



Microvascular Damage Reflects Underlying Cerebral Pathology in Alzheimer's Disease and Cerebral Small Vessel Disease

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INTRODUCTION

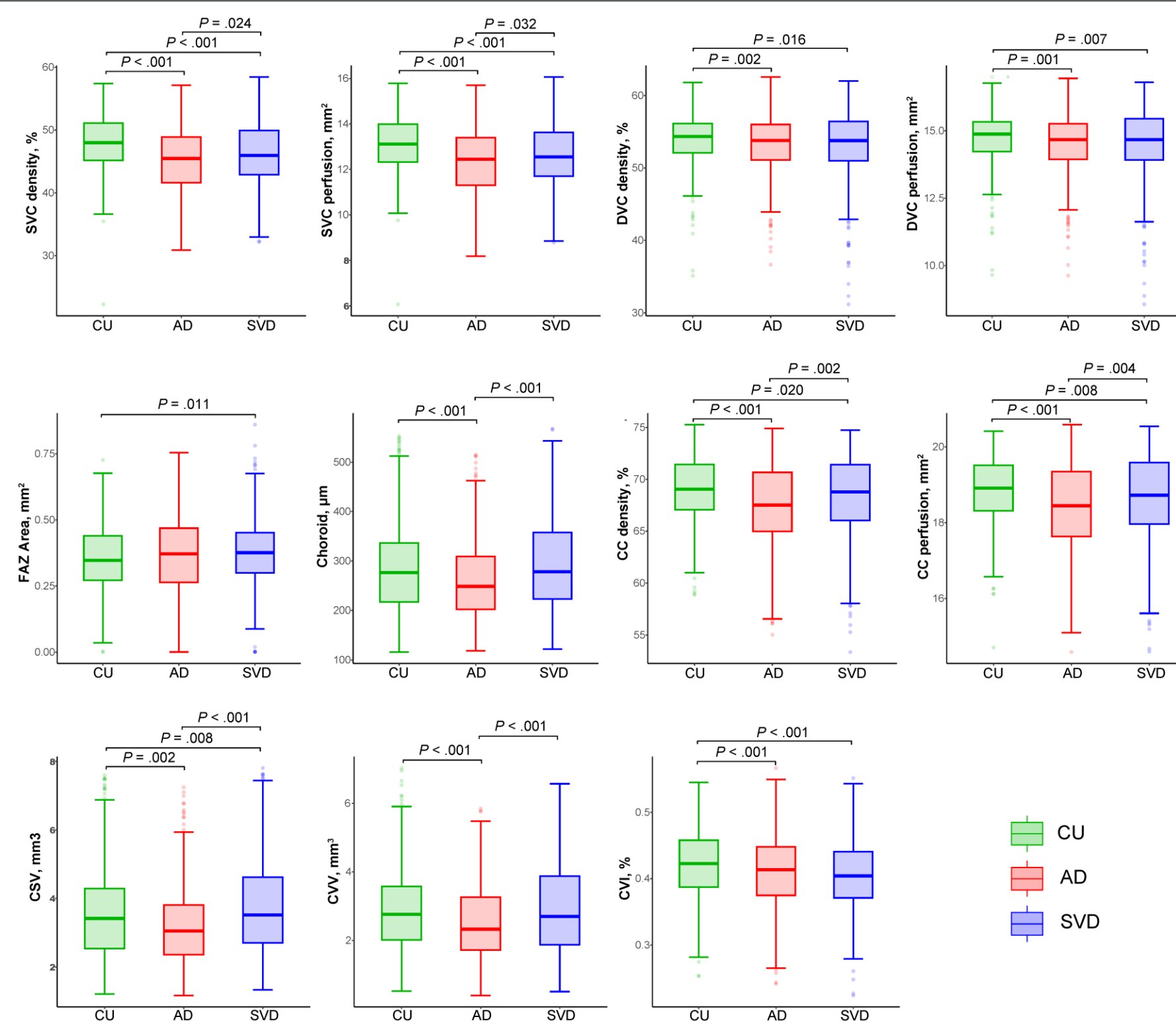
Optical coherence tomography angiography (OCTA) has revealed ocular microvascular alterations in both Alzheimer's disease (AD) and cerebral small vessel disease (SVD). However, whether these retinal and choroidal changes reflect disease-specific cerebral pathophysiology remains unclear.

METHODS

In this cross-sectional study, we included 149 patients with AD, 276 patients with SVD, and 225 cognitively unimpaired controls. All participants underwent swept-source OCTA, brain magnetic resonance imaging, and blood biomarker assessments. Quantitative ocular microvascular metrics were analyzed to characterize microvascular phenotypes associated with hallmark AD proteinopathy and SVD-related vascular injury.

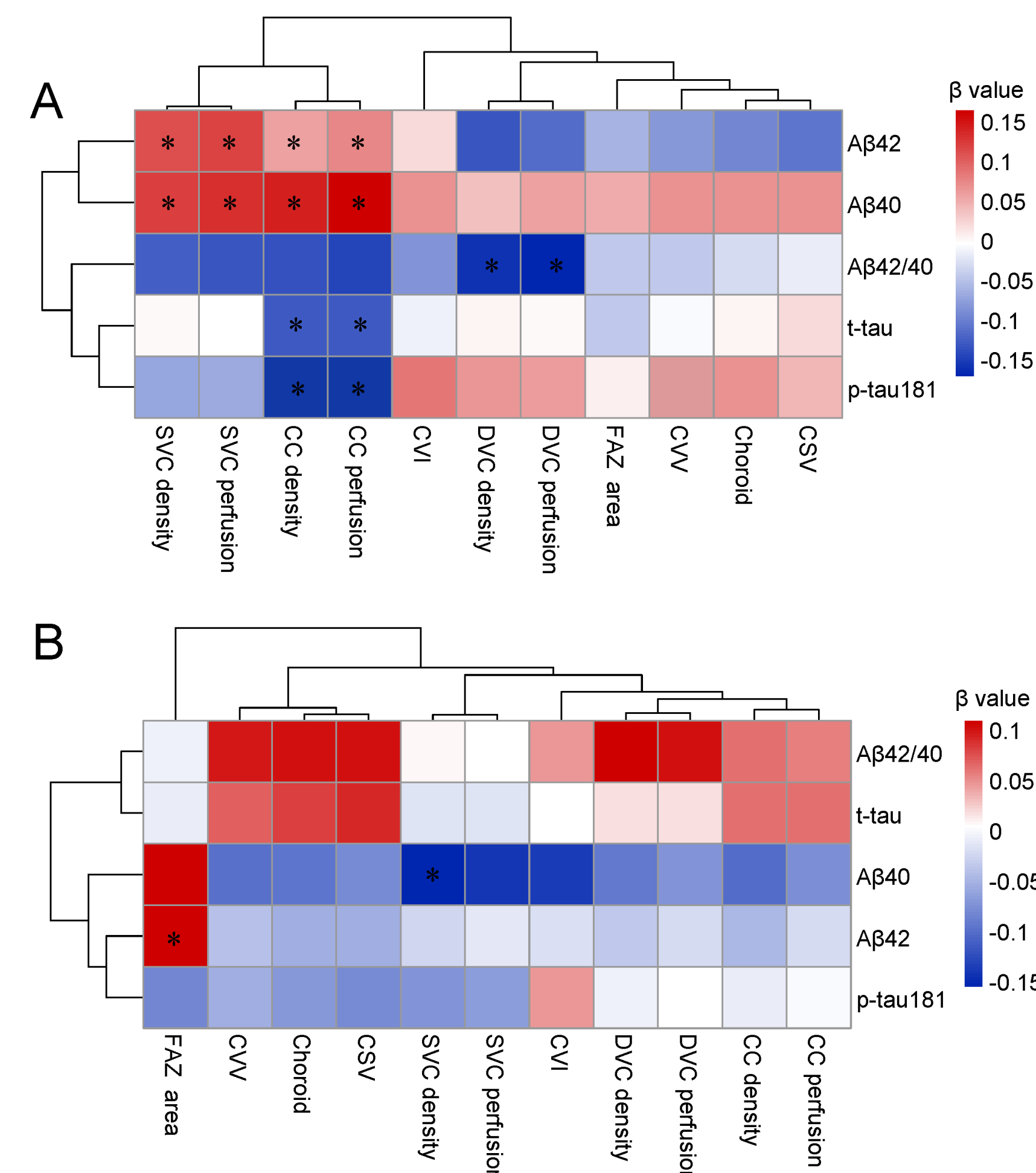
RESULTS

Fig 1. Comparison of ocular microvascular metrics among AD, SVD and cognitively unimpaired controls.



Compared with SVD, AD patients exhibited significantly reduced density and perfusion in retinal superficial vascular complex and choriocapillaris. In contrast, retinal ischemic perivascular lesions (RIPLs) were markedly more prevalent in SVD than in AD and were significantly associated with overall SVD burden ($p = 0.049$).

Fig 2. Correlations between ocular microvascular metrics and blood biomarkers.



A, Associations between OCTA metrics and blood biomarkers in AD. B, Associations between OCTA metrics and blood biomarkers in SVD.

Choriocapillaris impairment was selectively associated with lower serum Aβ42 and Aβ40 levels and higher phosphorylated tau 181 levels in AD, but not in SVD.

Table 1. Machine learning performance for disease classification.

Variables	AUC	ACC	Sensitivity	Specificity
AD - SVD group				
LASSO logistic	0.751	0.719	0.664	0.782
RF	0.864	0.759	0.804	0.760
SVM	0.883	0.802	0.800	0.800
MLP	0.863	0.773	0.782	0.800
XGBoost	0.874	0.820	0.818	0.818
AD - CU group				
LASSO logistic	0.799	0.739	0.831	0.564
RF	0.839	0.775	0.867	0.636
SVM	0.867	0.761	0.723	0.818
MLP	0.846	0.790	0.855	0.655
XGBoost	0.856	0.812	0.867	0.745
SVD - CU group				
LASSO logistic	0.879	0.807	0.807	0.804
RF	0.914	0.856	0.831	0.866
SVM	0.939	0.828	0.735	0.990
MLP	0.923	0.867	0.867	0.866
XGBoost	0.906	0.834	0.843	0.835

Machine learning models incorporating OCTA-derived microvascular features reliably differentiated AD from SVD and cognitively unimpaired individuals.

HIGHLIGHTS

- SVD shows increased RIPLs, while AD shows reduced CC density.
- RIPLs correlate with overall SVD burden; reduced CC density associates with elevated p-tau181 in AD.
- Selected OCTA metrics help ML models distinguish AD from SVD.

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CONCLUSION

Distinct ocular microvascular signatures differentiate AD from SVD. Choriocapillaris dysfunction appears to reflect AD-related proteinopathy, whereas RIPLs preferentially indicate SVD-related vascular injury. These findings support ocular microvasculature as a noninvasive biomarker of disease-specific cerebral pathology and vascular mechanisms underlying cognitive impairment.