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Regional Brain Atrophy Evolves Differently in Patients with Multiple Sclerosis According to Clinical Phenotype

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BACKGROUND AND PURPOSE: **Progressive brain atrophy is a well-known feature of multiple sclerosis (MS). We characterized the spatial evolution of atrophy in different MS phenotypes.**

METHODS: **Dual-echo and T1-weighted MR images were obtained in 70 patients with MS and 10 healthy control subjects at entry and after 15 months. Within-group changes in regional atrophy were assessed by applying Structural Image Evaluation Using Normalization of Atrophy software and statistical parametric mapping analysis. Reported differences are for $P < .001$.**

RESULTS: **During follow-up, patients with relapsing-remitting MS (RRMS) differences significant atrophy around the ventricular system; pericerebellar spaces; cerebellar tentorium; putamen; corpus callosum; cingulate sulcus; hippocampus; parieto-occipital fissure; lateral fissure; and frontal, parietal, temporal, and occipital cortex. Patients with secondary progressive MS developed significant atrophy of the cingulate sulcus; pulvinar; caudate nucleus; anterior orbital gyrus; mammillary body; fourth ventricle; and regions of frontal, parietal, temporal, and occipital cortex. Patients with primary progressive MS developed significant atrophy of the bilateral central sulcus; caudate nucleus; prepontine and quadrigeminal cisterns; lateral ventricle; and regions of frontal, parietal, temporal, and occipital cortex. In all phenotypes, the development of atrophy in some regions was significantly correlated with the accumulation of T2- and T1-visible lesions and clinical disability ($r = -0.57$ to -0.86).**

CONCLUSION: **In MS, brain atrophy develops involving different structures in the different phenotypes. While ventricular enlargement is predominant in RRMS, cortical atrophy seems to be more important in the progressive forms. Measures of regional brain atrophy were significantly correlated with disability, suggesting that this approach is promising for bridging the gap between clinical and MR imaging findings in MS.**

The progressive development of brain atrophy is a well-known feature of multiple sclerosis (MS) and viewed as a potential marker of irreversible tissue damage (1). Although the magnitude of brain atrophy seems to be greater in patients with the progressive forms than in those with relapsing-remitting MS (RRMS) (2–4), studies have demonstrated that considerable tissue loss also occurs in patients with early RRMS (5–8) and in patients with clinically isolated syndromes suggestive of MS (9, 10). Cross-sectional and longitudinal studies have shown that measurements of brain atrophy are better correlated with clinical disability (4, 11, 12) and neuropsychological impairment (13, 14) than are T2- and T1-lesion volumes. Recently, several automated techniques have been developed to measure brain atrophy (1). Among them, the Structural Image Evaluation Using Normalization of Atrophy (SIENA; University of Oxford, Oxford, UK) software (15) allows the estimation of the percentage of brain volume changes between two images obtained at different time points. This method requires little operator input, and as a consequence, offers high reproducibility.

Previous studies of patients with MS used either a global index of brain atrophy without considering the spatial localization of volume changes (4, 11, 12), or they evaluated volumes changes in only specific brain structures, such as the ventricles (9, 16, 17), the cor-

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Demographic clinical characteristics and MR imaging findings at baseline and after 15 months

	Healthy Subjects	Patients		
		RRMS	SPMS	PPMS
M/F	4/6	8/12	6/13	12/19
Mean age (years)	42.6 (31–58)	35.9 (25–43)	49.3 (35–58)	50.1 (25–68)
Median EDSS score	NA	3.0 (0.0–5.0)	6.0 (4.0–8.0)	6.0 (2.5–7.0)
Median disease duration (years)	NA	5 (0–20)	16 (6–34)	10 (2–26)
Baseline lesion volume (mL)				
On T2-weighted images	NA	13.9 (10.6)	21.7 (17.3)	21.0 (16.9)
On T1-weighted images	NA	3.1 (3.6)	8.5 (7.3)	8.2 (6.9)
Lesion volume change (%)				
On T2-weighted images	NA	9.4	3.8	4.9
On T1-weighted images	NA	3.4	11.0	4.3
Baseline NBV (mL)	1602 (80)	1517 (70)	1464 (90)	1473 (70)

Note.—Data in parentheses are the range or standard deviation. NA indicates not applicable.

pus callosum (16, 18, 19), or limited portions of the brain (2, 20). Few groups have specifically investigated changes in regional brain volume in MS patients (17, 21, 22); their results suggest that an accurate assessment of regional brain atrophy might be rewarding in terms of improving our understanding of the evolution of MS.

In this study, we combined SIENA and statistical parametric mapping (SPM) analysis that enables a voxel-wise comparison of spatially normalized images (15, 23). Our purpose was to characterize the evolution of regional brain atrophy to determine whether its development is an additional factor for characterizing the phenotypic variation of MS.

Methods

Patients

We examined 70 patients with clinically definite MS (24) (44 women, 26 men; mean age, 49.9 years; range, 25–68 years). Their median disease duration was 10 years (range, 0–34 years), and their median Expanded Disability Status Scale (EDSS) score (25) was 5.0 (range, 0.0–8.0). Twenty patients had RRMS, 19 had secondary progressive MS (SPMS) (26), and 31 had primary progressive MS (PPMS) (27). The Table shows the main demographic and clinical characteristics of the three groups.

Twenty-one patients (17 with PPMS and four with SPMS) were not receiving immunomodulatory-immunosuppressive drugs during the study. During follow-up, 10 RRMS patients and three SPMS patients had been treated with methylprednisolone 1 g every day for 5 days to treat acute relapse. At MR imaging, all patients had been relapse- and steroid-free for at least 3 months.

Ten healthy individuals with no previous history of neurologic dysfunction and with normal findings on neurologic examination served as control subjects. They included six women and four men (mean age, 42.6 years; range, 31–58 years).

MR Image Acquisition

In each subject, brain MR images were obtained at study entry and after 15 months (±2 weeks) by using the same 1.5-T units (Vision; Siemens, Erlangen, Germany) on a regular course of maintenance. During each session, we performed dual-echo turbo spin-echo imaging (TR/TE, 3300/16 and 98; echo train length, 5) and T1-weighted conventional spin-echo imaging (768/15). Twenty-four contiguous axial sections were acquired with 5-mm section thickness, a 256×256 matrix, and 250×250-mm^2 field of view. The sections were positioned to run parallel to a line that joins the most inferoanterior and most inferoposterior parts of the corpus callosum (28). At follow-up, subjects were carefully repositioned according to published guidelines (28).

MR Image Analysis

A single experienced observer (M.A.R.) blinded to the patients' identity performed the postprocessing. Hyperintense lesions on dual-echo images and hypointense lesions on T1-weighted images were identified, and lesion volumes were measured by using a segmentation technique based on local thresholding, as previously described (29). Whole brain cross-sectional normalized brain volume (NBV) and percentage brain volume change (PBVC) were estimated on T1-weighted images in each group by using SIENAx (30) and SIENA (15). NBV measured with SIENAx were obtained after brain volume was normalized by a factor accounting for intersubject brain-volume differences estimated through a transformation to a standard template. We also assessed changes in regional brain atrophy by using SIENA. The accuracy of this software was independent of section thicknesses, which ranged from 1 to 6 mm (15, 30); its error in measuring the PBVC between images acquired with the same pulse sequence is around 0.15 (15, 30).

After the software performed skull-based coregistration of the baseline and follow-up images, it automatically calculated boundary movement between the two. The boundaries for analysis were selected by using a gradient-based edge detector, which separated brain parenchyma from cerebrospinal fluid. Then, each boundary point was coupled with the corresponding anatomic boundary point on the follow-up image, and the distance between them was calculated. The resulting scalar values were then saved as an image file at the position of the boundary points and considered as maps of the spatial distribution of volume changes in subsequent analysis. At this stage, displacement maps were normalized into the standard Montreal Neurologic Institute space by using a completely automatic algorithm (FMRIB Linear Image Registration Tool) and the T1-weighted images to calculate the affine transformation. Then, normalized images with voxels of $2 \times 2 \times 2$ mm^3 were masked with a smoothed standard brain mask and smoothed with a 10 gaussian filter to reduce further anatomic differences.

Statistical Analysis

Changes in normalized and smoothed displacement maps were analyzed by using SPM99 software (Wellcome Department of Imaging Neuroscience, London, UK). Within-group analysis was performed by using a one-sample *t* test. To precisely define the anatomic regions of atrophy in each group, the

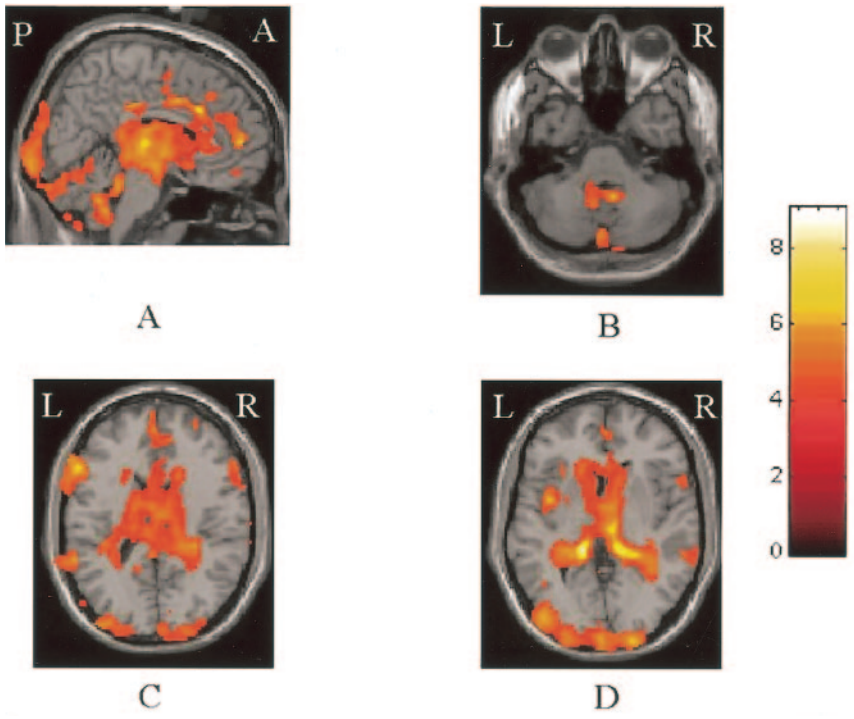

FIG 1. Color-coded areas (SPMt) of brain atrophy development in RRMS overlaid on a template T1-weighted image. All sections show extensive involvement of the ventricular system. Images *A* and *B* show involvement of the pericerebellar spaces and cerebellar tentorium. Images *A*, *C*, and *D* show involvement of the putamen; corpus callosum; insula; cingulate sulcus; and frontal, parietal, temporal, and occipital cortex.

results of these analyses were superimposed onto a high-resolution T1-weighted image available in the SPM package. A 3D anatomic atlas was used to increase confidence in the definition of these anatomic locations (31).

To assess the correlation between changes in regional brain volume and clinical- and MR imaging–derived metrics, these quantities were entered into the SPM design matrix by using basic models and linear regression analysis (32). We reported differences below a height threshold of $P < .001$, which was corrected for multiple comparisons (cluster extent threshold, $P < .05$).

Results

The Table shows lesion volumes and NBVs in the three groups of patients and in the control subjects.

Control Subjects

During follow up, no significant changes in regional brain atrophy were observed in healthy control subjects.

Relapsing-Remitting MS

During follow-up, patients with RRMS developed significant atrophy ($P < .001$) around the ventricular system, including the aqueduct and the lateral, third, and fourth ventricles (Fig 1). Also involved were the putamen; corpus callosum; cingulate sulcus, hippocampus, parieto-occipital fissure, lateral fissure; and regions of bilateral frontal (superior frontal sulcus and inferior frontal gyrus), parietal (precuneus, superior parietal gyrus, and supramarginal gyrus), and occipital (lingual gyrus, middle occipital gyrus, cuneus, and calcarine sulcus) cortex. These patients also had significant atrophy ($P < .001$)of the pericerebellar spaces and along the tentorium of the cerebellum, the right middle temporal gyrus, and the left insula (Fig 1).

Enlargement of the ventricular system was significantly correlated with changes in T2 ($r = -0.72$ to -0.81) and T1 ($r = -0.69$ to -0.76) lesion volumes during follow-up. Changes in EDSS scores during the study period were significantly correlated with development of atrophy in the lateral ventricles ($r = -0.69$ to -0.73), left superior parietal gyrus ($r = -0.82$), left calcarine sulcus ($r = -0.79$), left lingual gyrus ($r = -0.71$), left pericerebellar spaces ($r = -0.80$), and right lateral fissure ($r = -0.71$).

Secondary-Progressive MS

During follow-up, patients developed significant atrophy ($P < .001$) of the left cingulate sulcus, bilateral pulvinar; head and tail of the left caudate nucleus; tail of the right caudate nucleus; bilateral anterior orbital gyri; left middle temporal gyrus; left insula; left mammillary body; left thalamus; right inferior portion of the lateral fissure; right fourth ventricle; and regions of the frontal (superior, middle, and inferior frontal gyri), parietal (supramarginal and angular gyri), and occipital (middle occipital and intraoccipital gyri) cortex (Fig. 2).

Changes in T2 lesion volumes were significantly correlated with the development of atrophy in the left cingulate sulcus ($r = -0.74$), left inferior frontal gyrus ($r = -0.71$), left orbital gyrus ($r = -0.75$), left insula ($r = -0.71$), and right inferior portion of the lateral fissure ($r = -0.76$). Changes in EDSS scores were significantly correlated with the development of atrophy of the bilateral intraoccipital gyri ($r = -0.86$), right supramarginal gyrus ($r = -0.83$), right superior frontal gyrus ($r = -0.70$), left cingulate sulcus ($r =$

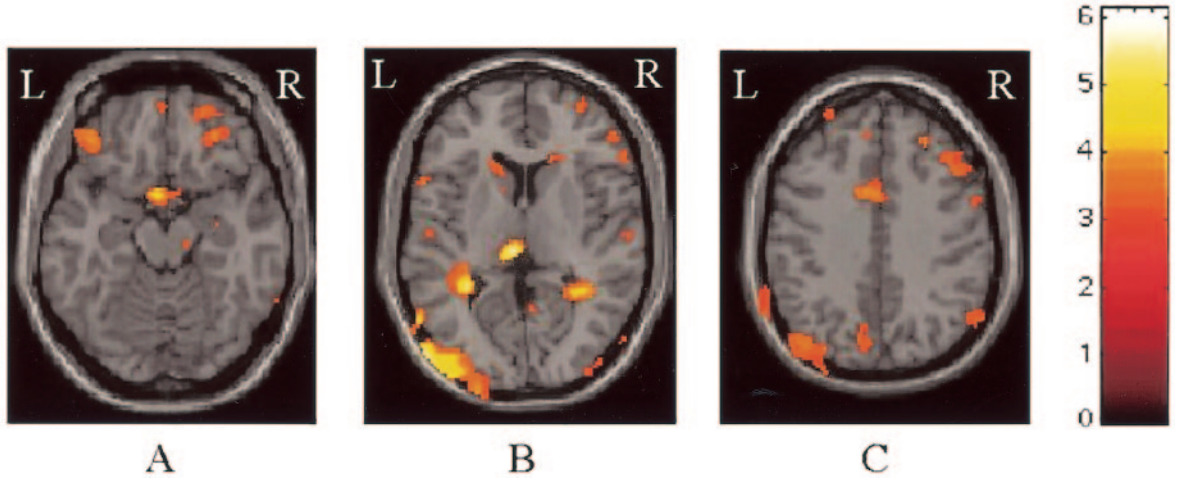

FIG 2. Color-coded areas (SPMt) of brain atrophy development in SPMS overlaid on a template T1-weighted image. Image *A* shows the involvement of the bilateral anterior orbital gyrus and left mammillary body. *B* shows the involvement of the caudate nuclei; left middle temporal gyrus; left thalamus; and frontal, parietal, temporal and occipital region. *C* shows the involvement of the cingulate sulcus and regions of frontal and parietal cortex.

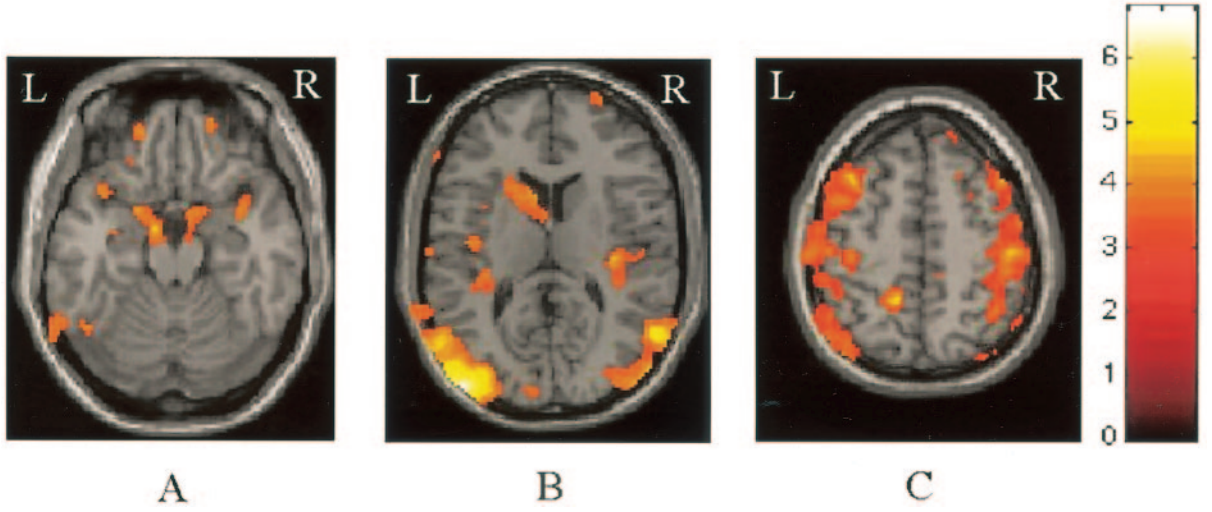

FIG 3. Color-coded areas (SPMt) of brain atrophy development in PPMS overlaid on a template T1-weighted image. *A* shows the involvement of the left middle occipital gyrus, bilateral parahippocampal gyri, and bilateral prepontine and quadrigeminal cisterns. *B* shows the involvement of the head of the left caudate nucleus, insula, and bilateral middle temporal gyrus. *C* shows the involvement of the bilateral central sulci (precentral and postcentral gyri) and regions of frontal and parietal cortex.

−0.70), and tail of the left caudate nucleus ($r = -0.73$).

Primary Progressive MS

During follow-up, patients with PPMS developed significant atrophy ($P < .001$) of the bilateral central sulci (precentral and postcentral gyri); head of the left caudate nucleus; bilateral insula; bilateral middle temporal gyri; bilateral middle occipital gyri; bilateral parahippocampal gyri; prepontine and quadrigeminal cisterns; right lateral ventricle; right lateral fissure; and regions of frontal (superior, middle, and inferior frontal gyri) and parietal (precuneus and angular gyrus) cortex (Fig 3).

Changes in T1 lesion volume during follow-up were significantly correlated with the development of atrophy of the bilateral central sulci ($r = -0.58$ to -0.65), left angular gyrus ($r = -0.69$), and head of the left caudate nucleus ($r = -0.61$). Changes in EDSS scores were significantly correlated with the development of atrophy of the right middle frontal gyrus ($r = -0.59$), right lateral fissure ($r = -0.57$), left angular gyrus ($r = -0.60$), and prepontine cistern ($r = -0.57$).

Discussion

Several studies have demonstrated that, on average, brain volume decreases by about 0.6–1% yearly in patients with MS (1, 12, 19, 33, 34). We attempted to define the evolution of regional brain atrophy in the main clinical courses of MS, with the background hypothesis that damage to different brain structures over time might be associated with phenotypic variations in MS. To test this hypothesis, we used an automated method (SIENA) to calculate longitudinal

changes between two MR imaging time points and then applied SPM to perform a group analysis. SIENA is a fully automated method with a high level of robustness and accuracy (15, 30), and it is not influenced by routinely used section thicknesses.

All disease groups had tissue loss around the lateral fissure, insula, middle temporal gyrus, frontal lobes (particularly the superior frontal sulcus and the inferior frontal gyrus), and several other regions in the parietal and occipital lobes. Sailer et al (21) have shown involvement of regions of frontal and temporal cortex in patients with MS. These structures are affected early in the course of the disease. Our results confirm and extend these by showing that atrophy in these regions is typical of the disease, as it was detected in all groups studied and it tends to be more evident in the progressive forms. No regional brain tissue loss was observed in healthy control subjects. The discrepancy between this latter finding and those of previous longitudinal studies in healthy individuals (35, 36) is probably related to the relative youth and narrow age range of subjects examined.

In agreement with previous investigators who studied clinically isolated syndromes suggestive of MS (17) or RRMS (19, 37), we found that the enlargement of the ventricular system is an early and conspicuous phenomenon, since it was detected almost exclusively in RRMS. This does not mean that the other disease phenotypes do not show absolute enlargement of the ventricular system; rather, the development of brain atrophy tends to involve different structures in the progressive forms, probably because ventricular enlargement has already reached a plateau. This finding is in contrast with the results of Kalkers et al (38), who found the largest yearly increase in ventricular fraction among SPMS patients, as compared with RRMS or PPMS patients. This discrepancy might be due to the different demographic characteristics of the SPMS patients in the previous study; they were younger than our patients and they had shorter disease durations and lower EDSS scores. This fits with the demonstration that, independent of disease subtype, ventricular enlargement seems to be greater in younger patients than in older patients with MS (38).

One of the main advantages of this method is that we were able to automatically obtain a global picture of regional changes in the brain. This allowed us to extend the findings of Brex et al (17) by showing that ventricular enlargement is not limited to the lateral ventricles in RRMS; instead, it diffusely involves the entire ventricular system, including the third and fourth ventricles and the pericerebellar spaces. The demonstration of early involvement of the posterior fossa structures in the course of the disease agrees with findings in patients with RRMS (19, 39).

Patients with the progressive disease phenotypes tended to develop atrophy in several cortical and subcortical regions. In SPMS particularly, we observed involvement of the cingulum, deep gray matter nuclei (e.g., pulvinar and caudate), orbital gyri, and mammillary bodies, whereas PPMS resulted in extensive involvement of the regions located around the bilateral central sulci. This last finding might be explained by the presence of cortical lesions in these specific regions in PPMS or by the retrograde degeneration of afferent and efferent tracts passing through the damaged spinal cord in these subjects (40). Tissue loss in these regions, which represent the origin of the corticospinal tract, might be one of the factors responsible for the progressive clinical worsening of pyramidal functions in these patients (27). The demonstration of progressive atrophy of the deep gray matter nuclei in SPMS agrees with pathologic (41) and MR imaging (42, 43) results showing neuronal loss of up to 30–35% in these structures (41). It also confirms the widespread involvement of gray matter, which seems to be more pronounced in the more advanced phases (44). Interestingly, in SPMS, regional brain atrophy also tended to affect regions that are not usually considered to be involved in MS; examples included the mammillary bodies and the inferior portions of the frontal lobes. Involvement of these structures might be another factor contributing to the impairment of memory and other cognitive functions often encountered in these patients (45).

Considering the relationship between brain atrophy and disability, previous studies have provided conflicting results. While some authors found a good correlation between a reduction of brain volume and the progression of disability (11, 33), others failed to demonstrate any relationship (2, 37, 46, 47). These discrepancies might be related to the limitations in the EDSS, which is heavily influenced by locomotor deficits, or to the fact that only global brain atrophy was measured. In our study, measurements of regional brain atrophy were significantly correlated with changes in disability, suggesting that our technique might improve the magnitude of correlation between clinical and MR imaging findings in MS.

The correlation between the development of regional brain atrophy and changes in T2 and T1 lesion volumes in our three groups suggests that new lesion formation—as well as progressive tissue damage in pre-existing lesions—might contribute to the loss of brain tissue. Further work is warranted to investigate the relationship between regional atrophy and the location of T2-visible lesions of MS.

Conclusion

In MS, brain atrophy develops involving different structures in the different phenotypes of the disease. Correlations between measures of regional brain atrophy and disability suggest that our approach is a promising tool to bridge the gap between clinical and MR imaging findings in MS.

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