Regional Magnetic Resonance Imaging Lesion Burden and Cognitive Function in Multiple Sclerosis

A Longitudinal Study

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Objective: To investigate the relationship between magnetic resonance imaging regional lesion burden and cognitive performance in multiple sclerosis (MS) over a 4-year follow-up period.

Design: Twenty-eight patients with MS underwent magnetic resonance imaging and took the Brief, Repeatable Battery of Neuropsychological Tests in Multiple Sclerosis at baseline, 1-year, and 4-year follow-up. An automated 3-dimensional lesion detection method was used to identify MS lesions within anatomical regions on proton density T2-weighted images. The relationship between magnetic resonance imaging regional lesion volumes and the Brief, Repeatable Battery of Neuropsychological Tests in Multiple Sclerosis results was examined using regression analyses.

Results: At all time points, frontal lesion volume represented the greatest proportion of total lesion volume, and the percentage of white matter classified as lesion was also highest in frontal and parietal regions. On neuropsychological testing, when compared with age- and educational level–matched control subjects, patients with MS showed significant impairment on tests of sustained attention, processing speed, and verbal memory ($P < .001$). Performance on these measures was negatively correlated with MS lesion volume in frontal and parietal regions at baseline, 1-year, and 4-year follow-up ($R = −0.55$ to $−0.73$, $P < .001$).

Conclusions: Multiple sclerosis lesions show a propensity for frontal and parietal white matter. Lesion burden in these areas was strongly associated with performance on tasks requiring sustained complex attention and working verbal memory. This relationship was consistent over a 4-year period, suggesting that disruption of frontoparietal subcortical networks may underlie the pattern of neuropsychological impairment seen in many patients with MS.

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Cognitive dysfunction is common in patients with multiple sclerosis (MS), with estimates ranging from 40% to 65% of patients with MS showing impairment on tests of attention, speed of information processing, and recent memory.1-4 Several recent studies5-13 have investigated the relationship between MS lesion burden as assessed by magnetic resonance imaging (MRI) and degree of cognitive impairment, with general agreement that poor cognitive performance is associated with increased total lesion volume.

The contribution of regional vs total lesion burden to cognitive dysfunction remains controversial in the literature, and the neuroanatomical basis of the cognitive dysfunction in MS remains to be fully elucidated. White matter lesions, which likely affect connections between cortical regions thought to be crucial for specific cognitive processes, may be particularly difficult to characterize. Several studies8,11,12,14 have attempted to examine the relationship of regional lesion burden to cognitive function; however, most of these studies only examined frontal lesion volume.

Even less is known about the relationship of regional or total lesion volume with specific cognitive deficits over time. Very few studies10,15,16 have examined longitudinal cognitive performance with serial MRI measurements of total lesion volume and, to our knowledge, there are no longitudinal studies of regional lesion burden and cognitive function. Because depression is frequent in patients with MS17 and because depression can have significant effects on cognitive function, we were also interested in examining the relationship of depressive symptoms to regional lesion burden and cognitive function.

Our group has been investigating the relationship between serial MS lesion vol-
SUBJECTS AND METHODS

PATIENTS AND CONTROL SUBJECTS

Forty-four patients with MS were initially enrolled in a National Institutes of Health–sponsored 1-year study. Four years later, 28 patients consented to participate in a follow-up study; 9 patients had either moved out of the area or were too physically incapacitated to participate in follow-up testing; 7 patients declined to participate in the follow-up study. Eligible patients for the initial study were between 20 and 55 years of age, fulfilled Poser et al criteria for definite MS, had an Expanded Disability Status Scale score of 6.5 or less, and an MRI of the brain demonstrating lesions consistent with the diagnosis of MS. Patients with a history of other central nervous system disease or significant medical illnesses were excluded. Patients with MS were also excluded if they had received immunosuppressive, cytotoxic, or experimental immunomodulatory therapy at any time prior to their initial enrollment, or corticosteroid or corticotropin or corticosteroid therapy within 2 months prior to enrollment. Treatment with disease-modifying therapy, including corticosteroids and later interferon beta, was allowed during the course of the study.

Healthy control subjects were recruited from the community for the follow-up study. Controls were selected to match patients with MS within 3 years of age and within 2 years of overall educational level. The 2 groups were also similar in gender composition and handedness. Patient and control demographics are summarized in Table 1. The initial and follow-up studies were approved by the Institutional Review Board of Brigham and Women’s Hospital, Boston, Mass. Informed consent was obtained from all patients and controls.

Table 1. Demographic and Clinical Data

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group Mean (SD)</th>
<th>Controls (n = 28)</th>
<th>Patients With MS (n = 28)</th>
<th>P†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>38.3 (8.4)</td>
<td>39.3 (7.3)</td>
<td>.66</td>
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</tr>
<tr>
<td>Gender, F/M</td>
<td>17/11</td>
<td>19/9</td>
<td>.78</td>
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<td>Handedness, R/L</td>
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<td>.73</td>
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<tr>
<td>Educational level, y</td>
<td>16.5 (2.8)</td>
<td>15.4 (2.4)</td>
<td>.13</td>
<td></td>
</tr>
</tbody>
</table>

†P value was determined using either the Wilcoxon rank sum test or Fisher exact test. P < .05 was considered statistically significant.

MAGNETIC RESONANCE IMAGING

Twenty-eight patients with MS underwent MRI at baseline, 1-year, and 4-year follow-up. Magnetic resonance imaging was performed on a 1.5-T unit (Signa; General Electric Medical Systems, Milwaukee, Wis.). Proton density and T2-weighted images were obtained using 2 interleaved dual-echo (echo times = 30 and 80 ms) long repetition (3000-ms) sequences yielding contiguous 3-mm-thick slices of the whole brain.

Anatomical regions were defined using surface landmarks on a 3-dimensional display of each patient’s baseline MRI study. An operator (R.A.S.) blinded to patient identity used standard cortical landmarks to divide each hemisphere into 4 large sectors. A plane was drawn from the superior extent of the rolandic sulcus to the anterior extent of the brainstem and perpendicular to the midsagittal plane. A second plane was drawn along the angle of the sylvian fissure also perpendicular to the midsagittal plane. These intersecting planes resulted in a crude division of each hemisphere into 4 regions roughly corresponding to the frontal, parietal, and temporal lobes, and a posterior region that included the occipital lobe, cerebellum, and brainstem (Figure). This procedure was repeated for each hemisphere, yielding a total of 8 anatomical regions of interest per MRI study.

Volumes of abnormal signal intensity (MS lesions) within each of these regions were identified using an automated image analysis algorithm. A template-driven segmentation technique, described in detail elsewhere, was used to identify major tissue types (gray matter, white matter, and cerebrospinal fluid). Each white matter voxel was then classified as normal white matter or white matter with abnormal signal intensity. The white matter classified as having abnormal signal intensity is believed to be consistent with MS lesions, and is, henceforth, referred to as lesion volume.

RESULTS

For the 28 patients with MS who participated in the follow-up study, mean time elapsed from baseline to follow-up assessment was 4.1 ± 0.7 years. Neuropsychological testing of patients with MS was performed within a mean of 8.3 days (range, 0–32 days) of baseline MRI, 6.9 days (range, 0–22 days) of 1-year follow-up MRI, and 0.2 days (range, 0–3 days) of 4-year follow-up MRI.

At study enrollment, mean disease duration was 8.3 ± 5.7 years. Mean Expanded Disability Status Scale score at baseline was 4.0 ± 1.8, 4.2 ± 1.3 at 1-year, and 4.8 ± 1.7 at 4-year follow-up (P = .09, Wilcoxon signed rank test). Fifteen of the patients with MS were classified as having relapsing-remitting MS and 13 as having chronic progressive MS at the time of enrollment. Fifteen of the patients with MS received immunomodulatory therapy at some point during the 4-year follow-up period. Eight patients received corticosteroid treatment, 3 of these in combination with cyclophosphamide. Seven patients received interferon beta therapy.
A mask defining the anatomical regions on each patient's baseline MRI was aligned with the segmented images for each time point (baseline, 1 year, and 4 years) using an automated image registration method. This procedure yielded volumes of lesion, healthy white matter, gray matter, and cerebrospinal fluid for each of the 8 anatomical regions.

NEUROPSYCHOLOGICAL TESTING

The Brief, Repeatable Battery of Neuropsychological Tests in Multiple Sclerosis (BRB) was administered to the patients with MS at baseline, 1-year, and 4-year follow-up. Alternate, equivalent, published forms of the revised BRB were used at each follow-up visit to minimize practice effects. The baseline BRB form was administered to the control subjects to allow comparison with the initial cognitive performance of the patients with MS.

The BRB is composed of 5 subtests: (1) The Bushke Verbal Selective Reminding Test is a measure of verbal learning and delayed recall of a 12-word list. The Long-Term Storage score represents the sum of words recalled on 2 consecutive trials without reminding, and the Consistent Long-Term Retrieval (CLTR) is the sum of words recalled on all subsequent trials without reminding. Total Delay is the number of words recalled after a 10-minute delay. (2) The 10/36 Spatial Recall Test measures visuospatial learning and delayed recall using a checkerboard pattern. Three learning trials and 1 delayed trial are scored for the total number of correct responses. (3) The Symbol Digit Modalities Test assesses sustained attention and information processing speed. The written form of the test was used to score the number of correct pairs. (4) The Paced Auditory Serial Addition Task (PASAT) is a measure of complex attention and concentration. A prerecorded audiocassette plays a series of single-digit numbers presented every 3 seconds. The subject is asked to add each number to the digit immediately preceding it, rather than a cumulative sum. The percentage of correct additions is recorded. (5) Word List Generation is a measure of verbal fluency and sustained attention. Subjects are instructed to generate as many words as possible that begin with a given letter in 60 seconds. The total number of admissible words is scored.

BECK DEPRESSION INVENTORY

The Beck Depression Inventory (BDI) is a self-reported index of subjective feelings. The BDI consists of 21 groups of statements, asking the subject to choose the statement in each group that best describes his or her feelings over the past week. The statements are assigned numerical value, with higher numbers assigned to more severe symptoms of depression. The BDI was added to the end of the neuropsychological test battery for patients with MS at the 4-year follow-up study and was administered to all controls at the end of their baseline battery.

STATISTICAL METHODS

Nonparametric statistics were used for all comparisons as assumptions of normality were not uniformly met. Demographic and neuropsychological measures of patients with MS and controls were compared using the Kruskal-Wallis test. The Fisher exact test was used to compare dichotomous variables (gender and handedness). The Wilcoxon signed rank test was used to compare baseline and follow-up BRB test scores and MRI lesion volumes in patients with MS. All correlations between MRI lesion volumes and neuropsychological test scores were examined using the Spearman rank correlation, yielding a Spearman ρ coefficient. All significance values were subjected to correction for multiple comparisons where appropriate. All values are expressed as mean±SD.

MRI LESION VOLUMES

Mean total lesion volume was 19.4±15.1 mL at baseline, increasing to 21.5±15.3 mL at 4-year follow-up (P=.48 Wilcoxon signed rank test). Frontal lesion volume represented the greatest percentage of total lesion volume (mean, 51.8%±8.3%; P<.01, Wilcoxon signed rank test), and this proportion did not change over the 4 years. The percentage of white matter classified as lesion was significantly higher in frontal and parietal regions (6.1% and 7.1%, respectively) compared with temporal (1.6%) and posterior (3.0%) regions (P<.005, Wilcoxon signed rank test). Regional and total lesion volumes were highly correlated, particularly frontal and parietal regions with total lesion volume (R=0.95-0.97, P<.001 Spearman rank correlation). Relative proportions of white matter classified as lesion and correlations for regional lesion volumes to total lesion volume are given in Table 2.

Patients with relapsing-remitting MS had a baseline total lesion volume of 14.0±5.4 mL compared with 24.1±19.1 mL for patients with chronic progressive MS (P<.08, Wilcoxon signed rank test). The mean change in total lesion volume over 4 years was 0.70±3.2 mL for patients with relapsing-remitting MS and 3.3±4.1 mL for patients with chronic progressive MS (P<.07, Wilcoxon signed rank test). We did not find any significant relationship between handedness and total or regional lesion volumes.

NEUROPSYCHOLOGICAL PERFORMANCE

Patients with MS were impaired on all baseline BRB tests compared with age- and educational level-matched controls. The most significant differences were found on tests of sustained attention (PASAT), processing speed (Symbol Digit Modalities Test), and the sustained working memory component of verbal memory (CLTR) (P<.001, Kruskal-Wallis test). Table 3 summarizes the BRB results for controls and patients with MS. Disease duration and Expanded Disability Status Scale scores were not significantly related to baseline or follow-up cognitive performance.

Overall, at both 1- and 4-year follow-up, patients with MS did not show significant changes on neuropsychological testing. Only 1 BRB subtest showed a modest decline at 4-year follow-up: the Delayed Verbal Memory score on the Selective Reminding Test (P=.02,
Wilcoxon signed rank test). No significant differences were found in the baseline or follow-up cognitive performance between patients with relapsing-remitting MS and patients with chronic progressive MS.

RELATIONSHIP OF MRI LESION BURDEN TO COGNITIVE MEASURES

Cognitive performance was significantly correlated with specific regional and total lesion volumes at baseline, 1-year, and 4-year follow-up MRI. Poor performance on tests of complex attention (PASAT), processing speed (Symbol Digit Modalities Test), and verbal memory (Bushke Verbal Selective Reminding Test) was associated with greater lesion volume in regions, but not with lesion volume in the temporal, occipital, brainstem, or cerebellar regions. Even after stringent correction for multiple comparisons, performance on the PASAT and Bushke Verbal Selective Reminding Test-CLTR remained significantly correlated with frontal, parietal, and total lesion burden ($R = -0.55$ to $-0.74$; $P < .001$, Spearman rank correlation). We also performed this analysis using lesion volume expressed as a fraction of the total white matter in each anatomical region with similar findings. Table 4 gives the correlations between all regional and total lesion volumes and cognitive performance at 4-year follow-up.

The relationship between regional lesion volume and neuropsychological performance was highly stable over the 4-year period. Table 5 gives the correlation between left and right frontal regions and the PASAT at all 3 time points.

As above, patients with MS did not demonstrate a significant change in lesion volume or a significant decline in most cognitive domains over the 4-year period. Overall, we did not find significant correlations between a change in lesion volume and a change in the BRB scores. The only cognitive subtest with a statistical trend toward decline over the 4 years, the Bushke Verbal Selective Reminding Test delayed verbal memory measure, did show a modest correlation with change in both frontal ($R = -0.40$; $P < .03$, Spearman rank) and total lesion volumes ($R = -0.39$; $P < .04$, Spearman rank), but these were not significant after correction for multiple comparisons.

BECK DEPRESSION INVENTORY

The BDI was administered at 4-year follow-up to patients with MS, and at baseline to all controls. Patients with MS reported a significantly higher BDI score than controls ($P < .001$, Wilcoxon signed rank test). However, the BDI scores did not show significant correlation with cognitive performance or with regional and total lesion volumes.

This longitudinal study demonstrated a robust and highly consistent association between MRI lesion burden in fron-
Our findings suggest that the regional distribution of lesions in MS is not random, and lesions show a clear predilection for frontal and parietal regions. Over half the total lesion volume was contained within frontal regions as we defined them, and frontal and parietal regions showed a significantly higher percentage of lesioned white matter than temporal and posterior regions. Lesion volumes in frontal and parietal regions were most strongly associated with the PASAT, a measure which requires sustained attention, working memory, and the ability to inhibit automatic responses. We also found a strong correlation of frontal and parietal lesion burden with the CLTR, a measure of verbal memory that also requires sustained attention and continuous retrieval of newly acquired information. Notably, the PASAT and CLTR were also among the tests showing the greatest impairment in patients with MS compared with age- and educational level-matched controls.

These findings suggest that the pattern of cognitive dysfunction frequently observed in patients with MS is directly related to lesion burden in frontal and parietal white matter. Several previous studies have reported marked dysfunction in patients with MS on tasks, such as the PASAT and CLTR.
as the Wisconsin Card Sort Test, that are thought to be dependent on the integrity of frontal attentional systems.\textsuperscript{2,20} Impairment in sustained attention, working memory, and executive function is frequently seen in patients with both cortical and subcortical frontal lobe damage from a variety of neurological conditions. More recently, functional imaging studies\textsuperscript{27,28} have also documented activation in parietal cortical regions with complex attention and memory tasks. It is also likely that disruption of circuits traversing the parietal white matter may disconnect frontal areas from other cortical regions involved in sustained task performance.

Our findings are supported by several other studies that have examined the relationship of regional MS lesion burden to specific cognitive tests. Swirsky-Sacchetti et al\textsuperscript{8} reported that left frontal lobe lesion burden was associated with poor performance on the Wisconsin Card Sort Test and several memory tests. Arnett et al\textsuperscript{20} found that patients with MS who had a "high" frontal lobe lesion burden performed poorly on the Wisconsin Card Sort Test when compared with patients with a "low" frontal lesion burden. Foong et al\textsuperscript{14} found moderately robust correlations between several neuropsychological measures of executive function and frontal lesion volume, but did not examine lesion volume in other anatomical regions. Similar to our findings, Foong et al\textsuperscript{14} did not find a robust relationship between spatial working memory and frontal lesion burden.

Our data also address the controversy concerning the relative contribution of regional lesion burden vs total lesion burden to cognitive impairment in MS. Swirsky-Sacchetti et al\textsuperscript{8} reported that total lesion volume was actually the strongest predictor of cognitive function, despite strong correlations of regional lesion area with specific cognitive tests. Foong et al\textsuperscript{14} attempted to elucidate the specific contribution of frontal lesion volume by controlling for total lesion volume, which resulted in nonsignificant correlations with all cognitive measures. We also found a strong relationship between cognitive performance and total lesion volume. This finding is not particularly surprising, however, given the extremely high correlation between lesion volumes in frontal and parietal regions and total lesion volume ($R=0.95$ and 0.97, Spearman rank correlation, respectively at both baseline and follow-up). The most robust associations with cognitive performance were seen with frontal and parietal regional lesion burden, while temporal, occipital, cerebellar, and brainstem regions did not show significant correlations with cognitive performance.

The distribution of regional lesion burden remained consistent over the 4-year follow-up. Although there was a modest increase in lesion burden over this time, it was not significantly different from baseline, and concomitantly, we did not observe much change in cognitive function. Many of our patients were treated with a variety of therapeutic agents over the course of the 4 years, and this may have influenced the rate of disease progression.

Although the presence of cognitive impairment in MS is well documented, the course of cognitive decline in MS remains controversial in the literature, and at least 1 other longitudinal study reported stable cognitive status for up to 4 years of follow-up.\textsuperscript{29} There are several explanations as to why we did not detect significant cognitive deterioration over the course of this study. First, several of the patients from the original cohort recruited for this study were unable to participate in the 4-year follow-up study because of physical incapacity, and may have represented the subgroup likely to show significant cognitive decline. Another possibility is the "critical threshold model" first suggested by Rao et al.\textsuperscript{9} It is conceivable that once this lesion burden threshold has been crossed, further cognitive deterioration may be slow. At baseline, our patients demonstrated marked cognitive impairment compared with age- and educational level–matched controls, and thus we may have missed the "window" of decline. A longitudinal study of cognitive function with MRI correlation of patients in earlier stages of the disease would likely yield more change in cognition and in lesion volume over a similar time period. It is also possible, that although we attempted to control for "practice effects" by using alternate versions of the BRB testing materials, repeated exposure or practice effects may have obscured some subtle decline in cognitive functioning. Finally, the course of cognitive decline may be variable among patients, and a much larger sample size may be required to detect a definitive pattern. We did not detect significant differences between patients with relapsing-remitting MS and patients with chronic progressive MS in the degree of cognitive impairment at baseline or over time, but had a small sample of patients in each group. Although we did not detect significant change on most cognitive measures, interestingly, the only subtest with a significant decline at follow-up (delayed verbal memory) did show a modest association with the small increase in frontal and total lesion volume.

Our findings suggest that although mood was clearly affected in many MS patients, the cognitive impairment seen in MS can not be attributed to the "pseudodementia" sometimes seen with depression, and that cognitive performance is independently related to lesion burden. Similar to Foong et al,\textsuperscript{14} we did not find a significant correlation between the degree of depressive symptoms and cognitive function or regional lesion burden. Several of our patients were receiving antidepressants, given either for depression or nonmood-related symptoms, such as chronic pain or incontinence. These medications may have affected the self-report of depressive symptoms; however, our patients did have a significantly higher BDI score than the controls.

One of the strengths of our study is the use of an automated 3-dimensional lesion detection algorithm. This method allows an unbiased, volumetric assessment of lesion burden, and was particularly useful for regional analysis. Using conventional spin-echo imaging, white matter lesions appear as areas of increased signal intensity. However, the segmentation of these scans can be difficult because the MRI intensity range of white matter lesions overlaps that of normal tissue (particularly, of gray matter). Template-driven segmentation allows automated classification of white matter voxels into healthy white matter or MS lesion with less interference from gray matter.\textsuperscript{24} In this study, we chose to use large anatomical divisions, as the exact anatomy of white matter connect-
tivity is poorly understood. We wanted to devise a method that was unbiased and easily reproducible across subjects, without requiring manual editing of subcortical structures. Thus, we chose to divide the hemispheres into quadrants and group lesions in the occipital lobe, cerebellum, and brainstem into a posterior region, which did not require any further manual editing. Future studies with more detailed methods of anatomical lesion localization may yield better understanding of the regional distribution of lesion burden, and the relationship to specific patterns of cognitive dysfunction in MS.

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