

Automated Quantification of Enlarged Perivascular Spaces and Associations with Demographics and Cognition

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BACKGROUND

- Enlarged perivascular spaces (ePVS) are a hallmark of cerebral small vessel disease and CAA.
- Impaired glymphatic clearance associated with ePVS may contribute to neuroinflammation and neurodegeneration.
- ePVS assessment relies mostly on visual review, although quantitative MRI approaches using T1- and T2-weighted imaging are being developed.
- We aimed to evaluate the reproducibility of a T1-only quantitative method and to investigate associations between ePVS burden, clinical characteristics and cognitive performance across the AD continuum.

METHODS

Data

- 1433 ADNI subjects were included: 839 cognitively normal (CN), 473 with MCI and 121 with AD.
- 199 additional MRI scans from 46 ADNI-2 subjects were analyzed for test-retest reproducibility (accelerated vs. non-accelerated 3DT1 scans).
- Cognitive performance was assessed using MMSE, ADAS-Cog and CDR-SB.

Image analysis (Fig. 1)

- 3DT1 data were segmented with a deep-learning method¹ trained to detect ePVS.
- Midbrain ePVS were additionally assessed using Frangi filtering to improve sensitivity.
- ePVS count/volume were calculated in the basal ganglia, cerebral white-matter, midbrain and whole brain.

Statistical analysis

Test-retest

- Test-retest reproducibility was assessed using Pearson correlation (r) and intraclass correlation coefficient (ICC(2,1), two-way random, absolute agreement).
- Absolute agreement was further evaluated using Bland–Altman analysis, including mean bias and 95% limits of agreement.
- For midbrain counts, where values were low and discrete, reproducibility was additionally summarized using exact and ± 1 agreement.

Associations with clinical characteristics

- Baseline associations between ePVS and demographic, genetic and clinical variables were assessed.
- ePVS counts and volumes were derived for the basal ganglia (BG), white matter (WM), midbrain (MB) and whole brain (Total).
- ePVS volumes and counts were log-transformed to account for skewness (except midbrain volume due to small magnitude).
- Multivariable linear regression models included age, sex, intracranial volume (ICV), APOE $\epsilon 4$ carrier status and cognitive measures as predictors.
- Model performance was compared across regions and metrics using R^2 .
- Group differences (CN, MCI, AD) were assessed using ANOVA with post-hoc tests, and effect sizes were quantified using η^2 .
- To assess independent effects of sex and head size, ICV was residualized with respect to sex.
- Standardized regression coefficients were computed to compare relative predictor importance.

RESULTS

Test-retest (Figs. 2 and 3)

- Reproducibility was excellent for basal ganglia, white matter and total measures, with high correlations ($r = 0.92-0.98$, $p < 0.001$) and ICC values (0.89-0.97).
- Volume measures demonstrated particularly high reliability across all regions (ICC ≥ 0.79), with near-perfect agreement in volume (ICC $\approx 0.96-0.97$).
- Bland-Altman analysis showed small biases and no systematic differences.
- Midbrain measures showed lower reproducibility for counts ($r = 0.49$, ICC = 0.47), with 38% exact agreement and 80% agreement within ± 1 count, reflecting low and discrete burden, while volume retained good reliability ($r = 0.79$, ICC = 0.79).

Associations with clinical characteristics

Regional comparison (Fig. 4 top left)

Model performance varied markedly by region.

- Basal ganglia ePVS volume showed the strongest associations ($R^2 = 0.17$).
- Midbrain showed moderate performance ($R^2 \approx 0.11$)
- White matter and total measures showed weak associations ($R^2 \approx 0.02-0.04$).
- Volume and count metrics performed similarly across regions.

Age effects (Fig. 4 top right)

Age was strongly associated with BG ePVS volume ($R^2 = 0.13$, $p < 0.001$), with a clear positive relationship.

Clinical group differences (Fig. 4 bottom left)

Group differences were statistically significant (ANOVA $p < 0.001$), but effect size was very small ($\eta^2 = 0.006$).

- MCI showed slightly higher ePVS than CN.
- No differences were observed for AD.

In multivariable models:

- MCI vs CN remained significant ($\beta \approx 0.09$, $p < 0.001$)
- AD showed no association.

Determinants of ePVS (Fig. 4 bottom right)

- In the multivariate analysis using standardized coefficients:
- Age was the dominant predictor ($\beta = 0.33$).
 - ICV showed a moderate positive association ($\beta = 0.18$)
 - Sex showed a small independent effect after accounting for head size ($\beta = 0.08$).
 - APOE $\epsilon 4$ carrier status showed a small negative association ($\beta = -0.08$, $p < 0.05$).
 - Cognitive associations were weak and inconsistent:
 - CDR-SB showed a small positive association ($\beta = 0.12$, $p < 0.001$).
 - MMSE and ADAS-Cog were not associated.

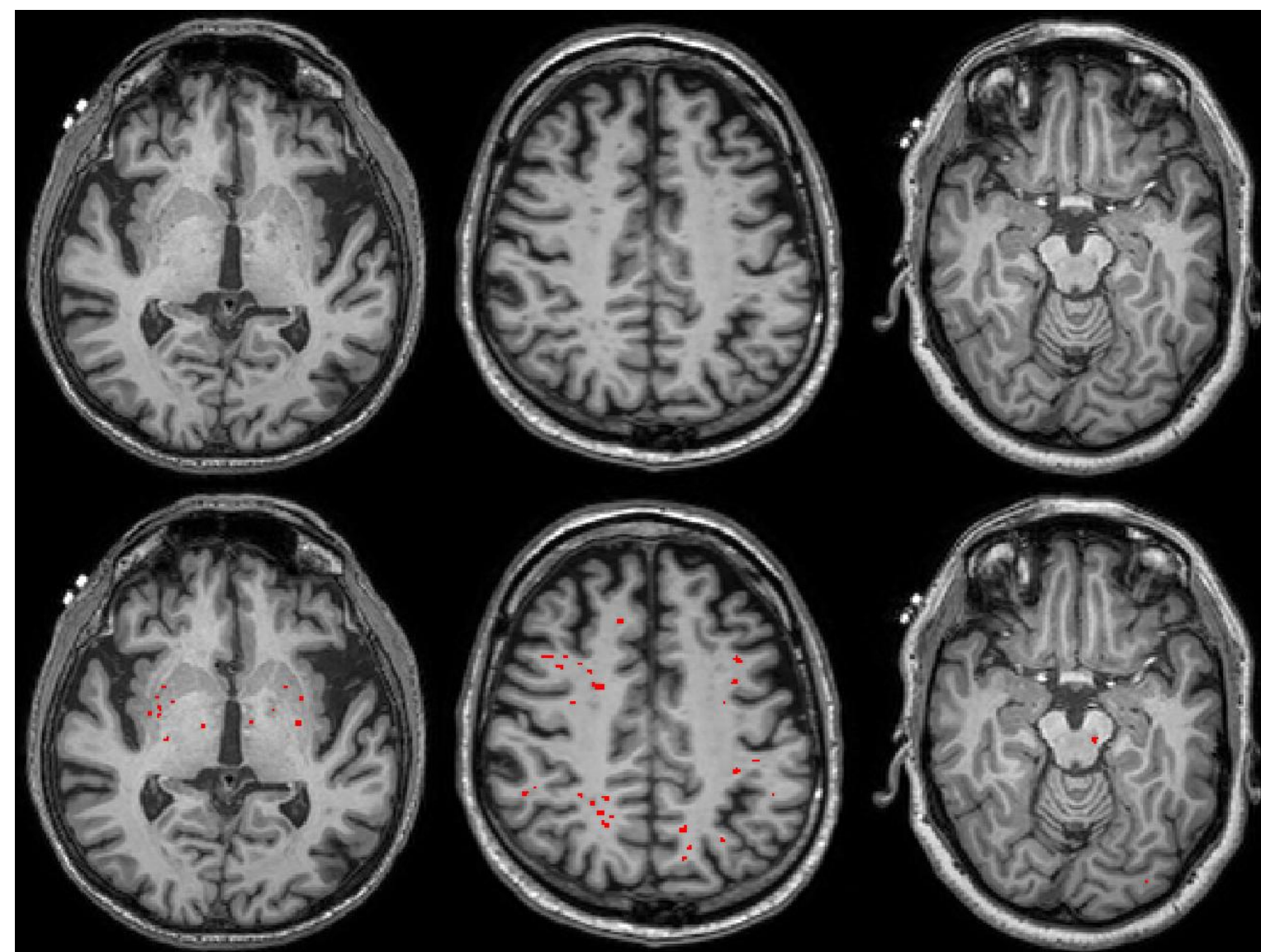


Fig. 1 - Example of ePVS segmentations

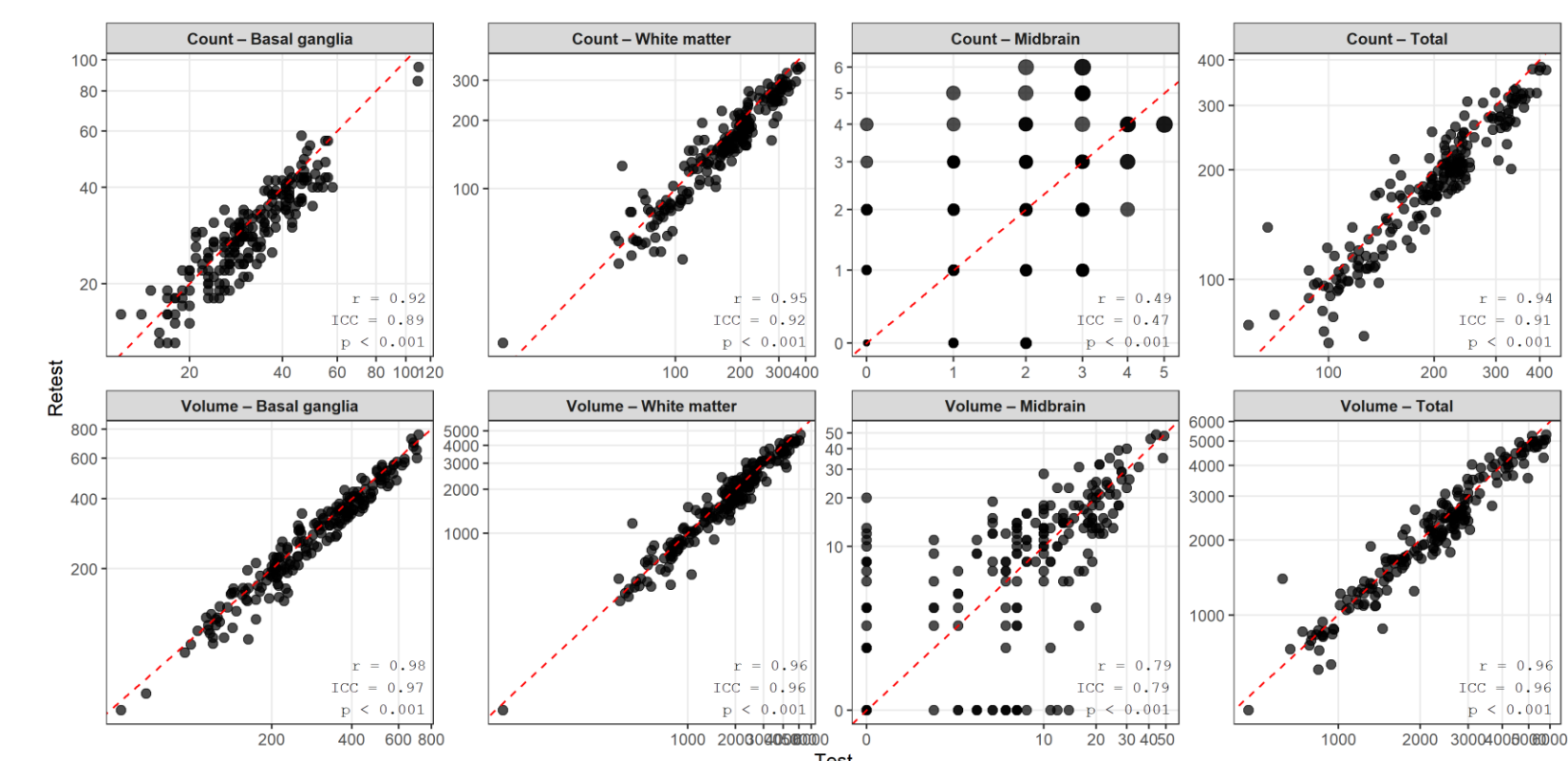


Fig. 2 - Test-Retest reproducibility

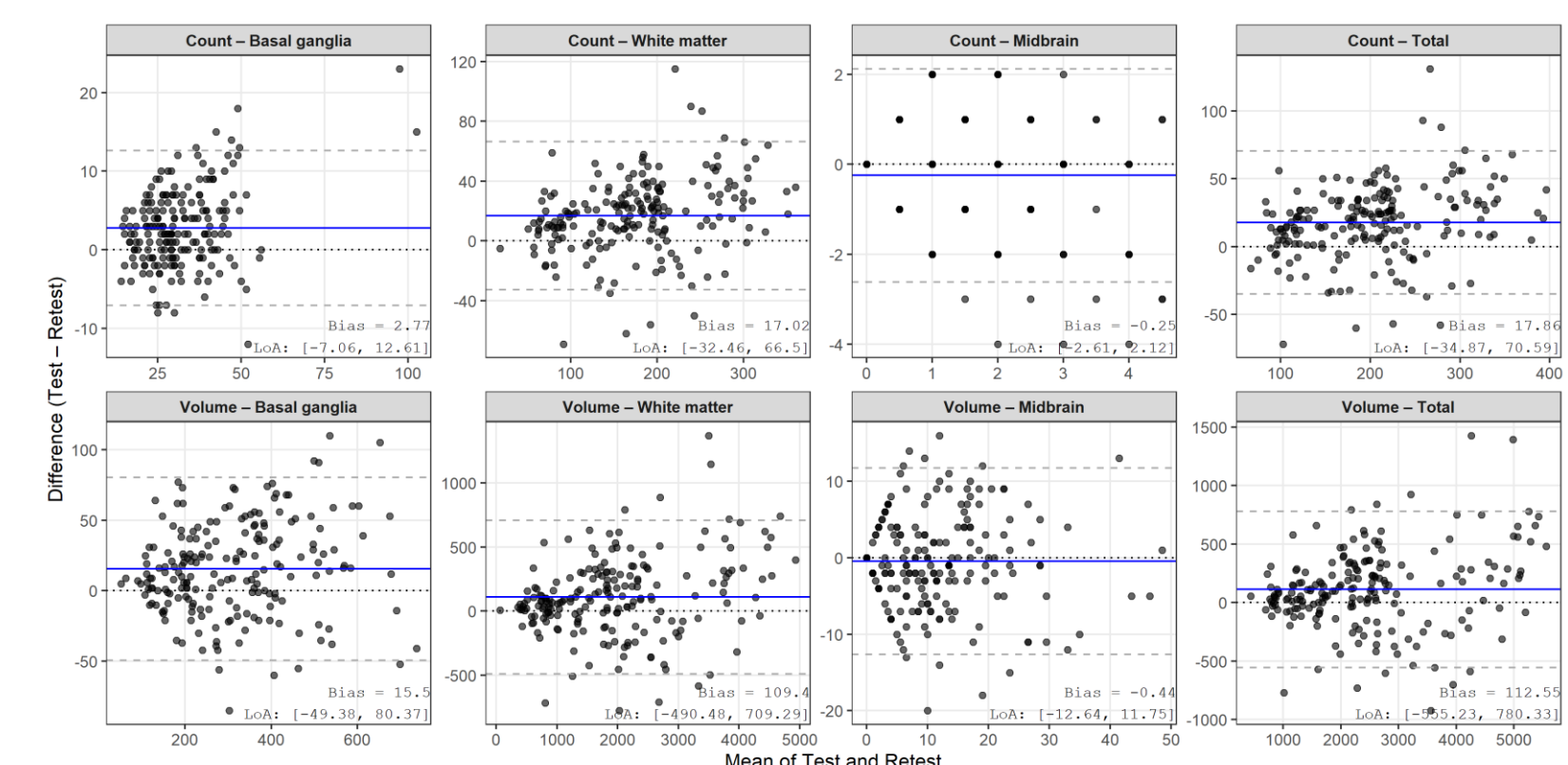


Fig. 3 - Test-Retest agreement (Bland-Altman analysis)

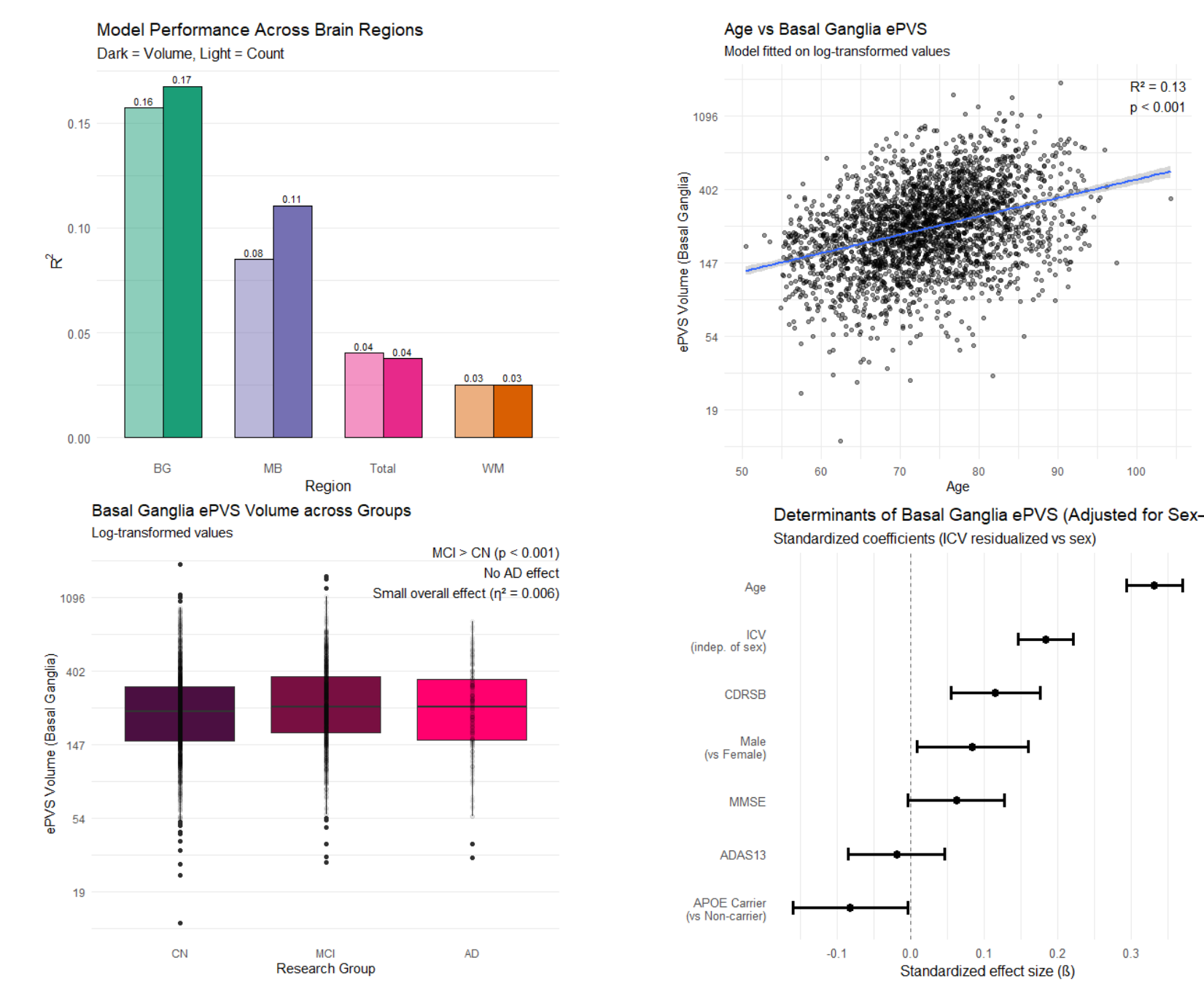


Fig. 4 - ePVS associations with demographic and clinical factors

CONCLUSIONS

- Although 3D T1-weighted MRI data alone may not be optimal for ePVS assessment, a T1-only quantitative method showed good reproducibility and robust associations with biological factors.
- ePVS burden is primarily driven by aging, with secondary contributions from head size and sex, and only weak associations with APOE $\epsilon 4$ status and cognitive measures.
- Basal ganglia volume provides the most sensitive measure in this analysis.
- Future work will investigate potential longitudinal associations.

REFERENCES

- Huang P. et al., *Development and validation of a perivascular space segmentation method in multi-center datasets*, Neuroimage. 2024.