Decreased Frontal Lobe Gray Matter Perfusion in Cognitively Impaired Patients with Secondary-Progressive Multiple Sclerosis Detected by the Bookend Technique

BACKGROUND AND PURPOSE: There is increasing evidence implicating microvascular impairment in MS pathogenesis. Perfusion imaging offers a unique opportunity to investigate the functional impact of GM pathology. We sought to quantify differences in MR imaging–based bookend-derived cerebral perfusion between cognitively impaired and nonimpaired patients with SPMS.

MATERIALS AND METHODS: Patients were prospectively recruited and assessed using MR imaging and the standard cognitive battery called the Minimal Assessment of Cognitive Function in MS. Patients exhibiting impairment on ≥2 individual tests were classified as cognitively impaired. Healthy controls were prospectively recruited and assessed using MR imaging to validate bookend assumptions. Structural and perfusion scans were coregistered and partitioned into anatomic brain regions and tissue compartments. Clinical and radiologic characteristics were compared between patients with and without impairment to identify potential confounders. A Bonferroni adjusted P value threshold (P < .005) was used for lobar and sublobar level analyses to correct for multiple comparisons.

RESULTS: Thirty-seven patients with SPMS (age 56 ± 9 years; 23 women, 14 men) and 10 age- and sex-matched healthy controls were recruited. Bookend assumptions were found to be valid in MS. GM and WM qCBV were all globally reduced in impaired patients. After adjusting for potential confounders while examining sublobar level perfusion, only GM qCBV was significantly different between cognitive groups, and this hypoperfusion localized to the bilateral medial superior frontal regions and left inferior, middle, and superior frontal regions (P < .005) of impaired patients compared with nonimpaired patients. GM qCBV accounted for 22.5% of the model variance compared with a model including only confounders (P = .0007).

CONCLUSIONS: Bookend-derived GM qCBV was significantly reduced in cognitively impaired patients with SPMS in functionally relevant brain regions.

ABBREVIATIONS: BPF = brain parenchymal fraction; DSC = dynamic susceptibility contrast; GM = gray matter; qCBF = quantitative cerebral blood flow; qCBV = quantitative cerebral blood volume; rCBF = relative cerebral blood flow; rCBV = relative cerebral blood volume; SPMS = secondary-progressive MS; TNF-α = tumor necrosis factor alpha

Cognitive dysfunction is common in MS and occurs most frequently in patients with SPMS. Multiple cognitive domains are affected, which can negatively impact social relationships, employment, and activities of daily living. Although MS is regarded primarily as a subcortical WM disease, GM disease burden is being increasingly emphasized.3-5 The underlying etiology of MS is largely unknown, though mounting evidence implicates microvascular impairment in MS pathogenesis. Pathologically, MS lesions demonstrate a perivenular distribution,6 lymphocytic cuffing,7 and wall hyalinization.8 Mechanisms of injury include cytotoxic T-cell inflammatory response and antigen-antibody mediated complement activation. Chronic ischemia may be mediated by edema and microcirculation disturbance, obliterator vasculitis, or the release of excitotoxins producing vascular tone dysregulation.9

MR imaging is the most frequently used neuroimaging technique in studies of cognitive impairment in patients with MS.10 However, only modest associations between T2-weighted hyperintense or T1-weighted hypointense WM lesion load and cognitive performance have been reported.11 In terms of assessing GM involvement, sequences that can identify cortical lesions, such as double inversion recovery, have highlighted the etiological role that GM may play.12,13 GM, particularly the cerebral cortex, is highly vascular, with significant metabolic activity, and thus is inherently sensitive to perfusion perturbations induced by pathologic change. As such, perfusion imaging offers a unique opportunity to investigate the functional impact of GM pathology.

The bookend technique is a novel DSC calibration method-ology that more accurately quantifies cerebral perfusion through the use of pre- and postgadolinium scans.14-16 These

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“bookend” scans allow DSC calibration by quantifying parenchymal and blood pool T1 changes while correcting for intravascular and extravascular water exchange. The bookend technique does not require normalization for comparative measurements and is reproducible, reliable, and accurate compared with PET. The goal of this study was to quantify differences in bookend-derived cerebral perfusion between cognitively impaired and nonimpaired patients with SPMS. We hypothesized that perfusion metrics would be significantly reduced within functionally relevant brain regions, such as the prefrontal cortex, in cognitively impaired patients with SPMS.

Materials and Methods

Patients and Healthy Controls

This study was approved by the research ethics boards of both Sunnybrook Health Sciences Centre and St. Michael’s Hospital. SPMS subjects were prospectively recruited over 1 year from 2 tertiary referral MS clinics. Written informed consent was obtained from all participants. The charts of potential subjects were examined by 2 senior neurologists (20 years’ experience) before recruitment. Exclusion criteria were history of drug/alcohol abuse, disease-modifying drug or steroid use within 6 months, premorbid (pre-MS) psychiatric history, head injury with loss of consciousness, concurrent medical diseases (eg, cerebrovascular disease), and MR imaging contraindications. Demographic data included age, sex, education level, and disease duration. MR imaging, neurologic examination, and Expanded Disability Status Scale assessment were completed on the same day.

To validate bookend assumptions regarding use of the water correction factor in patients with MS and to assess WM T1 differences in normal and diseased states, age- and sex-matched healthy controls were prospectively recruited and scanned before and after intravascular contrast administration with the bookend protocol. Healthy controls were assessed after being subjected to similar exclusion criteria as patients with MS. The Sunnybrook research ethics board did not authorize a DSC study in healthy controls because of the need for power injection.

Cognitive Testing

The Minimal Assessment of Cognitive Function in MS was administered under the supervision of a senior neuropsychiatrist (20 years’ experience). This 90-minute cognitive battery was recommended by an expert panel for clinical monitoring and research purposes. The Minimal Assessment of Cognitive Function in MS comprises 7 tests covering 5 cognitive domains, including processing speed, memory, executive function, visuospatial perception, and verbal fluency. Impairment for a single test was defined as a z score $< -1.5$. A composite outcome was used whereby patients with $\geq 2$ test impairments were considered impaired. Individual test results were not correlated with perfusion metrics in this study, as we sought to assess clinically relevant cognitive impairment that impacted multiple domains. The Beck Depression Inventory was also administered to account for the well-known association between depression and cognition.

MR Imaging Acquisition

MR imaging was performed on a 3T scanner (Philips, Best, the Netherlands) with a 16-channel phased array coil. Imaging parameters included volumetric T1 turbo field echo (TR/TE/flip angle: 9.5 ms/2.3 ms/12°; number of averages: 1; FOV: 24 cm; matrix size: 256 × 164; section thickness: 1.4 mm); proton density/T2 (TR/TE/flip angle: 1280 ms/90°; FOV: 23 cm; matrix: 256 × 261; section thickness: 3 mm); field-echo echo-planar imaging DSC (TR/TE/flip angle: 1610 ms/30 ms/60°; FOV: 22 cm; section thickness: 4 mm; matrix: 128 × 128; in-plane voxel size: 1.7 × 1.7 mm; no gap; signal bandwidth: 1260 Hz/pixel; sections: 25). Ten mL of Gadobutrol (Gadovist; Bayer, Toronto, Canada) (1 mmol/mL) was administered by a power injector at a rate of 5 mL/s, followed by a 25 mL bolus of saline at 5 mL/s. A total of 60 images were acquired at 1.6-second intervals with the injection occurring at the 10th volume. A segmented inversion recovery look-locker EPI sequence was performed immediately before and after the DSC sequence, as previously described (TR/TE/flip angle: 14.4 ms/7 ms/16°; inversion time: 15.8 ms; FOV: 22 cm; matrix: 128 × 128; 15 lines in k-space per acquisition; section thickness: 5 mm; 120 time points; scan time: 73 seconds). A 3000-ms delay was placed after the last imaging time point to facilitate longitudinal magnetization recovery. DSC acquisition achieved 10-cm coverage (25 sections at 4 mm per section) and was positioned such that the most superior section reached the vertex, while, inferiorly, the lowest section extended at least to the midbrain. Section placement was supervised by an experienced neuroradiologist to ensure consistent coverage across patients.

Image Processing

The On-line Appendix details the calculation of qCBV and qCBF. Briefly, bookend-derived qCBV in WM (qCBV$_{WM}$) is calculated based on the quantification of T1 changes in normal WM relative to blood pool changes. Careful modeling of the effects of intravascular and extravascular water exchange is required, as such exchange is a documented confounding effect in determining qCBV from pre- and postgadolinium T1 changes. To validate use of the water correction factor in patients with MS and negate its measurement as a source of bias for qCBV differences, we compared water correction factor calibration curves in patients with MS and healthy controls. This qCBV$_{WM}$ value is used to quantify the relative CBV and CBV values extracted during DSC analysis. To assess the potentially confounding effect of permeability differences between impaired and unimpaired patients with MS, relative recirculation, which is a validated index of BBB permeability, was calculated from the DSC acquisition data, as previously described.

Structural T1- and proton density/T2-weighted images were coregistered and parcellated by using validated proprietary software (SABRE). This technique combines manual tracing of a few important anatomic landmarks, such as the central sulcus, with automated Talairach grid divisions. ROIs defined by the SABRE technique demonstrated a high degree of correspondence with manually traced ROIs and were reproducible with high inter- and intrarater reliabilities. This parcellation methodology delineates 13 ROIs per hemisphere: superior frontal, medial superior frontal, middle frontal, medial middle frontal, inferior frontal, medial inferior frontal, superior parietal, inferior parietal, occipital, anterior temporal, posterior temporal, anterior basal ganglia, and posterior basal ganglia. Intracranial tissue was segmented according to 3 classifications: GM, WM, and CSF. WM lesion ROIs were manually traced on the proton density/T2 images by an experienced neuroradiologist (8 years’ experience) using Analyze 8.0 (Mayo Clinic, Rochester, Minnesota). These structural space object maps were coregistered to perfusion space using the FMRRIB Software Library (http://www.fmrib.ox.ac.uk/fsl) and combined in MATLAB (MathWorks, Natick, Massachusetts) to provide structural volumes (ie, GM, WM, CSF, and WM lesion) and perfusion
parameters (ie, qCBF, qCBV, and MTT) for every brain lobe and region (Fig 1).

**Statistical Analysis**

The validity of the water correction factor model (observed versus expected) in healthy controls, impaired patients with MS, and nonimpaired patients with MS was determined using the F-test. WM T1 values between these 3 groups were similarly compared. Patient clinical data, including age, sex, education level, disease duration, Expanded Disability Status Scale score, and Beck Depression Inventory score, and radiologic data, including GM fraction (GM/GM+WM+CSF), WM fraction (WM/GM+WM+CSF), CSF fraction (CSF/GM+WM+CSF), brain parenchymal fraction (GM+WM/GM+WM+CSF), WM lesion volume, qCBF, qCBV, MTT, WM T1, and relative recirculation, were compared between patients with and without impairment using the Student t test for independent samples, the Wilcoxon rank-sum test, or Pearson χ² test, as appropriate to the data type. Continuous data were expressed as mean ± SD or median with interquartile range, depending on the data type, while dichotomous data were expressed as proportions. Clinical and radiologic variables found to be significantly different between cognitive groups were considered as potential confounders and included as covariates in the regression analyses. Natural log transformation was used to normalize the nonparametric distribution of WM lesion volumes for the purpose of linear regression.

To investigate the relationship between cognitive impairment and qCBF or qCBV in brain lobes or regions, and to account for identified potential confounders, a generalized linear model with log link function was developed. Generalized linear models differ from traditional linear models in that they allow a dataset to statistically depend on a linear predictor through the application of a nonlinear link function, while traditional linear models make no such allowance. The logit function is the inverse of the logistic function, which is a common sigmoid curve. The dependent variable was impairment (ie, impaired versus nonimpaired) and the independent variables were lobar or sublobar values of qCBF or qCBV. The GENMOD procedure from SAS version 9.2 (SAS Institute, Cary, North Carolina) was performed to fit the generalized linear model.24 Goodness of fit was assessed by deviance and Pearson χ² test. A Bonferroni adjusted P value threshold (P < .005) was used to establish statistical significance, which reflected a maximum of 9 independent variables and covariates in any model. To minimize the severity of multiple comparison correction, sublobar qCBV and qCBF were nested within lateralized brain lobes as discrete analyses.

To quantify the impact of identified potential confounders on cognitive impairment within the lobar and sublobar level models, we considered a model to be a null model only if the “intercept” was included. To determine the predictive effects of potential confounders on impairment, the coefficient of determination (R²) was calculated using the following equation: \( R^2 = (L_M - L_0)/L_M \), where \( L_0 \) and \( L_M \) represent the maximized log-likelihood of the null model and the fitted model, respectively. Akaike Information Criterion (\( L_0 + 2 \times \) number of parameters) was also used for comparing models (the lower the Akaike Information Criterion, the better the model). All statistical analyses were conducted using SAS v9.2.

**Results**

**Clinical Characteristics**

Thirty-seven patients with SPMS were prospectively recruited from 2 tertiary referral MS clinics. Eighteen patients (48.6%) were cognitively impaired. The clinical characteristics of this patient cohort, including age, sex, education level, disease duration, Expanded Disability Status Scale score, and Beck Depression Inventory score, were not significantly different between those with and without cognitive impairment (P > .05) (Table 1). There was a trend toward longer disease duration in impaired patients (P = .08). Ten age- and sex-matched healthy controls were also prospectively recruited. Mean age (54 ± 7 years) and sex (6 women, 4 men) did not significantly differ from those of the patients with SPMS (P > .05).

**Radiologic Characteristics**

Water correction factor validation demonstrated no significant differences between the expected water correction factor model values and the observed uncorrected data points for healthy controls (F = 0.26, P > .05), impaired patients with MS (F = 0.27, P > .05), or nonimpaired patients with MS (F = 0.90, P > .05). An expected difference was detected between the WM T1 values for healthy controls (595 ± 22), impaired patients with MS (670 ± 25), and unimpaired patients (600 ± 20; P < .01). WM T1 (P = .12), relative recirculation (P = .5), and water correction factor (P = .83) were not significantly different between impaired and nonimpaired patients (Table 1). Table 1 demonstrates that BPF (P = .01) was significantly reduced, while WM lesion volume (P = .02) and CSF fraction (P = .04) were significantly increased in impaired patients. There were trends toward lower GM fraction (P = .09) and WM fraction (P = .09) in impaired patients. BPF and WM lesion volume were therefore included as covariates in the regression analyses, though CSF fraction was not significant (P = .83) in impaired patients, impaired versus nonimpaired patients (54.05).
include because of the redundancy with BPF. Global GM, and WM qCBV and qCBF, were all significantly reduced in impaired patients compared with their nonimpaired counterparts (P < .05), though MTT was similar between cognitive groups (P > .05). However, neither lobar WM qCBF nor qCBF were significantly associated with cognitive impairment after regression-based adjustment for potential confounders (ie, BPF and WM lesion volume) as covariates and correction for multiple comparisons (P > .005) (Table 2). Similar to lobar WM qCBF, lobar GM qCBF was not significantly associated with cognitive impairment (P > .005) (Table 3). The calculated deviance per df (deviance, df = 1.14) and Pearson χ² statistic per df (χ², df = 0.94) both indicated a good model fit, which confirmed the validity of this finding.

Lobar GM qCBV was significantly decreased in impaired patients in each observed brain lobe (P < .005) (Table 4). The calculated deviance per df (deviance, df = 1.11) and Pearson χ² statistic per df (χ², df = 0.93) both indicated a good model fit. In terms of the sublobar SABRE ROIs, cognitively impaired patients exhibited significantly attenuated GM qCBV in the bilateral medial superior frontal regions and left superior, middle, and inferior frontal regions (P < .005) (Table 5). The calculated deviance per df and Pearson χ² statistic per df for both the left and right frontal region-of-interest models indicated a good fit. GM qCBV improved prediction of cognitive impairment and accounted for 22.5% of the model variance (Akaike Information Criterion 286.21 versus 295.49, χ² = 11.3, df = 1, P = .0007).

Discussion

We have demonstrated that frontal lobe GM qCBV is significantly reduced in cognitively impaired patients with SPMS relative to nonimpaired patients with SPMS. Perfusion differences localized to the bilateral medial superior frontal regions and the left inferior, middle, and superior frontal regions. Impaired patients also exhibited significant decreases in GM and WM qCBF and qCBV at the global level. However, at the lobar and sublobar levels, significant hypoperfusion was only detected in GM qCBV. BPF, WM lesion volume, and CSF fraction were significantly different between impaired and nonimpaired patients, but frontal GM qCBV remained significantly attenuated at the lobar and sublobar levels when these potential structural confounders were accounted for. The lack of significant differences between impaired and nonimpaired patients with respect to WM T1, relative recirculation, water correction factor, GM fraction, and WM fraction highlights the relevance of bookend-derived qCBV to cognitive impairment in MS and heightens the importance of the reported perfusion dissimilarities. Akaike Information Criterion analysis demonstrated that GM qCBV improved prediction of cognitive impairment and accounted for approximately 23% of the model variance.

There has been a single prior study that examined cerebral perfusion in cognitively impaired patients with MS. Inglese et al reported significant correlations between subcortical GM CBF and the Rey Complex Figure Test score, and subcortical GM CBF and the Delis-Kaplan Executive Function System.
serving of discussion. We propose that advanced perivascular
versus qCBF may appear superficially discrepant and is de-
lterior and sublobar levels. This differential reduction in qCBF
may appear superficially discrepant and is de-
inguished metabolism in their bilateral prefrontal
cortices compared with patients with MS without memory
impairment. This supports the bilateral frontal lobe hypoper-
fusion in the impaired patients that we found. In terms of
further support, patients with traumatic brain injury with bi-
lateral superior-medial frontal lobe damage have been shown to
demonstrate slowed reaction time and an increased rate of
errors on neuropsychological tests.27 Further, it is well known
that the frontal lobes contain neural substrates that mediate
many cognitive processes.28

Global GM and WM qCBF and qCBV were all significantly
attenuated in our cohort of impaired patients. However, only
GM qCBF was significantly reduced in these patients at the
lobe and sublobar levels. This differential reduction in qCBF
versus qCBV may appear superficially discrepant and is de-
serving of discussion. We propose that advanced perivascular
inflammation, venous obliteration, and local endothelial fac-
tors may have greater impact on qCBV relative to qCBF and
explain its stronger association with cognitive impairment. In
support of this assertion, a recent study using susceptibility-
weighted imaging, which is particularly sensitive to venous
blood, demonstrated significantly reduced visibility of peri-
testicular WM venous vasculature in patients with MS com-
pared with healthy controls.29 The authors suggest that this
susceptibility reduction could be attributed to a global reduc-
tion in vein number or size secondary to venous occlusion and
perivenular inflammation. Such pathology may also be driven
by obliterator vascularis that preferentially disrupts the ve-
nous system.7,9 These venous changes are well described in MS
and would be expected to be most severe in advanced disease
states such as SPMS. Approximately 70% of CBV is accounted
for by venous capacitance,30 and its quantitative equivalent,
quadratic qCBV, should exhibit a similar relationship. By virtue of this
association, qCBV should be greatly impacted by pa-

Table 3: Relationship between cognitive impairment and lobar GM qCBF

| Parameter       | Impaired                  | Nonimpaired               | Estimate | SE   | \( \chi^2 \) | P Value |
|-----------------|---------------------------|---------------------------|----------|------|--------------|---------|
| GM qCBF Intercept | 16.7642 | 3.1318 | 28.65 | <.0001* |
| 1.11; Pearson \( \chi^2 \), df = 1.14 | 1.012 | 3.75 | 0.0527 |
| 1.0104 | 3.69 | 0.0546 |
| 1.0109 | 3.90 | 0.0483 |
| 0.0104 | 3.78 | 0.0519 |
| 1.0109 | 3.51 | 0.0610 |
| BPF 0.79 ± 0.03 | 0.009 ± 0.009 | 0.6119 | 1.492 | 16.82 | <.0001* |
| 1.14; Pearson \( \chi^2 \), df = 1.14 | 0.82 | 3.70 | 0.0545 |
| 0.0087 | 3.53 | 0.0604 |
| 0.0001* |
| WML volumea | 0.02 ± 0.01 | 0.099 ± 0.009 | 0.6119 | 1.492 | 16.82 | <.0001* |

Note:—WML indicates white matter lesion.

* Significant result (\( P < .005 \), Bonferroni adjusted).

Table 4: Relationship between cognitive impairment and lobar GM qCBV

| Parameter       | Impaired                  | Nonimpaired               | Estimate | SE   | \( \chi^2 \) | P Value |
|-----------------|---------------------------|---------------------------|----------|------|--------------|---------|
| GM qCBF Intercept | 18.9634 | 3.7690 | 25.31 | <.0001* |
| 1.11; Pearson \( \chi^2 \), df = 1.11 | 1.0234 | 8.95 | 0.0028* |
| 1.0776 | 8.91 | 0.0028* |
| 1.0434 | 8.94 | 0.0028* |
| 0.1601 | 9.08 | 0.0028* |
| 0.1665 | 8.74 | 0.0031* |
| BPF 0.79 ± 0.03 | 0.009 ± 0.009 | 0.6323 | 0.1692 | 13.96 | 0.0003* |
| 1.43 | 8.78 | 0.031* |
| 0.1339 | 8.78 | 0.031* |
| 0.1380 | 8.59 | 0.034* |
| 0.1753 | 13.01 | 0.0034* |
| WML volumea | 0.02 ± 0.01 | 0.009 ± 0.009 | 0.6323 | 0.1692 | 13.96 | 0.0002* |

Note:—WML indicates white matter lesion.

* Significant result (\( P < .005 \), Bonferroni adjusted).
factors may also have greater impact on qCBV than qCBF. A model simulating advanced MS, which was developed by direct intrastral application of TNF-α, demonstrated that TNF-α–mediated destabilization of endothelial nitric oxide synthase caused significant reductions in nitric oxide and CBV.32 By means of these various mechanisms, particularly those related to venous changes, it is plausible for one to observe more marked reductions in qCBV than qCBF.

This is the first reported use of the bookend technique in MS. This multiscan protocol is readily implemented on any MR imaging scanner by adding “bookend” scans before and after a DSC sequence, which is widely available in the clinical setting. This technique obviates the need for relative perfusion measurement or normalization, which is not feasible in diffuse disease processes like MS. As in other perfusion techniques, patients with recent bouts of active inflammation are excluded because of the perfusion and permeability alterations known to coincide with acute, demyelinating lesions. Such alterations affect the accuracy of perfusion techniques that do not apply contrast leakage correction algorithms. Previously published studies examining the variability and repeatability of results generated using the bookend technique have reported a test-retest intraclass coefficient of 0.90 and coefficient of variation of 0.09.15,16,20

Potential limitations include differences in WM properties between patients with MS and healthy controls that could theoretically invalidate the bookend assumptions. However, no significant differences were identified between the expected values from the water correction factor model and the observed data points for healthy controls, impaired patients with MS, and nonimpaired patients with MS. In addition, WM T1, relative recirculation, and water correction factor were not significantly different between impaired and nonimpaired patients. WM T1 was expectedly dissimilar between patients and controls, but this is irrelevant, as CBV quantification is based on changes in T1 before and after contrast administration, not the absolute T1 values. In addition, by relying on T1 differences and ratios, any large systematic errors in T1 determination would affect both pre- and postcontrast values equally and thus cancel out in a relative comparison. In terms of another potential limitation, we did not assess cognition in healthy controls, as a recent report suggested that comparing cognitively impaired patients with MS to nonimpaired patients with MS is more appropriate than comparing them to healthy controls.33

SPMS is less frequently studied than relapsing-remitting MS because of the relatively advanced disease severity and limited benefit from immunosuppressive therapeutics. We specifically enrolled patients with SPMS because of the higher incidence of cognitive impairment, which facilitated a balanced sample of impaired patients.1 The selection of advanced-stage patients with MS (ie, those with SPMS) and exclusion of patients with recent steroid or disease-modifying drug usage reduced the possibility of any confounding effects resulting from active inflammation. Our results should be considered preliminary and require further validation in a larger dataset. However, the present sample does not represent the largest SPMS cohort examined in terms of either cerebral perfusion or cognition. Although our qCBV results appear promising, a significant amount of cognitive test result variance could be caused by factors other than those measured in this study.

Conclusions

Cognitively impaired patients with SPMS demonstrated significant reductions in global GM and WM qCBV and qCBF compared with nonimpaired patients with SPMS. After correcting for potentially confounding differences in BPF and WM lesion volume, and adjusting for multiple comparisons, significantly decreased GM qCBV was demonstrated in the bilateral medial superior frontal regions and left inferior, middle, and superior frontal regions of impaired patients. It is plausible that hyperperfusion in such functionally relevant brain regions is associated with cognitive impairment.

Table 5: Relationship between cognitive impairment and sublobar GM qCBV

| Lobe and Parameter | Estimate | SE       | χ²  | P Value |
|--------------------|----------|----------|-----|---------|
| Frontal, left (goodness of fit: deviance, df = 11; Pearson χ², df = 0.95) | Intercept | 18.7597 | 4.0521 | 21.43 | <.0001 |
|                    | qCBV     |          |     |         |
|                    | IF       | -0.5396  | 0.1886 | 8.19  | 0.0042 |
|                    | MidF     | -0.4740  | 0.1664 | 8.11  | 0.0044 |
|                    | MF       | -0.5185  | 0.1917 | 7.32  | 0.0068 |
|                    | MMidF    | -0.4598  | 0.1668 | 7.60  | 0.0058 |
|                    | MSF      | 0.4872   | 0.1708 | 8.13  | 0.0043 |
|                    | SF       | -0.5387  | 0.1902 | 8.02  | 0.0046 |
|                    | BPF      | -17.5403 | 5.2881 | 11.00 | 0.0009 |
|                    | WML volumea | 0.6301 | 0.1833 | 11.82 | 0.0006 |
| Frontal, right (goodness of fit: deviance, df = 11; Pearson χ², df = 0.95) | Intercept | 18.1061 | 3.9819 | 20.68 | <.0001 |
|                    | qCBV     |          |     |         |
|                    | IF       | -0.5166  | 0.1986 | 6.67  | 0.0093 |
|                    | MidF     | -0.4865  | 0.1719 | 7.43  | 0.0064 |
|                    | MF       | -0.5398  | 0.2100 | 6.61  | 0.0101 |
|                    | MMidF    | -0.4317  | 0.1594 | 7.34  | 0.0068 |
|                    | MSF      | -0.4906  | 0.1741 | 7.94  | 0.0048 |
|                    | SF       | -0.5638  | 0.2039 | 7.65  | 0.0057 |
|                    | BPF      | -16.5799 | 5.2116 | 10.12 | 0.0015 |
|                    | WML volumea | 0.6532 | 0.1843 | 12.56 | 0.0004 |

Note.—IF indicates inferior frontal, MidF, middle frontal; MF, medial inferior frontal; MMidF, medial middle frontal; MSF, medial superior frontal; SF, superior frontal; WML, white matter lesion.

a Natural logarithmic transformation was applied.

b Significant result (P < .005; Bonferroni adjusted).

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