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Regional Lobar Atrophy Predicts Memory Impairment in Multiple Sclerosis

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BACKGROUND AND PURPOSE: **In recent studies, measures of whole brain atrophy were strongly correlated with neuropsychological testing, explaining more variance than measures of lesion burden in patients with multiple sclerosis. The relationship between regional lobar atrophy and cognitive impairment is yet to be examined. We endeavored to assess the clinical significance of regional lobar atrophy in multiple sclerosis.**

METHODS: **In a cross-sectional study, we evaluated 31 patients with multiple sclerosis with brain MR imaging and neuropsychological testing. Impairment was determined by comparison with demographically matched healthy controls. MR imaging generated measures of lesion burden (fluid-attenuated inversion recovery hyperintense volume), general atrophy (brain parenchymal fraction), central atrophy (lateral ventricle volume), and lobar atrophy (regional brain parenchymal fraction of frontal, temporal, parietal, and occipital lobes in each hemisphere). Neuropsychological testing emphasized measures of processing speed and memory, because these are commonly affected in multiple sclerosis.**

RESULTS: **Patients with multiple sclerosis showed significant atrophy and impairment on all neuropsychological tests. Regional atrophy accounted for the most variance in all regression models predicting memory performance. Left temporal atrophy was the primary predictor of auditory/verbal memory (partial *r*'s = 0.55–0.61), and both left and right temporal atrophy predicted visual/spatial memory performance (partial *r*'s = 0.51–0.67). Models predicting learning consistency retained frontal lobe atrophy measures (partial *r*'s = 0.44–0.68). Central and general atrophy measures were the primary predictors in modeling processing speed (partial *r*'s = 0.42–0.64).**

CONCLUSION: **Regional atrophy accounts for more variance than lesion burden, whole brain atrophy, or lateral ventricle volume in predicting multiple sclerosis–associated memory dysfunction.**

Multiple sclerosis is characterized by inflammation, demyelination, and neurodegeneration in the brain and spinal cord. In addition to motor and sensory dysfunction, impairments are common, causing considerable caregiver distress (1), unemployment and social dysfunction (2, 3), and poor quality of life (4). Slowed processing speed and defective retrieval from recent memory storage are the most frequently observed cognitive deficits in multiple sclerosis (5–8).

MR imaging is a valuable tool for characterizing multiple sclerosis lesions and atrophy (9, 10). Although modest correlations between MR imaging lesion ratings and cognitive dysfunction have been reported (11–16), recent research has found that cognitive dysfunction is more closely associated with brain atrophy than lesion burden (17–21). In one such study (21), third ventricular width accounted for significant variance in multiple sclerosis performance on processing speed and memory tests, after controlling for age and premorbid intelligence (partial $r = -0.71$). When regression models were repeated with the third ventricle removed, a measure of whole brain atrophy (brain parenchymal fraction) accounted for most variance.

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Despite the strong association between brain atrophy and cognitive dysfunction in multiple sclerosis, little is known about the clinical meaning of regional parenchymal atrophy. Recently, Zivadinov et al (22), in a study of 45 patients with relapsing-remitting multiple sclerosis, calculated a normalized measure, the regional brain parenchymal fraction, by a ratio of regional parenchymal volume divided by parenchyma plus cerebrospinal fluid. This normalized regional measure was more strongly correlated with lesion burden than the absolute volume. Another study by the same group (23), asked whether, in a cross-sectional study, absolute or normalized measures of frontal atrophy would correlate best with neuropsychological tests. The results showed that normalized measures yield stronger associations. However, the only study showing correlation between regional lobar atrophy (dorsal frontal) and concordant (executive function) neuropsychological dysfunction was based on semiquantified, visual inspection of MR imaging scans (24).

Therefore, in this article, we aimed to explore the relationship between neuropsychological impairment and regional lobar atrophy after accounting for the influence of generalized lesion and atrophy measurements in patients with multiple sclerosis. We predicted that regional lobar atrophy would account for more variance in neuropsychological tests in a pattern that is concordant with widely accepted brain-behavior relationships.

Methods

Subjects

We studied 31 patients meeting diagnostic criteria for definite multiple sclerosis (25), with a mean age (± SD) of 41.8 ± 9.1 years. The sample included 22 women (71%) and 29 whites (94%). Mean education level was 15.2 ± 2.1 years. Median Expanded Disability Status Scale score was 2.5 (range, 1–7). Mean disease duration was 10.1 ± 8.3 years, and 26 patients (84%) had a relapsing-remitting versus secondary progressive ($n = 5$) course.

Two independent groups of healthy volunteers served as control subjects to determine the extent of impairment in the multiple sclerosis group. Sixteen subjects, who did not differ from the multiple sclerosis group on demographic characteristics by analysis of variance and χ^2 tests (age, 38.3 ± 9.6 years; education, 15.1 ± 1.6 years; 69% women; 88% white), underwent brain MR imaging. Also studied were 34 healthy controls volunteering for neuropsychological evaluation. These subjects also approximated the patients on demographic characteristics (age, 41.3 ± 9.7 years; education, 14.3 ± 2.0 years; 65% women; 100% white), as demonstrated by nonsignificant statistical tests.

Procedures

Brain MR imaging was performed on a 1.5-T scanner (Philips Gyroscan ACS-NT, Best, the Netherlands) using axial T1-weighted (TR/TE, 400/10) and fast fluid-attenuated inversion recovery (TR/TE/TI, 8000/120/2200) images, 5-mm nongapped sections, and coronal 3D gradient echo T1-weighted (3D-T1) (TR/TE, 24/7) 2.5-mm nongapped sections. Image analysis was performed at two analysis centers where all investigators were blinded to patients' clinical characteristics and neuropsychological status.

For analysis of hyperintense lesions on T2-weighted images, we used fluid-attenuated inversion recovery (FLAIR) scans, which have higher sensitivity and lower interobserver variability than fast spin-echo T2-weighted images in the detection of areas of T2 prolongation in multiple sclerosis (26, 27). In brief, a masking and thresholding technique was used to determine the FLAIR lesion volume, as previously described (28). All FLAIR axial sections from the midpoint of the cerebellum to the vertex were analyzed. Extracranial tissue was first removed using a masking function involving an automated contour-tracing tool designed to trace the brain contour, given a user-specified point along the cortical surface. A second part of the masking procedure involved removing nonlesional extra-axial hyperintensities from within the brain surface contour, primarily the result of FLAIR artifacts in the ventricles and subarachnoid space. A threshold was then applied to separate hyperintense lesions from the nonlesional tissue. Through development of this technique, the optimal threshold was determined from a 24 × 24 mm region of interest in the cingulate gyrus as identified on the superiormost axial section containing the central portion of the lateral ventricles. The software then automatically calculated the total brain lesion burden by multiplying lesion area by section thickness.

Brain parenchymal fraction was measured on the basis of a semiautomated computer-assisted technique, using masking and thresholding, as previously described (28). This semiautomated method has been validated against a fully automated method of measuring brain parenchymal fraction (29). Brain parenchymal fraction was defined as the ratio of brain parenchymal volume (tissue compartment) to the total brain volume within the surface contour (total intracranial volume): [brain parenchymal fraction = volume of brain parenchyma/volume within brain surface contour (parenchyma + cerebrospinal fluid)]. All sections from the inferior cerebellum (where the vermis is first visible) to the upper section above the full skull were analyzed. Extracranial tissue was removed from each section using a semiautomated edge-finding tool with manual adjustment as necessary to ensure accuracy. The result was a single region of interest that included only the brain and cerebrospinal fluid surrounded by a smoothly contoured brain surface. The choroid plexus was manually added to the cerebrospinal fluid compartment by setting the masking value to the cerebrospinal fluid pixel value. Cerebrospinal fluid within the brain volume was then separated from the parenchyma by intensity thresholding. The mean pixel value of a 6 × 6 mm square region of interest of normal-appearing white matter was measured from the section where the full lateral ventricles were most visible. A constant threshold of 60% of the average value of normal-appearing white matter was the threshold whereby all values higher than this calculated pixel value were designated as parenchyma and values lower than this as cerebrospinal fluid. The thresholding procedure separated the image into datasets consisting of parenchymal pixels and cerebrospinal fluid pixels. The software program determined compartmental volumes by multiplying the total area of pixels by the section thickness.

Regional parenchymal volume and lateral ventricle volume were calculated using a Sun Ultra 10 Promo workstation (Sun Microsystems, Mountain View, CA), from coronal 3D T1-weighted images, as described elsewhere (22, 23). A digital 3D version of the Harvard Medical School atlas (30) was used as a reference for segmenting the 4 lobes. The lobar boundaries were traced on each anatomic section in accordance with previously published research (31), using an atlas composed of 1-mm sections. The edges were determined by a semiautomated iterative morphologic outlining of the external cerebrospinal fluid spaces. In particular, the cortex superior to the lateral fissure and anterior to the central sulcus was defined as the frontal lobe boundary. Boundaries were outlined on each anatomic section from the precentral, inferior, middle, and superior frontal gyri to the section anterior to the optic chiasm.

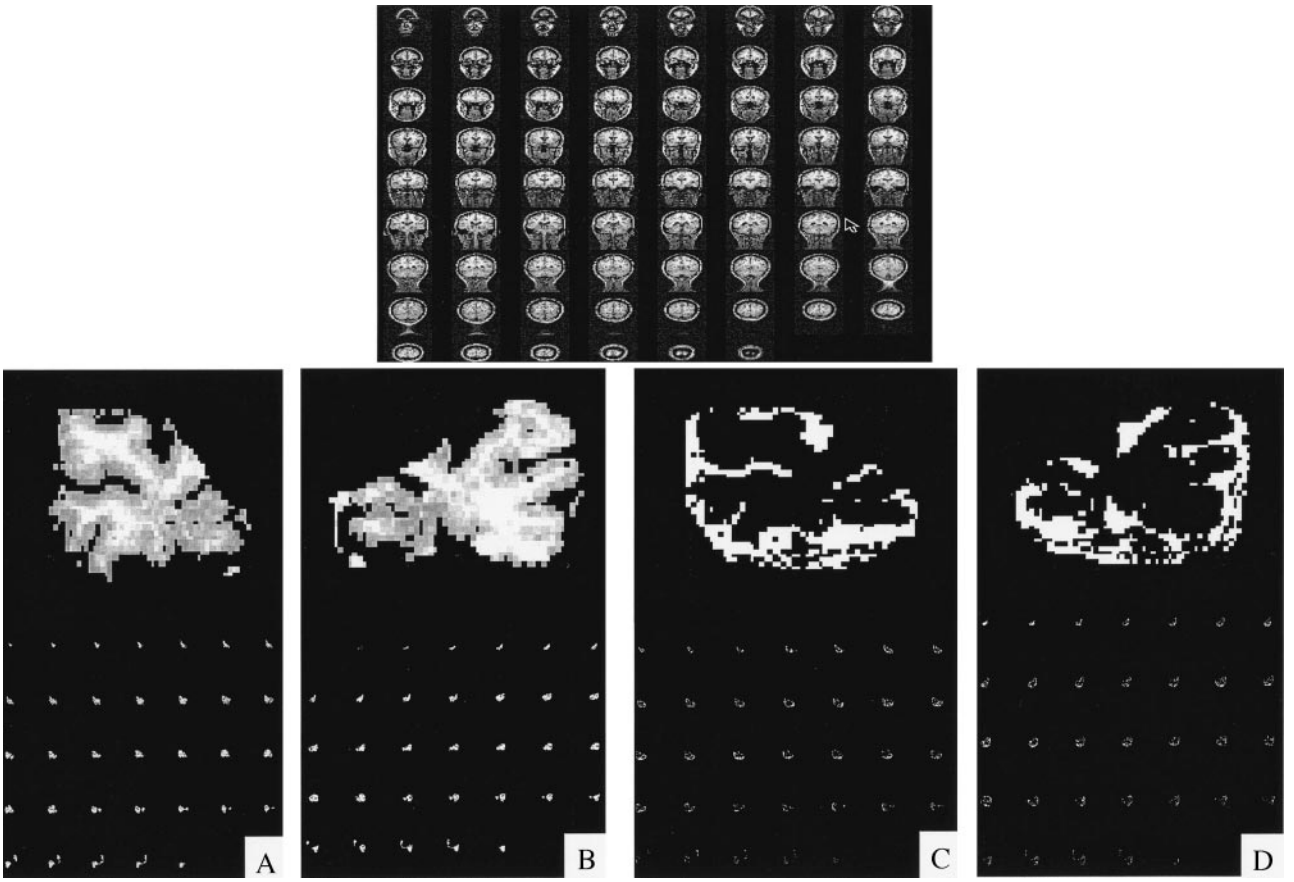

FIG 1. Regional brain atrophy measurement of the temporal lobes in a patient with secondary progressive multiple sclerosis. The top figure shows coronal 3D spoiled gradient-recalled acquisition in the steady state T1-weighted source image used for the segmentation of the temporal lobes. Panels *A* and *C* show the brain parenchyma–only and cerebrospinal fluid–only images of the right temporal lobe. Panels *B* and *D* show the same type of segmentation outputs in the left temporal lobe.

The cortex inferior to the lateral fissure was defined as residing in the temporal lobe. These boundaries were outlined from the superior temporal, anterior, and posterior gyri, to the middle temporal gyrus, the inferior temporal gyrus, and the fusiform and cingulate gyri. Because there is no definite landmark to delineate the temporal from the occipital lobe, a line was drawn from the parietooccipital fissure to the preoccipital notch (31). Sections above the sylvian fissure were considered to reside in the parietal lobe. The cortex superior to the lateral fissure and caudal to the central sulcus, but rostral to the occipital cortex, was defined as residing in the parietal lobe. The boundaries were outlined from the postcentral gyrus, the supramarginal gyrus, and the superior parietal lobule. The average number of sections was 46 ± 2.1 for the frontal, 35 ± 2.1 for the temporal, 30 ± 1.1 for the parietal, and 26 ± 0.8 for the occipital lobe. Segmentation of the cerebrospinal fluid spaces and brain parenchyma was performed via an automated algorithm based on thresholding (18, 19, 22, 23). This segmentation automatically created brain parenchyma (Fig 1*A* and *B*) and cerebrospinal fluid–only images (Fig 1*C* and *D*) and calculated the volumes of brain parenchyma and cerebrospinal fluid. A normalized measure, the regional brain parenchyma fraction, was calculated as the ratio of regional brain parenchyma volume to the regional volume of the parenchyma and the cerebrospinal fluid in each lobe (total intraregional volume). The lateral ventricle volume was determined from coronal 3D T1-weighted images using the same semiautomated contouring method, and the volume was automatically calculated from the outlined regions by multiplying the outlined area by the section thickness.

The reliability of these MR imaging measures has been reported previously. The intra- and interrater coefficients of variation for FLAIR lesion volume are 1.2% and 3.1% (29), and, for brain parenchymal fraction, are 0.31% and 0.34% (28). Test-retest (scan-rescan) within-subjects coefficient of variation for brain parenchymal fraction is 0.41% (28). The mean coefficient of variation for lateral ventricle volume intrarater reproducibility is 0.53% (range, 0.27–0.88). The mean coefficient of variation for regional brain parenchyma of the 4 lobes ranges from 3.2% to 3.5% for scan-rescan variability, 1.3% to 1.7% for intrarater variability and 2.2% to 2.9% for interrater variability, and the mean intraclass correlation coefficient for the four lobes ranges from 0.88 to 0.92 (23).

Neuropsychological testing conformed to consensus panel recommendations (32) regarding the assessment of processing speed and memory. Rao adaptations (33, 34) of the *Paced Auditory Serial Addition Test* (35) and the *Symbol Digit Modalities Test* (36) were used to evaluate processing speed. The *Paced Auditory Serial Addition Test* involved rapid additions of successive single digits presented aurally at either a 2- or 3-second interstimulus interval. On the *Symbol Digit Modalities Test*, patients were asked to voice a number matching an associated symbol presented in a key at the top of an 8 × 11.5 inch sheet. For each test, the dependent measures were the total number of correct responses. Auditory/verbal learning and memory were assessed with the second edition of the *California Verbal Learning Test* (37). The *California Verbal Learning Test-II* required learning a 16-item word list, presented aurally, five times. Patients were asked to recall as many words as possible after each presentation. Total Recall was the sum of all words recalled during the five learning trials. The Delayed Recall trial, 25 minutes later, required recalling the list without cues or repeated presentation. The *Brief Visuospatial Memory*

Test-Revised (38) measured visual/spatial learning in a similar format. Patients viewed a matrix of six abstract designs, presented for 10 seconds. After the display was removed from view, participants rendered the designs as accurately as possible and in correct locations, using paper and pencil. Total Recall, the number of points earned during the three immediate learning trials, was followed by the Delayed Recall trial 25 minutes later. Research has shown that these traditional tests are reliable (37–39) and sensitive to the effects of multiple sclerosis (21, 40–41).

We then assessed the consistency of recall during the learning trials from each memory test, wherein the denominator was equal to the sum of points earned on all but the last recall trial and the numerator was the sum of identical points earned on two consecutive trials. The *California Verbal Learning Test-II* consistency was calculated automatically using a computer program. The number of words recalled on any trial and subsequently recalled on the following trial (i.e., trial 1 to 2, trial 2 to 3, trial 3 to 4, trial 4 to 5) was summed are then divided by the total number of words recalled on the first four learning trials. The *Brief Visuospatial Memory Test-Revised* learning consistency was calculated manually, using an analogous method—that is, the same points earned on one trial and the next (ie, trial 1 to 2, trial 2 to 3) were summed and divided by the total points earned on trials 1 and 2. These calculations yielded proportions, ranging from 0 to 1, with higher values indicating better consistency of learning. Finally, depression was quantified by using the *Beck Depression Inventory* (43).

Analysis

For demographics, group comparisons were performed by analysis of variance and χ^2 tests. Pearson *r* was calculated for correlation analysis. Effect sizes were calculated using the statistic *d*, in the traditional manner (44). Because age was significantly correlated with lateral ventricle volume ($r = 0.41$, $P = .02$) and both left ($r = -0.41$, $P = .02$) and right ($r = -0.37$, $P = .04$) frontal regional brain parenchyma, all subsequent analyses controlled for the effects of age. Thus, we compared MR imaging measures and neuropsychological testing from patients and controls with analysis of covariance, controlling for age. Stepwise linear regression models predicting neuropsychological tests from lesion burden and whole brain, central, and regional atrophy measures controlled for the effects of age and depression. This aspect of the research design was based on the well-established correlation between depression and cognitive function in multiple sclerosis (45, 46). Two models (*P* to enter = .05 and *P* to exit = .10) were calculated for each outcome measure, one controlling for age and the other controlling for both age and depression (ie, the *Beck Depression Inventory*). These covariates were entered in block 1 and retained, followed by the forward stepwise procedure for the MR imaging predictors.

Results

There were no significant differences between patients and controls on any demographic measure. Analyses of covariance were significant for all group MR imaging comparisons, indicating brain atrophy in patients with multiple sclerosis versus controls. Effect sizes were calculated in accordance with the Cohen (44) formula [$\text{mean}_x - \text{mean}_y/\text{SD}_{xy}$]. For general and central atrophy measures, effect sizes ranged from d = 0.7 for lateral ventricle volume (mean for multiple sclerosis = 35.56 ± 20.19; normal = 21.47 ± 16.63; $P = .014$), to $d = 1.1$ for brain parenchymal fraction (multiple sclerosis = 0.834 ± 0.039; normal = 0.884 ± 0.034; $P < .001$). Similarly, regional lobar atrophy was present in multiple sclerosis with effect sizes ranging from $d = 0.9$ for right temporal regional brain parenchyma (multiple sclerosis: absolute = 76.174 ± 10.390, normalized = 0.698 ± 0.074; normal: absolute = 80.099 ± 8.136, normalized = 0.770 ± 0.065; $P = .031$) to $d = 1.2$ for left temporal regional brain parenchyma (multiple sclerosis: absolute = 76.055 ± 12.612, normalized = 0.722 ± 0.083; normal: absolute = 82.921 ± 10.151, normalized = 0.799 ± 0.046; $P = .003$). Patients with multiple sclerosis were also impaired on all neuropsychological tests. Effect sizes ranged from $d = 0.6$ ($P = .009$) for *Brief Visuospatial Memory Test-Revised* consistency to $d = 1.3$ ($P < .001$) for *Brief Visuospatial Memory Test: Revised* Total Recall.

Within the patient sample, volumetric indexes were significantly intercorrelated. The correlation between brain parenchymal fraction and lateral ventricle volume was −0.74 ($P < .001$). Correlations between brain parenchymal fraction and regional brain parenchyma fractions ranged from 0.47 ($P = .008$) for right occipital to 0.73 ($P < .001$) for left frontal regional brain parenchyma. Correlations between lateral ventricle volume and regional brain parenchyma fractions ranged from −0.31 ($P = .090$) for right parietal to −0.69 ($P < .001$) for left temporal regional brain parenchyma. Paired contralateral regional brain parenchyma fractions (right/left) were strongly intercorrelated as follows: frontal $r = 0.95$, temporal $r = 0.97$, parietal $r = 0.69$, occipital $r = 0.88$, all $P < .001$.

The results of the regression models are summarized in Table 1. Beginning with processing speed, both the *Paced Auditory Serial Addition Test* ($R^2 = 0.22$, $P=.020$) and the *Symbol Digit Modalities Test* ($R^2 = 0.61$, $P < .001$) were significantly predicted by MR imaging indexes, and in each case, at least one measure of central or general atrophy was retained. Both models predicting *Paced Auditory Serial Addition Test* retained lateral ventricle volume (partial $r = 0.47$) as the primary MR imaging predictor. Different results were obtained for the *Symbol Digit Modalities Test* depending on whether the *Beck Depression Inventory* was entered as a covariate. In the model controlling only for age, lateral ventricle volume was the primary predictor (partial $r = 0.63$). In the model controlling for age and the *Beck Depression Inventory*, left (partial $r = 0.64$) and right temporal regional brain parenchyma were retained, as well as brain parenchymal fraction.

The models predicting auditory/verbal memory were consistent, with left temporal regional brain parenchyma being the primary independent variable in each case. Partial *r*'s ranged from 0.55 (Total Recall controlling for age) to 0.61 (Delayed Recall controlling for age and the *Beck Depression Inventory*).

There were no statistically significant correlations between the *Brief Visuospatial Memory Test-Revised* Total Recall and MR imaging when only age was entered in block 1; however, when the model controlled for age and *Beck Depression Inventory*, both left and right temporal regional brain parenchyma predicted performance, accounting for 48% of the

Linear regression analysis results

	Block 1 Covariates	Retained MRI Variables	Partial *r* for primary predictor	Change in R^2 from Block 1	Mulitple R^2	*P* Value
Processing Speed and Working Memory						
Paced Auditory Serial Addition Test	Age	LVV	0.42	0.16	0.17	.030
	Age, BDI	LVV	0.47	0.21	0.22	.020
Symbol Digit Modalities Test	Age	LVV; Left Parietal	0.63	0.32	0.50	.001
	Age, BDI	Left Temporal; BPF; Right Temporal	0.64	0.31	0.61	.001
Auditory/Verbal Learning and Recent Memory						
CVLT-II Total Learning	Age	Left Temporal	0.55	0.17	0.30	.006
	Age, BDI	Left Temporal	0.57	0.17	0.32	.014
CVLT-II Delayed Recall	Age	Left Temporal; Left Occipital	0.56	0.15	0.45	.001
	Age, BDI	Left Temporal; Left Occipital	0.61	0.20	0.50	.001
Visual/Spatial Learning and Recent Memory						
BVMT-R Total Learning	Age	—	0.31			
	Age, BDI	Left Temporal; Right Temporal	0.51	0.18	0.48	.001
BVMT-R Delayed Recall	Age	Left Temporal; Right Temporal	0.62	0.22	0.58	<.001
	Age, BDI	Left Temporal; Right Temporal	0.67	0.29	0.59	.001
Consistency of Learning						
CVLT-II Learning Consistency	Age	Left Frontal	0.44	0.17	0.19	.030
	Age, BDI	Left Frontal	0.44	0.16	0.20	.030
BVMT-R Learning Consistency	Age	Left Temporal	0.66	0.29	0.43	<.001
	Age, BDI	Left Temporal; Left Frontal	0.68	0.31	0.55	<.001

Note.—For each regression model, table shows the partial r between the first predictor controlling for variables entered in block 1 and the change in R^2 after block 1. CVLT-II = California Verbal Learning Test second edition, BVMT-R = Brief Visuospatial Memory Test-Revised, BDI = Beck Depression Inventory, LVV = Lateral Ventricle Volume, BPF = Brain Parenchyma Fraction. Lobar region labels reflect regional brain parenchyma fractions.

variance (left temporal partial $r = 0.51$). Nearly identical results were obtained for *Brief Visuospatial Memory Test-Revised* Delayed Recall. When both age and the *Beck Depression Inventory* were entered into this model, temporal lobe regional brain parenchyma accounted for 59% of the variance.

Finally, learning consistency measures were also significantly predicted by MR imaging indexes. For *California Verbal Learning Test-II* consistency, left frontal regional brain parenchyma was the only MR imaging variable retained in models accounting for either age ($R^2 = 0.19$, $P = .030$) or age and the *Beck Depression Inventory* ($R^2 = 0.20$, $P = .030$). For *Brief Visuospatial Memory Test-Revised* consistency, left temporal regional brain parenchyma was the most significant predictor (age-controlled $R^2 = 0.43$, $P < .001$; age and *Beck Depression Inventory*–controlled $R^2 = 0.55$, $P < .001$). In the model accounting for age and the *Beck Depression Inventory*, left frontal regional brain parenchyma was also retained.

FLAIR lesion volume was not retained in any of the regression models predicting cognitive impairment.

Discussion

This study was designed to determine whether regional parenchymal atrophy accounts for significant variance in multiple sclerosis cognitive performance. To our knowledge, this is the first report of temporal lobe atrophy being associated with memory impairment in multiple sclerosis, a disease in which precise focal brain/cognition associations are rarely reported (47, 48). Correlations between frontal lobe pathology and executive function defects are better known (14, 24), although an association between a quantitative measure of frontal atrophy and cognitive impairment was only recently reported (23). In this study, we found that regional atrophy accounts for more variance than whole brain lesion volume, whole brain atrophy, or central atrophy, in predicting multiple sclerosis–associated memory dysfunction.

Measures of whole or central brain atrophy (ie, brain parenchymal fraction and lateral ventricle volume) were only retained in models predicting processing speed and working memory. These functions are mediated by widely dispersed cortical regions interconnected by long white matter tracts (49). Thus, it is of no surprise that a more general measure of degenerative change correlates strongly with such impairment. In contrast, memory may be more cortically mediated and affected by regional (ie, temporal lobe) atrophy. There is support for this idea in other areas of the literature. For example, poor memory is predicted by mild age-related shrinkage of entorhinal

cortex (50, 51), and hippocampal and temporal lobe cortical gray matter volume are associated with impaired memory in patients with Korsakoff's syndrome and Alzheimer disease (52–54),

We were somewhat surprised to find correlations between left temporal atrophy and impairment on a test of visual/spatial memory; however, when human subjects are confronted with spatial learning tasks, some degree of verbal mediation might be expected. In support of this notion, functional MR imaging work has shown that word-encoding tasks give rise to activity in the left frontal and temporal lobes, whereas visual stimuli that can be verbalized produce bilateral frontal and temporal lobe activation (55). Other work (56) suggests that verbal mediation may be crucial for the coordination of different aspects of visual-spatial processing. The *Brief Visuospatial Memory Test-Revised* requires memory for location and identification and, as such, may require such mediation by the left hemisphere. There is also support for this hypothesis from the clinical literature. For example, in patients with epilepsy, left hippocampal and left perirhinal cortex volumes predict verbal memory performance, whereas bilateral entorhinal cortex volumes predict visual memory performance (57).

Consistency of learning would be expected to correlate with frontal lobe function, and indeed, we find evidence of this in models predicting learning consistency on the *California Verbal Learning Test-II* and the *Brief Visuospatial Memory Test-Revised*, with left frontal regional brain parenchyma being the most consistent predictor. Previous studies have associated frontal lobe function with organized learning processes such as semantic clustering for verbal material (58, 59), and such organizational schemes are associated with better recall consistency (60). In the present study, we found an expected association between left frontal atrophy and poorer *California Verbal Learning Test-II* recall consistency. That the *Brief Visuospatial Memory Test-Revised* recall consistency was associated with left frontal and temporal atrophy suggests that such encoding consistency is at least partly dependent on verbal mediation.

When we controlled for age and depression, left temporal lobe atrophy was the primary predictor of *Symbol Digit Modalities Test* performance. Such was not the case for the *Paced Auditory Serial Addition Test*, in which lateral ventricle volume was the primary predictor. The contribution of left temporal lobe functioning to the *Symbol Digit Modalities Test* performance may be explained by the fact that short-term memory for number/symbol pairings is involved in this task. There is no such paired-associate learning required for the *Paced Auditory Serial Addition Test.* That *Paced Auditory Serial Addition Test* performance depends on many, widely-dispersed cortical regions is now firmly established (49).

As in other cognition/MR imaging correlation studies, the effects reported here are of medium strength and leave unexplained much variance in neuropsychological test performance. At present, structural brain MR imaging can account for roughly half of the variance in multiple sclerosis–associated cognitive dysfunction (20, 21). In the near future, we will see continuing efforts to build optimal statistical models that better predict neuropsychological phenomena using these and newly developed measures of magnetic transfer imaging (61, 62), iron deposition (63), and diffusion-weighted imaging (64), among others. In addition, functional brain imaging shows great potential to account for additional variance in cognitive function after brain injury. Cortical reorganization can be seen during motor (65) and various cognitive (66–68) challenges, and individual differences in such potential for neural plasticity may explain why patients with multiple sclerosis with similar degrees of lesion burden and atrophy appear to differ in neuropsychological competence.

There are limitations to this work that bear further consideration. First, patients were compared with 2 different normal control samples, separately studied with MR imaging and neuropsychological testing. Thus, we were unable to determine if these regional volume/neuropsychological correlations were specific to multiple sclerosis. Second, we did not measure regional lesion volume, limiting conclusions that can be drawn regarding the relative predictive power between lesion volume and atrophy, as done elsewhere. In this regard, it is important to acknowledge previous work (16) showing correlations between frontal and parietal lesion volume and performance on tests of attention and working memory. Third, this is a cross-sectional study based on a modest sample of 31 patients, and although the calculation of parenchymal fractions was automated, the lobar tracings were performed manually. Therefore, the stability of regional brain parenchyma findings may not be maintained in longitudinal work. As more automated and specific regional parcellation techniques are developed, we hope to predict neuropsychological impairment with greater accuracy. Such a study is underway at our center.

In conclusion, we compared measures of regional, whole brain, and central atrophy to determine which explained more variance in cognitive performance in patients with multiple sclerosis. Temporal lobe atrophy explained most of the variance in memory performance, whereas whole brain or central atrophy best accounted for tasks emphasizing processing speed. Frontal atrophy contributed to the prediction of learning consistency. We believe that regional atrophy is more promising than general atrophy in explaining cognitive dysfunction in multiple sclerosis.

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