

Regional MRI lesion burden and cognitive function in MS: A longitudinal study

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Abstract

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

Design: Twenty-eight patients with MS underwent MRI and the Brief Repeatable Battery of Neuropsychological Tests in MS [1] (BRB) at baseline, 1 year and 4 year follow-up. An automated 3-D lesion detection method was used to identify MS lesions within anatomic regions on proton density/T2-weighted images. The relationship between MRI regional lesion volumes and BRB tests 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 to age and education matched control subjects, MS patients showed significant impairments on tests of sustained attention, processing speed, and verbal memory ($p < 0.001$). 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 , $p < 0.0001$).

Conclusions: MS 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 quite consistent over a four year period, suggesting that disruption of frontoparietal subcortical networks may underlie the pattern of neuropsychological impairment seen in many MS patients.

Introduction

Cognitive dysfunction is common in patients with multiple sclerosis (MS), with estimates ranging from 40% to 65% of MS patients showing impairment on tests of attention, speed of information processing, and recent memory [2] [3] [4]. Several recent studies 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. [5-13] .

The contribution of regional versus total lesion burden to cognitive dysfunction remains controversial in the literature, and the neuroanatomic 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 studies have attempted to examine the relationship of regional lesion burden to cognitive function [14] [8] [11] [12], however, the majority 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 studies have examined longitudinal cognitive performance with serial MRI measurements of total lesion volume [15] [10] [16], and to our knowledge, there are no longitudinal studies of regional lesion burden and cognitive function. As depression is frequent in MS [17], and depression can have significant effects on cognitive function, we were also interested in examining the relationship of depressive symptomatology to regional lesion burden and cognitive function.

Our group has been investigating the relationship between serial MRI lesion volumes and multiple clinical parameters in MS [18]. We have previously published a report of serial neuropsychological assessment and MRI measures over a one year period [10], demonstrating robust correlations between baseline cognitive testing and total lesion volume. In the initial study, only the relationship of total lesion volume and cognitive tests was assessed, and no significant changes in cognitive function were observed at one year follow-up. We undertook this 4 year follow-up study to further investigate the relationship between MRI lesion volumes, examined regionally, and longitudinal cognitive performance.

Subjects and Methods

Patients and Control Subjects

Forty-four MS patients were initially enrolled in a National Institutes of Health sponsored one 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 criteria for definite MS [19], had a Kurtzke Expanded Disability Status Scale (EDSS) of 6.5 or less [20], and an MRI of the brain demonstrating lesions consistent with the diagnosis of MS [21]. Patients with a history of other central nervous system disease or significant medical illnesses were excluded. MS Patients were also excluded if they had received immunosuppressive, cytotoxic or experimental immunomodulatory therapy at any time prior to initial enrollment, or corticotropin or corticosteroid therapy within 2 months prior to enrollment. Treatment with disease-modifying therapy, including corticosteroids and later beta-interferon, 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 MS patients within 3 years of age and within 2 years of overall length of education. The 2 groups were also similar in gender composition and handedness. Patient and

control subject 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. Informed consent was obtained from all patients and control subjects.

Magnetic Resonance Imaging

Twenty eight MS patients underwent magnetic resonance imaging (MRI) at baseline, 1 year and 4 year follow-up. MRI was performed on a 1.5T unit (Signa, General Electric Medical Systems, Milwaukee, Wisconsin). Proton density and T2-weighted images were obtained using two interleaved dual-echo (TE=30 and 80 msec) long TR (3,000 msec) sequences yielding contiguous 3mm thick slices of the whole brain.

Anatomic regions were defined using surface landmarks on a 3-dimensional display of each patient's baseline MRI study. An operator 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 which included the occipital lobe, cerebellum and brainstem (see [Figure 1](#)). This procedure was repeated for each hemisphere, yielding a total of 8 anatomic regions of interest per MR study.

Volumes of abnormal signal intensity (MS lesions) within each of these regions were identified using an automated image analysis algorithm [22]. A template driven segmentation technique, described in detail elsewhere [23] 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 [22]. The white matter classified as having abnormal signal intensity is felt to be consistent with MS lesions, and is henceforth referred to lesion volume.

A mask defining the anatomic regions on each patient's baseline MRI was aligned with the segmented images for each timepoint (baseline, 1 year, and 4 year follow-up imaging) using an automated image registration method [23]. This procedure yielded volumes of lesion, healthy white matter, gray matter and CSF for each of the 8 anatomic regions.

Neuropsychological Testing

The Brief, Repeatable Battery of Neuropsychological Tests in Multiple Sclerosis (BRB) [1] was administered to the MS patients 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 to initial cognitive performance of the MS patients. The order of presentation of the BRB subtests was identical for all subjects at all timepoints.

The BRB is comprised of five subtests:

1. The Bushke Verbal Selective Reminding Test (SRT) is a measure of verbal learning and delayed recall of a 12 word list. The long-term Storage (LTS) 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 one delayed trial are scored for total number of correct responses.
3. The Symbol Digit Modalities Test (SDMT) 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 pre-recorded audio-cassette 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 is a self-report index of subjective feelings [24]. The inventory consists of 21 groups of statements, asking the subject to choose the statement in each group which 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 Beck Depression Scale was added to the end of the neuropsychological test battery for the MS patients at the 4 year follow-up study, and was administered to all control subjects at the end of their baseline battery.

Statistical Methods

Non-parametric statistics were used for all comparisons as assumptions of normality were not uniformly met. Demographic and neuropsychological measures of MS patients and control subjects 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 MS patients. All correlations between MRI lesion volumes and neuropsychological test scores were examined using Spearman's rank correlation, yielding a Spearman's Rho coefficient. All significance values were subjected to correction for multiple comparisons [25] where appropriate.

Results

For the twenty-eight MS patients 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 MS patients 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 entry, mean disease duration was 8.3 ± 5.7 years. Mean EDSS at baseline was 4.0 ± 1.8, 4.2 ± 1.3 at 1 year, and 4.8 ± 1.7 at 4 year follow-up (Wilcoxon, $p=0.09$). Fifteen of the MS patients were classified as relapsing-remitting and 13 as chronic progressive at the time of enrollment. Nineteen of the MS patients received immunomodulatory therapy at some point during the four year follow-up period. Six patients received beta-interferon therapy.

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 (Wilcoxon, $p=0.48$). Frontal lesion volume represented the greatest percentage of total lesion volume (mean of 51.8% ± 8.3, Wilcoxon $p<0.01$), and this proportion did not change over the four years. The percentage of white matter classified as lesion was significantly higher in frontal and parietal regions (6.1% and 7.1% respectively) compared to temporal (1.6%) and posterior (3.0%) regions (Wilcoxon, $p<0.005$). Regional and total lesion volumes were highly correlated, particularly frontal and parietal regions with total lesion volume (Spearman Rank R .95-.97, $p<0.00001$). Relative proportions of white matter classified as lesion and correlations for regional lesion volumes to total lesion volume are shown in [Table 2](#).

Relapsing-remitting patients had a baseline total lesion volume of 14.0 ± 5.4 ml compared with 24.1 ± 19.1 ml for the chronic progressive patients (Wilcoxon, $p<0.08$). The mean change in total lesion volume over 4 years was 0.70 ± 3.2 ml for relapsing-remitting patients and 3.3 ± 4.1 ml for chronic progressive patients ($p<0.07$). We did not find any significant relationship between handedness and total or regional lesion volumes.

Neuropsychological Performance

MS patients were impaired on all baseline BRB tests compared to age and education matched control subjects. The most significant differences were found on tests of sustained attention (PASAT), processing speed (SDMT), and the sustained working memory component of verbal memory (CLTR) (Kruskal-Wallis, $p < 0.0002$). [Table 3](#) summarizes the BRB results for control subjects and MS patients. Disease duration and EDSS were not significantly related to baseline or follow-up cognitive performance.

Overall, at both 1 and 4 year follow-up, MS patients did not show significant changes on neuropsychological testing. Only one BRB subtest showed a modest decline at 4 year follow-up: the Delayed Verbal Memory score on the Selective Reminding Test (Wilcoxon, $p=0.024$). No significant differences were found in the baseline or follow-up cognitive performance between relapsing-remitting and chronic progressive patient groups.

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 MR imaging. Poor performance on tests of

complex attention (PASAT), processing speed (SDMT) and verbal memory (SRT) was associated with greater lesion volume in frontal and parietal regions, but not with lesion volume in temporal, occipital, brainstem or cerebellar regions. Even after stringent correction for multiple comparisons, performance on the PASAT and SRT-CLTR remained significantly correlated with frontal, parietal and total lesion burden (Spearman Rank Correlation; $R = -0.55$ to -0.74 $p < 0.0001$). We also performed this analysis using lesion volume expressed as a fraction of the total white matter in each anatomic region with very similar findings. [Table 4](#) shows 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](#) shows the correlation between left and right frontal regions and the PASAT at all 3 timepoints.

As above, MS patients did not demonstrate a significant change in lesion volume nor a significant decline in most cognitive domains over the 4 year period, and overall we did not find significant correlations between change in lesion volume and change in BRB scores. The only cognitive subtest with a statistical trend towards decline over the 4 years, the SRT delayed verbal memory measure, did show a modest correlation with change in both frontal (Spearman Rank $R = -.42$, $p < 0.03$) and total lesion volumes ($R = -.39$, $p < 0.04$), but these were not significant after correction for multiple comparisons.

Depression Inventory

The Beck Depression Inventory was administered at 4 year follow-up to the MS patients, and at baseline to all control subjects. MS patients reported a significantly higher Beck Depression Inventory score than controls (Wilcoxon, $p < 0.001$). However, the Beck scores did not show significant correlation with cognitive performance, or with regional and total lesion volumes.

Discussion

This longitudinal study demonstrated a robust and highly consistent association between MR lesion burden in fronto-parietal white matter and cognitive performance. 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 of 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 MS patients compared to age and education matched controls.

These findings suggest that the pattern of cognitive dysfunction frequently observed in MS patients is directly related to lesion burden in frontal and parietal white matter. Several previous studies have reported marked dysfunction in MS patients on tasks, such as the Wisconsin Card Sort Test, that are thought to be dependent on the integrity of frontal attentional systems [\[2\]](#) [\[26\]](#).

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 have also documented activation in parietal cortical regions with complex attention and memory tasks [27] [28]. 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 which have examined the relationship of regional MS lesion burden to specific cognitive tests. Swirsky-Sacchetti et al [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 [26] found that MS patients with a "high" frontal lobe lesion burden performed poorly on the Wisconsin Card Sort Test when compared to patients with a "low" frontal lesion burden. Foong et al [14] found moderately robust correlations between several neuropsychological measures of executive function and frontal lesion volume, but did not examine lesion volume in other anatomic regions. Similar to our findings, Foong et al 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 versus total lesion burden to cognitive impairment in MS. Swirsky-Sacchetti et al [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 [14] attempted to elucidate the specific contribution of frontal lesion volume by controlling for total lesion volume, which resulted in non-significant 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 ($R = .95$ and $.97$, 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 quite consistent over the 4 year follow-up. Although there was a modest increase in lesion burden over this time period, 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 four 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 one other longitudinal study reported stable cognitive status for up to 4 years of follow-up [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 due to 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 and colleagues. It is conceivable that once this lesion burden threshold has been crossed, further cognitive deterioration may be quite slow. At baseline, our patients demonstrated marked cognitive impairment compared to age and education 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, repeat exposure or "practice effects" may have obscured some subtle decline in cognitive functioning. Finally, the course of cognitive decline may be quite variable among patients, and a much larger sample size may be required to detect a definitive pattern. We did not detect significant differences between relapsing-remitting and chronic progressive groups in the degree of cognitive impairment at baseline or over time, but had a relatively 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 "pseudo-dementia" sometimes seen with depression, and that cognitive performance is independently related to lesion burden. Similar to Foong et al. [14], we did not find a significant correlation between degree of depressive symptomatology and cognitive function or regional lesion burden. Several of our patients were on antidepressants, given either for depression or non-mood related symptoms, such as chronic pain or incontinence. These medications may have affected the self-report of depressive symptomatology, however, our patients did report a significantly higher Beck Inventory score than the control subjects.

One of the strengths of our study is the use of an automated 3D 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 MR 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 [22]. In this study, we chose to use relatively large anatomic divisions, as the exact anatomy of white matter connectivity 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 anatomic lesion localization may yield better understanding of the regional distribution of lesion burden, and the relationship to specific patterns of cognitive dysfunction in MS.

Figures and Tables

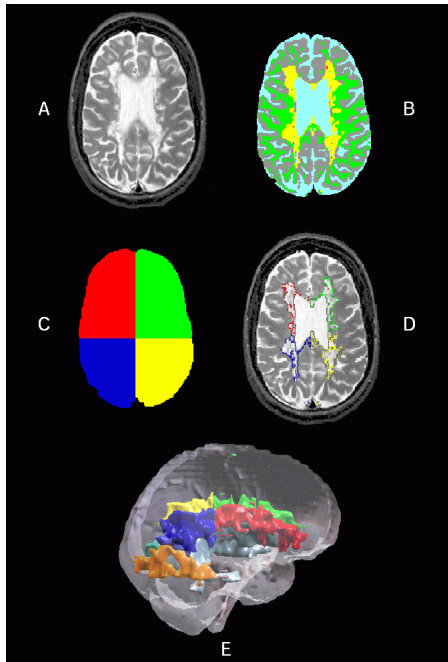


Image Processing and Lesion Segmentation.

- A.** T2-weighted magnetic resonance imaging axial section from the brain of a 33-year-old woman with multiple sclerosis.
- B.** Segmented image showing tissue classification into gray matter (grey), cerebrospinal fluid (aqua), normal white matter (green) and lesion (yellow).
- C.** Anatomical mask showing quadrants corresponding to right frontal (red), left frontal (green), right parietal (blue).
- D.** Overlay of regional lesion labels on T2-weighted magnetic resonance imaging with corresponding colors mentioned in C.
- E.** Three-dimensional reconstruction of ventricular cerebrospinal fluid (shown in light blue) and regional lesion volumes with corresponding colors to anatomical mask mentioned in C.

TABLE 1. Demographic and Clinical Data

	Group Mean (Standard Deviation)		p*
	Controls (n=28)	MS Patients (n=28)	
Age	38.3 (8.4)	39.3 (7.3)	0.66
Gender (F:M)	17:11	19:9	0.78
Handed (R:L)	24:4	22:6	0.73
Education	16.5 (2.8)	15.4 (2.4)	0.13

- p value from Wilcoxon Rank-Sum or Fisher Exact Test

Table 2. Relationship of Regional to Total Lesion Volumes

	% of Lesioned White Matter Within Region	% Region to Total Lesion Volume	Correlation of Regional to Total Lesion Volume
			Spearman Rho
<u>Baseline:</u>			
Frontal	6.1%	52.0%	.95
Parietal	7.1%	30.0%	.97
Temporal	1.6%	3.0%	.81
Posterior	3.0%	15.0%	.80
<u>4-Year:</u>			
Frontal	5.6%	51.2%	.96
Parietal	7.3%	29.4%	.96
Temporal	1.8%	3.3%	.75
Posterior	2.4%	16.4%	.84

TABLE 3. Baseline Brief Repeatable Battery and Serial Neuropsychological Test Results

	Control Subjects (n = 28)	MS Patients (n = 28)		
		Baseline	One Year	Four Year
Selective Reminding Test				
LTS	52.5 (10.5) ^a	42.6 (12.1)	44.6 (11.8)	42.5 (10.8)
CLTR	44.3 (11.8) ^a	27.7 (12.4)	32.5 (13.7)	27.9 (10.3)
Total Delay	9.4 (1.7) [*]	7.4 (2.3)	8.3 (2.8)	6.3 (3.0) ^b
10/36 Spatial Recall	29.2 (5.6)	24.7 (7.7)	25.9 (7.2)	26.4 (7.0)
Symbol Digit Modalities	62 (10.6) ^a	40.6 (10.5)	41.6 (10.9)	42.2 (13.9)
PASAT	87.8 (13.8) ^a	67.9 (22.8)	71.0 (23.4)	70.3 (20.5)
Word List Generation	34.8 (9.8) ^a	26.6 (6.6)	27.9 (7.3)	27.2 (7.6)
Beck Depression Scale	3.2 (4.1) ^a			11.5 (6.9)

^a p<.005, Wilcoxon Rank Sum Test comparing control subjects to Baseline BRB results for MS patients (significant after adjustment for multiple comparisons)

^b p=0.24 Wilcoxon Signed Rank Test comparing Baseline to Four Year Follow-up BRB in MS patients to baseline measures in the same patients (not significant after adjustment for multiple comparisons)

TABLE 4. Correlation between Cognitive Tests and Regional Lesion Volumes at 4 Year Follow-up

	Frontal	Parietal	Temporal	Posterior (Occipital, Brainstem, Cerebellar)	Total Lesion Volume
Selective Reminding Test:					
Long Term Storage	-0.37 (.05)	-0.28 (.15)	-0.02 (.93)	-0.14 (.48)	-0.33 (.08)
CLTR	-0.61* (<i><.001</i>)	-0.55* (.002)	-0.19 (.33)	-0.22 (.25)	-0.61* (<i><.001</i>)
Total Delay	-0.48 (.01)	-0.43 (.02)	-0.11 (.58)	-0.05 (.80)	-0.45 (.02)
10/36 Spatial Recall	-0.45 (.02)	-0.38 (.05)	-0.19 (.32)	.02 (.93)	-0.43 (.02)
Symbol Digit Modalities	-0.42 (.02)	-0.41 (.03)	.003 (.99)	-0.31 (.11)	-0.45 (.02)
PASAT	-0.67* (<i><.001</i>)	-0.69* (<i><.001</i>)	-0.13 (.51)	-0.21 (.28)	-0.66* (<i><.001</i>)
Word List Generation	-0.09 (.65)	-0.07 (.74)	.06 (.75)	-0.08 (.68)	.03 (.89)
Beck Depression Scale	.06 (.76)	.03 (.86)	-0.19 (.33)	.04 (.85)	.01 (.98)

Values shown are Spearman Rank correlation coefficients, with significance levels shown below in parentheses.

* p values <0.005 (significant after adjustment for multiple comparisons)

Table 5. Correlation coefficients for PASAT with left and right frontal regions

	Baseline	Year 1	Year 4
Left frontal	-0.68	-0.68	-0.73
Right frontal	-0.50	-0.47	-0.59

Spearman Rank

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