

Data-driven trajectories of atrophy capture clinical heterogeneity across the Lewy body disease spectrum

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AIMS

We aimed to determine whether transdiagnostic subtyping across the Lewy body disease continuum provides a biologically grounded framework for explaining heterogeneous clinical presentations.

BACKGROUND

- Lewy body diseases (LBDs), including Parkinson's disease (PD), PD dementia (PDD), dementia with Lewy bodies (DLB) and isolated REM sleep behaviour disorder (iRBD), share α -synuclein pathology but show marked clinical heterogeneity across motor, non-motor, cognitive and neuropsychiatric features.[1,2]
- Traditional cross-sectional neuroimaging studies often pool individuals with differing subtype profiles, disease stages and clinical severity, potentially obscuring subtype- or stage-specific effects and limiting reproducible biomarkers for complex symptoms such as visual hallucinations.
- Previous syndrome-based subtyping efforts in PD and iRBD [3,4] have shown limited clinical separability, and DLB remains relatively underexplored. **This motivates a transdiagnostic approach that can better capture biological progression [5]** across the Lewy body disease continuum.
- To address this, we applied a transdiagnostic subtyping approach to a large, balanced cohort spanning PD, DLB and prodromal iRBD, with detailed clinical and neuropsychological phenotyping.
- By combining subtype and model stage, this framework may **better capture biological progression across LBD and support improved stratification, risk enrichment and clinical trial design.**

METHODS

Subtype and Stage Inference (**SuStaln**) modelling was applied across all clinical Lewy body diseases, including PD, PDD, DLB, and prodromal iRBD, to identify shared and distinct neurodegenerative subtypes.

KEY FINDINGS

Four transdiagnostic atrophy trajectories were identified. Early cortico-limbic/late basal ganglia subtype was linked to cognitive impairment in PD, while both early limbic subtypes were associated with visual hallucinations.

METHODS

This study analysed a multi-cohort international dataset of 1,373 participants with T1-weighted MRI, including 506 healthy controls, 444 individuals with PD including 33 with PDD, 294 with DLB, and 129 with iRBD. Cohort composition is shown in Figure 1.

Cohort Composition

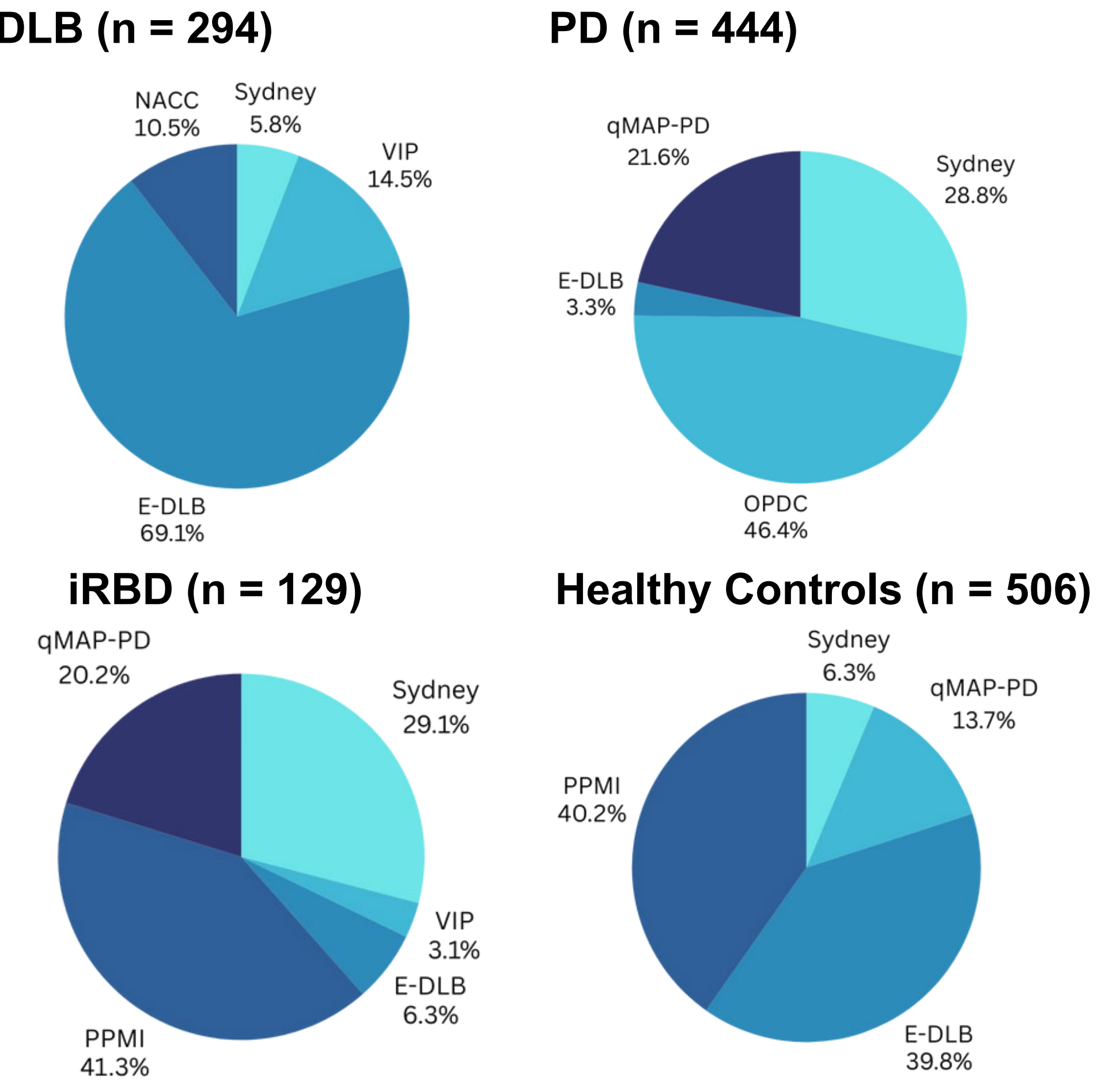


Figure 1. Pie charts show the contribution of each cohort to the Parkinson's disease (PD), dementia with Lewy bodies (DLB), isolated REM sleep behaviour disorder (iRBD) and healthy control (HC) groups.

Cohort Description:

- Multicenter Study: **12 centres**
- Balanced representation of all clinical LBD: **PD + PDD + DLB + iRBD**
- Biological progression of disease measured by: **Atrophy derived from structural T1 MRI scans**

Data also includes:

- Longitudinal clinical follow-ups of PD patients (n = 135, median follow-up = 4.9 years)
- iRBD phenoconversion data (n = 41, median follow-up = 3.6 years)

Subtype and Stage Inference

We used subtyping and stage inference (SuStaln), [6] an unsupervised machine learning approach that identifies data-driven subtypes and stages of disease progression from regional atrophy patterns.

Atrophy progression was modelled using z-score thresholds of 0.5, 1 and 2, representing increasing severity of regional involvement. Each subtype captures a distinct spatiotemporal sequence of atrophy, while the model stage reflects cumulative progression along that subtype-specific trajectory.

This model was applied to the entire spectrum of Lewy body diseases (PD + PDD + DLB + iRBD) to identify subtypes united by the measurable biological progression rather than clinical diagnoses.

RESULTS

#1 Four transdiagnostic subtypes of spatiotemporal atrophy patterns in LBD

- Four transdiagnostic LBD subtypes were identified, each defined by a distinct temporal ordering of regional brain atrophy.
- These biologically defined trajectories cut across the traditional canonical syndromes, with the clinical diagnoses represented across subtypes.
- Subtype membership captured clinically meaningful variation in cognition, motor impairment and visual hallucinations, supporting the relevance of transdiagnostic atrophy patterns for explaining LBD heterogeneity (Figure 2).

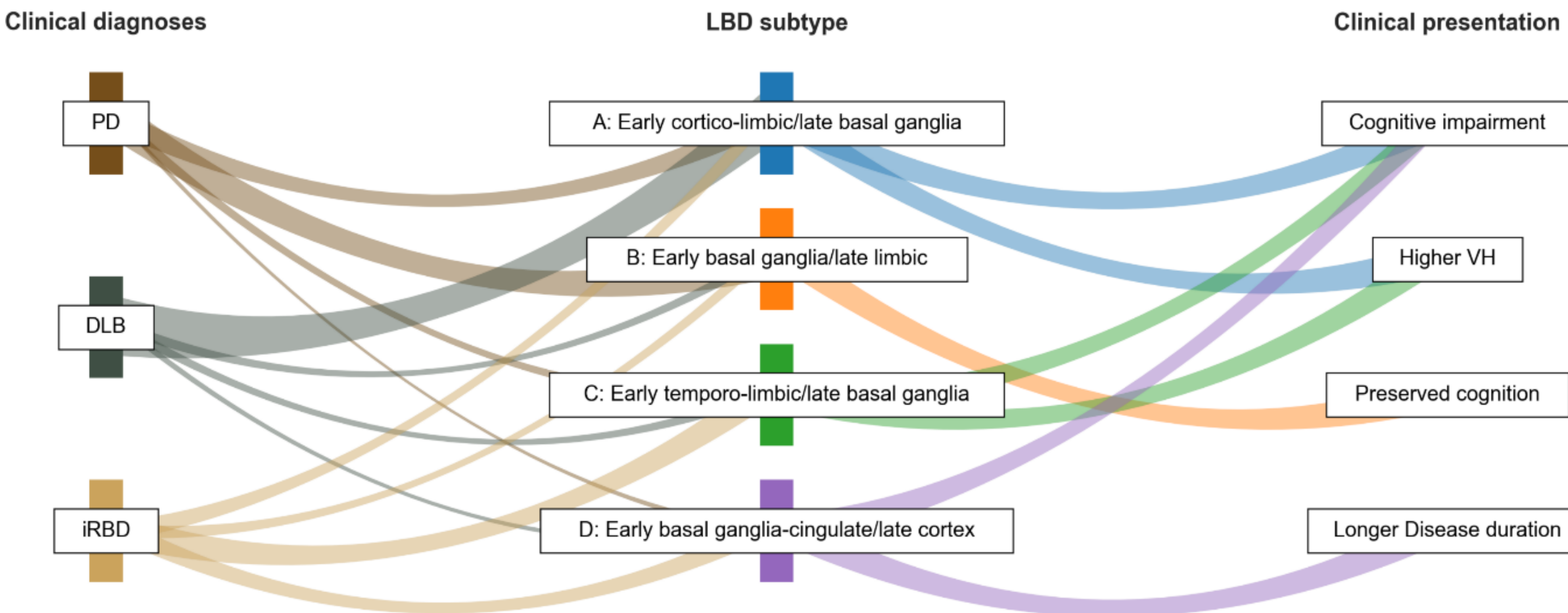


Figure 2. Sankey plot showing the relationship between clinical diagnosis, LBD subtype and clinical presentation. Four subtypes were identified: A, early cortico-limbic/late basal ganglia; B, early basal ganglia/late limbic; C, early temporo-limbic/late basal ganglia; and D, early basal ganglia-cingulate/late cortex. Flow widths represent the relative contribution of each diagnostic group to each subtype and the association of each subtype with key clinical features.

#2 Subtypes predict individuals with PD at risk of cognitive decline

- Across the LBD cohort, **Subtype B showed better MMSE performance than Subtypes A, C and D** (all $pFDR \leq 0.006$; Figure 3A), while cognition declined with advancing disease stage ($\beta = -0.16$, 95% CI $[-0.22, -0.09]$, $pFDR < 0.001$).
- In PD participants with longitudinal MoCA data, Subtype A converted faster than Subtype B ($pFDR = 0.020$) and **showed a nearly three-fold higher adjusted risk of cognitive impairment** ($HR = 2.91$, 95% CI $[1.52, 5.59]$, $pFDR = 0.007$).

#3 Hallucinations in PD are associated with limbic trajectories and amygdala atrophy

- VH were most prevalent in early limbic subtypes A and C (47.7% and 47.8%) and less frequent in early basal ganglia subtypes B and D (17.7% and 26.3%).
- VH were associated with reduced amygdala volume ($pFDR < 0.001$), while **prevalence rose steeply after moderate amygdala atrophy** (Figure 3D).
- A combined **model including subtype, amygdala volume and stage best predicted hallucinations** ($AUC = 0.73$, 95% CI $[0.64, 0.81]$) and outperformed amygdala volume alone ($\chi^2 = 16.26$, $p = 0.003$).

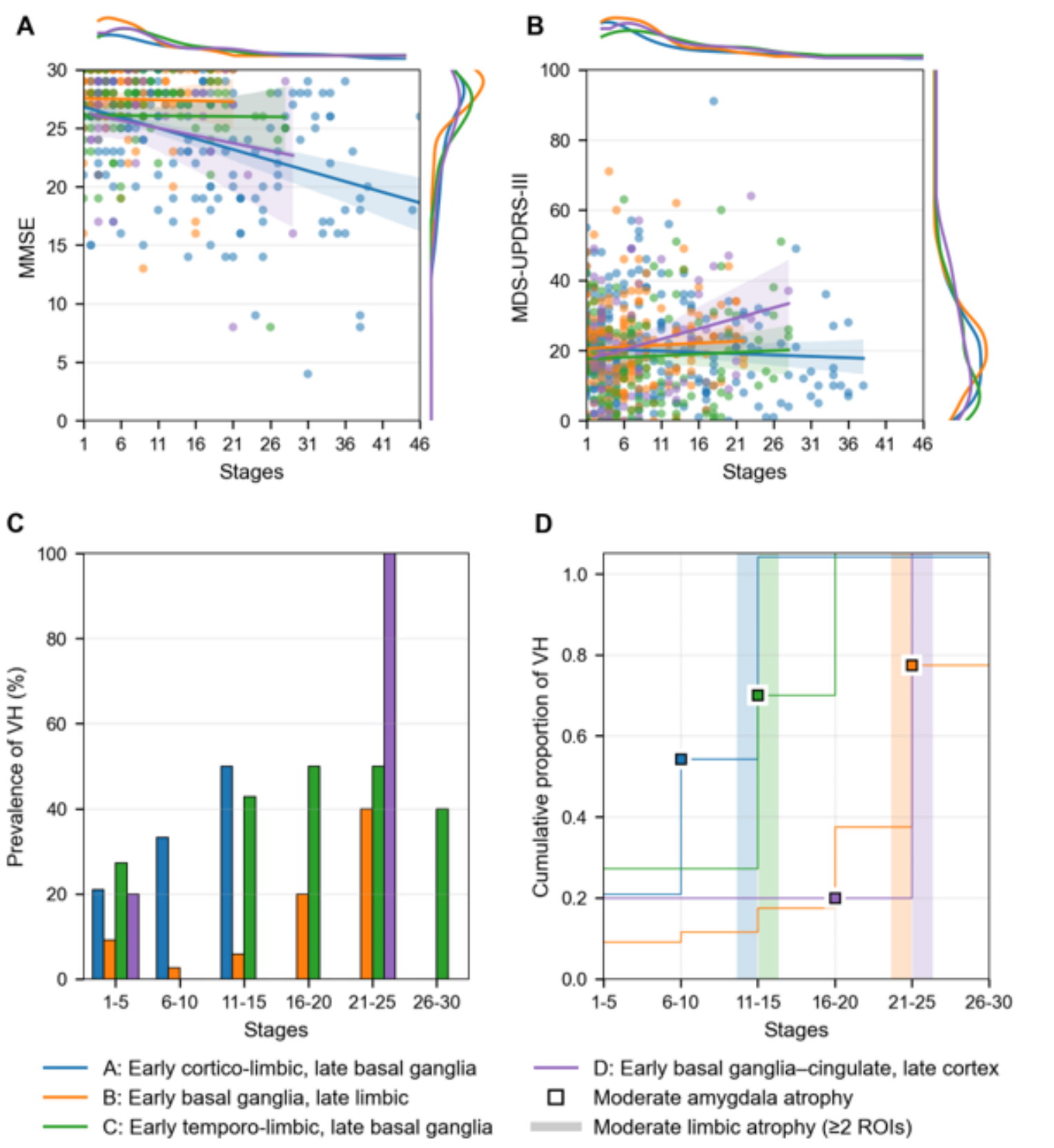
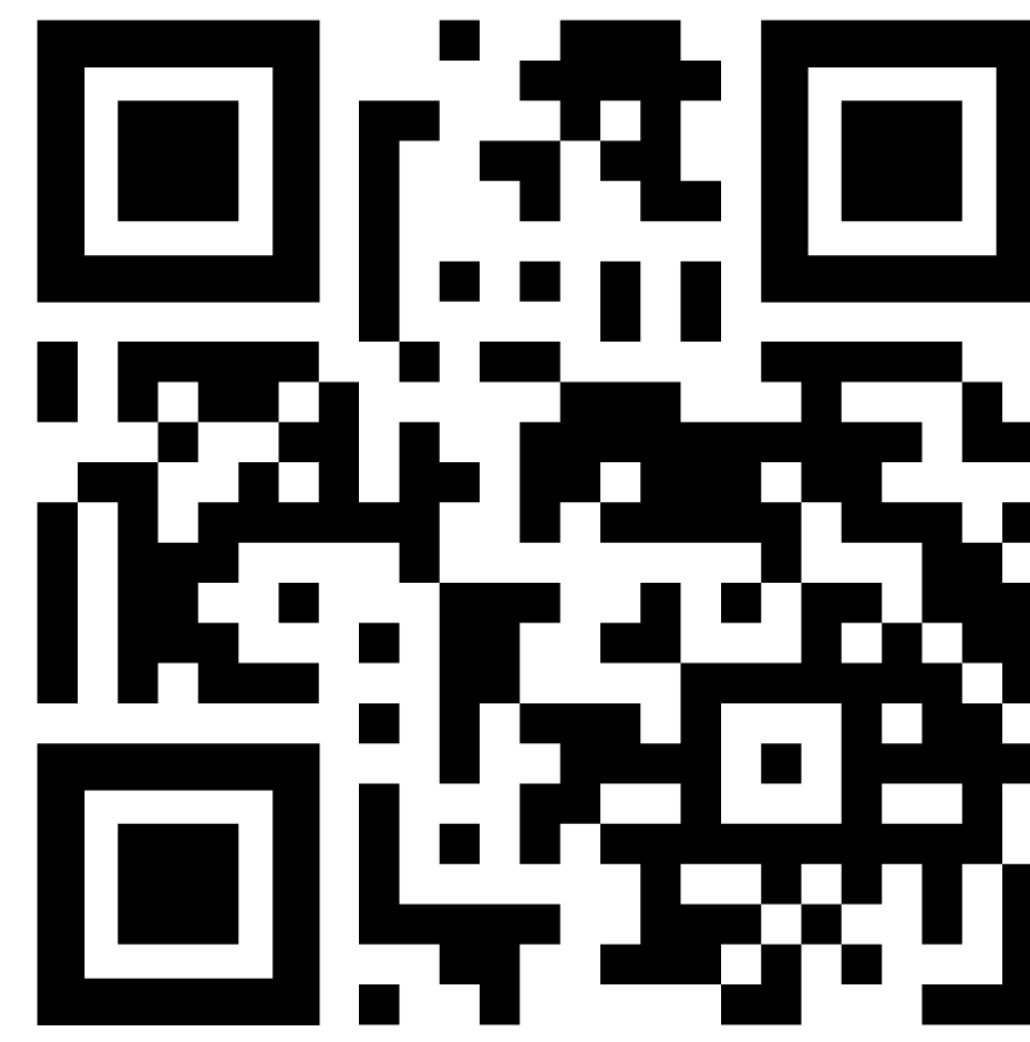


Figure 3. A, MMSE declined with increasing stage B, Motor scores showed subtype-specific differences in motor progression. C, VH prevalence varied across subtype and stage, with higher prevalence in Subtypes A and C. D, cumulative VH prevalence increased around the transition to moderate limbic (vertical bars) and amygdala (squares) atrophy.

Conclusion

This study supports a transdiagnostic, biologically grounded framework for understanding heterogeneity across LBD. Imaging-derived atrophy subtypes revealed overlapping yet distinct trajectories that captured variation in cognition, VH and iRBD phenoconversion risk, moving beyond traditional clinical distinctions. By modelling the temporal sequence of atrophy, this approach may help identify conversion-prone iRBD individuals, stratify PD patients by cognitive risk and reduce heterogeneity in clinical trials through biologically informed recruitment.

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