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ORIGINAL RESEARCH

Neurovascular Decoupling Is Associated With Lobar Intracerebral Hemorrhages and White Matter Hyperintensities

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BACKGROUND: Neurovascular coupling is a fundamental aspect of brain function by regulating cerebral blood flow in response to regional neuronal activity. Increasing evidence suggest neurovascular decoupling occurs early in the progression of Alzheimer disease (AD), potentially reflecting early vascular damage. Therefore, understanding the relationship between neurovascular coupling and established vascular risk factors for AD is essential to gain deeper insights into the vascular mechanisms underlying AD.

METHODS: This cross-sectional observational study investigated the association between neurovascular coupling and vascular risk factors for AD, specifically small vessel disease magnetic resonance imaging markers, cardiovascular risk factors, and the apolipoprotein E genotype. The cohort included 119 participants diagnosed with subjective cognitive impairment, mild cognitive impairment, and AD-related dementia, as well as individuals without cognitive complaints. Neurovascular coupling was measured by blood-oxygen-level-dependent functional magnetic resonance imaging amplitude in response to visual stimulation.

RESULTS: Our findings revealed that decreased neurovascular coupling is linked to structural brain changes typically seen in small vessel disease; specifically we found an association between neurovascular coupling and white matter hyperintensities load (β=−0.199, P=0.030) and presence of lobar intracerebral hemorrhage (β=−0.228, P=0.011).

CONCLUSIONS: This raises the suggestion that a decreased neurovascular coupling in the disease process of AD is related to comorbid small vessel disease.

Key Words: Alzheimer disease ■ cerebral amyloid angiopathy ■ functional magnetic resonance imaging ■ neurovascular coupling ■ small vessel disease

Neurovascular coupling reflects the interaction between regional neuronal activity and subsequent cerebral blood flow response,[1] and is a fundamental aspect of brain function. This mechanism plays a vital role in maintaining cognitive function by ensuring the adequate delivery of oxygen and nutrients to activated brain regions in response to changing neural demands.[2,3] Impairment of neurovascular coupling has been linked to brain dysfunction and damage,[2] which has raised interest in exploring its contribution to neurodegenerative diseases.

In the presymptomatic phase of Alzheimer disease (AD), patients exhibit reduced hemodynamic responses to neural activation.[4] Additionally, neurovascular coupling to visual stimulation, measured by blood-oxygen-level-dependent functional magnetic

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RESEARCH PERSPECTIVE

What Is New?

- This study reveals an association between neurovascular coupling impairment and small vessel disease markers (white matter hyperintensities and lobar intracerebral hemorrhages) in a cohort including participants with a diagnosis of subjective cognitive impairment, mild cognitive impairment, and Alzheimer disease–related dementia, as well as individuals without cognitive complaints.

What Questions Should Be Addressed Next?

- Future research should investigate whether impaired neurovascular coupling predicts the progression of small vessel disease magnetic resonance imaging markers and cognitive decline over time and explore the underlying mechanisms.
- Additionally, studies should assess whether improving vascular health can preserve neurovascular coupling and slow cognitive decline in Alzheimer disease and at-risk populations.

resonance imaging (BOLD fMRI), is impaired in early-stage AD-related dementia.[5] These findings suggest that neurovascular decoupling occurs early in the disease process of AD, contributing to a growing body of evidence that neurovascular dysfunction is a critical factor in AD pathogenesis and may even precede the development of AD pathology.[6] Because impairment of neurovascular coupling in AD is postulated to reflect early vascular damage,[5] it is important to assess how neurovascular coupling relates to established vascular risk factors for AD to provide deeper insight into the vascular mechanisms underlying the disease.

Pathological studies reveal that most patients with AD exhibit mixed pathologies, including cerebral small vessel disease (SVD).[7,8] A very frequent finding in these cases is cerebral amyloid angiopathy (CAA), one of the most common pathologies underlying SVD caused by deposition of amyloid β (Aβ) in small to medium-sized cerebral blood vessels and leptomeningeal arteries.[9–11] Up to 98% of patients with AD show moderate to severe CAA.[12] Additionally, there is evidence of comorbid nonamyloid small vessel disease in AD,[13] sometimes referred to as hypertensive SVD. These vascular pathologies are a risk factor for AD.[14] Neuroimaging markers of SVD, such as white matter hyperintensities (WMHs), lacunar infarcts, microbleeds, and enlarged dilated perivascular spaces, are indicators of this increased risk.[15] Epidemiological studies also suggest a pathogenic role for vascular factors in AD, indicating that cerebrovascular disease and AD share similar risk factors, such as hypertension, diabetes, and hyperlipidemia, and the apolipoprotein E (APOE) ε4 genotype.[9,16]

As impairment of neurovascular coupling has become increasingly recognized as an early vascular factor in the pathophysiology of AD, exploring its associations with established vascular risk factors is essential to gain a better understanding of the vascular mechanisms underlying AD. Therefore, this study aims to assess the associations between neurovascular coupling and vascular risk factors for AD. Specifically, we will investigate the relationship between neurovascular coupling and SVD MRI markers, cardiovascular risk factors, and the APOE genotype in an existing memory clinic cohort including participants with a diagnosis of subjective cognitive impairment (SCI), mild cognitive impairment (MCI), and dementia (including probable AD or mixed-type dementia), as well as in participants without cognitive complaints.

METHODS

Data Availability

The data that support the findings of this study are available from the principal investigator upon reasonable request (s.van_rooden@lumc.nl).

Study Design and Participants

Between September 2019 and December 2021, we recruited patients from the memory clinic of the Leiden University Medical Center (Leiden, the Netherlands) and the memory clinic of the Haaglanden Medical Center (The Hague, the Netherlands) who were diagnosed with SCI, MCI, or dementia (probable AD or mixed-type dementia). Patients with other types of dementia or significant neurological or psychiatric disorder were not included for this study. The diagnosis was made at the memory clinic in a multidisciplinary consensus meeting using the National Institute of Neurological and Communicative Disorders and Stroke and Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria.[17] Participants without cognitive complaints were recruited via various advertisements. Exclusion criteria were MRI contraindications, specific contra-indications to fMRI such as seizure within prior year and noncorrectable visual impairment, incapacitated to give informed consent, and age >90 years. All participants underwent MRI, neuropsychological assessment, and collection of 2 mL saliva for DNA genotyping. Medical history and cardiovascular risk factors were recorded (ie, hypertension, hyperlipidemia, diabetes, and current smoking status). For this current study, the Mini Mental State

Examination score is reported as a measure for cognitive function. Our findings on the association between neurovascular coupling and cognitive function, assessed across various cognitive domains, have been published previously.[5] The medical ethics committee of Leiden Den Haag Delft approved the study. Written informed consent was obtained from all participants. The followed procedures were in accordance with institutional guidelines and the World Medical Association Declaration of Helsinki.

Image Acquisition and Processing

Imaging was performed on a 3-Tesla scanner (3T Achieva Philips Medical Systems, Eindhoven, the Netherlands) using a standard 32-channel head coil. For each participant, 3D T1-weighted images, T2-weighted images, fluid-attenuated inversion recovery scan, T2*-weighted images, and visually stimulated BOLD fMRI scans were obtained. Parameters have been described previously.[5] The visual stimulus was presented in a block-design schedule with an 8 Hz flashing radial black and white checkerboard pattern for 20 seconds (stimulus), alternated with 28 seconds of gray screen (rest), as described previously.[18] Each scan consisted of 4 cycles of stimulus and rest conditions.

Before analysis, a visual quality control check was performed on all MRI scans to ensure that no gross artifacts were present in the data. Lobar microbleeds (location as described by the Boston criteria[19]) and deep microbleeds were scored on T2*-weighted images according to criteria as described previously.[20] Lobar intracerebral hemorrhages (ICHs) were scored on T2*-weighted images and defined as parenchymal defects with hemosiderin evidence in their wall[21] and located in one of the cerebral lobes. Cortical superficial siderosis was characterized by linear blood residues in the superficial cortex layers on T2*-weighted images, and classified as focal (3 or fewer sulci) or disseminated (4 or more sulci).[22] Lacunar infarcts were defined as round or oval lesion with a diameter between 3 mm and 15 mm, appearing hypointense with a surrounding rim of hyperintensity on fluid-attenuated inversion recovery images and hyperintense on T2-weighted images.[23] Dilated perivascular spaces in the basal ganglia and dilated perivascular spaces in the centrum semiovale were assessed on axial T2-weighted images in line with STRIVE (standards for research into SVD) definitions.[24] Dilated perivascular spaces in the basal ganglia were scored using a 1 to 4 point semiquantitative scale as previously described.[25] Dilated perivascular spaces in the centrum semiovale were rated on a 0 to 4 point semiquantitative scale.[26] WMHs were defined and analyzed using a semiautomated and validated method using fluid-attenuated inversion recovery images, as previously described.[27] Gray matter volume was calculated using Structural Image Evaluation, using Normalization, of Atrophy,[28] part of the FMRIB Software Library.[29] The analysis of BOLD fMRI scans, which utilized a checkerboard stimulus, included the determination of the neurovascular coupling parameter (ie, BOLD amplitude), following previously established methods.[18] BOLD amplitude is a robust measurement of neurovascular coupling and is the preferred parameter over other neurovascular coupling parameters (ie, time to peak or time to baseline).[30]

APOE ε Genotyping

APOE genotyping was performed on all participants. Polymerase chain reaction (PCR) amplification of the SNP-containing DNA region was performed in a final volume of 25 μL, using 5 pmol APOE primers: Forward: 5′-TAA GCT TGG CAC GGC TGT CCA AGG A-3′ and Reverse: 5′-ACA GAA TTC GCC CCG GCC TGG TAC ACT GCC-3′ (IDT), 5 nmol each dNTP (Solis Biodyne, ref. 02-21-00100), 1X PCR Buffer B1, 1.5 mmol/L $MgCl_2$, 5 U FIREPol DNA Polymerase (Solis Biodyne, ref. 01-02-01000), 10% dimethyl sulfoxide, and 125 ng genomic DNA in 25 μL. PCR was performed using the following amplification protocol: initial step of 15′ 95°C, 1 cycle of: 30″ 95°C, 30″ 66°C, 1″72°C, 2 cycles of: 30″ 95°C, 30″ 64°C, 1″72°C, 3 cycles of: 30″ 95°C, 30″ 62°C, 1″72°C, 4 cycles of: 30″ 95°C, 30″ 60°C, 1″72°C and 30 cycles of 30″ 95°C, 30″ 58°C, 1″72°C and a final step of 10′ 72°C. PCR amplification was followed by specific restriction enzyme cleavage of the PCR product to generate allele-discriminating DNA fragments. In a final volume of 50 μL, using 5 μL PCR-product, 5 μL rCutSmart-Buffer and 20 U HhaI, recombinant restriction enzyme (NEB; ref. R0139L), the PCR-product was cleaved by overnight incubation at 37° C. Products were visualized by Agarose Gel electrophoresis, using 4% low melting Agarose (Fisher Scientific; ref. BP1360-100) in 1X TBE. A volume of 20 μL cleaved DNA was loaded on gel, followed by a 1-hour run at 140V. Restriction fragment length polymorphism results were confirmed by Sanger sequencing.

Statistical Analysis

All statistical analyses were performed with the Statistical Package of Social Sciences (SPSS, version 29.0). For our primary objective, we assessed the associations between neurovascular coupling and various MRI markers of SVD, cardiovascular risk factors, and the APOE genotype in the entire sample using linear regression analyses. Neurovascular coupling was used as dependent variable, and all models were adjusted for age and sex. Microbleeds, lobar ICHs, lacunar infarcts, and cardiovascular risk factors were dichotomized (present or not present). Dilated perivascular

spaces were dichotomized by separating high scores (3 and 4) from low scores (0, 1, and 2). WMH volumes were log transformed. APOE genotype was classified as follows: participants carrying at least 1 ε4 allele were classified as APOE ε4, those with ε2/2 or ε2/3 were classified as APOE ε2, and ε2/4 heterozygotes were grouped with ε4 due to the stronger association of ε4 with AD.[31] To further investigate whether the significant associations identified in the primary objective varied by cognitive status, we included an interaction term with cognitive status in our regression models. Cognitive status was treated as a categorical variable with 4 groups (no cognitive complaints, SCI, MCI, and AD-related dementia), and the models were adjusted for age and sex. The goodness of fit of the models was evaluated using the coefficient of determination (R^2). To verify that the assumptions for linear regression were met, linearity was assessed for continuous predictors through scatterplots of the predictor versus dependent variable. For binary predictors, linearity was assumed, because the model compares the mean difference between groups. Homoscedasticity was examined by inspecting a plot of residuals versus fitted values, while normality of residuals was visually assessed using Q-Q plots. Moreover, no influential outliers were identified.

In our secondary analysis, we examined whether the associations identified in the primary objective differed based on CAA status, as defined by the modified Boston MRI criteria.[32] First, we included an interaction term with CAA status (probable CAA yes/no) in our linear regression model. Subsequently, we stratified our sample into the 2 CAA status groups (probable CAA yes/no) and conducted separate linear regression analyses for each group to evaluate the relationship between BOLD amplitude and variables identified in the primary objective. All models included the same covariates, age and sex, to ensure a consistent comparison across groups.

We reported unstandardized regression coefficients and their CIs, standardized regression coefficients, and *P* values. An uncorrected *P* value <0.05 was deemed statistically significant.

RESULTS

Table 1 describes the demographic and clinical characteristics of the study sample. There was a broad cognitive range in the group of 119 participants (Mini-Mental State Examination range 18–30) and broad BOLD amplitude range (mean 1.0%, SD 0.3, range 0.3–1.8). Approximately half of the participants were found to have 1 or more lobar microbleeds, while 8 participants displayed 1 or more lobar ICH. None of the participants were found to have disseminated cortical superficial siderosis, and 1 SCI participant presented with focal cortical superficial siderosis (3 sulci or less). Associations between BOLD amplitude and SVD MRI markers, cardiovascular risk factors, and APOE genotype are shown in Table 2.

Lower BOLD amplitude was associated with larger WMH volume (β=−0.199, *P*=0.030) and the presence of lobar ICH (β=−0.228, *P*=0.011) within the whole sample when adjusted for age and sex (Figures 1 and 2, respectively). The models showed modest explanatory power, with R^2 values of 0.164 and 0.168, respectively. No associations were found with regard to the other SVD MRI markers. Furthermore, there was no association between BOLD amplitude and cardiovascular risk factors or APOE ε4 and ε2 genotype.

Additionally, to explore whether the associations between BOLD amplitude and WHMs and ICHs varied across different cognitive status groups (no cognitive complaints, SCI, MCI, and AD-related dementia), we included interaction terms between WMHs, lobar ICH, and cognitive status in the linear regression models. The interaction terms with cognitive status were not statistically significant for lobar ICH (*P*=0.060) or for WMHs (*P*=0.583), indicating that the association between neurovascular coupling and both WMHs and lobar ICH did not differ significantly among the cognitive subgroups.

For our secondary analyses, to explore whether the associations between BOLD amplitude and WHMs varied across CAA status, an interaction term between WMHs and CAA status (probable CAA yes/no) was included in the linear regression model. Table 3 describes the demographic and clinical characteristics of the CAA group (n=32) and non-CAA group (n=87) separately. The interaction term was statistically significant (*P*=0.050), indicating that the association between neurovascular coupling and WMHs did differ significantly among the CAA status subgroups. Subsequently, to examine the relationship between BOLD amplitude and WMHs for each group separately, stratified analysis was performed. The association between BOLD amplitude and WMH volume found in the total sample remained significant in stratified analyses for the CAA group (β=−0.370, *P*=0.046), with the model showing modest explanatory power (R^2=0.227). However, this association was not observed in the non-CAA group (β=−0.116, *P*=0.274) (Figure 3).

DISCUSSION

We explored the association between neurovascular coupling and a comprehensive set of SVD MRI markers, cardiovascular risk factors, and APOE genotype in a cohort including participants with a diagnosis of SCI, MCI, and AD-related dementia, as well as in participants without cognitive complaints. Our data show

Table 1. Demographic and Clinical Characteristics of the Study Sample

	Whole sample	No cognitive complaints	SCI	MCI	Dementia
N	119	44	25	33	17
Age, y	71.6 (8.8; 51–89)	67 (9.0; 51–86)	70.8 (8.1; 53–85)	76.1 (6.1; 63–87)	76.7 (7.2; 59–89)
Female sex	49 (41%)	26 (59.1%)	8 (32.0%)	9 (27.3%)	6 (35.3%)
MMSE, median (IQR)	28 (18–30)	29 (28–29)	29 (28–30)	27 (26–29)	27 (23–27)
Neurovascular coupling					
BOLD amplitude, % change	1.0 (0.3; 0.3–1.8)	1.1 (0.2; 0.7–1.8)	1.1 (0.2; 0.7–1.6)	0.9 (0.3; 0.3–1.5)	0.8 (0.2; 0.3–1.3)
SVD risk factors					
Hypertension	31 (26.1%)	9 (20.5%)	6 (24.0%)	12 (36.4%)	4 (23.5%)
Hyperlipidemia	32 (26.9%)	6 (13.6%)	9 (36.0%)	13 (39.4%)	4 (23.5%)
Diabetes	14 (11.8%)	2 (4.5%)	5 (20.0%)	6 (18.2%)	1 (5.9%)
Smoking (current)	15 (12.6%)	5 (11.4%)	4 (16.0%)	5 (15.2%)	1 (5.9%)
SVD MRI markers					
≥1 Lobar ICH	8 (6.7%)	0 (0%)	1 (4%)	4 (12.1%)	3 (17.7%)
1 Lobar ICH	4	0	1	3	0
2 Lobar ICH	2	0	0	1	1
3 Lobar ICH	2	0	0	0	2
≥1 Lobar microbleeds	59 (49.6%)	16 (36.4%)	12 (48%)	21 (84%)	10 (58.8%)
Cortical superficial siderosis	1 (0.8%)	0 (0%)	1 (4%)	0 (0%)	0 (0%)
Focal (≤3 sulci)	1	0	1	0	0
Disseminated (≥4 sulci)	0	0	0	0	0
≥1 Deep microbleeds	13 (10.9%)	5 (11.4%)	3 (12.0%)	5 (15.2%)	0 (0%)
≥1 Lacunar infarcts	46 (38.7%)	14 (31.8%)	8 (32.0%)	17 (51.5%)	7 (41.2%)
DPVS-CSO – high count	75 (63.0%)	36 (81.8%)	8 (32.0%)	17 (51.5%)	14 (82.4%)
DPVS-BG – high count	48 (40.3%)	14 (31.8%)	9 (36.0%)	17 (51.5%)	8 (47.1%)
WMH volume, cm^3	6.7 (7.6; 0.3–47.0)	4.5 (4.3; 0.7–18.0)	6.0 (8.3; 0.9–42.1)	7.6 (7.0; 0.3–23.7)	11.4 (11.7; 1.2–47.0)
Gray matter volume, cm^3	694.3 (47.5; 572.9–788.1)	725.6 (37.5; 640.4–788.1)	703.7 (38.7; 624.3–769.5)	670.7 (33.4; 602.6–733.0)	645.1 (43.4; 572.9–734.5)
APOE genotype					
APOE ε4 carrier	51 (55.3%)	12 (27.3%)	10 (40%)	17 (51.5%)	12 (70.6%)
4/4	9	0	1	3	5
3/4	38	11	8	12	7
2/4	4	1	1	2	0
APOE ε2 carrier	11 (9.2%)	4 (9.1%)	6 (24.0%)	1 (3.0%)	0 (0%)
2/2	1	1	0	0	0
2/3	10	3	6	1	0
APOE 3/3	52 (43.7%)	28 (63.6%)	9 (36%)	10 (30.3%)	5 (29.4%)

APOE indicates apolipoprotein E; BOLD, blood-oxygen-level dependent; DPVS-BG, dilated perivascular spaces-basal ganglia; DPVS-CSO, dilated perivascular spaces-centrum semiovale; ICH, intracerebral hemorrhage; IQR, interquartile range; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; MRI, magnetic resonance imaging; SCI, subjective cognitive impairment; SVD, small vessel disease; and WMH, white matter hyperintensity. Values are number (%) or mean (SD; range). APOE status is missing for 5 patients with MCI.

that decreased neurovascular coupling is linked to structural brain changes typically seen in SVD, which are particularly associated with higher WMH load and the presence of lobar ICH.

This study shows that a lower BOLD amplitude is associated with a higher volume of cerebral WMHs. This aligns with the consistently observed finding of reduced neurovascular coupling in patients with WMHs when compared with controls, and in patients with more severe WMHs when compared with severe WMHs.[33] Directly stimulating the dilation of cerebral blood vessel (eg, by inhalation of carbon dioxide [CO_2]–enriched air) shows comparable associations between dilation of the vessel wall and WMH volume in older subjects,[34–36] patients with AD,[37] and patients with SVD and a mild stroke.[38] This indicates a strong relationship between dysfunction of the vessel wall and the development of WMHs. In our cohort, the association between BOLD

Table 2. Associations Between Neurovascular Coupling and SVD MRI Markers, Cardiovascular Risk Factors, and APOE Genotype in the Whole Sample

	BOLD amplitude		
	B (95% CI)	*β* (Standardized)	*P* value
SVD MRI markers			
Lobar ICH	−0.246 (−0.435 to −0.057)	−0.228	0.011
Lobar microbleeds	0.005 (−0.092 to 0.102)	0.009	0.917
Deep microbleeds	0.035 (−0.116 to 0.186)	0.040	0.651
Lacunar infarcts	−0.025 (−0.130 to 0.081)	−0.044	0.645
DPVS-CSO high count	0.026 (−0.080 to 0.131)	0.044	0.630
DPVS-BG high count	−0.001 (−0.104 to 0.102)	−0.002	0.984
WMHs (ln)	−0.054 (−0.104 to −0.005)	−0.199	0.030
Gray matter volume	1.036×10^{-7} (-1.261×10^{-6}, 1.469×10^{-6})	0.018	0.881
Cardiovascular risk factors			
Hypertension	0.074 (−0.034 to 0.182)	0.119	0.179
Hyperlipidemia	0.020 (−0.089 to 0.130)	0.033	0.712
Diabetes	0.059 (−0.089 to 0.207)	0.070	0.432
Smoking (current)	−0.085 (−0.229 to 0.059)	−0.104	0.243
APOE genotype			
APOE ε4 carrier	−0.085 (−0.183 to 0.013)	−0.157	0.087
APOE ε2 carrier	0.068 (−0.095 to 0.231)	0.074	0.410

Linear regression analyses all adjusted for age and sex.

APOE indicates apolipoprotein E; BOLD, blood-oxygen-level dependent; DPVS-BG, dilated perivascular spaces-basal ganglia; DPVS-CSO, dilated perivascular spaces-centrum semiovale; ICH, intracerebral hemorrhage; MRI, magnetic resonance imaging; SVD, small vessel disease; and WMHs, white matter hyperintensities.

amplitude and WMHs did not differ among the spectrum of cognitive impairment, from no complaints to AD-related dementia. The interaction between neurovascular decoupling and formation WMHs may therefore represent a fundamental cerebrovascular process in neurodegenerative disease, occurring before or alongside cognitive change.

Although this relationship with WMHs does not imply causation, it is postulated that impaired neurovascular coupling may contribute to the formation of WMHs.[39] Neurovascular coupling is responsible for the tight coordination between neuronal activity and blood flow regulation in the brain. Impairment in this process could lead to prolonged insufficient blood flow (ie, cerebral hypoperfusion,

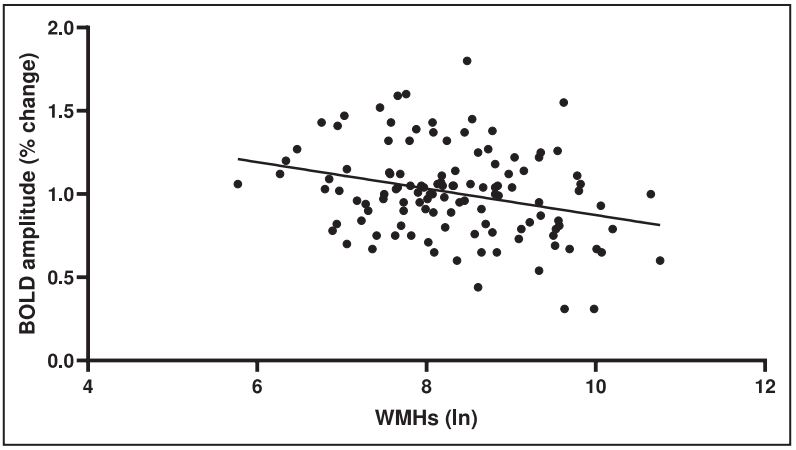

Figure 1. Scatterplot of the neurovascular coupling parameter BOLD amplitude plotted on the *y*-axis against WMHs load plotted on the *x*-axis.
Lower BOLD amplitude is associated with larger WMH volume (β=−0.199, *P*=0.030) in the whole study sample. BOLD indicates blood-oxygen-level-dependent; and WMHs, white matter hyperintensities.

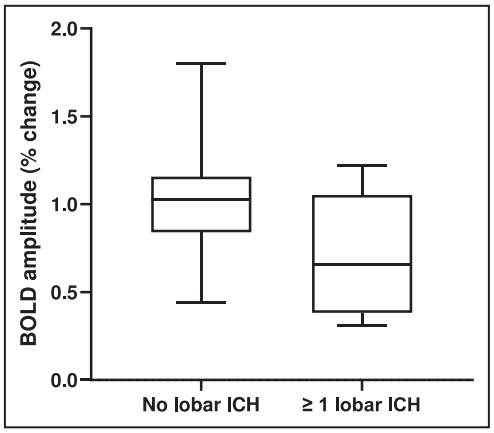

Figure 2. Boxplot of the neurovascular coupling parameter BOLD amplitude plotted on the *y*-axis and presence of lobar ICH plotted as a dichotomous variable on the *x*-axis.
Lower BOLD amplitude is associated with the presence of lobar ICH (β=−0.228, *P*=0.011) in the whole study sample. BOLD indicates blood-oxygen-level-dependent; and ICH, intracerebral hemorrhage.

leading to ischemic injury to the white matter and contributing to the development of WMHs). In CAA, amyloid deposition in cerebral vessel walls damages smooth muscle and endothelial cells, which may directly impair neurovascular coupling by reducing vessel wall elasticity and impairing the ability of blood vessels to dilate in response to neural activity. Impaired neurovascular coupling in CAA precedes nonhemorrhagic brain injuries, including WMHs,[40] and the effect of vascular amyloid on WMHs appears to be mediated by vascular dysfunction as measured by changes in the fMRI response.[41]

In this context, a recent study on neurovascular coupling in AD and CAA has demonstrated a relation between BOLD amplitude to visual stimulation and WMHs volume in patients with CAA only, because this association was not observed in patients with MCI or AD without hemorrhagic markers indicative of CAA.[42] This association between a decreased BOLD response to visual stimulation and WMHs is consistently observed in patients with CAA,[18,42,43] as highlighted in a recent meta-analysis.[33] In this respect, our secondary analysis revealed that the association between the BOLD amplitude and WMHs volume was only present in the subgroup with hemorrhagic markers indicative of CAA. These findings raise the suggestion that the observed relationship in our cohort may reflect concurrent CAA pathology. This is further supported by the association between neurovascular coupling and the presence of lobar ICH, with CAA being a primary pathology associated with such hemorrhagic events.

However, we did not find an association between neurovascular coupling and lobar microbleeds, which are also considered a marker for CAA. Previous studies on patients with sporadic CAA have reported

Table 3. Demographic and Clinical Characteristics of the Non-CAA and CAA Subgroups

	Non-CAA group	CAA group
N	87	32
Age, y	70.6 (8.7; 52–87)	74.6 (8.5; 51–89)
Female sex	41 (47.1%)	8 (25.0%)
MMSE, median (IQR)	29 (27–29)	27 (25–29)
Neurovascular coupling		
BOLD amplitude, % change	1.03 (0.25; 0.44–1.60)	0.96 (0.33; 0.31–1.80)
SVD risk factors		
Hypertension	22 (25.3%)	9 (28.1%)
Hyperlipidemia	23 (26.4%)	9 (28.1%)
Diabetes	11 (12.6%)	3 (9.4%)
Smoking (current)	9 (10.3%)	6 (18.8%)
Modified Boston CAA MRI markers		
≥1 Lobar ICH	0 (0.0%)	8 (25.0%)
1 Lobar ICH	0	4
2 Lobar ICH	0	2
3 Lobar ICH	0	2
≥1 Lobar microbleeds	27 (31.0%)	32 (100%)
1 Lobar microbleed	27	1
2 or more Lobar microbleeds	0	31
Cortical superficial siderosis	0 (0%)	1 (3.1%)
Focal (≤3 sulci)	0	1
Disseminated (≥4 sulci)	0	0
Significant association from whole study sample		
WMH volume cm^3	5.4 (4.9; 0.3–23.4)	10.2 (11.6; 0.6–47.0)

Values are number (%) or mean (SD; range).
BOLD indicates blood-oxygen-level dependent; CAA, cerebral amyloid angiopathy; ICH, intracerebral hemorrhage; IQR, interquartile range; MMSE, Mini-Mental State Examination; MRI, magnetic resonance imaging; SVD, small vessel disease; and WMH, white matter hyperintensity.

conflicting results regarding this association.[18,43] Variances in CAA severity might account for these divergent findings between studies. Since our cohort was not specifically selected for the presence of CAA, the average lobar microbleeds count in our cohort was substantially lower than in a previous study that did find an association.[43] Moreover, various pathophysiological mechanisms likely underlie the development of the different vascular lesions in the brain, although the precise pathways are not yet fully understood. For instance, it is hypothesized that lobar microbleeds are caused by vascular remodeling processes.[44,45] This suggests that factors other than impaired neurovascular coupling, such as structural alterations of blood vessels, may play a more significant role in the formation of these lesions. Therefore, to better elucidate the impact of decreased neurovascular coupling on the development

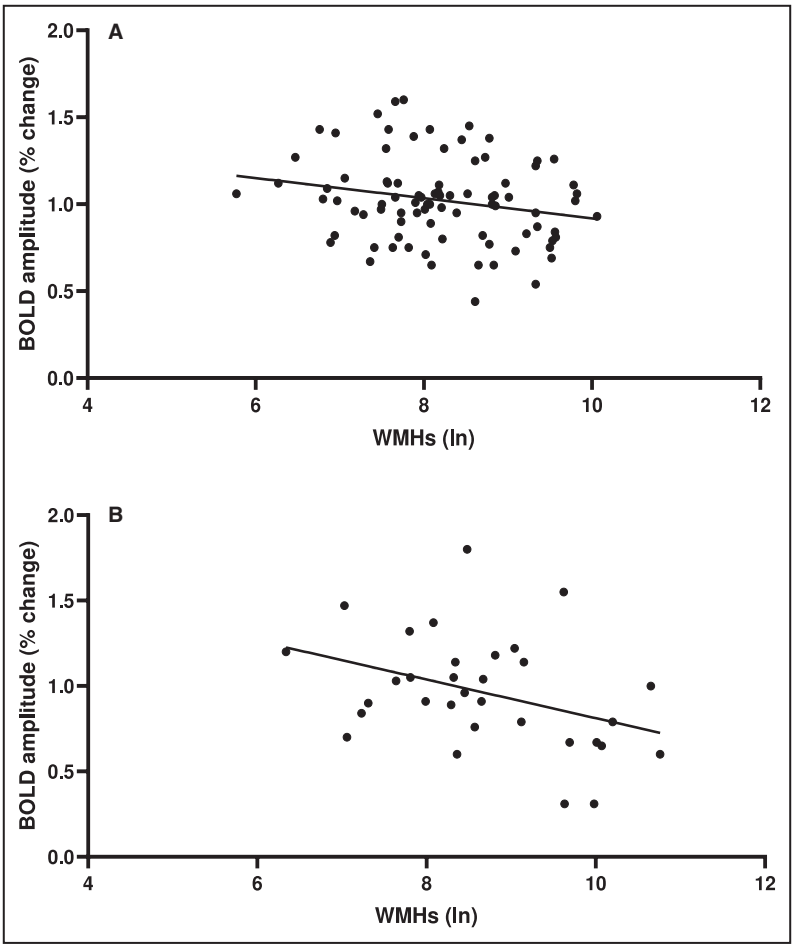

Figure 3. Scatterplots of the neurovascular coupling parameter BOLD amplitude plotted on the *y*-axis against WMHs load plotted on the *x*-axis for the (A) non-CAA subgroup and (B) CAA subgroup.
In the non-CAA subgroup **(A)**, BOLD amplitude is not significantly associated with WMHs load (β=−0.116, *P*=0.274). In the CAA subgroup **(B)**, lower BOLD amplitude is significantly associated with larger WMH volume (β=−0.370, *P*=0.046). BOLD indicates blood-oxygen-level-dependent; CAA, cerebral amyloid angiopathy; and WMHs, white matter hyperintensities.

of different types of vascular brain lesions, future longitudinal studies are crucial.

With regard to APOE genotype, we found no association with BOLD amplitude. Studies focusing on the link between APOE ε4 genotype and neurovascular coupling are scarce. In line with our finding, no significant influence of APOE genotype on the hemodynamic responses to a visual stimulation task was reported in healthy adults.[46] On the other hand, reduced cerebrovascular reactivity to CO_2 inhalation has been observed in young adult APOE e4 carriers by BOLD fMRI[47] and in older adult APOE ε4 carriers by transcranial Doppler ultrasonography,[48] suggesting that APOE ε4 does affect the vasoactive ability of cerebral blood vessels. Studies with greater sample sizes are needed to provide more insight into the potential relationship with the APOE ε4 genotype.

An advantage of challenging the vessel wall using BOLD fMRI with a visual stimulus, rather than CO_2 inhalation, is that it includes a neuronal component to activate the cerebral blood flow response, thereby providing a physiologically relevant measure of the vascular response to brain activity. However, a limitation of this method is the uncertainty regarding the precise vascular and neuronal contribution to the signal. Therefore, it is important to interpret the BOLD signal with caution, because it represents a complex interaction of various brain functions.[49] Moreover, it is important to acknowledge that the study period coincided with the early stages of the COVID-19 pandemic. Although we did not specifically assess the impact of the pandemic on participants' care, cognitive status, or vascular health, we recognize the potential for such effects. This uncertainty should be considered when

interpreting our findings, because the pandemic may have introduced variables that were not accounted for in our analysis.

CONCLUSIONS

In conclusion, impaired neurovascular coupling is associated with a higher load of WMHs and the presence of lobar ICH in a cohort including participants with a diagnosis of SCI, MCI, and AD-related dementia, as well as in participants without cognitive complaints. Notably, neurovascular coupling appears not to be related to other SVD MRI markers, cardiovascular risk factors, or the APOE ε4 genotype. Taken together, our findings raise the suggestion that a decreased neurovascular coupling in the disease process of AD may be related to comorbid SVD, most probably of the CAA type. This highlights the importance of considering small vessel damage in understanding the vascular contributions to the disease process of AD. For example, therapies aimed at amyloid lowering in CAA might improve cerebrovascular function (ie, neurovascular coupling), and have the potential to prevent (at least part of) the subsequent vascular lesions. These preventive interventions aimed at modifying neurovascular coupling could also prove their potential in AD treatment trials in order to reduce dementia risk, in which neurovascular coupling to visual stimulation can serve as an outcome marker.

ARTICLE INFORMATION

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Disclosures

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