

Intravoxel Incoherent Motion Imaging in Small Vessel Disease

Microstructural Integrity and Microvascular Perfusion Related to Cognition

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Background and Purpose—Cerebral small vessel disease (SVD) is associated with cognitive impairment. This may be because of decreased microstructural integrity and microvascular perfusion, but data on these relationships are scarce. We determined the relationship between cognition and microvascular perfusion and microstructural integrity in SVD patients, using intravoxel incoherent motion imaging—a diffusion-weighted magnetic resonance imaging technique designed to determine microvascular perfusion and microstructural integrity simultaneously.

Methods—Seventy-three patients with SVD and 39 controls underwent intravoxel incoherent motion imaging and neuropsychological assessment. Parenchymal diffusivity D (a surrogate measure of microstructural integrity) and perfusion-related measure fD^* were calculated for the normal appearing white matter, white matter hyperintensities, and cortical gray matter. The associations between cognitive performance and D and fD^* were determined.

Results—In SVD patients, multivariable analysis showed that lower fD^* in the normal appearing white matter and cortical gray matter was associated with lower overall cognition ($P=0.03$ and $P=0.002$, respectively), lower executive function ($P=0.04$ and $P=0.01$, respectively), and lower information-processing speed ($P=0.04$ and $P=0.01$, respectively). D was not associated with cognitive function. In controls, no association was found between D , fD^* , and cognition.

Conclusions—In SVD patients, lower cognitive performance is associated with lower microvascular perfusion in the normal appearing white matter and cortical gray matter. Our results support recent findings that both cortical gray matter and normal appearing white matter perfusion may play a role in the pathophysiology of cognitive dysfunction in SVD.

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Key Words: cerebral blood flow ■ cerebral small vessel disease ■ cognition

Cerebral small vessel disease (SVD) causes lacunar stroke syndrome and is an important contributor to cognitive impairment and dementia. Radiological markers of SVD, such as white matter hyperintensities (WMH) and lacunes, are found mainly in the subcortical white matter and have been associated with impaired cognitive function.^{1,2} Recent studies suggest that cortical changes, such as a lower cortical thickness and lower total cortical volume, may also play a role in SVD.³

The exact pathophysiology of cognitive deterioration in SVD remains unclear. It has been proposed that microstructural damage and reduced cerebral perfusion may play an integral part in this process. Diffusion tensor imaging studies found

diminished microstructural integrity and network efficiency of the white matter in SVD patients compared with controls.⁴ Moreover, lower microstructural integrity in the white matter was found to be associated with lower cognitive function.^{5,6} In addition to microstructural changes, multiple studies showed reduced cerebral perfusion in patients with SVD.⁷⁻⁹ Most of these studies examined perfusion differences between patients with cognitive impairment and a control group, whereas studies on the direct relationship between cognition and perfusion in patients with SVD are scarce.

Intravoxel incoherent motion (IVIM) imaging is a diffusion-weighted magnetic resonance imaging (MRI) technique

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designed to determine microvascular perfusion and microstructural integrity simultaneously. IVIM generates many measures concurrently, including D (parenchymal diffusivity) and fD^* . A higher D indicates less restricted water diffusion, which is surrogate for a decreased microstructural integrity. A higher fD^* is surrogate for a higher microvascular perfusion.^{10–12} Earlier studies using dynamic susceptibility contrast MRI and arterial spin labeling MRI in patients with gliomas found that perfusion-related parameters in IVIM correlated with cerebral blood volume and cerebral blood flow.^{13–15} The IVIM technique enables concurrent analysis of microstructural integrity and microvascular perfusion and the possibly combined contribution to cognition.

We used IVIM to examine microvascular perfusion and microstructural integrity in the white matter and cortical gray matter (CGM) and their association with cognition in patients with SVD and in controls. To have a broad clinical spectrum linked to SVD, we included patients with lacunar stroke and patients with SVD-related vascular cognitive impairment.¹

Methods

Patient Population

We included clinically overt SVD patients and age- and sex-matched controls. Patients with SVD consisted of consecutively included first-ever lacunar stroke patients and patients with mild vascular cognitive impairment (mVCI) who consented to participate in the study. Participants were included from the Maastricht University Medical Center and Zuyderland Medical Center, The Netherlands, between April 2013 and December 2014. Lacunar stroke patients were recruited from the Stroke Unit. Lacunar stroke was defined as an acute stroke syndrome with a compatible recent small subcortical infarct on clinical brain MRI. This was determined as a round or ovoid hyperintense lesion on a diffusion weighted imaging sequence or a hyperintense lesion on both fluid-attenuated inversion recovery and T2-weighted sequences, all with a diameter of <20 mm in the axial plane.¹⁶ If no such lesion was visible on MRI or only computed tomography was performed, established clinical criteria for lacunar stroke syndrome were used.¹⁷ Exclusion criteria included a potential cardiac embolic source (eg, atrial fibrillation), symptomatic carotid stenosis of $\geq 50\%$, or recent cortical infarct on brain MRI or computed tomography. Stroke patients were included at least 3 months post-stroke to avoid acute stroke changes.¹⁸ mVCI patients were recruited from the outpatient clinic of the Department of Neurology and from the Memory Clinic. Criteria of mVCI were met when patients had (1) subjective complaints of cognitive functioning, (2) objective cognitive impairment in at least one cognitive domain at neuropsychological testing, (3) a Clinical Dementia Rating of ≤ 1 and a Mini Mental State Examination score of ≥ 20 , and (4) vascular lesions on brain MRI, which suggest a link between the cognitive deficit and SVD¹⁹: moderate-to-severe WMH (Fazekas score deep >1 and periventricular >2) or mild WMH (Fazekas score deep=1 and periventricular=2) combined with lacune(s) and microbleeds.²⁰

Age- and sex-matched controls were recruited from the outpatient clinic of the Department of Neurology. We included 1 control per 2 SVD patients. Controls had no overt cerebrovascular diseases and cognitive impairment. Most of them had lumbar radicular syndrome or peripheral neuropathy. Additional exclusion criteria for all participants include neurodegenerative diseases, multiple sclerosis, epilepsy, systemic inflammatory diseases, alcohol abuse, psychiatric disorders or use of medication that may influence the accuracy of neuropsychological testing, and the presence of a contraindication for MRI (eg, pacemaker and claustrophobia).

Characteristics of all participants were recorded, including age; sex; educational level; and the presence of cardiovascular risk factors such as hypertension (history of hypertension and use of blood

pressure-lowering drugs), hypercholesterolemia (history of hypercholesterolemia and use of statin), diabetes mellitus (history of diabetes mellitus or use of blood sugar-lowering drugs), smoking (current smoking), and body mass index (weight divided by the square of length).

The Medical Ethical Committee of the Maastricht University Medical Center approved the study. All participants were included after written informed consent.

Magnetic Resonance Imaging

All participants underwent standard brain imaging on a 3.0 T MRI system. The MR protocol consisted of a T1-weighted, T2-weighted, and fluid-attenuated inversion recovery sequences.

After this standard protocol, IVIM imaging was performed using a Stejskal–Tanner diffusion-weighted single-shot echo-planar-imaging spin echo pulse sequence.²¹ Fifteen diffusion-weighted images were acquired in the anterior–posterior direction using multiple diffusion-sensitive b values. More sequence and image-processing details can be found in the [online-only Data Supplement](#)

Image Processing

Using Freesurfer software, white matter and CGM were segmented on T1-weighted scans.²² WMH were automatically segmented, with manual correction, on fluid-attenuated inversion recovery scans to differentiate between normal appearing white matter (NAWM) and WMH.²³ WMH volume was quantified and normalized to the intracranial volume. Parenchymal brain volume, normalized to total intracranial volume was used as a measure for atrophy.²⁴

A 2-compartment diffusion model was used to quantitatively model the diffusion-attenuated signal.¹² This model describes intravascular and parenchymal (nonvascular) compartments. The intravascular compartment represents the fast water motion in blood flowing into a network of small vessels. This compartment provides a perfusion-related measure, fD^* , in which D^* is the pseudodiffusivity of water in the flowing blood, and f is the fractional volume of blood. The extravascular compartment is described by the water diffusion in the parenchymal microstructure and gives rise to the parenchymal diffusivity D .

To account for the prepulse to suppress CSF and also differences in relaxation time of blood and tissue, we used the modified IVIM model proposed by Hales and Clark.²⁴

To calculate D and fD^* , model fitting was performed voxel by voxel using the 2-step method introduced by Federau et al.¹³ Subsequently, values were obtained of D and fD^* for the NAWM, WMH, and CGM. In this study, we focus on D and fD^* as a surrogate measure for parenchymal microstructural integrity and microvascular perfusion, respectively.

Neuropsychological Assessment

All participants received extensive neuropsychological testing covering 3 main cognitive domains. The memory domain was measured with the Rey Auditory Verbal Learning Test (immediate recall, delayed recall, and delayed recognition) and the Digit Span Forward. Executive function domain was tested using the Stroop Color-Word Test interference score (time of part 3 minus mean time of part 1 and 2), Trail Making Test interference score (time of part B minus time of part A), Category (animals and professions) and Letter Fluency, Letter-Number Sequencing, and Digit Span Backward. Information-processing speed was determined using the Symbol Substitution Coding, Trail Making Test part A, and Stroop Color-Word Test parts 1 and 2. The Z scores were calculated for each test by dividing the difference between the individual raw score and the sample mean by the sample SD. Compound scores were determined for each participant by averaging the Z scores within each domain. An overall cognition compound score was calculated taking the average of the 3 domain compound scores. When not all tasks could be performed, compound scores were calculated from the scores of the remaining tasks. We used the Hamilton Anxiety and Depression Scale test (range 0–42) to record depression and anxiety symptoms.

Statistical Analysis

To examine the relationship between the compound scores of the different cognitive domains (dependent variables) and D and fD^* (independent variables) in the NAWM, WMH, and CGM, we used univariable and multivariable linear regression, corrected for age, sex, educational level, and Hamilton Anxiety and Depression Score. Significant associations were further corrected for normalized WMH volume and normalized brain volume (markers for macrostructural brain damage). These analyses were performed for SVD patients and controls and also for the SVD subgroups lacunar stroke and mVCI separately. A possible interaction effect of D and fD^* on cognition in SVD patients was tested by adding an interaction term in the multivariable linear regression analysis. Statistical analysis was performed using SPSS 22.0. Statistical significance was inferred for $P < 0.05$.

Results

We included 73 patients with SVD—40 patients with lacunar stroke and 33 patients with mVCI—and 39 age- and sex-matched controls. We initially included 80 patients and 40 controls, but because of imaging complications and image artifacts, we had to exclude 7 patients and 1 control for the final analysis. Of the 40 lacunar stroke patients, 31 had a recent lesion visible on MRI and 9 (5 with MRI and 4 with computed tomography) were included based on clinical presentation. Characteristics of these participants are presented in Table 1.

For cognitive scores on all individual tests, see [online-only Data Supplement](#). In 6 SVD patients, 1 or 2 neuropsychological tasks were not performed because of mild motor deficit or insufficient comprehension of the task instructions.

Microstructural Integrity (Parenchymal Diffusivity D)

In patients with SVD, univariable analysis showed that higher D in NAWM, WMH, and CGM was significantly associated with lower scores on overall cognition, executive function,

information-processing speed, and memory, except for cortical D and memory and speed (Table 2). After correcting for age, sex, educational level, and Hamilton Anxiety and Depression Score, D was no longer associated with any cognition measure (Table 3). Age and educational level seemed to be important confounders because they largely explained the observed associations between D and cognition in the univariable analysis.

In a separate multivariable analysis for each subgroup (lacunar stroke and mVCI), D was not associated with cognitive function ([online-only Data Supplement](#)).

In controls, univariable analysis showed that higher D in the NAWM and CGM was associated with lower scores on executive function ($\beta = -0.436$; $P = 0.01$ for NAWM and $\beta = -0.338$; $P = 0.04$ for CGM). After correcting for age, sex, education level, and Hamilton Anxiety and Depression Score, these associations were no longer significant ([online-only Data Supplement](#)).

Microvascular Perfusion (fD^*)

In patients with SVD, lower fD^* in the CGM was significantly associated with lower performance in all cognitive domains in univariable analysis (Table 2). After correcting for age, sex, educational level, and Hamilton Anxiety and Depression Score, fD^* in the NAWM and CGM was significantly associated with overall cognition, executive function, and information-processing speed (Table 3). After additional correction for WMH volume and brain volume, the associations remained significant between fD^* in the CGM and overall cognition, executive function, and information-processing speed ($\beta = 0.246$; $P = 0.009$, $\beta = 0.247$; $P = 0.01$, and $\beta = 0.234$; $P = 0.02$, respectively).

In lacunar stroke patients, similar associations between fD^* and cognitive function were found in multivariable analysis, whereas no significant associations were found in mVCI patients ([online-only Data Supplement](#)).

In controls, univariable and multivariable analyses showed no association between fD^* and cognition ([online-only Data Supplement](#)).

There was no interaction effect between D and fD^* in the NAWM, WMH, or CGM on the association with cognitive function, in patients with SVD (data not shown).

Discussion

We examined the parenchymal microstructural integrity and microvascular perfusion concurrently in relation to cognitive function in SVD patients and age- and sex-matched controls, using IVIM imaging. We found that in SVD patients, lower microvascular perfusion in the NAWM and CGM was independently associated with lower overall cognitive function, executive function, and information-processing speed. This association was not observed in controls. Microstructural integrity was not associated with cognition.

The observed association between decreased microvascular perfusion in the NAWM and lower cognitive function supports earlier findings that NAWM in SVD may be affected before morphological abnormalities (ie, WMH) become evident and that NAWM changes may relate to clinical decline.^{8,25} In our study,

Table 1. Characteristics of SVD Patients and Controls

	SVD Patients (n=73)	Controls (n=39)
Age, y (SD)	70 (11)	69 (12)
Male sex, %	43 (59)	23 (59)
Educational level, %		
Low	34 (47)	13 (33)
Average	26 (36)	20 (51)
High	13 (18)	6 (15)
WMH volume (SD)*	0.014 (0.014)	0.005 (0.010)
Brain volume (SD)*	0.670 (0.050)	0.693 (0.039)
Hypertension, %	46 (63)	18 (46)
Hypercholesterolemia, %*	47 (64)	13 (33)
Diabetes mellitus, %	12 (16)	4 (10)
BMI, kg/m ² (SD)	25 (4)	27 (3)
Smoking, %*	18 (24)	3 (8)

Brain volume is brain volume normalized to intracranial volume, and WMH volume is WMH volume normalized to intracranial volume. BMI indicates body mass index; SVD, small vessel disease; and WMH, white matter hyperintensities.

* $P < 0.05$ for SVD patients compared with controls.

Table 2. Association Between Cognition and *D* and *fD in SVD Patients, Uncorrected**

	Overall		Executive		Speed		Memory	
	β	<i>P</i> Value	β	<i>P</i> Value	β	<i>P</i> Value	β	<i>P</i> Value
<i>D</i>								
NAWM	-0.376	0.001*	-0.380	0.001*	-0.285	0.02*	-0.309	0.01*
WMH	-0.356	0.002*	-0.406	<0.001*	-0.239	0.04*	-0.280	0.02*
CGM	-0.245	0.04*	-0.251	0.03*	-0.229	0.05	-0.161	0.17
<i>fD</i> *								
NAWM	0.142	0.23	0.121	0.31	0.141	0.23	0.106	0.37
WMH	-0.136	0.25	-0.177	0.14	-0.175	0.14	-0.018	0.88
CGM	0.311	0.01*	0.271	0.02*	0.281	0.02*	0.251	0.03*

β values represent standardized regression coefficients. CGM indicates cortical gray matter; NAWM, normal appearing white matter; SVD, small vessel disease; and WMH, white matter hyperintensities.

**P*<0.05.

the association between microvascular perfusion in the NAWM and cognitive function was no longer significant after correcting for WMH volume and brain volume. Apparently, WMH volume and particularly brain volume are strong confounders, and increases in WMH volume and decreases in brain volume possibly occur concurrently with changes in microvascular perfusion.

The strong association between cortical perfusion and cognition in SVD patients in our study, independent of WMH volume and brain volume, supports the currently evolving view that SVD is not a disorder solely restricted to the white matter. Increasing evidence suggests that cortical changes are integral in the disease process of SVD.^{1,26} Cortical thinning and cortical microinfarcts have recently been described in SVD and in relation to cognitive function.²⁷⁻³¹ A reduction of capillaries and venous density in the CGM have also been reported in SVD patients.^{32,33} It is presumable that although MRI abnormalities in the white matter are markers for SVD and associated with cognitive functioning, cortical thinning and cortical hypoperfusion are the main mediators for cognitive decrements in SVD patients. Whether reduced cortical perfusion is a cause or consequence of cortical changes in SVD cannot be deduced from our study.

Our finding that microvascular perfusion did not relate to cognition in age-matched controls may suggest that the association in SVD is not merely related to aging. However, it may also be because of the small variance of cognitive scores in our cognitive healthy controls.

In subgroup analysis, the association between microvascular perfusion and cognition was significant in lacunar stroke patients but not in mVCI patients. We presume that the underlying pathophysiology in both groups is SVD. However, differences may exist. The lacunar stroke group may be a more homogenous SVD group compared with the mVCI group as some of the mVCI patients may have coexisting pathologies such as amyloid angiopathy or Alzheimer pathology that also can affect cognitive function.³⁴

We found no association between microstructural integrity and cognitive function in SVD patients. Age and educational level had a strong confounding effect. Recently, a study using IVIM imaging examined the microstructural integrity in patients with WMH, and similarly, no significant association was found between microstructural integrity and cognitive function.³⁵ However, our finding is partly dissimilar to

Table 3. Association Between Cognition and *D* and *fD, in SVD Patients, Corrected for Age, Sex, Educational Level, and Hamilton Anxiety and Depression Score**

	Overall		Executive		Speed		Memory	
	β	<i>P</i> Value	β	<i>P</i> Value	β	<i>P</i> Value	β	<i>P</i> Value
<i>D</i>								
NAWM	-0.093	0.41	-0.130	0.27	-0.003	0.98	-0.108	0.39
WMH	-0.081	0.48	-0.191	0.10	0.005	0.97	-0.036	0.78
CGM	-0.021	0.84	-0.054	0.63	-0.009	0.94	-0.027	0.98
<i>fD</i> *								
NAWM	0.202	0.03*	0.197	0.04*	0.220	0.04*	0.115	0.28
WMH	-0.142	0.16	-0.160	0.12	-0.164	0.15	-0.055	0.62
CGM	0.289	0.002*	0.271	0.01*	0.304	0.01*	0.183	0.09

β values represent standardized regression coefficients. CGM indicates cortical gray matter; NAWM, normal appearing white matter; SVD, small vessel disease; and WMH, white matter hyperintensities.

**P*<0.05.

earlier diffusion tensor imaging studies showing an association between cognitive function and microstructural integrity in the WMH and in the NAWM.^{4,6} The difference is that the patients of these aforementioned studies were selected on extensive WMH on brain imaging, whereas ours was primarily based on clinical symptoms of SVD (ie, including lacunar stroke patients without any WMH). Therefore, it is possible that the group composition differs with regard to the stage of the disease process. Moreover, microstructural integrity (in terms of D) measured by IVIM is not confounded by the vascular components, whereas the diffusivity measure acquired by diffusion tensor imaging is contaminated by blood space contribution. Another methodological difference is that earlier DTI studies used multidirectional protocols, whereas our protocol was unidirectional. Some structures including white matter tracts are directionally oriented, and a unidirectional protocol might be less sensitive to provide D values that relate to cognition. However, an earlier IVIM study using a unidirectional protocol found an association between higher D and lower cognitive scores in patients with diabetes mellitus.²¹ Thus, although theoretically a protocol using multiple diffusion-sensitizing directions may provide more information, a unidirectional protocol should also be able to detect an association between D and cognition. Another study found an association between microstructural integrity in the NAWM and executive function in patients with lacunar stroke and extensive WMH.²⁵ However, they did not correct for educational level, which is an important determinant for cognitive function.

There was no interaction between microstructural integrity and microvascular perfusion on cognition. This suggests that in patients with SVD, the association between cognition and microvascular perfusion is independent of the microstructural integrity.

Our study has several strengths. We used clearly defined inclusion and exclusion criteria for SVD patients. This enabled us to have a well-represented spectrum of clinically overt SVD patients. By using IVIM imaging, we could examine microvascular perfusion and microstructural integrity simultaneously in their relation with cognitive performance. In addition, IVIM imaging has less contamination from large vessel signals and is, therefore, more targeted at microvascular perfusion compared with other MR perfusion sequences including dynamic susceptibility contrast MRI, making it a useful technique in studying SVD.^{11,36} Furthermore, in contrast to many other perfusion methods, IVIM imaging does not use exogenous contrast agents to measure perfusion, and it is, therefore, safe and patient friendly. Apart from the technical advantages, we performed extensive neuropsychological assessment, enabling us to examine a spectrum of cognitive domains. Moreover, in contrast to many earlier studies, we not only examined the white matter but also the CGM.

This study was limited by a single-axis (diffusion sensitization) IVIM protocol, as commented above. This may have led to less accurate IVIM values for the white matter. For the CGM, which is more isotropic at the imaging resolution scale, the use of a single-axis diffusion sensitization is not expected to have any influence. Furthermore, we did not perform carotid imaging in the nonstroke and control groups. IVIM imaging focuses on local microcirculation, but we cannot exclude an effect of arterial stenosis on the IVIM imaging

measures. Finally, as our study has a cross-sectional design, it is not possible to determine whether the relation between microvascular perfusion and cognition is of causative nature.

In conclusion, we have demonstrated that lower microvascular perfusion, but not microstructural integrity, in the NAWM and CGM is related to lower cognitive performance in SVD. Our results confirm the involvement of NAWM and emphasize the importance of cortical involvement in cognitive changes in SVD. Future, longitudinal studies with IVIM imaging should determine whether microvascular perfusion might be apparent before microstructural changes occur and can be used as a marker for disease progression in SVD.

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Disclosures

None.

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Supplemental Material

Intravoxel Incoherent Motion Imaging in SVD: Microstructural Integrity and Microvascular Perfusion Related to Cognition

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Supplemental Methods

Magnetic Resonance Imaging

All participants underwent standard brain imaging on a 3.0 Tesla MRI system (Achieva TX, Philips Healthcare, Best, The Netherlands). The MR protocol consisted of a T1 weighted, T2 weighted and fluid-attenuated inversion recovery (FLAIR) sequence.

After this standard protocol, IVIM imaging was performed using a Stejskal-Tanner diffusion weighted single-shot echo-planar-imaging spin echo pulse sequence (TR/TE = 6800/84 ms; FOV 221x269 mm²; acquisition matrix 110x112; 58 slices; 2.0x2.4x2.4 mm cubic voxel size; acquisition time 5:13 minutes).¹ To minimize the signal contamination of cerebral spinal fluid (CSF), an inversion recovery pulse (TI = 2230 ms) was given prior to the diffusion sensitization.² Fifteen diffusion weighted images were acquired in the anterior-posterior direction using multiple diffusion sensitive *b*-values (0, 5, 7, 10, 15, 20, 30, 40, 50, 60, 100, 200, 400, 700, and 1000 s/mm²). To increase the signal-to-noise ratio the numbers of signal averages for the highest two *b*-values were two and three respectively, whereas for all other *b*-values this was one.

Image Processing

Using Freesurfer software, white matter and CGM were segmented on T1 weighted scans.³ WMH were automatically segmented, with manual correction, on FLAIR scans to differentiate between normal appearing white matter (NAWM) and WMH.⁴ WMH volume was quantified and normalized to the intracranial volume. Parenchymal brain volume, normalized to total intracranial volume was used as a measure for atrophy.²⁴

IVIM images were corrected for image distortion and subject motion.⁵ Subsequently, the images were realigned with the T1-weighted image (FSL version 5.0) and smoothed with a 3-mm full-width-at-half-maximum Gaussian kernel (Statistical Parametric Mapping software application, Wellcome Department of Cognitive Neurology, UK).⁶

A two-compartment diffusion model was used to quantitatively model the diffusion attenuated signal.⁷ This model describes an intravascular and parenchymal (non-vascular) compartment. The intravascular compartment represents the fast water motion in blood flowing into a network of small vessels. This compartment provides a perfusion related measure, fD^* , in which D^* is the pseudo-diffusivity of water in the flowing blood and f is the fractional volume of blood. The extravascular compartment is described by the water diffusion in the parenchymal microstructure and gives rise to the parenchymal diffusivity D .

To account for the pre-pulse to suppress CSF and also differences in relaxation time of blood and tissue, we employed the modified IVIM model proposed by Hales and Clark.²

To calculate D and fD^* , model fitting was performed voxel-by-voxel using the two-step method introduced by Federau et al.⁸ Subsequently, values were obtained of D and fD^* for the NAWM, WMH and CGM. In this study we focus on D and fD^* as a surrogate measure for parenchymal microstructural integrity and microvascular perfusion, respectively.

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Supplemental Tables

Table I. Neuropsychological test scores in SVD patients and controls

	SVD	Controls
	Mean Score (SD)	Mean Score (SD)
Rey Auditory Verbal Learning Test		
Immediate recall*	32.1 (10.3)	36.1 (7.7)
Delayed recall*	5.4 (3.5)	6.6 (2.5)
Delayed recognition*	11.4 (3.2)	12.6 (2.0)
Stroop Colour-Word Test Part 1#*	57.8 (14.8)	50.1 (10.0)
Stroop Colour-Word Test Part 2#*	76.3 (20.1)	65.7 (13.5)
Stroop Colour-Word Test Part 3#*	153.9 (60.1)	119.5 (48.8)
Trail Making Test A#*	66.1 (34.5)	44.2 (15.3)
Trail Making Test B#*	179.2 (117.2)	106.4 (48.4)
Category Fluency*	30.3 (10.6)	39.0 (12.3)
Letter Fluency	24.8 (12.6)	28.7(10.5)
Symbol Substitution - Coding*	42.5 (18.7)	53.5 (18.3)
Digit Span Forward	7.4 (2.0)	7.8 (1.6)
Digit Span Backward	5.2 (1.8)	5.9 (1.5)
Letter Number Sequencing	6.7 (3.3)	7.6 (2.9)

Test score unit is in seconds

*p<0.05 when comparing SVD and Controls

Table II. Association between cognition and D and fD^* , in lacunar stroke patients, corrected for age, sex, educational level, Hamilton Anxiety and Depression Score

	Overall		Executive		Speed		Memory	
D	β	p -value	β	p -value	β	p -value	β	p -value
NAWM	-0.186	0.24	-0.183	0.29	-0.189	0.24	-0.121	0.48
WMH	-0.163	0.35	-0.302	0.11	-0.025	0.89	-0.106	0.57
CGM	-0.079	0.60	-0.111	0.50	-0.117	0.45	0.007	0.97
fD^*	β	p -value	β	p -value	β	p -value	β	p -value
NAWM	0.322	0.02*	0.310	0.04*	0.277	0.04*	0.261	0.08
WMH	-0.217	0.13	-0.231	0.14	-0.266	0.07	-0.091	0.56
CGM	0.370	0.01*	0.371	0.01*	0.320	0.02*	0.284	0.06

β values represent standardized regression coefficients. NAWM – normal appearing white matter; WMH – white matter hyperintensities; CGM – cortical grey matter

Table III. Association between cognition and D and fD^* , in mVCI patients, corrected for age, sex, educational level, Hamilton Anxiety and Depression Score

	Overall		Executive		Speed		Memory	
D	β	p -value	β	p -value	β	p -value	β	p -value
NAWM	0.122	0.55	0.019	0.91	0.334	0.13	-0.085	0.69
WMH	0.160	0.41	-0.022	0.90	0.244	0.25	0.097	0.63
CGM	0.050	0.81	0.029	0.87	0.151	0.51	-0.063	0.77
fD^*	β	p -value	β	p -value	β	p -value	β	p -value
NAWM	0.180	0.33	0.185	0.24	0.255	0.21	-0.023	0.90
WMH	-0.289	0.14	-0.307	0.07	-0.207	0.35	-0.139	0.51
CGM	0.160	0.42	0.125	0.46	0.317	0.14	-0.073	0.724

β values represent standardized regression coefficients. NAWM – normal appearing white matter; WMH – white matter hyperintensities; CGM – cortical grey matter

Table IV. Association between cognition and D and fD^* , in controls, corrected for age, sex, educational level, Hamilton Anxiety and Depression Score

	Overall		Executive		Speed		Memory	
D	β	p -value	β	p -value	β	p -value	β	p -value
NAWM	0.028	0.85	-0.212	0.18	0.079	0.67	0.193	0.16
WMH	0.010	0.94	-0.033	0.83	0.056	0.75	-0.006	0.96
CGM	-0.061	0.64	-0.204	0.16	-0.110	0.53	0.183	0.15
fD^*	β	p -value	β	p -value	β	p -value	β	p -value
NAWM	-0.087	0.50	-0.078	0.59	-0.167	0.33	0.056	0.66
WMH	0.035	0.80	0.212	0.17	-0.171	0.35	0.055	0.69
CGM	-0.105	0.414	-0.158	0.28	-0.137	0.43	0.060	0.64

β values represent standardized regression coefficients. NAWM – normal appearing white matter; WMH – white matter hyperintensities; CGM – cortical grey matter