was predominantly confined to WM.[14] With use of the same segmentation method in 50 patients with RR MS, a significant reduction of GM-f was found, whereas WM-f was not significantly different between patients and control subjects.[13] The lack of significant WM atrophy may be due to the small sample of RR patients studied.[13] A T1-weighted segmentation method was used to separate segmented GM into neocortical and non-neocortical in 90 RR and PP patients, and a significant reduction of neocortical GM was found in both groups of patients.[12] A different approach to the assessment of GM atrophy was recently described by a novel method of automated surface reconstruction to measure cortical thickness, and a significant focal and overall cortical thinning in 20 patients with MS was found.[20] Compared with previous studies, we produced more comprehensive evidence that there is significant atrophy of both GM and WM in patients with MS, thus confirming the pathologic evidence[1-4] of GM involvement in MS.

Among the studies based on automated MR segmentation methods, only one[12] assessed differences between patients with different disease courses and found no significant differences in neocortical GM between RR and PP patients. In the current study, we showed that SP patients, with respect to RR ones, have significantly more atrophy of both GM and WM, thus suggesting that brain atrophy may be relevant in determining the course of the disease and eventually disease progression. No differences were found in the small group of PP patients.

So far, the intercorrelations between lesion load and WM and GM have been only partially addressed. In 26 patients with MS, T1- and T2-weighted lesion volumes were inversely related to GM-f but not to WM-f.[11] In 50 RR patients, AWM-f was inversely correlated to GM-f but not to global WM-f.[13] In patients with RR MS, a significant correlation between neocortical atrophy and T2 lesion volume was found, whereas no correlation was found in PP patients.[12] A significant correlation between thinning of the cerebral cortex and T1-T2 lesion volume was found in 20 patients with MS.[20] We showed that lesion load is significantly correlated with both GM and WM atrophy; however, a significantly stronger relationship was found with GM-f than with gWM-f. These results support the hypothesis that GM atrophy is heavily dependent on lesion load, possibly owing to retrograde degeneration of GM neurons secondary to fibers traversing WM lesions,[21,22] although we cannot ignore the possibility of both discrete and diffuse independent GM lesions that may be undetectable by conventional MRI.[2,4]

Measurements of MRI-segmented volumes were significantly correlated to disability and age at disease onset and, to a lesser extent, drug treatment. So far, the studies addressing the relationship between MRI and disability have reported conflicting results, and this has been attributed to the poor sensitivity of the EDSS, although, more recently, functional MRI studies[23] suggested that the possible impact of plasticity may play a key role in determining the resulting disability. Significant correlations between disability and WM and GM atrophy were not found in 30 patients with RR MS.[14] A significant correlation between neocortical atrophy and EDSS was described in both RR and PP patients, whereas the correlation with disease duration was found only in RR patients.[12] A significant correlation between GM atrophy and EDSS was reported, but there was no correlation between WM atrophy and disease duration.[11] We produced very strong evidence that lesion load and both WM and GM atrophy are significantly correlated with disability. The existence of a close relationship between GM atrophy and disability is

further supported by the significant association found in the analysis of predictors of disability. This correlation supports the role that GM involvement may play in the pathogenesis of MS and urges us to focus on neurodegeneration as a key feature of MS.

The correlation with age at disease onset suggests that the younger the age at disease onset, the worse the lesion load and brain atrophy (especially of WM) will be. These data suggest that brain atrophy is related to what happens at the very beginning of the disease rather than during the disease course. This hypothesis is in accordance with previous reports. Global brain atrophy (as derived from the parenchymal fraction) and central atrophy (as derived from the ventricular fraction) were longitudinally measured in 83 patients with MS at an interval of 2 to 4 years.[24] The main observations were that clinical characteristics (such as duration of symptoms and ΔEDSS) did not predict the variance in the rate of global or central atrophy, whereas the rate of central atrophy was significantly higher in younger patients. Twenty-eight patients with MS were followed for up to 14 years after the first onset of symptoms,[25] and lesion load in the first 5 years was more closely correlated with disease-related brain atrophy at 14 years than were later changes in lesion load. Furthermore, in a cohort of patients with RR MS, lesion load (as derived from the average number of total and new gadolinium-enhanced lesions) decreased significantly with increasing patient age, independently of disease duration and relapse rate.[26]

In line with the use of IFNβ in clinical practice, in a cross-sectional survey, it was found that patients assigned to treatment with IFNβ had a higher lesion load (adjusted mean of 1.6%; 95% CI 1.4 to 1.7) than those who had never received this drug because a watchful-waiting approach had been preferred (1.2%; 95% CI 1.0 to 1.5).

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