

Mapping the differential role of small vessel disease in aging and dementia

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KEY MESSAGE

Automatic quantification tools of small vessel disease markers show moderate-to-strong agreement with visual ratings. Best performance was found for white matter hyperintensities, followed by cerebral microbleeds and perivascular spaces. Associations among regional markers differed between a ***population-based*** and a ***memory clinic cohort***. Greater small vessel disease burden generally corresponded with worse cognitive outcomes, with associations being more pronounced for WMH than the other markers.

BACKGROUND

Small vessel disease (SVD) is a major contributor to dementia. Improved understanding of SVD can facilitate the early identification of individuals at risk of cognitive decline and dementia. Yet, the inter-relationship and clinical correlates of SVD markers are still poorly understood. Manual segmentation of SVD markers is time-consuming, expensive and subject to inter-rater reliability. To accelerate research, automatic segmentation models have been developed and need to be evaluated across heterogeneous datasets.

AIMS

1. Validate existing automatic segmentation tools against visual ratings in diverse independent cohorts and, thereby, evaluate their generalizability.
2. Comprehensively characterize the regional and global distribution of SVD markers.
3. Outline the region-specific associations between individual SVD markers and cognitive domains.

METHODS

Study population. 790 individuals from population-based Gothenburg H70 Birth Cohort and 790 from Karolinska University memory clinic cohort.

Data. Demographics, cognitive tests, CSF biomarkers (A β 42/A β 40), APOE genotype. T1-weighted, FLAIR, and SWI MRI. Visual ratings of SVD markers using Fazekas¹, Potter², and STRIVE-2³ criteria.

Automated segmentation. White matter hyperintensities (WMH), enlarged perivascular spaces (EPVS), and cerebral microbleeds (CMB) were segmented from T1-weighted, FLAIR, and SWI MRI, respectively (Figure 1).

Regional quantification. WMH: Global, deep, and periventricular volume (ICV-normalized). EPVS: Global, basal ganglia, and centrum semiovale burden (normalized to regional volume). CMBs: Global, lobar, and deep count and presence.

Statistical Analysis. Spearman correlation: automatic versus visual SVD markers. Partial Spearman correlations: regional automatic SVD markers versus cognitive domains. Covariates: age and sex (MemClin), sex (H70), education (cognition models).

Table 2. Agreement of automated markers and visual ratings of small vessel disease.

Automated SVD marker	Visual assessment	Cohort	N	Spearman's ρ	p-value _{FDR}
Global WMH volume fraction	Fazekas scale	H70	788	0.63 [0.58; 0.67]	<0.001
		Memclin	650	0.76 [0.73; 0.79]	<0.001
Centrum semiovale EPVS volume fraction	Potter scale	H70	790	0.46 [0.41; 0.52]	<0.001
		Memclin	785	0.53 [0.48; 0.58]	<0.001
Basal ganglia EPVS volume fraction		H70	789	0.41 [0.36; 0.47]	<0.001
		Memclin	785	0.59 [0.55; 0.64]	<0.001
Lobar CMB counts	Visual count	H70	788	0.62 [0.58; 0.66]	<0.001
		Memclin	782	0.65 [0.61; 0.69]	<0.001
Deep CMB counts		H70	788	0.59 [0.54; 0.63]	<0.001
		Memclin	782	0.50 [0.45; 0.55]	<0.001

REFERENCES

[1] Fazekas F, et al. AJR. 1987;149:351-356. [2] Potter GM, et al. Cerebrovascular Diseases. 2015;39:224-231. [3] Duering M, et al. The Lancet Neurology. 2023;22:602-618. [4] Gibson E, et al. *Human Brain Mapping*. 2024;45:e70104. [5] Gibson E, et al. Human Brain Mapping. 2026;47:e70462. [6] Tsuchida A, et al. Scientific Reports. 2024;14:30901.

Table 1. Description of the population-based H70 cohort and the Karolinska University memory clinic cohort.

	N H70	Stat H70	N Memclin	Stat Memclin	Effect Size
Demographic					
Age (years)	789	70.5 [70.4-70.8]	788	60.0 [56.0-63.0]	r = -0.95 [-0.97; -0.92]
Female (N, %)	790	414 (52.4%)	788	445 (56.5%)	RD = 0.04 [-0.01; -0.09]
Education (years)	789	13.0 [10.0-16.0]	631	13.0 [11.0-16.0]	r = 0.05 [-0.01; 0.11]
APOE ϵ 4 carrier (N, %)	773	257 (33.3%)	694	314 (45.2%)	RD = 0.12 [0.07; 0.17]
MMSE	784	29.0 [29.0-30.0]	476	27.0 [24.0-29.0]	r = -0.56 [-0.61; -0.50]
Dementia (N, %)	789	13 (1.7%)	788	162 (20.6%)	RD = 0.19 [0.16; 0.22]
Automatic SVD marker					
Global WMH volume fraction (%)	790	0.2 [0.1-0.4]	789	0.14 [0.1-0.3]	r = -0.13 [-0.19; -0.08]
Periventricular WMH volume fraction (%)	790	0.2 [0.1-0.3]	789	0.1 [0.1-0.3]	r = -0.18 [-0.24; -0.12]
Deep WMH volume fraction (%)	790	0.0 [0.0-0.0]	789	0.0 [0.0-0.0]	r = 0.08 [0.03; 0.14]
Global EPVS volume fraction (%)	790	0.1 [0.1-0.1]	789	0.1 [0.0-0.1]	r = -0.47 [-0.52; -0.42]
Basal ganglia EPVS volume fraction (%)	790	1.5 [1.1-1.9]	789	0.8 [0.6-1.2]	r = -0.57 [-0.61; -0.52]
Centrum semiovale EPVS volume fraction (%)	790	0.2 [0.1-0.4]	789	0.1 [0.0-0.3]	r = -0.20 [-0.25; -0.14]
Global CMB present (N, %)	788	239 (30.3%)	790	253 (32.0%)	RD = 0.01 [-0.03; 0.05]
Lobar CMB present (N, %)	788	179 (22.7%)	790	188 (23.8%)	RD = 0.01 [-0.03; 0.05]
Deep CMB present (N, %)	788	100 (12.7%)	790	121 (15.3%)	RD = 0.03 [-0.01; 0.06]

Figure 1. Automated segmentation of small vessel disease: (A) segcsvdWMH⁴, (B) segcsvdPVS⁵, and (C) SHiVAi⁶

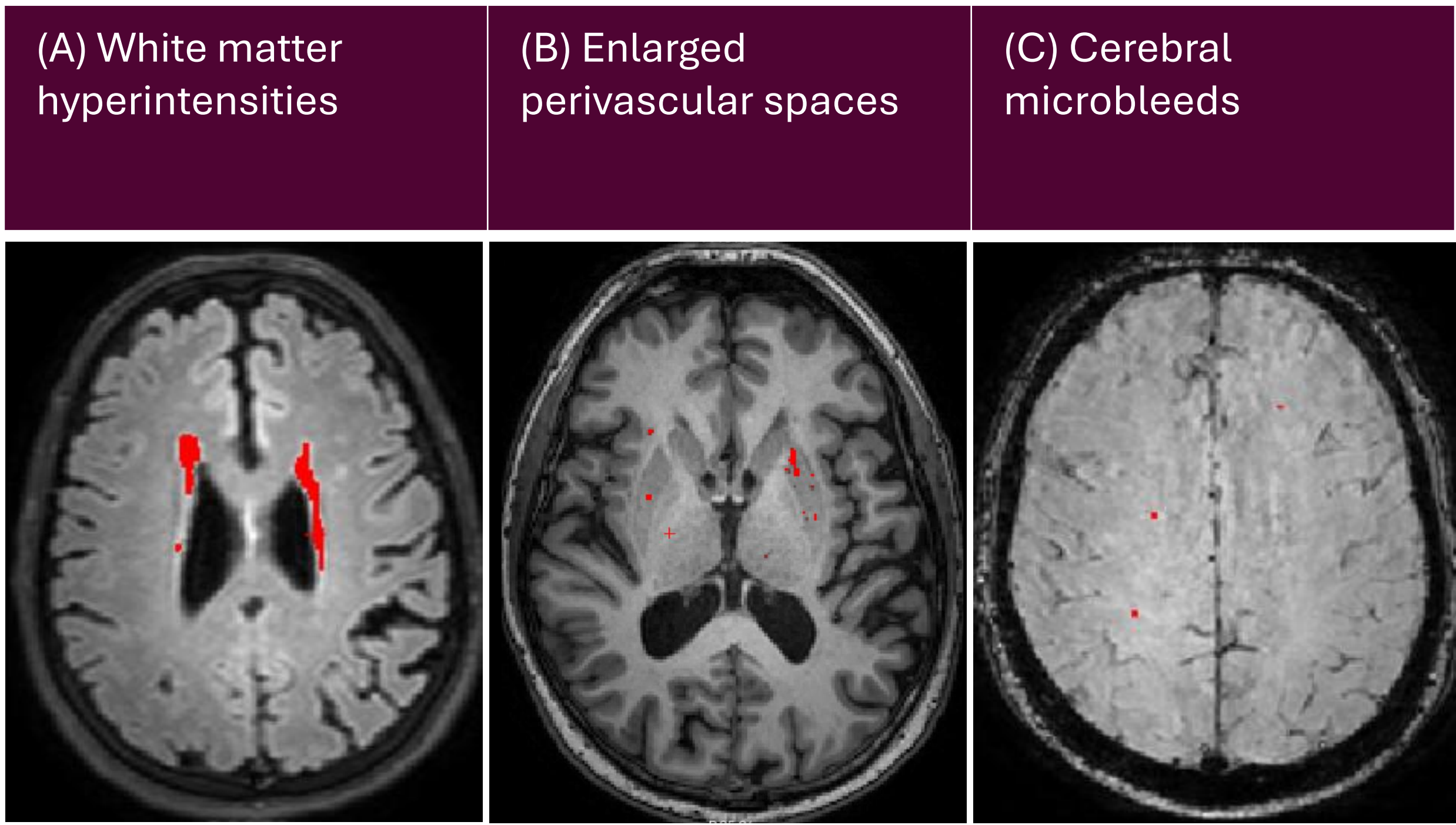
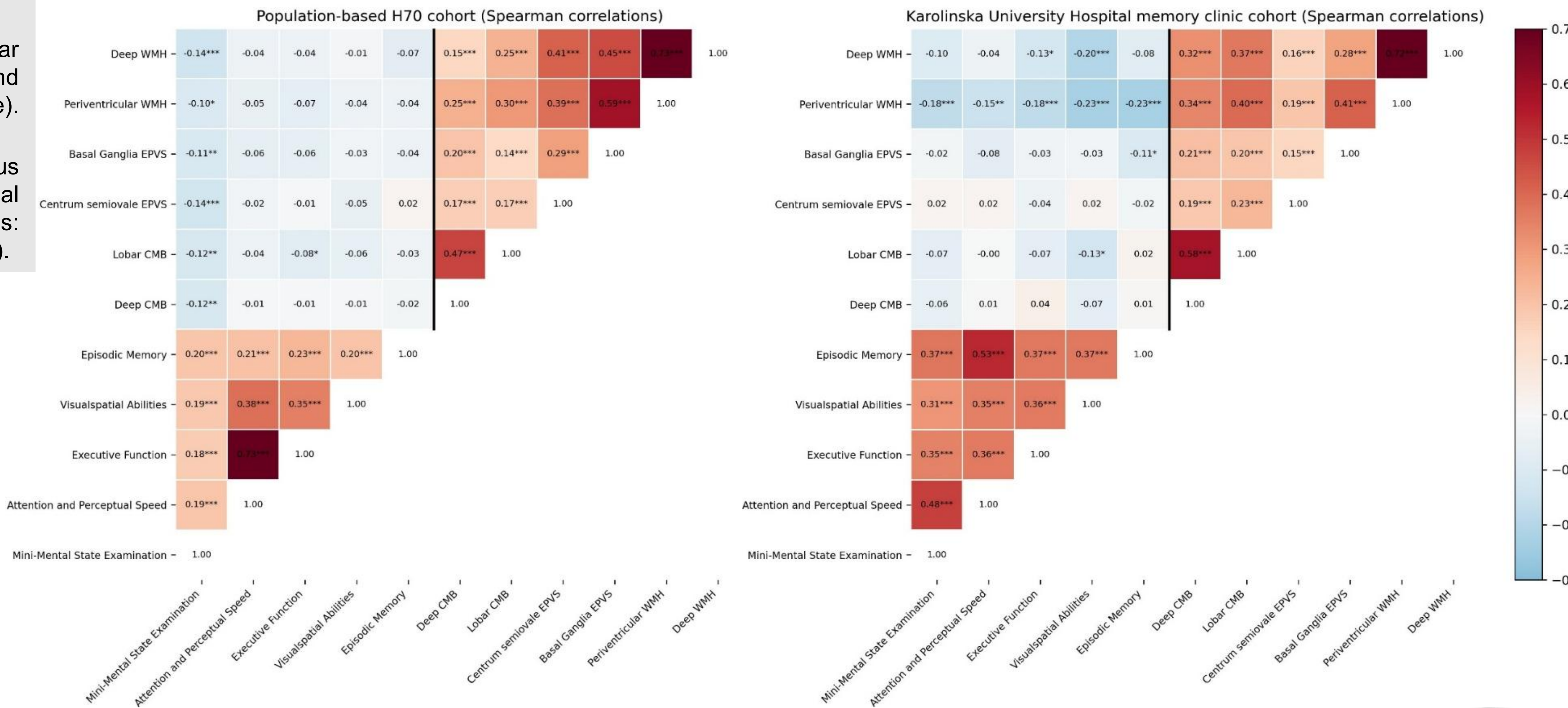


Figure 2. Association between regional small vessel disease markers and cognition in two independent cohorts



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