

Structural Heterogeneity in Isolated Executive-Predominant Cognitive Impairment Across Dementia Etiologies

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Background

- Alzheimer's disease (AD), cerebrovascular disease (VasD), and dementia with Lewy bodies (DLB) can present with overlapping early clinical features, particularly executive dysfunction, complicating differential diagnosis.
- Standard voxel-based morphometry (VBM) detects group-level gray matter (GM) differences but may not fully capture within-diagnosis structural heterogeneity.
- Mapping both group-level GM differences and within-group variability may provide complementary imaging biomarkers across dementia etiologies.

Objective

- To characterize diagnosis-related gray matter differences and within-group structural heterogeneity among individuals with isolated executive-predominant cognitive impairment due to AD, VasD, or DLB.

Materials and Methods

We included 54 participants from the National Alzheimer's Coordinating Center database with isolated mild executive-predominant cognitive impairment and available T1-weighted brain MRI.

Participants were grouped by clinical diagnosis:

- AD: n = 6; age 74.0 ± 6.5 years; 4F/2M
- VasD: n = 36; age 75.6 ± 6.9 years; 12F/24M
- DLB: n = 12; age 69.9 ± 7.9 years; 9F/3M

Cognitive impairment was defined using:

- Clinical Dementia Rating: CDR = 0.5–1
- MMSE: 17–29 or MoCA: 17–26

T1-weighted MRI scans were processed using CAT12/SPM12 VBM.

A one-way ANOVA tested the main effect of diagnosis on voxel-wise GM density, adjusting for total intracranial volume. Post-hoc pairwise t-tests evaluated diagnosis-specific GM differences.

Statistical threshold: $p < 0.001$, uncorrected.

To evaluate within-group structural heterogeneity, voxel-wise maps of the following metrics were generated separately for each diagnostic group:

- Mean GM density
- GM variance
- Coefficient of variation

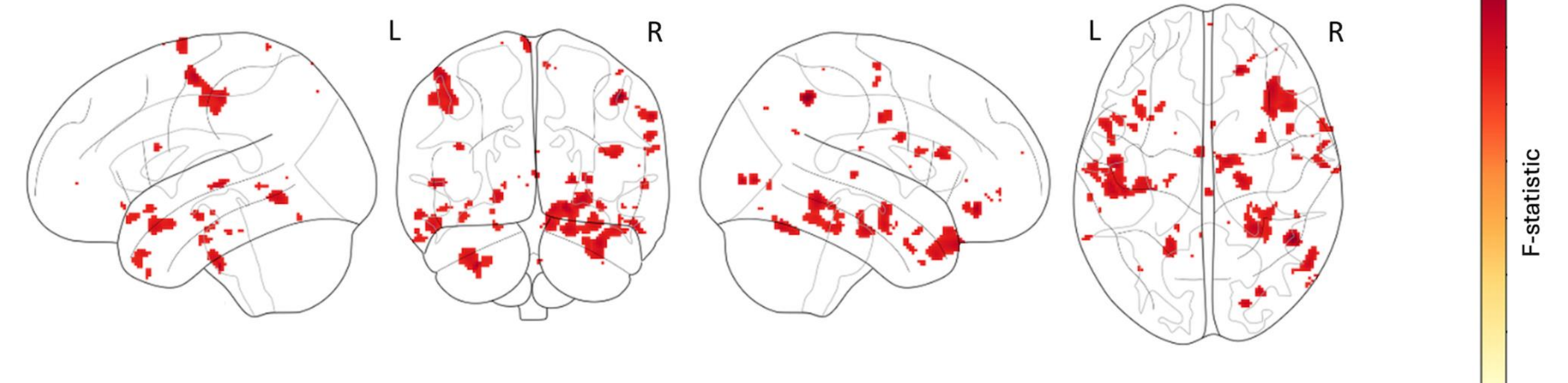
Conclusions

- AD, VasD, and DLB show distinct GM patterns in isolated executive-predominant cognitive impairment. Beyond mean VBM contrasts, variance-based metrics reveal diagnosis-specific structural heterogeneity that may reflect subtype diversity or mixed disease mechanisms.
- Integrating within-group variability with conventional VBM may improve characterization of mixed-etiology cognitive impairment and support stratification in mechanism-focused clinical trials.

Results

The omnibus ANOVA showed widespread diagnosis-related GM differences involving inferior parietal, fusiform, orbitofrontal, postcentral, and calcarine regions:

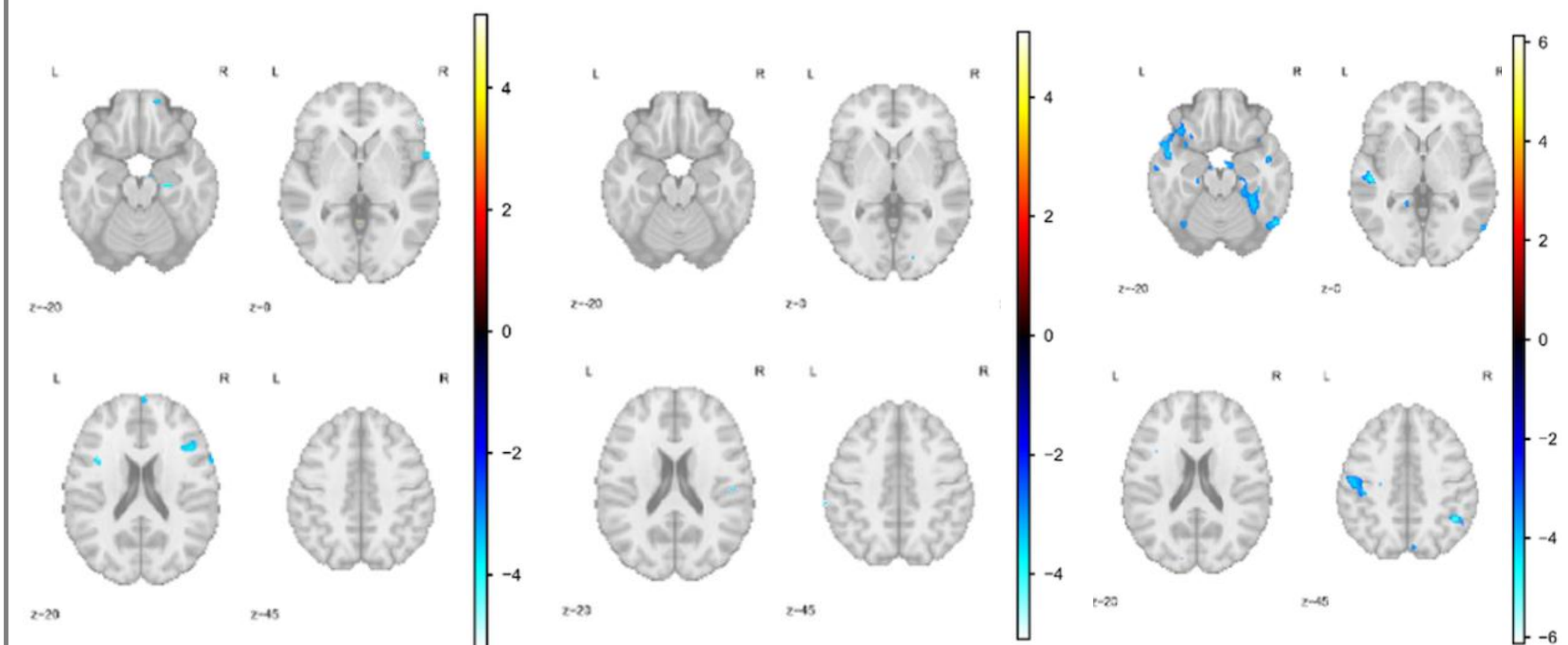
Main Effect of Group (F-test) – Glass Brain View



Post-hoc analyses showed distinct diagnosis-linked GM reduction patterns:

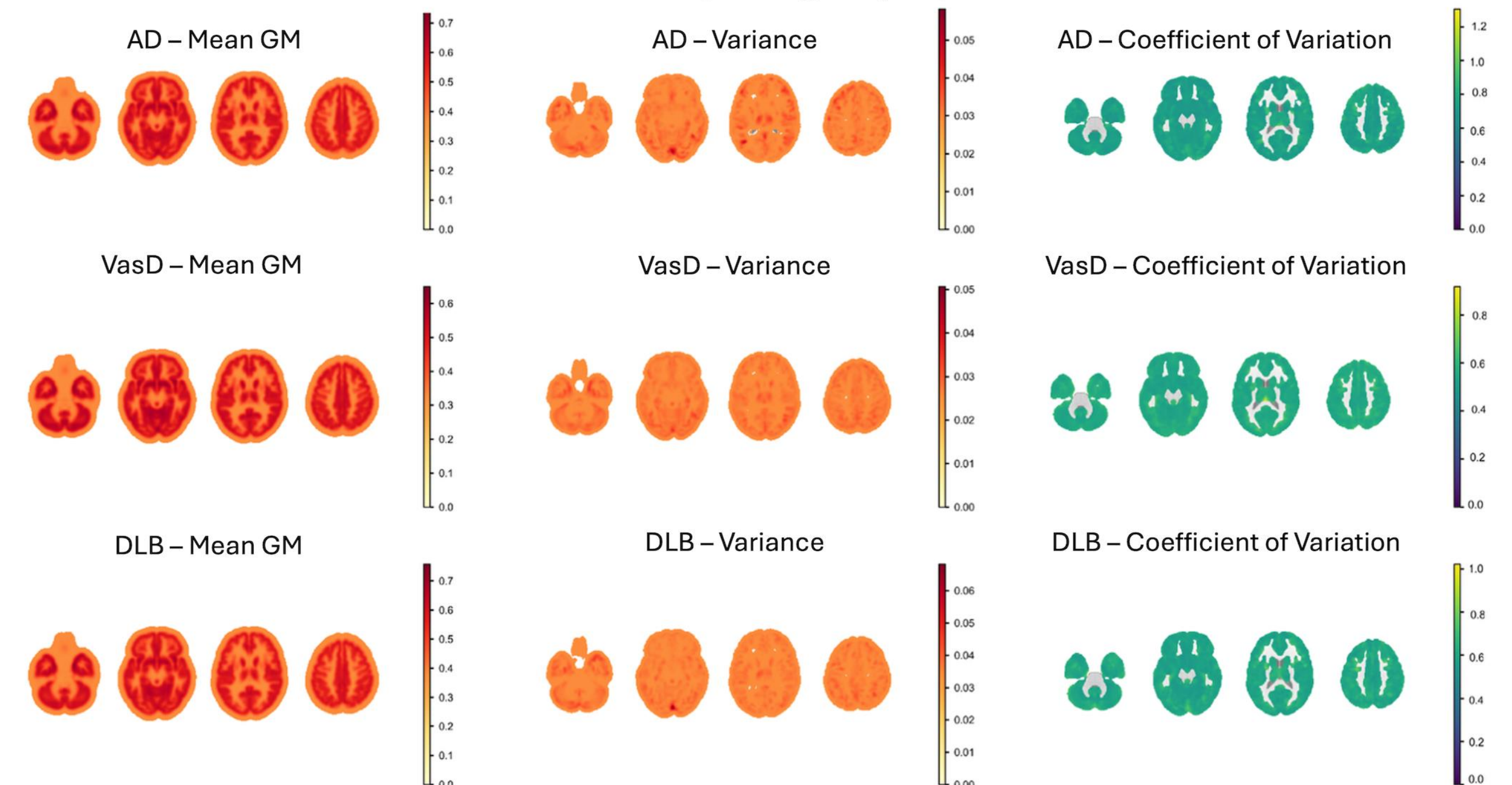
- AD < VasD: AD showed lower GM density relative to VasD.
- AD < DLB: AD showed lower GM density relative to DLB.
- DLB < VasD: DLB showed lower GM density relative to VasD, with prominent posterior involvement.

Pairwise Group Comparisons (VBM)



Within-group heterogeneity analyses revealed diagnosis-specific spatial patterns, with AD, VasD, and DLB showing distinct variance and CV profiles.

Within-Group Homogeneity Maps



Takeaways

- Executive-predominant impairment overlaps across AD, VasD, and DLB.
- Standard VBM detects mean GM differences but may miss within-group heterogeneity.
- Variance and CV maps reveal diagnosis-specific structural variability.
- Combining mean- and variability-based VBM may improve mixed-dementia characterization.