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ORIGINAL RESEARCH

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

R.I. Aviv
P.L. Francis
R. Tenenbein
P. O'Connor
L. Zhang
A. Eilaghi
L. Lee
T.J. Carroll
J. Mouannes-Srour
A. Feinstein

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.[1] Multiple cognitive domains are affected, which can negatively impact social relationships, employment, and activities of daily living.[2] 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, obliterative 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 methodology that more accurately quantifies cerebral perfusion through the use of pre- and postgadolinium scans.[14-16] These

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From the Departments of Psychiatry (A.F.), Neurology (L.L.), and Medical Imaging (P.L.F., R.T., L.Z., A.E., R.I.A.), Sunnybrook Health Sciences Centre, Toronto, Ontario, Canada; Department of Neurology (P.O.), St. Michael's Hospital, Toronto, Ontario, Canada; Departments of Medical Imaging (R.I.A., P.F., R.T.) and Medicine (L.L., A.F., P.O.), University of Toronto Toronto, Ontario, Canada; Department of Biomedical Engineering (T.J.C., J.M.-S.), Northwestern University, Evanston, Illinois; Department of Radiology (T.J.C.), Northwestern University, Chicago, Illinois.

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Please address correspondence to Richard Aviv, MBChB, Sunnybrook Health Sciences Centre, 2075 Bayview Ave, Room AG-31, Toronto, ON, M4N 3M5 Canada; e-mail: richard.aviv@sunnybrook.ca

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"bookend" scans allow DSC calibration by quantifying parenchymal and blood pool T1 changes while correcting for intra-to-extravascular water exchange.[15] The bookend technique does not require normalization for comparative measurements and is reproducible, reliable,[15,16] and accurate compared with PET.[17] 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 intravenous 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.[18] 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.[19] A composite outcome was used whereby patients with ≥ 2 test impairments were considered impaired.[19] 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: 2900 ms/10.7 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).[14] 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.[20] Careful modeling of the effects of intra-to-extravascular water exchange is required, as such exchange is a documented confounding effect in determining qCBV from pre- and postgadolinium T1 changes.[21] 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 CBF 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.[22]

Structural T1- and proton density/T2-weighted images were coregistered and parcellated by using validated proprietary software (SABRE).[23] 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.[23] 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 FMRIB 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

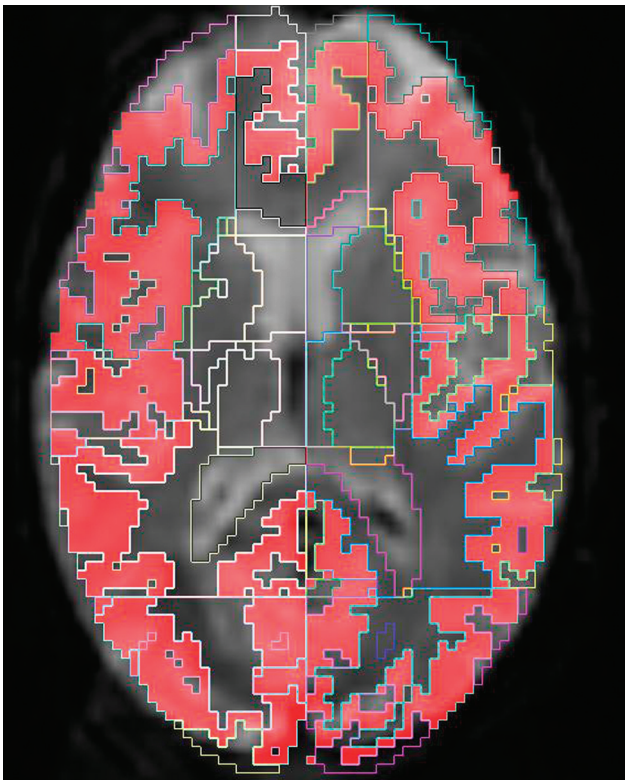

Fig 1. DSC map with coregistered regions of interest delineating multiple brain structures and tissue types. Global gray matter is illustrated by the red flood fill.

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 χ^2 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 logit 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 χ^2 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 (R^2) was calculated using the following equation: $R^2 = (L_O - L_M)/L_O$, where L_O and L_M represent the maximized log-likelihood of the null model and the fitted model, respectively. Akaike Information Criterion ($L_M + 2 \times$ 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

Table 1: Clinical and radiologic characteristics of patients with SPMS

Parameter[a]	Impaired $n = 18$	Nonimpaired $n = 19$	*P* value
Age (years)	58 ± 10	55 ± 6	0.32
Gender (F/M)	12/6	11/8	0.73
Education level (years; median [IQR])	15.5 (13–17.5)	16 (13–17.5)	0.99
Disease duration (years; median [IQR])	23 ± 12	17 ± 6	0.08
BDI (score; median [IQR])	9 (7.25–10)	5.5 (5–10.25)	0.21
EDSS (score; median [IQR])	6.5 (6.13–6.5)	6 (6–6.5)	0.29
GM qCBF (ml/100 g/min)	57 ± 17	60 ± 18	0.003[b]
WM qCBF (ml/100 g/min)	38.4 ± 15.4	40.3 ± 18.5	0.04[b]
GM qCBV (ml/100 g)	3.8 ± 1.1	4.1 ± 1.4	0.0001[b]
WM qCBV (ml/100 g)	2.6 ± 0.6	2.9 ± 0.9	0.004[b]
GM MTT (seconds)	4.11 ± 0.75	4.18 ± 0.76	0.18
WM MTT (seconds)	4.43 ± 0.84	4.46 ± 0.79	0.63
WML volume	0.02 ± 0.01	0.009 ± 0.009	0.02[b]
Brain parenchymal fraction	0.79 ± 0.03	0.82 ± 0.03	0.01[b]
CSF fraction	0.17 ± 0.04	0.15 ± 0.03	0.04[b]
GM fraction	0.43 ± 0.01	0.45 ± 0.03	0.09
WM fraction	0.36 ± 0.02	0.38 ± 0.03	0.09
rR	0.11 ± 0.01	0.11 ± 0.02	0.50
WM T1	670.32 ± 25.38	600.02 ± 20.52	0.12
WCF	1.31 ± 0.58	1.26 ± 0.41	0.83

Note:—BDI indicates Beck Depression Inventory; EDSS, Expanded Disability Status Scale; IQR, interquartile range; rR, relative recirculation, WCF, water correction factor; WML, white matter lesion.
[a] Value is mean ± standard deviation unless otherwise stated.
[b] Significant result ($P < .05$).

Table 2: Relationship between cognitive impairment and lobar WM qCBV and qCBF

Parameter	Estimate	SE	χ^2	*P* Value
Goodness of fit: deviance, $df = 1.12$; Pearson χ^2, $df = 0.95$				
Intercept	18.5684	3.7342	24.73	<.0001[b]
WM qCBV				
Frontal				
Left	−0.6978	0.2727	6.55	0.0105
Right	−0.6824	0.2634	6.71	0.0096
Occipital	−0.4850	0.1835	6.98	0.0082
Parietal				
Left	−0.6966	0.2619	7.07	0.0078
Right	−0.6918	0.2648	6.83	0.0090
Temporal				
Left	−0.3924	0.1542	6.48	0.0109
Right	−0.3924	0.1515	6.71	0.0096
BPF	−17.7085	4.8537	13.31	0.0003[b]
WML volume[a]	0.5986	0.1679	12.72	0.0004[b]
Intercept	16.5159	3.2686	25.53	<.0001[b]
WM qCBF				
Frontal				
Left	−0.0305	0.0174	3.06	0.0803
Right	−0.0305	0.0173	3.13	0.0769
Occipital	−0.0276	0.0144	3.65	0.0560
Parietal				
Left	−0.0346	0.0186	3.45	0.0631
Right	−0.0344	0.0189	3.31	0.0687
Temporal				
Left	−0.0173	0.0099	3.07	0.0796
Right	−0.0188	0.0101	3.48	0.0620
BPF	−15.8110	4.3555	13.18	0.0003[b]
WML volume[a]	0.6016	0.1579	14.51	0.0001[b]

Note:—WML indicates white matter lesion.
[a] Natural logarithmic transformation was applied.
[b] Significant result ($P < .005$, Bonferroni adjusted).

included 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 qCBV 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 χ^2 statistic per *df* (χ^2, $df = 0.94$) 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 χ^2 statistic per *df* (χ^2, $df = 0.93$) 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 χ^2 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, $\chi^2 = 11.3$, $df = 1$, $P = .0007$).

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.[25] Inglese et al reported significant correlations between subcortical GM CBF and the Rey Complex Figure Test score, and subcortical GM CBV and the Delis-Kaplan Executive Function System

Table 3: Relationship between cognitive impairment and lobar GM qCBF

Parameter	Impaired	Nonimpaired	Estimate	SE	χ^2	*P* Value
Goodness of fit: deviance, $df = 1.14$; Pearson χ^2, $df = 0.94$						
Intercept			16.7642	3.1318	28.65	<.0001[b]
GM qCBF						
Frontal						
Left	54.71 ± 14.27	55.71 ± 12.95	−0.0197	0.0102	3.75	0.0527
Right	56.00 ± 16.29	58.91 ± 16.84	−0.0199	0.0104	3.69	0.0548
Occipital	55.39 ± 14.41	57.36 ± 15.38	−0.0214	0.0109	3.90	0.0483
Parietal						
Left	51.90 ± 11.5	59.40 ± 14.52	−0.0202	0.0104	3.78	0.0519
Right	56.46 ± 13.24	62.20 ± 19.48	−0.0204	0.0109	3.51	0.0610
Temporal						
Left	67.92 ± 24.54	70.42 ± 27.54	−0.0159	0.0083	3.70	0.0545
Right	53.95 ± 13.83	66.94 ± 23.60	−0.0164	0.0087	3.53	0.0604
BPF	0.79 ± 0.03	0.82 ± 0.03	−16.0231	4.1471	14.93	0.0001[b]
WML volume[a]	0.02 ± 0.01	0.009 ± 0.009	0.6119	0.1492	16.82	<.0001[b]

Note:—WML indicates white matter lesion.
[a] Natural logarithmic transformation was applied.
[b] Significant result ($P < .005$, Bonferroni adjusted).

Table 4: Relationship between cognitive impairment and lobar GM qCBV

Parameter	Impaired	Nonimpaired	Estimate	SE	χ^2	*P* Value
Goodness of fit: deviance, $df = 1.11$; Pearson χ^2, $df = 0.93$						
Intercept			18.9634	3.7690	25.31	<.0001[b]
GM qCBV						
Frontal						
Left	3.42 ± 0.95	3.79 ± 1.27	−0.5343	0.1787	8.95	0.0028[b]
Right	3.46 ± 0.94	3.81 ± 1.25	−0.5301	0.1776	8.91	0.0028[b]
Occipital	4.26 ± 0.99	4.67 ± 1.43	−0.4289	0.1434	8.94	0.0028[b]
Parietal						
Left	3.82 ± 0.90	4.27 ± 1.27	−0.4824	0.1601	9.08	0.0026[b]
Right	3.41 ± 0.95	3.80 ± 1.27	−0.4923	0.1665	8.74	0.0031[b]
Temporal						
Left	4.46 ± 1.50	4.87 ± 1.91	−0.3963	0.1338	8.78	0.0031[b]
Right	4.43 ± 1.29	4.69 ± 1.78	−0.4044	0.1380	8.59	0.0034[b]
BPF	0.79 ± 0.03	0.82 ± 0.03	−17.6498	4.8933	13.01	0.0003[b]
WML volume[a]	0.02 ± 0.01	0.009 ± 0.009	0.6323	0.1692	13.96	0.0002[b]

Note:—WML indicates white matter lesion.
[a] Natural logarithmic transformation was applied.
[b] Significant result ($P < .005$, Bonferroni adjusted).

score.[25] While we did not corroborate their results in terms of our anterior and posterior basal ganglia regions, that study did not examine cortical GM, so there is no basis for comparison with respect to our frontal lobe findings. Paulesu et al[26] examined cerebral metabolic rates in patients with MS with memory impairment using PET imaging and identified significantly diminished metabolism in their bilateral prefrontal cortices compared with patients with MS without memory impairment. This supports the bilateral frontal lobe hypoperfusion in the impaired patients that we found. In terms of further support, patients with traumatic brain injury with bilateral 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 qCBV was significantly reduced in these patients at the lobar and sublobar levels. This differential reduction in qCBV versus qCBF may appear superficially discrepant and is deserving of discussion. We propose that advanced perivascular inflammation, venous obliteration, and local endothelial factors 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 periventricular WM venous vasculature in patients with MS compared with healthy controls.[29] The authors suggest that this susceptibility reduction could be attributed to a global reduction in vein number or size secondary to venous occlusion and perivenular inflammation. Such pathology may also be driven by obliterative vasculitis that preferentially disrupts the venous 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, qCBV, should exhibit a similar relationship. By virtue of this strong association, qCBV should be greatly impacted by pathologies that decrease venous capacitance, such as those discussed here. In addition, drugs such as dihydroergotamine demonstrate that venous changes may primarily impact qCBV, with less-marked qCBF alteration.[31] Local endothelial

Table 5: Relationship between cognitive impairment and sublobar GM qCBV

Lobe and Parameter	Estimate	SE	χ^2	*P* Value
Frontal, left (goodness of fit: deviance, $df = 1.11$; Pearson χ^2, $df = 0.95$)				
Intercept	18.7597	4.0521	21.43	<.0001
qCBV				
IF	−0.5396	0.1886	8.19	0.0042[b]
MidF	−0.4740	0.1664	8.11	0.0044[b]
MIF	−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[b]
SF	−0.5387	0.1902	8.02	0.0046[b]
BPF	−17.5403	5.2881	11.00	0.0009[b]
WML volume[a]	0.6301	0.1833	11.82	0.0006[b]
Frontal, right (goodness of fit: deviance, $df = 1.11$; Pearson χ^2, $df = 0.95$)				
Intercept	18.1061	3.9819	20.68	<.0001
qCBV				
IF	−0.5166	0.1986	6.77	0.0093
MidF	−0.4685	0.1719	7.43	0.0064
MIF	−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[b]
SF	−0.5638	0.2039	7.65	0.0057
BPF	−16.5799	5.2116	10.12	0.0015[b]
WML volume[a]	0.6532	0.1843	12.56	0.0004[b]

Note:—IF indicates inferior frontal; MidF, middle frontal; MIF, 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).

factors may also have greater impact on qCBV than qCBF. A model simulating advanced MS, which was developed by direct intrastriatal 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 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 qCBF and qCBV 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 hypoperfusion in such functionally relevant brain regions is associated with cognitive impairment.

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