ORIGINAL ARTICLE

Gray Matter Atrophy Is Related to Long-Term Disability in Multiple Sclerosis

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Objective: To determine the relation of gray matter (GM) and white matter (WM) brain volumes, and WM lesion load, with clinical outcomes 20 years after first presentation with clinically isolated syndrome suggestive of multiple sclerosis (MS).
Methods: Seventy-three patients were studied a mean of 20 years from first presentation with a clinically isolated syndrome (33 of whom developed relapsing-remitting MS and 11 secondary-progressive MS, with the rest experiencing no further definite neurological events), together with 25 healthy control subjects. GM and WM volumetric measures were obtained from three-dimensional T1-weighted brain magnetic resonance images using Statistical Parametric Mapping 2.
Results: Significant GM ($p < 0.001$) and WM atrophy ($p = 0.001$) was seen in MS patients compared with control subjects. There was significantly more GM, but not WM atrophy, in secondary-progressive MS versus relapsing-remitting MS ($p = 0.003$), and relapsing-remitting MS versus clinically isolated syndrome ($p < 0.001$). GM, but not WM, fraction correlated with expanded disability status scale ($r_s = -0.48$; $p < 0.001$) and MS Functional Composite scores ($r_s = 0.59$; $p < 0.001$). WM lesion load correlated with GM ($r_s = -0.63$; $p < 0.001$), but not with WM fraction. Regression modeling indicated that the GM fraction explained more of the variability in clinical measures than did WM lesion load.
Interpretation: In MS patients with a relatively long and homogeneous disease duration, GM atrophy is more marked than WM atrophy, and reflects disease subtype and disability to a greater extent than WM atrophy or lesions.

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Magnetic resonance imaging (MRI)–detectable white matter (WM) lesions are usually seen early in relapse onset multiple sclerosis (MS), and in people who develop a clinically isolated syndrome (CIS) suggestive of MS, they are associated with conversion to clinically definite MS,[1,2] although they predict subsequent disability only to a limited degree.[3,4]

Brain atrophy is also seen from clinical disease onset in MS[5]; it is prominent in the later stages of the disease, and is more marked in secondary progressive (SP) compared with relapsing-remitting (RR) phenotypes of MS,[6,7] although the relative influence of disease phenotype and disease duration on such atrophy is uncertain.

From pathological studies extensive cortical damage has been observed predominantly in progressive forms of MS, suggesting that GM pathology may be an important determinant of irreversible disability.[8] Although whole-brain atrophy has been well explored, the advent of new MRI acquisition and analysis tools now makes it possible to determine the relative extent of both GM and WM atrophy. Recent work investigating the progression of tissue-specific atrophy, measured using methods based on Statistical Parametric Mapping (SPM) segmentations, after first presentation with a CIS showed significantly greater GM compared with WM atrophy in those patients who developed clinically definite MS within 3 years.[9] Furthermore, in patients with early RRMS, GM atrophy over 2 years was more rapidly progressive than WM atrophy.[10] These studies suggest that progressive GM atrophy occurs early in the clinical course of MS, and in the case of CIS, is of direct and immediate clinical relevance. Although some studies have detected predominantly GM atrophy,[9,11–14] not all have; indeed, some observed mostly WM atrophy,[15] and it remains to be definitively determined which tissue is most affected at any given stage of the disease, particularly in the longer term.

The relation between WM lesions and brain atrophy also remains unclear, with current evidence suggesting

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a partial discordance between these pathological manifestations of MS[16] both in cross-sectional and longitudinal studies.[9,11,12,17–21] The suggestion that there is at least a partial discordance between T2 lesion load (T_2LL) and atrophy measures during the evolution of MS is supported by the observation that, although disease-modifying therapies such as β-interferon are relatively effective in preventing new WM lesion formation, their effect in reducing atrophy has been modest,[22,23] and in some studies, not evident at all.[24,25]

With this context, the *primary objective* of this study was to estimate GM and WM volumes in a cohort of CIS patients followed-up 20 years from clinical disease onset, and to assess the relation between these measures of tissue-specific atrophy, clinical course, and disability, in particular, investigating the hypothesis that GM atrophy will correlate better with clinical disease severity. *Secondary objectives* were as follows: (1) to evaluate the relation of GM and WM volumes with T_2LL, and (2) to investigate the relative contributions of GM and WM volumes and T_2LL to disability.

Methods

Subjects

This report is based on 20-year follow-up data of a cohort who had clinical and MRI assessments at approximately 5-yearly intervals after presenting with a CIS suggestive of MS.[3,4] Clinical status was documented at the 20-year follow-up in 107 patients,[4] of whom 75 had an MRI examination, with data from two patients excluded (one who developed cerebrovascular disease and one who did not complete the scanning protocol). The remaining 73 patients are the subject of this report.

Clinically definite MS was diagnosed on clinical grounds alone.[26] Disability was assessed using the expanded disability status scale (EDSS)[27] and MS functional composite (MSFC) scores.[28] The clinical course of MS (RRMS or SPMS) was defined by Lublin and Reingold criteria.[29] Those clinically definite MS patients with an EDSS ≤ 3 were defined as benign MS. Patients were studied a mean (standard deviation [SD]) of 20 [1.5] range, (18–27) years after the CIS (49 women and 24 men; mean age, 51.4 [7.2] years); 29 were still classified as CIS (mean disease duration, 20.4 [2.06] years; mean age, 51.5 [8.4] years), 33 had developed RRMS (mean disease duration, 19.7 [1.1] years; mean age, 51 [6.1] years) and 11 SPMS (mean disease duration, 19.8 [0.68] years; mean age, 52 [7.3] years). The median EDSS was 2.5 (range, 0–8) for all patients and 3.25 (range, 1–8) for MS patients only. Three patients were receiving disease-modifying treatments. MRI was also performed in 25 healthy control subjects (14 women and 11 men; mean age, 41.7 [7.7] years).

The study was approved by the National Hospital for Neurology and Neurosurgery and Institute of Neurology Joint Research Ethics Committee. All study participants gave written informed consent.

Image Acquisitions and Processing

Whole-brain MRI was performed on a 1.5-Tesla GE Signa scanner (General Electric, Milwaukee, WI) as follows: (1) two-dimensional, dual-echo proton density (TE, 17 milliseconds) and T2 (TE, 103 milliseconds)-weighted fast spin-echo (repetition time [TR], 2,000 milliseconds; 28 × 5mm slices; field of view, 24 × 18cm; in-plane resolution of 1.1 mm); and (2) three-dimensional, axial, T1-weighted, inversion-prepared, fast spoiled gradient recall (TR, 10.9 milliseconds; TE, 4.2 milliseconds; inversion time, 450 milliseconds; 124 × 1.5mm slices; imaging matrix, 256 × 160, interpolated to a final in-plane resolution of 1.1mm). An experienced neuroradiologist (K.A.M.), blinded to clinical details, identified lesions on hard copies of the proton density–weighted images, with reference to the T2-weighted images. This was then used as a reference for contouring of the lesions on the proton density–weighted digital images, using a semiautomated local thresholding technique implemented in the image display package DispImage (Plummer, Department of Medical Physics and Bioengineering, University College London, London, United Kingdom).[30] Then a computer program summed all the individual lesion volumes (calculated as surface area of each lesion multiplied by slice thickness), and T_2LLs were generated.

Segmentation of the axial, three-dimensional, T1-weighted images into WM, GM, and cerebrospinal fluid was performed using SPM2 (Statistical Parametric Mapping; Wellcome Department of Cognitive Neurology, Institute of Neurology, London), following a previously described method[11] (software available free to the research community at www.nmrgroup.ion.ucl.ac.uk/atrophy). The processing parameters for SPM2 were set to 0.01 for the bias correction and 30 for the bias cutoff. WM and GM fraction volumes (GMF) relative to total intracranial volume were derived, corrected for lesion misclassification as GM.[11] The tissue masks were inspected by an experienced operator, and no significant segmentation errors were detected.

To assess the robustness of results obtained using SPM2, we reprocessed our data using SIENAX (Structural Image Evaluation, using Normalization, of Atrophy for cross-sectional measurement), a fully automated technique, to obtain the normalized GM and WM volumes.[31] SIENAX methodology and results are provided in an Appendix.

Statistical Analyses

Group comparisons of the brain tissue volumes were performed using linear regression with group indicator and age and sex covariates. To assess the associations between the brain volume measurements, T_2LL, and disability (EDSS and MSFC and its components), we used Spearman's rank correlation.

To assess the relative contribution of the WM and GM volume loss and T_2LL to accrued disability, we used ordinal logistic regression (for EDSS) and linear regression (for MSFC). Both EDSS (categorized as follows: ≤ 1.5; >1.5, and ≤ 3; >3 and ≤ 6; >6) and MSFC (as a continuous variable) were modeled as response variables, with tissue volumes, lesion load, age, and sex as covariate predictors. Lesion load was log-transformed to improve normality before inclusion in the regression models; where the T_2LL was zero (10 subjects), the log volume was given a value of 0.01 to in-

Table 1. **Mean and Median (Standard Deviation) of Brain Volume Measurements**

Group (n)	GMF Mean; Median (SD)	WMF Mean; Median (SD)
Control subjects (25)	0.51; 0.52 (0.01)	0.29; 0.29 (0.01)
All patients (73)	0.49; 0.49 (0.03)	0.28; 0.28 (0.01)
CIS (29)	0.50; 0.50 (0.02)	0.28; 0.28 (0.01)
MS (44)	0.47; 0.48 (0.03)	0.28; 0.28 (0.01)
RRMS (33)	0.48; 0.49 (0.02)	0.28; 0.28 (0.01)
Benign MS (22)[a]	0.49; 0.49 (0.02)	0.28; 0.28 (0.01)
Nonbenign MS (22)[b]	0.46; 0.46 (0.30)	0.28; 0.27 (0.01)
SPMS (11)	0.45; 0.45 (0.03)	0.27; 0.27 (0.01)

[a]Benign multiple sclerosis (MS) = expanded disability status scale (EDSS) ≤ 3.
[b]Nonbenign MS = EDSS > 3.
GMF = gray matter fraction; WMF = white matter fraction; CIS = clinically isolated syndrome; MS = multiple sclerosis (RRMS and SPMS); RRMS = relapsing-remitting MS; SPMS = secondary progressive MS.

clude these subjects. Changing the EDSS category intervals, or the small value given for the log volume where the T_2LL was zero, did not materially change the results.

MRI covariates were entered together and removed singly by manual backward stepwise exclusion until all model predictors were significant at $p < 0.1$. Age and sex were added to the final models but omitted if the adjusted coefficients were both nonsignificant and not materially different from unadjusted coefficients. Models were applied to the whole cohort of patients and the MS subgroup separately.

The data were analyzed using SPSS 11 (SPSS, Chicago, IL) and Stata 9.2 (Stata Corporation, College Station, TX). Statistical significance was taken at $p < 0.05$.

Results

Tissue-Specific Volumes and Clinical Subgroups

Tissue-specific volumes were significantly lower in MS patients and MS subgroups (RRMS and SPMS) versus control subjects (Tables 1 and 2). Significant GM and WM atrophy was seen in MS patients compared with control subjects. There was significantly more GM atrophy, but not WM atrophy, in SPMS versus RRMS and RRMS versus CIS. There was significantly greater GM atrophy, but not WM atrophy, in those (nonbenign) MS patients with an EDSS > 3 (22 patients) compared with those (benign) MS patients with an EDSS ≤ 3 (22 patients). There were no significant differences for any of the volume measurements between the control subjects and those remaining classified as a CIS after first presentation.

Magnetic Resonance Imaging Measures and Disability

GMF correlated significantly with EDSS and MSFC for all patients and for the MS subgroup alone (Table 3). WM fraction volumes showed no such correlations. T2LL also correlated with EDSS ($r_s = 0.49$; $p < 0.001$) and MSFC ($r_s = -0.53$; $p < 0.001$) for all patients, as well as in the MS subgroup ($r_s = 0.38$, $p = 0.009$; and $r_s = -0.42$, $p = 0.005$, respectively).

Correlations of Lesions with Gray and White Matter Volumes

T_2LL correlated significantly with GMF ($r_s = -0.63$; $p < 0.001$) but not with WM fraction volumes ($r_s = -0.15$; $p = 0.19$) for the whole cohort of patients and for the MS subgroup only ($r_s = -0.66$, $p < 0.001$, and $r_s = -0.18$, $p = 0.22$, respectively).

Predicting Disability

For the whole cohort of patients, only GMF and log-transformed T_2LL independently predicted EDSS category, with GMF the stronger predictor: There was an estimated 64% ($p = 0.001$) reduction in the odds of having greater disability per 1 SD greater GMF, and a 52% odds reduction ($p = 0.05$) per 1 SD greater log-transformed T_2LL.

Only GMF independently predicted disability as measured by MSFC scores; there was an estimated 0.61 increase ($p < 0.001$) in MSFC per 1 SD greater GMF.

Restricting regression models to the MS subgroup of patients, only GMF independently predicted disability, whether EDSS or MSFC: There was a 59% ($p = 0.007$) reduction in the odds of being in more severe EDSS category per 1 SD greater GMF, and there was a 0.67 increase ($p = 0.001$) in MSFC per 1 SD greater GMF.

The findings using SIENAX measured tissue volumes were similar to those obtained using SPM2 (see the Appendix for further details).

Discussion

This study builds on previous work,[20,32,33] characterizing tissue-specific brain atrophy in a group of people with MS or CIS who have a uniquely long and homogeneous disease duration (approximately 20 years). It has allowed an exploration of the associations and role as predictors of MRI measures, tissue-specific (GM and WM) atrophy and WM lesion load, with clinical phenotype and disability, relatively free of confounding by variability in disease duration.

In this cohort of patients, both GM and WM atrophy was seen in MS patients compared with control subjects, and the extent of GM atrophy was greater than that of WM atrophy in keeping with some previous studies.[9,11–14] Furthermore, there was significantly more GM, but not WM, atrophy in SPMS versus RRMS, and RRMS versus those remaining CIS

Table 2. **Age- and Sex-Adjusted Mean Difference between Patient Subgroups and Control Subjects**

Group Comparisons	GMF		WMF	
	Adjusted Mean Difference (95% CI)	*p*	Adjusted Mean Difference (95% CI)	*p*
MS-control subjects	**−0.027 (−0.041 to (−0.014))**	**<0.001**	**−0.009 (−0.017 to (−0.001))**	**0.017**
MS-CIS	**−0.028 (−0.039 to (−0.017))**	**<0.001**	−0.003 (−0.010 to 0.003)	0.318
SPMS-control subjects	**−0.046 (−0.063 to (−0.028))**	**<0.001**	**−0.013 (−0.024 to (−0.002))**	**0.018**
RRMS-control subjects	**−0.021 (−0.035 to (−0.008))**	**0.002**	**−0.008 (−0.017 to (−0.001))**	**0.042**
SPMS-CIS	**−0.046 (−0.062 to (−0.030))**	**0.001**	−0.006 (−0.016 to 0.003)	0.179
RRMS-CIS	**−0.022 (−0.033 to (−0.010))**	**<0.001**	−0.002 (−0.009 to 0.004)	0.540
SPMS-RRMS	**−0.024 (−0.040 to (−0.008))**	**0.003**	−0.004 (−0.014 to 0.005)	0.361
Benign-nonbenign MSa	**0.022 (0.004–0.040)**	**0.01**	0.004 (−0.004 to 0.013)	0.328
CIS-control subjects	0.001 (−0.013 to 0.015)	0.089	−0.006 (−0.015 to 0.002)	0.142

Benign MS = expanded disability status scale (EDSS) ≤ 3; nonbenign MS = EDSS > 3.
GMF = gray matter fraction; WMF = white matter fraction; CI = confidence interval; MS = multiple sclerosis (RRMS and SPMS); CIS = clinically isolated syndrome; SPMS = secondary progressive MS; RRMS = relapsing-remitting MS.

patients. It should be noted that GM atrophy has not been a universal finding in MS, and that a definitive consensus on the location and timing of brain atrophy has yet to be reached; however, a significant number of recent studies suggest that GM atrophy is a consistent finding throughout the clinical course of MS, seemingly mirroring clinical status.[9,10,32,34] The apparent discrepancy in some previous studies may represent a combination of cohort-related and technical factors. Although there is no universally accepted gold standard method for measuring GM and WM volumes, the SPM-based approach has provided consistent findings in several previous studies,[9–11,32] and in this study, the robustness of the results obtained using SPM-based methods have been consolidated by similar findings with another widely used segmentation method (SIENAX technique; see Appendix).

Given the relatively homogeneous disease duration and age distribution of the clinical subgroups included in this work, the association of GM atrophy with clinical status is not explained by these factors; rather, the findings suggest a direct link between GM atrophy and clinical disease severity.

Differential tissue-specific atrophy in MS may be partially explained by variable degrees of inflammatory activity in WM and GM,[35,36] with relatively greater compensation of cell loss by inflammatory infiltrates and edema in WM compared with GM. Differential inflammatory noise in the volumetric measures may also lead to greater attenuation of WM compared with GM associations with clinical parameters. However, it may be expected that eventually atrophy, if progressive, would reach a magnitude where it would no longer be disguised by inflammatory interference; given this, our observations in MS patients with relatively long disease duration suggest that WM atrophy is truly less progressive than that of GM, and not simply the result of compensation by, and short-term fluctuations associated with, inflammation. In addition, although we detected no clear evidence of an association between WM atrophy and disability, 50% of MS patients in this cohort had a benign clinical course, and

Table 3. **Correlations of Brain Volume Measurements with Clinical Features**

	rs (p)				
	EDSS (n = 73)[a] (44[b])	MSFC (n = 67)[a] (41[b])	Z-PEG (n = 70)[a] (42[b])	Z-WALK (n = 68)[a] (40[b])	Z-PASAT (n = 68)[a] (42[b])
GMF[a]	**−0.48 (<0.001)**	**0.56 (<0.001)**	**0.59 (<0.001)**	**−0.40 (0.001)**	**0.27 (0.026)**
GMF[b]	**−0.41 (0.005)**	**0.55 (<0.001)**	**0.44 (0.003)**	**−0.49 (0.001)**	**0.32 (0.038)**
WMF[a]	−0.20 (0.086)	0.03 (0.784)	0.16 (0.176)	−0.11 (0.337)	−0.07 (0.537)
WMF[b]	−0.11 (0.443)	0.10 (0.526)	0.28 (0.071)	−0.09 (0.560)	−0.04 (0.761)

[a]All patients.
[b]Multiple sclerosis (MS) subgroup only.
rs = Spearman's rank correlation coefficient; EDSS = expanded disability status scale; MSFC = multiple sclerosis functional composite score; GMF = gray matter fraction; WMF = white matter fraction.

it is conceivable that larger cohort with more severe disability (eg, EDSS score ≥ 7) might exhibit more WM atrophy; further work is required to explore this possibility. Considered overall, our findings suggest that measures of GM atrophy will be more useful than WM volume in natural history studies or treatment trials, for example, in a study of potentially neuroprotective agents, although serial studies should further investigate the relation between longitudinal GM volume and clinical changes.

GM, but not WM volume measurements, correlated with clinical disability (EDSS, MSFC, and its components). Although T2LL correlated significantly with disability, GMF was a better predictor of disability when included in the regression models. Whereas noting the caveats about inflammatory noise discussed previously, these data suggest that GM atrophy has more clinical relevance in the long term than either lesion load or WM atrophy in people with MS, being more closely related to long-term disability and clinical course. This study's findings consolidate and extend the observation made in several previous studies that MRI markers of GM involvement correlate more strongly with measures of physical disability than WM lesion load.[8,32,33,37]

The amount of tissue loss in MS probably represents a balance between several pathological processes: irreversible neuronal and axonal loss, myelin loss, and reversible neuroaxonal atrophy, on the one hand, with partial compensation by inflammation-associated cellular infiltrates, and cellular (including axonal[38]) and interstitial edema on the other. With regard to the mechanisms of brain atrophy, there may be: (1) antegrade and retrograde neuroaxonal tract degeneration associated with focal WM inflammatory lesions,[39] with a potentially significant delay between axonal demyelination and subsequent neuroaxonal degeneration; and (2) a more widespread process directly targeting neurons, myelin (including cortical demyelination[35,36]), and glia.

GM (but not WM) volume measurements correlated with WM lesion load, which is in keeping with other studies.[9–11,32] This correlation may reflect secondary degeneration from WM lesions to GM. That the degree of correlation is only moderate suggests that processes independent of WM lesions are also contributing to GM atrophy in MS. One such explanation might be that GM demyelinating lesions, although not visible on conventional MRI, are commonly found at autopsy.[35,36] Our findings emphasize that further research to elucidate pathogenic mechanisms in MS should focus on GM as well as WM pathology.

When considering the significance of the findings observed in our study, it is important to take into account a few limitations. First, neither WM lesion volume nor tissue-specific brain atrophy measurement is pathologically specific. WM lesions on T2-weighted MRI may contain variable amounts of inflammation, demyelination, edema, and axonal loss. The brain volume measurements, although affected by the same factors, are thought to be more specifically weighted toward neurodegeneration. Second, our brain volume measurement data are cross sectional and do not provide any direct information on the temporal evolution of atrophy, information that can be gathered using only serial MRI data. We therefore cannot determine whether the atrophy observed in this study occurred immediately before or many years before this study. Although the patients were scanned at earlier time points,[3] there has been a major scanner hardware upgrade since then, rendering it difficult to directly compare measurements from earlier scanning with that obtained at 20 years. Third, some of the more disabled patients were not able to be scanned, so our data are relatively biased toward a less disabled subset of the patients previously studied.[4] Fourth, spinal cord involvement makes an important contribution to locomotor disability in MS and was not included in this investigation. Finally, with the SPM-based methods, misclassification of lesions or nonbrain tissue as GM may lead to a relative underestimation of the apparent magnitude of GM disease effects; however, correction for lesion misclassification was performed, and quality assurance review of the scans found no additional significant segmentation errors; thus, there should not have been significant misclassification effects.

Notwithstanding these caveats, the study clearly found that in MS patients with a relatively long and homogeneous disease duration (approximately 20 years), GM atrophy is greater than WM atrophy, and reflects disease subtype and disability. It also helps to understand why a limited relation between WM lesions and disability in MS has been evident in many previous MRI clinical studies of both natural history and therapeutic intervention, and highlights a need to better understand and monitor GM pathology in MS.

Appendix: Gray and White Matter Volumes Measured Using SIENAX and Their Relationship with Clinical Subgroups and Disability

SIENAX Methodology

SIENAX was used to obtain the normalized (per subject head size) GM and WM brain volumes (NGMV and NWMV). In brief, SIENAX first extracts brain and skull voxels from the input MR data, using the Brain Extraction Tool (www.fmrib.ox.ac.uk/fsl). The brain image is then affine-registered to standard space brain and skull images, derived from the MNI152 standard space reference set, with the skull registration used to determine the head size normalization factor. Next, tissue type segmentation, with partial volume estimation, is performed to calculate the total volume of brain tissues, including

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