Lower cerebral blood flow is associated with impairment in multiple cognitive domains in Alzheimer's disease

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Abbreviations

AD	Alzheimer's disease
PCASL	Pseudo-continuous arterial spin labeling
CBF	Cerebral blood flow
MCI	Mild cognitive impairment
MMSE	Mini mental state examination
MRI	Magnetic resonance imaging
PVC	Partial volume corrected
SCD	Subjective cognitive decline
WMH	White matter hyperintensities

1. Introduction

Alzheimer's disease (AD) is the most common neurodegenerative disease that causes dementia. Hallmark of AD is severe cognitive impairment with interference in daily living. In addition to structural brain changes such as volume loss, AD patients have decreased cerebral blood flow (CBF) [1–3]. Regional CBF mapping can be accomplished with MRI-based arterial spin labeling (ASL). ASL is a non-invasive MRI-technique that uses magnetically labeled water as a tracer for blood flow.

Decreased CBF is thought to reflect neuronal dysfunction and synaptic failure, the latter is considered to be the best correlate of cognitive decline in AD [4–7]. Decreased CBF as a reflection of synaptic failure is possibly one of the determinants of cognitive impairment. In a former study, we found that in mild cognitive impairment (MCI) and AD patients lower ASL-measured CBF was related to more severe global cognitive impairment (measured with the Mini-Mental State Examination (MMSE)) [3]. Several previous studies have investigated the association between CBF and cognitive impairment and found a relationship between lower CBF and worse cognitive performance [3,8–11]. Comparability is hampered however, by small sample sizes and the use of only a cognitive screening test, or a few neuropsychological tests to evaluate cognitive impairment.

Based on earlier findings, we hypothesized that whole-brain and regional CBF would correlate with cognitive functioning in a memory clinic population. We expected this association most prominently in AD providing support for ASL-CBF as a measure for disease severity. To test this hypothesis, we investigated the associations between ASL-CBF and performance in specific cognitive domains in a large sample of patients with subjective cognitive decline (SCD), MCI and AD using an extensive and standardized neuropsychological test battery.

2. Methods

2.1 Subjects

We included 399 patients (143 SCD, 95 MCI, 161 AD patients) with available ASL and standardized neuropsychological assessment from the memory clinic based Amsterdam Dementia Cohort [12]. All patients visited our memory clinic between October 2010 and November 2012 and underwent standardized brain MR imaging at 3T, organized in a one-day standardized dementia screening that included medical history, physical and neurological examinations, screening laboratory tests and neuropsychological assessment. Clinical diagnosis was established by consensus in a multidisciplinary team [12]. AD patients met the NINCDS-ADRDA criteria (proposed by National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association) for probable AD [13], and also met the core clinical criteria for probable AD proposed by the National Institute on Aging-Alzheimer's Association (NIA-AA) workgroup [14]. Diagnosis of MCI was based on the Petersen and NIA-AA criteria for MCI [15,16]. Patients were considered to have SCD when they presented with cognitive complaints, and results of clinical assessments were normal (i.e. criteria for MCI or psychiatric disorder were not fulfilled and other underlying neurological or psychiatric diseases were ruled out) [17,18]. For all patients, the presence of vascular risk factors (i.e. hypertension, hypercholesterolemia, and diabetes mellitus) was determined based on self-reported medical history and medication use. Smoking status was defined as never, former or current. Level of education was classified according to the system of Verhage ranging from 1 to 7 (low to highly educated) [19]. The study was approved by the medical ethics committee of the VU University Medical Center. All patients provided written informed consent for their clinical data to be used for research purposes.

2.2 Neuropsychological assessment

Cognitive functioning was assessed by a standardized neuropsychological test battery. We assessed global cognition and five cognitive domains. For global cognition, we used the MMSE [20]. For memory, we used the Visual Association Test (VAT) and the total immediate recall and delayed recall of the Dutch version of the Rey Auditory Verbal Learning Test (RAVLT) [21,22]. To examine language, we used the VAT naming, category fluency (animals), the Dutch version of the Controlled Oral Word Association Test (COWAT) [letter fluency], and the comparative questions and naming condition of the Arizona Battery for Communication Disorders (ABCD) [21,23–26]. For attention we used the Trail Making Test (TMT) part A, the Letter Digit Substitution Task (LDST), the forward condition of the Digit Span and the Stroop Test card I and II [27–30]. To examine executive functioning, we used the TMT part B, the backward condition of the Digit Span, Stroop Test card III and the Frontal Assessment Battery (FAB) [27–29,31]. To assess visuospatial functioning we used three subtests of the Visual Object and Space Perception (VOSP) battery, namely (i) incomplete letters, (ii) dot counting and (iii) number location [32].

Neuropsychological data were standardized into z-scores. TMT A and B and the Stroop Test scores were log-transformed due to non-normal distribution and inverted by computing $-1*z$-score, so that higher scores imply a better performance. In patients where the TMT B was aborted (n = 81), we estimated TMT B by multiplying the time needed to complete TMT A with the mean B/A index. The mean B/A index for all patients who completed both TMT A and B (n = 318) was 2.99. On the other tests, 1 to 11% of the test scores were missing and these scores were not imputed. Raw neuropsychological test scores were standardized into z-scores across the entire group. Subsequently, available test scores were averaged to create five cognitive domains (i.e. memory, language, attention, executive functioning and visuo-spatial functioning).

2.3 MRI protocol

MR imaging was performed on a 3T whole body MR system (Signa HDxt, GE Medical Systems Milwaukee, WI, USA) using an 8-channel head coil. The MRI protocol included T1-weighted, T2-weighted, fluid attenuated inversion recovery (FLAIR) and gradient echo T2*-weighted images. Global cortical atrophy (GCA) was defined on axial FLAIR images (range: 0-3) [33] and the severity of white matter hyperintensities (WMH) using the Fazekas scale was determined on the FLAIR sequence (possible range: 0-3) [34], both were dichotomized into absent (0-1) or present (2-3). Medial temporal lobe atrophy (MTA) was determined on coronal T1-weighted images using the Scheltens scale (range: 0-4) [35], the mean of left and right MTA scores were dichotomized into MTA absent (<1.5) or MTA present (≥1.5). Lacunes

were defined as deep lesions (3-15mm) with CSF-like signal on all sequences. Lacunes were scored as absent or present.

Pseudo-continuous ASL (pcASL) perfusion images (3D-FSE acquisition with background suppression, post-label delay 2.0s, echo time=9ms, repetition time=4.8s, spiral readout 8 arms x 512 samples; 36x5.0mm axial slices, 3.2x3.2mm in-plane resolution, reconstructed pixel size 1.7x1.7mm, acquisition time 4 minutes) were calculated using a single compartment model after the subtraction of labeled from control images [36].

2.4 Pre-processing and MRI data analysis
Both T1-weighted and pcASL images were corrected for gradient non-linearities in all three directions. Further data analyses were carried out using FSL (version 4.1; http://www.fmrib.ox.ac.uk/fsl). Pre-processing of T1 images consisted of non-brain tissue removal [37], linear registration to standard space [38] and tissue segmentation [39]. PcASL images were linearly registered to the brain-extracted T1 images. The brain mask was used to calculate uncorrected mean whole-brain CBF. Partial volume estimates were transformed to the ASL data space and used in a regression algorithm [40], using a Gaussian kernel of 9.5mm full width at half maximum, to create partial volume corrected (PVC) cortical and white matter CBF maps. Partial volume estimates were subsequently used as a weighting factor to calculate mean cortical CBF. Additionally, the MNI152 atlas and the Harvard-Oxford cortical atlas (both part of FSL) were used to create regions-of-interest (ROIs) of the frontal, parietal, temporal and occipital brain areas, to extract mean regional uncorrected and PVC CBF values (Figure 1).

Figure 1: Regions-of-interest (ROIs) of the frontal (yellow), parietal (green), temporal (blue) and occipital lobe (red) following the MNI152 atlas and the Harvard-Oxford cortical atlas.

2.5 Statistics
PASW Statistics 22.0 for Mac (SPSS Inc., Chicago, IL) was used for all statistical analyses. Analyses of variance (ANOVA) and Pearson χ^2 tests were performed to compare groups when appropriate. ANOVA's were performed with age, gender and education as covariates. We then used linear regression analyses with CBF as independent variable, and cognitive domains as dependent variables (separate models for each cognitive domain). We adjusted for diagnosis (using dummy variables), age, gender, education, WMH and lacunes. To check if associations with CBF differed according to diagnostic group, interaction terms (dummy-diagnosis*CBF) were included in the model. When we found an interaction between diagnosis and CBF (p≤0.05), results were subsequently stratified for diagnosis and the standardized beta (stβ) was displayed for each diagnostic group separately. When no

significant interaction was found, the interaction term was removed from the model and we report overall stβ. The level of significance was set at $p<0.05$.

3. Results

Demographic data and MRI results are summarized per diagnostic group in Table 1. Patients with SCD were younger than MCI and AD patients. Furthermore, AD patients were more often female than patients with MCI and SCD and were less educated than patients with SCD.

AD patients had more severe GCA and MTA than patients with MCI and SCD. Furthermore, AD and MCI patients had more often WMH than patients with SCD, and MCI patients had more often lacunes than AD and SCD patients. Whole-brain PVC cortical CBF differed between groups ($p<0.01$). Post-hoc comparisons showed that AD patients had lower PVC cortical CBF than MCI patients, who in turn had lower PVC cortical CBF than individuals with SCD. When we evaluated regional CBF, results were comparable.

Figure 2: Examples of uncorrected whole-brain CBF maps in subject with SCD (56-year-old man, MMSE: 30, mean uncorrected CBF: 41 mL/100g/min), patient with MCI (63-year-old woman, MMSE: 25, mean uncorrected CBF: 30 mL/100g/min), and patient with AD (51-year-old man, MMSE: 18, mean uncorrected CBF: 25 mL/100g/min). Red to yellow/green colours represent CBF in millilitres per 100 g per minute.

Table 2 shows the raw neuropsychological test results and the z-scores of the cognitive domains per diagnosis. Adjusted for age, gender and education, AD patients had lower scores on all neuropsychological tests than patients with MCI and SCD. In addition, patients with MCI scored worse than SCD-patients on memory, attention, language and executive functions, but not on visuo-spatial functioning.

3.1 Association between PVC cortical CBF and cognitive domains

Table 3 shows the associations between whole-brain and regional PVC cortical CBF and performance in specific cognitive domains.

Adjusted for diagnosis, age, gender, education, WMH and lacunes in linear regression analyses, we found associations between whole-brain PVC cortical CBF and all cognitive domains (stβ's = 0.07-0.14, all $p<0.05$). These associations were attributable to a widespread reduction in CBF as we found associations between regional CBF with global cognition, memory, attention, visuo-spatial functioning, executive functioning and CBF. These associations were found for all regions, except for a trend between PVC occipital CBF and memory (stβ = 0.06, $p=0.06$), and for frontal CBF and attention (stβ = 0.07, $p=0.08$).

There were significant interactions between PVC cortical CBF in all regions and diagnosis for language ($p<.01$). After stratification, we found strong associations in AD patients (significant associations in all brain regions; stβ = 0.24-0.32, $p<0.001$), but not in MCI or SCD. Additionally, we found interactions between PVC parietal CBF and diagnosis for global cognition and executive functioning. After stratification we again observed strong associations in AD patients (PVC parietal CBF ~ global cognition: stβ = 0.23, $p<0.001$ and PVC parietal CBF ~ executive functioning: stβ = 0.25, $p<0.001$), while there were no significant associations in SCD or MCI.

Figure 3: Scatterplot of PVC parietal CBF against executive functioning.

3.2 Association between uncorrected CBF and cognitive domains
Subsequently, we repeated the analysis for whole-brain and regional uncorrected CBF estimations (table 4). These analyses largely showed a similar pattern of associations, with an even stronger preference for the strongest associations between decreased CBF and cognitive impairment to occur in the dementia stage. Moreover, these associations appeared to be more prominent than for PVC CBF.

4. Discussion
The main finding of this paper is that reductions in CBF are associated with cognitive functioning in all cognitive domains and across the full spectrum of cognitive decline, but most prominently in the stage of AD dementia. We observed these associations for both whole-brain and regional CBF and using both PVC cortical and uncorrected estimates of CBF.

Among the limitations of this study may be the use of partial volume correction. Although in theory it might be preferred to use PVC cortical CBF maps, the main drawback is no consensus on which method is best to correct for PVE [41]. The presence of cerebral atrophy in AD makes interpretation of ASL data complicated. An observation of cortical hypoperfusion could simply mirror cerebral atrophy. Therefore, in this study we used both uncorrected CBF, as well as PVC cortical CBF (actual grey matter CBF) to determine if the associations between CBF and cognition remained after correcting for PVE. In our previous work, we showed that CBF consistently increased after PVE but the proportional differences remained similar across groups [3]. In the present study, the uncorrected and PVC cortical CBF also yielded comparable results, which suggests that the detected associations of CBF with cognitive functioning are not merely a result of cerebral atrophy. Moreover, the most

important difference between PVC cortical and uncorrected CBF estimates was that the specificity of the associations for the AD stage was even more clear in the uncorrected estimates. This provides further proof that the uncorrected CBF estimates measure more than atrophy, since associations between atrophy and cognition tend to be more strong in the earlier, non-demented disease stages. Our results show a strong association between uncorrected CBF estimates (as available from the scanner in clinical practice) and disease severity, suggesting that PVE is not necessary to monitor disease severity in AD patients. ASL-MRI may therefore be a promising tool in the clinical practice.

Other possible limitations include that we did not scan with several delay times to account for differences in travel times between groups. However, we did use an age-adjusted delay time of 2.0 [42], which is assumed to be suitable to account for delayed blood arrival to the brain tissue. No correction for possible confounders on ASL-measured-CBF such as caffeine-intake, smoking and vasoactive medication were applied. Furthermore, we used large ROIs which may have obscured subtle regional associations. On the other hand, the use of smaller ROIs give less accurate and less reliable CBF estimates, because of the limitations of the low signal-to-noise ratio (SNR) and spatial resolution of ASL and results of larger ROIs may considered to be more robust [43]. The inclusion of relatively young patients could limit the generalizability of our findings to elderly AD patients and although we view the groups of SCD, MCI, and AD in some way as a continuum, this is not self-evident, as some of these patients will remain stable or develop non-AD dementias. Finally, the cross-sectional design prevents us from drawing conclusions about the future disease course of these patients, especially for the MCI-patients in this cohort. Among the strengths are the large cohort of SCD, MCI and AD patients with available pseudo-continuous ASL-MRI, which was obtained according to a standardized protocol. The use of a standardized neuropsychological test battery allowed looking at specific cognitive domains.

We found consistent associations of ASL-CBF and cognitive impairment in AD, while associations in MCI and SCD were less obvious. Previous literature suggests that functional and metabolic markers, such as glucose metabolism and CBF, show increasing changes during the progression from pre-dementia stages to MCI and finally the dementia stage of AD [2,3,44,45]. Our findings suggests that CBF may be less sensitive to early brain changes, but may have particular value in reflecting disease severity in more advanced disease stages. This suggests that CBF alterations and hypometabolism continue to change along the disease process of AD, without reaching a plateau in an early disease stage [44,46].

In this study we had an extensive and standardized neuropsychological test battery, covering five major cognitive domains. We found that CBF, both whole-brain and in specific regions,

was associated with functioning in all cognitive domains. Earlier studies describing associations between CBF and cognitive impairment often focused merely on screening instruments (MMSE) or a few neuropsychological tests only [3,8–10]. Chao et al. [11] investigated associations between ASL-CBF and cognitive domains, but only in MCI-patients. They found that MCI patients with a different pattern of cognitive impairment (i.e. memory or executive functioning) exhibited specific patterns of hypoperfusion. In our study, we expected to find associations of reduced CBF in a specific anatomical region and cognitive impairment in a specific domain. By contrast, our results suggest a more global or nonspecific effect of CBF on cognitive domains, indicating that decreased CBF in a particular region does not have a localized effect on a cognitive domain. These results support the hypothesis that global cognitive impairment in AD patients is related to widespread brain changes. The strongest associations were observed in the stage of AD, when a lot of damage to the brain has occurred, and the relationship between cognitive impairments and the regional distribution of disease is less obvious. A second explanation of our results could be that although cognitive tests are selected to measure a specific cognitive domain, reality is that each test taps on more than one cognitive domain. For example worse performance on the Trail Making Test B not only measures executive functioning, but also requires attention and relies heavily on intact visuo-spatial functioning. The latter could explain the association between reduced CBF in the posterior regions and executive functioning. Another example is that tests to assess visuo-spatial functioning (i.e. Visual Object and Space Perception (VOSP) battery) tap on a variety of abilities, such as visual and color discrimination, visuo-perceptual organization, visual construction and visual neglect. In addition, they require intact planning, organization and sequencing (i.e. executive functioning). This long list of cognitive functions may explain widespread associations between VOSP tests and reduced CBF.

In particular for parietal CBF, we found that associations with global cognition and executive functioning were most prominent in AD patients. This seems in line with previous findings that [18F]FDG-PET-hypometabolism in AD is most pronounced in the posterior regions [47]. Moreover, these findings also seem in line with previous longitudinal findings that the posterior regions are associated with cognitive decline in AD patients [48,49]. Changes in CBF and glucose metabolism are closely linked, and a decrease in CBF is thought to reflect synaptic failure [5,6]. Synaptic failure is thought to cause network disturbance and connectivity research shows that the posterior brain region is a highly active network region [50]. Probably the association that we found between parietal CBF and cognitive impairment reflects network disruption. Finally, we found a strong association between lower CBF in all regions and worse performance on language in AD patients. These results are consistent

with earlier findings and provides further evidence for the reflection of network disruption in AD [50], or that multiple brain regions contribute to different aspects of cognitive processes.

Earlier studies have well established the association between decreased CBF and AD. However, it is still not completely clarified whether decreased CBF is a cause, consequence or epiphenomenon of underlying AD pathology. Future research with repeated measurements of CBF could explore the relationship between change in CBF and cognition in the earlier non-demented disease stage and in more advanced disease stages. ASL could be of additional value in this line of research. In addition, whereas the detection of amyloid in living patients has a large diagnostic value, the level of deposition does not correlate well with cognitive impairment [51]. It is therefore not certain whether amyloid represents a useful outcome measure in clinical trials. Our results suggest that ASL-measured-CBF is a functional marker of disease severity. In addition to the absolute units of CBF measurement, ASL-measured-CBF could be a possible useful imaging marker of therapeutic efficacy in clinical trials. Finally, future research could exploit the potential for a (non-)pharmacological treatment for the regulation of CBF and prevention of AD. Identifying the possible mechanism underlying the effect of decreased CBF on cognition, could support the recommendation of changing lifestyle factors, such as regular exercise, as a preventative therapy to prevent or delay dementia.

In conclusion, our study investigated ASL-CBF in the entire cognitive spectrum – from SCD to AD – and our results show associations across all cognitive domains. Of note, these associations were strongest for AD patients. Our findings support the potential role of CBF as a functional marker of disease severity, with ASL as non-invasive, easily-obtained method of CBF measurement.

5. Acknowledgements

6. Disclosures

7. References

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Table 1: Demographics and MR imaging findings

	Total (n = 399)	**SCD** (n = 143)	**MCI** (n = 95)	**AD** (n = 161)
Age	63.53 ± 8.23	59.69 ± 8.69	65.24 ± 7.28[a]	65.93 ± 7.04[a]
Women, n (%)	184 (46.1%)	63 (44.1%)	33 (34.7%)	88 (54.7%)[ab]
Education	5.15 ± 1.29	5.45 ± 1.19	5.14 ± 1.35	4.89 ± 1.30[a]
MMSE	24.75 ± 4.78	28.22 ± 1.53	26.57 ± 1.93[a]	20.60 ± 4.76[ab]
Vascular risk factors				
Hypertension, n (%)	136 (34.1%)	39 (27.3%)	39 (41.1%)[a]	58 (36%)
Hypercholesterolemia, n (%)	106 (26.6%)	26 (18.2%)	36 (37.9%)[a]	44 (27.3%)
Diabetes mellitus, n (%)	36 (9%)	12 (8.4%)	13 (13.7%)	11 (6.8%)
Smoking status:				
Never, n (%)	161 (40.4%)	63 (44.1%)	42 (44.2%)	56 (34.8%)
Former, n (%)	170 (43.8%)	61 (43.5%)	34 (37.3%)	75 (47.7%)
Current, n (%)	57 (14.3%)	16 (11.2%)	15 (15.8%)	26 (16.1%)
MRI characteristics				
GCA (%)	46 (11.5%)	3 (2.1%)	6 (6.3%)	37 (23%)[ab]
MTA (%)	52 (13%)	0 (0%)	6 (6.3%)[a]	46 (28.6%)[ab]
WMH (%)	82 (20.6%)	12 (8.4%)	28 (29.5%)[a]	42 (26.1%)[a]
Lacunes (%)	31 (7.8%)	6 (4.2%)	16 (16.8%)[ac]	9 (5.6%)
PVC cortical CBF				
Whole-brain	44.72 ± 9.87	48.67 ± 9.80	44.28 ± 9.10[a]	41.47 ± 9.16[ab]
Regional PVC cortical CBF				
Frontal	45.35 ± 10.61	49.29 ± 10.47	44.75 ± 10.11[a]	42.20 ± 9.94[ab]
Temporal	41.07 ± 8.83	44.54 ± 8.88	41.32 ± 8.05[a]	37.83 ± 8.02[a]
Parietal	50.13 ± 11.90	55.35 ± 11.53	50.12 ± 10.95[a]	45.49 ± 10.85[ab]
Occipital	50.71 ± 11.91	55.09 ± 11.60	50.32 ± 11.11[a]	47.06 ± 11.42[ab]

AD, Alzheimer's Disease; MCI, mild cognitive impairment; SCD, subjective cognitive decline; GCA, global cortical atrophy; MTA, medial temporal lobe atrophy; WMH, high-signal-intensity areas in white matter (based on Fazekas score); MMSE, Mini Mental State Examination; CBF, cerebral blood flow; PVC, partial volume corrected. Availability for incomplete data: SCD: Smoking status 140/143, MCI: Smoking status 91/95, GCA, 94/95; MTA 94/95; WMH 94/95; AD: Smoking status 157/161. One-way ANOVA or χ^2 were performed, respectively. Data are presented as mean ± SD, number (percentage). Cerebral blood flow (CBF) values in mL/100g/min. Significant difference $p < 0.05$ to [a]SCD, [b]MCI and [c]AD.

Table 2: Raw neuropsychological test performance of diagnostic groups

	Total (*n* = 399)	**SCD** (*n* = 143)	**MCI** (*n* = 95)	**AD** (*n* = 161)
Memory *(z-score)*	-0 ± 0.9	0.8 ± 0.4	0 ± 0.5[a]	-0.8 ± 0.6[ab]
VAT	8.9 ± 3.7	11.6 ± 0.7	10.2 ± 2.4[a]	5.7 ± 3.8[ab]
RAVLT total immediate	32.5 ± 12.8	43.6 ± 9.4	32.3 ± 8.5[a]	21.9 ± 8[ab]
RAVLT delayed	5 ± 4.1	8.9 ± 3	4.2 ± 2.7[a]	1.8 ± 2.2[ab]
Attention *(z-score)*	-0 ± 0.8	0.5 ± 0.5	0.1 ± 0.5[a]	-0.5 ± 0.9[ab]
TMT A[*]	60.9 ± 55.4	35.7 ± 13.3	47.5 ± 24	93.6 ± 75.3[ab]
LDST	38 ± 13	46 ± 9.5	39.3 ± 10[a]	27.9 ± 11.7[ab]
Digit span (forward)	11.7 ± 3.3	13 ± 3.2	11.5 ± 2.8[a]	10.5 ± 3.2[ab]
Stroop I[*]	52 ± 17.8	44.3 ± 8.3	48.1 ± 10.2	62 ± 23.2[ab]
Stroop II[*]	75.6 ± 32.8	61.3 ± 13.7	67.5 ± 15.5[a]	95.5 ± 43.4[ab]
Language *(z-score)*	-0 ± 0.8	0.3 ± 0.5	0.2 ± 0.6	-0.5 ± 0[ab]
VAT naming	11.6 ± 1.2	11.9 ± 0.4	11.9 ± 0.4	11.1 ± 1.7[ab]
Animal fluency	17.1 ± 6.7	21.5 ± 5.7	18.6 ± 5.3[a]	12.3 ± 5[ab]
Letter fluency	30.1 ± 12.8	34.9 ± 12	31.7 ± 12	24.7 ± 12[ab]
Comparative questions	5.6 ± 0.7	5.8 ± 0.3	5.8 ± 0.4	5.4 ± 1[ab]
ABCD naming	17.1 ± 3	18.6 ± 1.4	17.8 ± 2.1[a]	15.1 ± 3.6[ab]
Visuospatial functioning *(z-score)*	-0 ± 0.8	0.3 ± 0.3	0.2 ± 0.3	-0.5 ± 1.1[ab]
Number location	8.6 ± 1.5	9.2 ± 1	9 ± 1.14	7.9 ± 1.8[ab]
Dot counting	9.4 ± 1.1	9.8 ± 0.4	9.6 ± 0.5	8.9 ± 1.7[ab]
Fragmented letters	17.5 ± 4	19.1 ± 1.4	18.5 ± 1.2	15 ± 5.7[ab]
Executive functioning *(z-score)*	-0 ± 0.9	0.6 ± 0.4	0.1 ± 0.5[a]	-0.8 ± 0.8[ab]
Digit span (backward)	7.8 ± 2.8	9.4 ± 2.6	7.9 ± 2.5[a]	6.3 ± 2.4[ab]
TMT B[*]	182.6 ± 173.9	88 ± 45.4	142.2 ± 91.5[a]	299.2 ± 219.6[ab]
FAB	15 ± 3.3	16.9 ± 1.4	15.9 ± 1.8	12.3 ± 3.8[ab]
Stroop III[*]	131.4 ± 63.5	98.6 ± 24.1	121 ± 36.3[a]	180.3 ± 63.5[ab]

AD, Alzheimer's Disease; MCI, mild cognitive impairment; SCD, subjective cognitive decline; MMSE, Mini Mental State Examination; VAT, Visual Association Test; RAVLT, Rey Auditory Verbal Learning Test; TMT, Trail Making Test; LDST, Letter Digit Substitution Test; ABCD, Arizona Battery for Communication Disorders; FAB, Frontal Assessment Battery.

Z-scores allow comparison of neuropsychological test results within patients. Higher z-scores imply better performance on all tests.

Raw neuropsychological data are presented as mean ± standard deviation. Univariate analyses of variances were performed with diagnosis as between-subject factor. Gender, age and education are entered as covariates.

Significant difference *p* <0.05 to [a]SCD, [b]MCI and [c]AD.

[*]Higher scores imply worse performance.

Table 3: Linear regression models for the association between PVC cortical CBF and cognitive domains

Region	Cognitive domain	All	SCD (*n* = 143)	MCI (*n* = 95)	AD (*n* = 161)
Whole-brain	Global	.10**			
	Memory	.07*			
	Attention	.09*			
	Executive functioning	.12**			
	Visuo-spatial functioning	.14**			
	Language		.01	.11	.28***
Parietal	Global		.06	.06	.23***
	Memory	.09**			
	Attention	.10*			
	Executive functioning		.07	.09	.25***
	Visuo-spatial functioning	.18***			
	Language		.01	.10	.32***
Frontal	Global	.10**			
	Memory	.08**			
	Attention	.07			
	Executive functioning	.11**			
	Visuo-spatial functioning	.12*			
	Language		.03	.11	.30***
Temporal	Global	.10**			
	Memory	.08**			
	Attention	.10*			
	Executive functioning	.12***			
	Visuo-spatial functioning	.13**			
	Language		.00	.11	.29***
Occipital	Global	.08*			
	Memory	.06			
	Attention	.05			
	Executive functioning	.10**			
	Visuo-spatial functioning	.18***			
	Language		-.02	.08	.24***

We used linear regression analyses with PVC cortical CBF as independent variable and cognitive domains as dependent variable. Cognition is expressed as a (composite) z-score. We corrected for diagnosis (using dummy variables), age, gender and education, white matter hyperintensities and presence of lacunes. To check if associations with CBF differed according to diagnostic group, interaction terms (dummy-diagnosis*CBF) were included in the model. When we found an interaction between diagnosis and CBF (p<0.05), results were subsequently stratified for diagnosis and the standardized beta (stβ) is displayed for each group separately. When no significant was found, the interaction term was removed from the model and the overall stβ is reported.

SCD, subjective cognitive decline; MCI, mild cognitive impairment; AD, Alzheimer's disease.

*p<0.05, **p<0.01, ***p<0.001

Table 4: Linear regression models for the association between uncorrected CBF and cognitive domains

Region	Cognitive domain	All	SCD (n = 143)	MCI (n = 95)	AD (n = 161)
Whole-brain	Global	.11**			
	Memory	.08**			
	Attention	.11*			
	Executive functioning	.13***			
	Visuo-spatial functioning	.15**			
	Language		.01	.12	.31***
Parietal	Global		.06	.06	.26***
	Memory	.09**			
	Attention		.04	.12	.25***
	Executive functioning		.07	.08	.31***
	Visuo-spatial functioning	.20***			
	Language		.01	.12	.34***
Frontal	Global	.11**			
	Memory	.08**			
	Attention	.08			
	Executive functioning	.12**			
	Visuo-spatial functioning	.11*			
	Language		.03	.12	.30***
Temporal	Global	.13***			
	Memory	.10**			
	Attention	.11**			
	Executive functioning	.14***			
	Visuo-spatial functioning	.14**			
	Language		.02	.11	.37***
Occipital	Global		.04	.08	.23***
	Memory	.06*			
	Attention		.01	.14	.22**
	Executive functioning	.10**			
	Visuo-spatial functioning		.05	.12	.42***
	Language		-.01	.07	.29***

We used linear regression analyses with uncorrected CBF as independent variable and cognitive domains as dependent variable. Cognition is expressed as a (composite) z-score. We corrected for diagnosis (using dummy variables), age, gender and education, white matter hyperintensities and presence of lacunes. To check if associations with CBF differed according to diagnostic group, interaction terms (dummy-diagnosis*CBF) were included in the model. When we found an interaction between diagnosis and CBF ($p<0.05$), results were subsequently stratified for diagnosis and the standardized beta (stβ) is displayed for each group separately. When no significant was found, the interaction term was removed from the model and the overall stβ is reported.

SCD, subjective cognitive decline; MCI, mild cognitive impairment; AD, Alzheimer's disease.

*$p<0.05$, **$p<0.01$, ***$p<0.001$