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Cerebral Blood Flow in Ischemic Vascular Dementia and Alzheimer's Disease By Arterial Spin Labeling MRI

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Abstract

Background—The objectives were first to compare the effects of subcortical ischemic vascular dementia (SIVD) and Alzheimer's disease (AD) on cerebral blood flow (CBF) and second to analyze the relationship between CBF and subcortical vascular disease, measured as volume of white matter lesions (WML).

Methods—Eight mildly demented patients with SIVD (77 ± 8 years, 26 ± 3 MMSE) and 14 patients with AD were compared to 18 cognitively normal elderly. All subjects had CBF measured using arterial spin labeling MRI and brain volumes assessed using structural MRI.

Results—AD and SIVD showed marked CBF reductions in frontal ($p = 0.001$) and parietal ($p = 0.001$) cortex. In SIVD, increased subcortical WML were associated with reduced CBF in frontal cortex ($p = 0.04$) in addition to cortical atrophy (frontal: $p = 0.05$; parietal: $p = 0.03$).

Conclusions—Subcortical vascular disease is associated with reduced CBF in the cortex, irrespective of brain atrophy.

Keywords

Magnetic Resonance Imaging; Cerebral blood flow; Subcortical ischemic vascular dementia; Alzheimer's disease; Cortex; Segmentation; White matter lesions

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1. Introduction

Subcortical ischemic vascular dementia (SIVD) and Alzheimer's disease (AD) cause neurodegeneration in various regions of the brain, leading to brain dysfunction (1). However, the specific mechanisms that lead to brain deficits and ultimately cognitive impairment are controversial and remain to be elucidated, especially in SIVD (2). Imaging studies using Fluorodeoxyglucose Positron Emission Tomography (FDG-PET) and Single Photon Emission Computed Tomography (SPECT) respectively have shown reduced cerebral glucose metabolism and cerebral blood flow (CBF) in both SIVD and AD (see review (3)). In AD, diminished glucose metabolism and CBF exhibit a characteristic regional pattern including bilaterally parietal and temporal cortices (4-6), that can be seen already in preclinical stages of the disease (7). In contrast to AD, no major coherent regional metabolic or CBF pattern has been described in SIVD, although changes in preferentially frontal lobe regions have been reported (8-12). Furthermore, metabolic or CBF reductions in SIVD may correlate only weakly with dementia severity (13,14). The prominent MRI features of SIVD include cortical atrophy, subcortical infarcts (lacunes) and white matter lesions (WML) (15), which have been shown to correspond to poor executive performance (16). It has therefore been suggested that ischemic WML, potentially disrupting subcortical-to-cortical connections, may explain the regional heterogeneity of metabolic and CBF patterns in SIVD and their complex relationship to dementia severity (17). This idea has been recently supported by a FDG-PET study, which found a strong relationship between WML and cortical metabolic reductions especially in frontal lobe regions in SIVD, irrespective of the location of WML (17). However, other studies failed to detect similar relations between WML and cortical glucose metabolism (18) or blood flow in SIVD (14,19,20). Since a disruption of subcortical-cortical connections by subcortical ischemic lesions could be a major mechanism for cognitive impairment in SIVD (21) that may also have profound consequences for developing effective treatment strategies, further investigations into the relationship between cortical deficits and subcortical WML are warranted.

A major technical complication for PET and SPECT, which may have contributed to inconsistent metabolic and CBF findings in SIVD, is the so-called partial volume effect (PVE) in which variable contributions of gray matter, white matter, and cerebrospinal fluid (CSF) may mimic metabolic or CBF variations. In particular for measurements in cortical regions, PVE can induce an artificial dependence on WML since WML are also associated with loss of cortical gray matter (15,22). Although a few PET and SPECT studies in SIVD considered PVE (17,18), the majority did not include corrections, which may have biased findings of reduced glucose metabolism and CBF in patients with WML. Moreover, no study before corrected simultaneously for gray matter, white matter and WML variations. Arterial spin labeling (ASL) MRI (23), which deploys magnetically labeled endogenous blood water as tracer and thus is entirely non-invasive, has been used recently to map CBF abnormalities in AD (24,25) and frontotemporal dementia (26). In this study, we used ASL-MRI to compare the pattern of CBF reduction between AD and SIVD. Moreover, we corrected ASL-MRI data for PVE from WML as well as for gray matter, white matter, and CSF variations using information from co-registered structural MRI data.

The main goals in this study were twofold: First, to measure the extent to which SIVD and AD are each associated with CBF reductions, irrespective of regional gray matter, white matter, and WML variations and second to determine if the CBF reductions of cortical gray matter are associated with subcortical disease, quantified as WML volumes.

2. Methods

2.1 Demographics

The sample was drawn from the vascular dementia program project, a prospective longitudinal study of SIVD, AD and normal aging at three university-affiliated dementia centers (27), and involved subjects who had successfully completed both structural MRI and ASL-MRI. The sample included 8 patients with a clinical diagnosis of SIVD (mean age 77 ± 8 years, 2 women and 6 men), 14 patients with AD (mean age 74 ± 5 years, 6 women and 8 men), and 18 cognitive normal (CN) subjects (mean age 73 ± 8 years, 8 women and 10 men). SIVD was diagnosed according to the criteria of the State of California Alzheimer's Disease Diagnostic and Treatment Centers (ADDTC) (28). However, the possibility that some or even all of the SIVD subjects might have had AD cannot be ruled out short of autopsy. The critical difference between the SIVD and AD groups was imaging evidence of lacunar infarction temporally related to cognitive decline in the former, and lack of lacunes in the latter group. We recognize that many patients with clinical diagnosis of SIVD by these criteria can have mixed AD/SIVD pathology at autopsy (29). AD was diagnosed according to NINCDS/ADRDA criteria (30). Dementia was established according to DSM-IV criteria (31). In one AD patient in this sample and one SIVD was the clinical diagnosis confirmed by autopsy. As part of the multicenter collaborative study, all subjects received a unified battery of neurological, neuropsychiatric, and cognitive evaluation at each center, as described in previous publications (27,32,33). All subjects gave written informed consent before participating in the study, which was approved by the Committees of Human Research at the Universities of California in San Francisco and Davis and the Veterans Administration Medical Center in San Francisco, where the MRI studies were performed.

2.2 MRI

Subjects had perfusion and structural MRI scans less than 30 minutes apart on a 1.5 Tesla MR scanner (Siemens Medical Systems, Inc), equipped with a single channel transmit/receive head coil. Perfusion was measured using the quantitative imaging of perfusion single subtraction method, termed QUIPSS II (34)-modified EPSTAR (35) sequence. The perfusion signal was mapped using a single shot echo planar imaging (EPI) sequence with $2.0 \times 2.0 \text{ mm}^2$ inplane resolution, 128×128 base matrix size and with 6/8 partial k-space acquisitions. Six contiguous slices, each 9 mm thick and axially oblique angulated along the anterior-posterior commissure, were collected in proximal to distal order from the labeling plane. The 6 slices of ASL-MRI covered the frontal, parietal, occipital and superior temporal lobes. The partial volume associated with 9mm thick slices was accounted for by co-analysis with structural MRI data, as described in more detail below. Average signal-to-noise of the unprocessed perfusion weighted images was usually higher than 15:1. The MRI scanner was monthly serviced, including calibration of RF and magnetic field gradients. ASL was achieved by selecting a 90mm tagging slab, positioned 65mm inferior to the center of the lowest image plane, approximately coinciding with the circle of Willis. Other parameters of the perfusion sequence were: 1700 ms repetition time (TR), 15 ms echo time (TE), 600ms interval (TI_1) between the tagging pulse and start of the bolus saturation pulse in QUIPPS II and 1500ms post tagging delay (TI_2). Fifty interleaved tag and control scans were averaged to obtain a sufficient signal to noise ratio for ASL-MRI. In addition to perfusion, structural MRI data were obtained using a volumetric magnetization prepared rapid gradient echo (MPRAGE) sequence (TR/TE/ TI =10/4/300ms, $1.0 \times 1.0 \text{ mm}$ inplane resolution and 1.5mm thick slices) and a double-spin echo (DSE) sequence (TR/TE1/TE2 = 5000/20/80ms, $1.0 \times 1.0 \text{ mm}$ inplane resolution and 3.0mm thick slices).

2.3 MRI Segmentation

Tissue segmentation was based on simultaneous evaluations of the T1-, T2-, and density-weighted image contrasts, as described in a previous publication with minor modifications (36). Furthermore, the main brain lobes were identified on each subject's MRI data using high dimensional brain warping of an anatomically labeled atlas brain to the individual brains, as previously described (37). In short, first-pass segmentation of whole-brain MRI data into the primary tissue categories of gray matter, white matter, and CSF was performed by an automated procedure based on K-means cluster analysis. The initial automated process was followed by manual editing of the axial segmented images on a slice by slice basis. Specifically, a trained technician reclassified pixels as white matter lesions (WML) that had been classified by the K-means procedure as either gray matter or CSF due to their relative hyperintensity, but were clearly white matter by anatomic location. In addition, gray matter was separated into cortical gray matter (cGM) and subcortical gray matter. Tissue volumes, including those of WML were computed by summing over all voxels with the corresponding tissue labels. The operators were blinded to all clinical information. Finally, a brain template of frontal, parietal, temporal, and occipital labels, was warped to each individual segmented MRI to identify cGM and WM by each main lobe (37). Atrophy was measured by computing lobe volumes based on the tissue segmented images.

2.4 CBF Quantification

Perfusion-weighted imaging (PWI) data were obtained by subtracting the labeled images from the control images. To minimize signal contamination from large blood vessels, PWI voxels with intensities brighter than 3 standard deviations of the median perfusion weighted signal in each subject were eliminated. For the remaining PWI voxels, CBF was computed based on a single compartment and instant equilibrium model for a blood tracer (34), according to:

$$\Delta M = 2M_{0b} \cdot f \cdot \frac{\alpha}{\lambda} \cdot TI_1 \cdot e^{(-TI_2 \cdot R_{1b})} \quad [1]$$

Here, ΔM is the perfusion weighted signal, derived from the difference between label and control scan, M_{0b} is the equilibrium magnetization of arterial blood and f represents cerebral blood flow in units of ml/100g/min. α and λ describe the labeling efficiency and the tissue-to-blood partition, respectively. It was assumed that α and λ have each a value of 0.95, are same for patients and controls, and hence their ratio is practically unity. TI_1 is the interval between the labeling pulse and the start of the bolus saturation pulses in QUIPPS II and TI_2 is the post labeling delay. Per definition, TI_2 is a function of the slice order as blood flow advances from the labeling gap to the distal slice position in the brain. R_{1b} is the longitudinal relaxation rate of arterial blood. For quantification of CBF, we assumed $1/R_{1b} = 1200\text{ms}$ (38) and derived M_{0b} - as described in reference (34) - from the signal of white matter M_{wm} in a single shot EPI images ($TR = \infty$) according to $M_{0B} = k \cdot M_{WM} \cdot e^{(R_{2WM} - R_{2B})TE}$. We assumed for $1/R_{2WM}$ and $1/R_{2B}$ values of 80ms and 200ms, respectively and for the scaling factor k a value of 1.06 to adjust for a lower WM than blood signal (34).

2.5 Structural and Perfusion MRI Co-Analysis

Image registration between structural and perfusion images was done in two steps. First labeled and control images of perfusion, which have T2 contrast, were registered to the structural T2-weighted image using normalized mutual entropy (39). Second, the T2-weighted image was then registered to the T1-weighted image and the same transformation was applied to the label and control image to finally align the perfusion image with the T1-weighted image and correspondingly with the segmented image data. The next goal of the analysis was to estimate

for each PWI voxel the tissue weight W^{Tissue} (in units of volume) for each tissue type (i.e. cGM or WM) and anatomical region (frontal, parietal, temporal, or occipital lobe) using information from the segmented MRI data, similar to a method that has previously been outlined in detail for spectroscopic imaging data (40). For this, the segmented MRI data was down-sampled to the resolution of the PWI data using nearest neighbor interpolation.

The next goal of the analysis is the formulation of a reliable method for the estimation of CBF of “pure” cortical gray matter or white matter in each brain region, i. e. left or right frontal, parietal, or temporal lobes for each subject. (The occipital lobe was not included in the final analysis, because it contributed only a few voxels compared to the other lobes and thus estimations for the occipital lobe had large margins of error). With the assumption that such levels exist and that predominantly gray matter and white matter give rise to the perfusion weighted signal, the simplified model for CBF becomes:

$$CBF_n = X^{cGM} * W_n^{cGM} + X^{WM} * W_n^{WM} + Bias(W_n^{cGM}, W_n^{WM}) + error. \quad [2]$$

Here, n runs through all voxels in one of the lobes. X^{cGM} and X^{WM} represent respectively the contributions of cortical gray matter and white matter to CBF and are synonymous with flow rates (ml/100mg/min) in this context. W_n^{cGM} and W_n^{WM} are the weights of cortical gray matter and white matter in the voxels, respectively. $Bias(W_n^{cGM}, W_n^{WM})$ represents spurious contributions of other tissue types, such as WML or subcortical gray matter to CBF. The bias term is, by hypothesis, a function of the weights W_n^{cGM} and W_n^{WM} , because the lower their sum for a voxel the more likely it is that WML or subcortical gray matter are contributing to CBF. A major exception to this is when the rest of the voxel contains CSF, which contributes nothing to the PWI signal. The error term represents simply the error from estimations of the PWI signal itself and is assumed to be reasonably Gaussian distributed. The model was fit using a multiterm linear regression algorithm (SPLUS, Mathsoft Inc, Seattle) to obtain estimations for X^{cGM} and X^{WM} . Furthermore, the accuracy for X^{cGM} and X^{WM} was determined, especially given the possibility of bias induced by WML using the width of 95% confidence intervals of the regression fits. These confidence intervals were constructed by refitting X^{cGM} and X^{WM} from a set of 1000 resample observations using a general nonparametric bootstrap procedure. Signal contributions corresponding to the bias term in Eq. [2] were discriminated by comparing mean and median values of the confidence intervals, according to $bias = (mean - median)/mean$. For bias values larger than ± 0.05 , some PWI voxels with high tissue weights of WML were removed before refitting the regressions until a bias of less than or equal to ± 0.05 was obtained. Note, that the error associated with perfusion measurements in white matter is substantially greater than that in gray matter given the relatively long transit times of white matter and short life of the spin labels at 1.5T. Since analyses of both perfusion and segmentation are performed on large areas (entire lobes), no additional spatial smoothing is required to reduce registration errors. Since complete coverage of the lobe was not possible with ASL-MRI, the intersection in volume between all subjects was used to make an analysis consistent.

A representative dataset of T1-weighted structural MRI, the corresponding tissue segmentation map, and the corresponding PWI data set, all co-registered to each other, is depicted in Figure 1. The color-coded maps represent cortical gray matter of different lobes. Similarly, white matter of different lobes represented in different gray scales. CSF is shown in dark gray. Representative linear regression plots of CBF against the cortical gray matter volume fraction in PWI voxels, described in Equ. 2, are shown in Figure 2, including the 95% confidence intervals of the regression estimates. The data are from the frontal lobe of a 77 years old cognitively normal male subject (A) and a 79 years old patient diagnosed with SIVD (B). This

shows first an overall reduction of CBF for the patient in both white matter and gray matter compared to the control subjects and second different regression slopes between white matter and gray matter perfusion for the two subjects. Other subjects showed similar patterns. The figures also illustrate that PVE correction is essential to accurately capture the difference in CBF between the patient and control.

2.6 Statistics

Multivariate analysis of variance (MANOVA) with Wilks' lambda approximation was used to determine if variations of CBF or volume measures in the different brain lobes were overall explained by diagnosis and WML. Wilks' lambda, a generalization of univariate F-distribution, was used to take correlations between the regional CBF measures into account when performing the significant tests (41). The MANOVA tests were followed by Scheffe post-hoc tests to account for multiple comparisons. Sex, age and MMSE were used as covariates when appropriate. Spearman rank correlation analysis was used to test relationships between CBF or cortical gray matter volumes and WML, which were log transformed to account for the skewed distribution of WML between the groups. The significance level of all tests was $\alpha < 0.05$. (SPLUS, Mathsoft Inc, Seattle) was used for all computations.

3. Results

Demographics and clinical information of the subjects, including amounts of WML and number of lacunes based on MRI evaluations, are summarized in Table 1. Differences in age, years of education, and gender distribution between the groups were not significant (all $p > 0.3$). Most SIVD and AD patients were mildly demented based on Mini-Mental State Examination (MMSE) and Clinical Dementia Rating (CDR) scores. As expected, AD and SIVD patients had significantly lower MMSE and CDR scores than control subjects ($p = 0.001$) but score differences between AD and SIVD patients were not significant ($p = 0.14$). Based on MRI results, SIVD subjects had on average substantially more WML compared to AD and controls (both $p < 0.001$), whereas AD and control subjects had similar amounts of lesions.

Table 2 lists the main results for CBF of cortical gray matter (in ml/100mg tissue/min) and volumes (in percentage of total intracranial volume) by groups, separately for the brain lobes. Overall, dementia was strongly associated with reduced CBF in the frontal cortex ($F(3,36) = 11.5$; $p < 0.002$) and in the parietal cortex ($F(3,36) = 15.6$; $p < 0.001$) and somewhat ($p = 0.08$) in the superior temporal cortex. The CBF reductions in frontal and parietal cortex remained significant after accounting for variations of log WML and age among the groups. Post-hoc tests revealed that both SIVD and AD patients had significantly reduced CBF values compared to CN subjects in the frontal and parietal cortex. Although CBF differences between SIVD and AD were not significant, the CBF values were quite a bit lower in SIVD than AD and more prominent than the volume reductions. In addition to diagnosis, increased log WML was separately associated with reduced CBF values across the groups. Specifically, log WML explained 11% ($F(4,35) = 6.6$; $p = 0.02$) of CBF reduction in the frontal cortex compared to diagnosis explaining 32% of the reduction. Similarly, log WML explained 18% ($F(4,35) = 12.5$; $p = 0.002$) of the CBF reduction in the parietal cortex, compared to diagnosis explaining 30% of the reduction. In SIVD, the CBF reduction in the frontal cortex correlated with log WML (frontal: $r = -0.76$, $p = 0.04$), whereas a similar correlation in the parietal cortex did not reach significance ($r = -0.59$, $p = 0.07$). No significant correlation between cortical CBF and log WML were found for AD and control subjects. The relationships between reduced CBF and increased log WML volumes are shown in Figure 3 for frontal and parietal cortex, separately for each group.

Results of brain volume loss (in percentage of total intracranial volume) in SIVD and AD are summarized in Table 2, separately for each lobe. Similar to CBF, dementia was associated with

marked volume loss of cortical gray matter in the frontal ($F(3,36) = 7.1$; $p = 0.003$), parietal ($F(3,36) = 15.5$; $p = 0.001$), and temporal lobe ($F(3,36) = 14.4$; $p = 0.001$), but not in the occipital lobe ($F(3,36) = 3.1$; $p = 0.06$). A significant association between increased log WML and cortical gray matter loss was found for the parietal lobe ($F(4,35) = 5.9$; $p = 0.02$), with log WML explaining 8% of the loss compared to 44% explained by diagnosis. In SIVD alone, cortical gray matter volumes in the frontal lobe correlated with increased log WML ($r = -0.74$, $p = 0.05$), similar to the finding for frontal lobe CBF. In addition, cortical gray matter in the parietal lobe also correlated with WML ($r = -0.78$, $p = 0.03$), in contrast to CBF findings. In AD and control subjects, no significant correlations between cortical gray matter volumes and WML were found.

4. Discussion

In this study we investigated differences in CBF between SIVD and AD and further explored if CBF reduction is modulated by subcortical vascular disease as evidenced by white matter lesions. The main findings are: First, SIVD and AD are associated with substantial CBF reductions in both frontal and parietal cortex, irrespective of brain atrophy, gray/white matter partial volumes, and WML. Second, cortical CBF reductions correlate with subcortical vascular disease, consistent with the hypothesis that dementia in SIVD is induced by subcortical-cortical disconnections.

To measure cortical CBF in SIVD and AD irrespective of cortical atrophy and WML, we performed PVE corrections based on a four compartment tissue model to account for variations of CSF, white matter, gray matter, and WML using segmented volumetric MRI data co-registered to ASL-MRI. Although most PET and SPECT studies in SIVD did not account for PVE, some have reported PVE corrections (17,42,43). However, previous PVE corrections were limited to either 2- compartment methods, accounting for diluting effect of CSF spaces or 3-compartment methods, considering partial volume averaging between gray and white matter in addition to CSF spaces, but none included partial volume averaging of WML. We further used bootstrapping to obtain unbiased estimates CBF of cortical gray matter without relying on a normal distribution of regional differences of tissue loss and WML. While our approach aimed eliminating PVE, we sacrificed resolving regional CBF variations within brain lobe since CBF needs to be regressed against many voxels with varying amounts of gray and white matter for robust estimates of CBF of pure gray or white matter. We have previously used a similar approach to obtain PVE corrected MR spectroscopic imaging data in SIVD (44).

Our first finding of substantial CBF reductions in frontal and parietal cortex in SIVD is consistent with many PET and SPECT reports of respectively reduced cortical glucose metabolism and CBF reduction in SIVD. Our results further indicate that CBF reduction and gray matter atrophy co-exist in cortical regions in SIVD. A $H_2^{15}O$ PET study of CBF patterns in SIVD and AD found regional CBF defects primarily in the frontal cortex in patients with SIVD, whereas AD patients had CBF deficits primarily in temporal and parietal lobe regions (45). The SIVD patients in our study had substantial CBF reduction in both frontal and parietal cortical regions, potentially indicating mixed pathology. Moreover, the distribution of cortical atrophy in these patients paralleled the distribution of CBF reduction. Our data agree with imaging-autopsy correlation studies showing AD pathology and cerebrovascular disease often coexist (27).

An unexpected finding in AD is that CBF reductions in the frontal cortex are similar to those in the parietal cortex. PET and SPECT find metabolic and CBF deficits typically in parietal and temporal regions in AD (4-6). In a previous ASL-MRI study in a different cohort of AD patients, we also found CBF reductions primarily in parietal brain regions (25). However,

findings of frontal lobe metabolic and CBF deficits in AD are not uncommon, especially in patients with concomitant psychiatric symptoms, including depression (46). Four of the 14 AD patients had a history of depression but the number of subjects was too small to determine with reasonable confidence whether those with depression had greater frontal involvement than the other patients. It is also possible that the AD patients presented mixed etiologies, including cerebrovascular disease and amyloid angiopathy, which are common in older AD patients (47). Eventually, it will be necessary to obtain autopsy information to exclude concurrent cerebrovascular disease and cerebral amyloid angiopathy as potential cause of frontal lobe hypoperfusion in these AD patients.

Our second finding of a strong correlation between decreased frontal lobe CBF and WML agrees with recent PET findings in SIVD (17,48). We also found a strong correlation between cortical gray matter loss and WML that involved both frontal and parietal lobe regions. There are several possible interpretations for these findings. First, subcortical infarctions may be responsible – at least in part – for cortical neurodegeneration and secondary reduction of CBF and gray matter loss. A second possibility is that WML represent generalized cerebrovascular disease, possibly causing CBF reduction due to limited blood supply, which then leads secondarily to cortical atrophy. Furthermore, this generalized cerebrovascular disease could be associated with cortical ischemia/infarction, which is not detected by structural MRI (47). However, the regional frontal effect of WML on cortical CBF in our study may speak against this assumption since cortical microinfarctions are typically symmetrically distributed throughout frontal and posterior cortical regions (47).

In contrast to our findings, several other studies failed to detect correlations between WML and cortical glucose metabolism (18) or blood flow (14,19,20). These studies have used global and in most cases semiquantitative measures of white matter lesions. Moreover, these studies did not account for PVE effects on PET and SPECT measures, which may have increased measurement variability and hence decreased power to detect an effect. These factors should be taken into account when looking for effects of WML on cortical deficits.

Several limitations of the study should be mentioned: We used clinical and not autopsy data for patient classification, although in two cases, one AD and another SIVD, diagnosis has been confirmed. It is generally recognized that an accurate prediction whether a patient has AD or SIVD is difficult to make antemortum. Furthermore, autopsied cases in this SIVD program project study show that many patients diagnosed with SIVD have mixed AD/SIVD pathology (27). Thus, some SIVD patients in this study may have had concurrent AD pathology, whereas some AD patients had likely vascular disease and may have lacked AD pathology. Another limitation is that some AD patients were taking cholinesterase inhibitors and anticholinergic drugs that could have altered brain function, potentially enhancing CBF differences between AD and SIVD. Another limitation is the small sample size, which limits confidence in the statistical significance of the findings. The findings need to be replicated in a larger cohort of patients. A technical limitation is that we did not control for potential differences of perfusion transit times between the groups to deliver labeled blood water to the imaging plane, which may have increased CBF differences. New technical developments in ASL, including full volumetric acquisitions, can circumvent problems with transit times by measuring the entire inflow dynamics of the ASL signal. Finally, detection of cortical atrophy and WML was compromised, because tissue segmentation involved T2-weighted MR images with relatively low resolution (4.2 mm³). It is possible that different results would be obtained if tissue segmentation were performed with MRI at higher resolution.

This study is the first using ASL-MRI to investigate regional CBF alterations in SIVD. As such, ASL-MRI yielded strikingly similar findings with those from PET and SPECT. ASL-MRI offers several advantages to PET and SPECT, including higher patient safety since no

injection of radioactive tracers is required, greater availability because ASL can be performed on standard clinical MRI scanners. Promising new technical innovations of ASL, such as full volumetric brain coverage at high spatial resolution and with improved sensitivity will greatly facilitate future investigations of regional CBF alterations in AD and vascular dementia (49). Future investigations with ASL-MRI also need to shed light on the extent to which altered perfusion predicts cognitive decline and dementia. As treatments for AD and vascular brain injury are under development, predictors of cognitive decline and dementia will play an important role for the assessment of effective treatment intervention.

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Figure 1.

Representative set of T1-weighted structural MRI (A), corresponding tissue segmentation map (B), and corresponding perfusion weighted imaging data (C), all co-registered to each other.

The color coded segmentation maps shows cortical gray matter of different lobes (frontal lobe: blue = left, red = right; parietal lobe: dark green = left, light green = right occipital lobe; orange = left). Similarly, white matter of different lobes is represented in different gray scales.

Cerebrospinal fluid is shown in dark gray. For the process of PVE correction, the segmentation map will be blurred to the resolution of the perfusion weighted image.

Figure 2.

Representative linear regression plots and 95% confidence intervals of cerebral blood flow (CBF) against volume fractions of cortical gray matter in perfusion weighted images voxels. Data in (A) are from the frontal lobe of a 77 years old cognitively normal male subject, those in (B) are from a 79 years old patient diagnosed with SIVD. This shows an overall reduction of CBF in both white matter and gray matter for the patient compared to the cognitive normal subjects. Furthermore, the patient has a flatter slope of the CBF regression than the control subject, indicating CBF of cortical gray matter is disproportionately more reduced compared to CBF of white matter in the patient than in the control subject. The confidence intervals of the regression reflect 1000 fold resampling the data by bootstrap to illustrate the actual procedures in this study for estimations of CBF.

Figure 3.

Relationship between cerebral blood flow of frontal (A) and parietal (B) cortex as a function of subcortical WML lesions. Note, the log of WML is plotted to reduce the skewed distribution of WML between the groups. Symbols indicate (●) SIVD, (○) AD and (□) control subjects. The arrows point to two subjects with confirmed diagnosis by autopsy.

Table 1

Demographics and Clinical Summary

Group	SIVD	AD	Control
N	8	14	18
Age (years)	77 ± 8	74 ± 5	73 ± 8
Women/Men	2/6	6/8	8/10
Years Education	13.7 ± 3.7	15.1 ± 3.4	15.4 ± 3.8
MMSE*	26.4 ± 2.8	23.0 ± 5.9	29.5 ± 0.5
CDR ^{\$}	0.7 ± 0.3	0.9 ± 0.6	0
WML volumes (%) [#]	1.9 ± 1.1	0.4 ± 0.2	0.5 ± 0.5

* Minimental State Examination score;

^{\$} Clinical Dementia Rating score;

[#] White matter lesion volumes in percentage of total intracranial volume;

Significance of differences between groups; more results in the main text.

Age: $F(2,37) = 1.36$; $p = 0.3$

Years of Education: $F(2,37) = 0.51$; $p = 0.6$

MMSE: $F(2,37) = 7.29$; $p = 0.001$

CDR: SIVD versus AD: $p = 0.31$

WML: $F(2,37) = 14.28$; $p < 0.001$;

Table 2
Cortical gray matter CBF and volumes in the major brain lobes by groups and group differences

Gray Matter	SIVD	AD	Normal	SIVD vs. Normal	AD vs. Normal	SIVD vs. AD
CBF *						
Frontal Lobe	38.9 ± 14.4	41.2 ± 10.9	56.4 ± 7.9	-31% (p = 0.002)	-27% (p = 0.001)	-6% (p = 0.2)
Parietal Lobe	35.5 ± 11.7	43.6 ± 11.7	58.7 ± 9.8	-39% (p = 0.001)	-26% (p = 0.001)	-18% (p = 0.1)
Temporal Lobe	37.6 ± 12.6	45.5 ± 15.2	52.7 ± 19.1	-28% (p = 0.1)	-13% (p = 0.3)	-17% (p = 0.2)
Volume[§]						
Frontal Lobe	14.0 ± 1.3	14.1 ± 1.2	15.1 ± 0.9	-7% (p = 0.03)	-7% (p = 0.04)	-1% (p = 0.8)
Parietal Lobe	6.2 ± 0.5	6.3 ± 0.5	7.1 ± 0.5	-13% (p = 0.02)	-11% (p = 0.02)	-2% (p = 0.6)
Temporal Lobe	8.4 ± 0.9	8.7 ± 0.7	9.8 ± 0.7	-14% (p = 0.02)	-11% (p = 0.03)	-3% (p = 0.4)

* CBF in ml/100mg tissue/min;

[§]Volumes in percentage of total intracranial volume;