

Mesoscale metabolic connectivity captures clinical heterogeneity in dementia with Lewy bodies

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- ✓ FDG-PET captures DLB clinical heterogeneity primarily through mesoscale metabolic organisation, rather than regional uptake and whole-brain graph metrics across cognitive, motor, behavioural and disease-stage outcomes.
- ✓ Somatomotor–associative network coupling emerges as a reproducible signature of individual disease phenotype.

INTRODUCTION

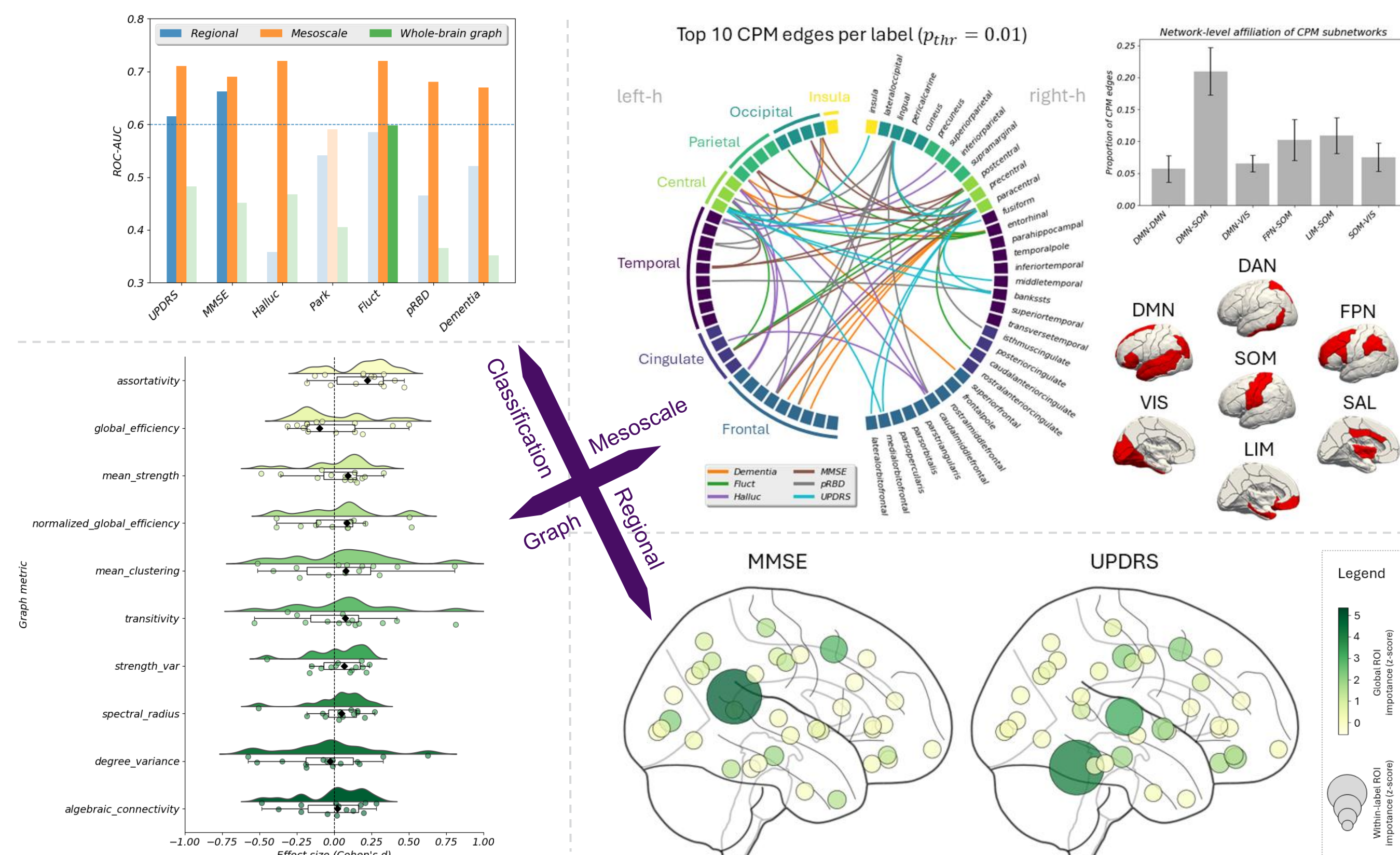
Dementia with Lewy bodies (DLB) shows marked clinical heterogeneity across cognitive, motor, neuropsychiatric and sleep domains, creating a **need for imaging biomarkers** able to support patient stratification beyond diagnosis. We **compared regional, connectome-based and graph-theoretical representations of FDG-PET data** to identify the level of brain organization that best captures DLB phenotypic variability and disease progression.

METHODS

We studied **94 patients** within the Lewy body disease spectrum using FDG-PET and multidimensional clinical assessment. PET data were analyzed at **three levels of brain organization—regional metabolism, metabolic connectivity, and global network topology**—and used to predict cognitive, motor, neuropsychiatric and disease-stage outcomes through **cross-validated machine-learning models**. Classification performance was assessed using ROC-AUC.

RESULTS

- **Connectome-based representations provided the highest and most consistent classification performance** across cognitive, motor and behavioural outcomes.
- **Regional FDG uptake** captured only selected phenotypes and produce **heterogeneous, outcome-specific patterns**.
- Predictive subnetworks were **dominated by somatomotor interactions with associative networks (default-mode, limbic and frontoparietal)**, whereas global graph metrics showed poor discriminative value.



CONCLUSIONS

- This study shows that **clinically relevant information in DLB FDG-PET is better captured by mesoscale metabolic relationships than by regional uptake values or whole-brain network summaries**. While regional analyses retain diagnostic relevance (e.g., cingulate island pattern), **clinical heterogeneity across cognitive, motor and neuropsychiatric domains appears to be encoded in distributed metabolic coupling between large-scale brain systems**.
- A consistent finding was the **involvement of somatomotor–associative network interactions**, suggesting that DLB phenotypes may emerge from network-level reorganization rather than focal metabolic abnormalities. These results support a **shift from region-based interpretation toward subject-specific metabolic connectome approaches** as a more sensitive framework to characterize disease expression.
- **Future work should focus on multicenter validation** and integration of subcortical and brainstem structures to assess clinical translation.

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