



BACKGROUND

Neuropsychiatric symptoms (NPS) affect most individuals with Alzheimer's disease (AD) and are associated with accelerated disease progression, increased caregiver burden, institutionalization, and higher mortality.¹ Despite their clinical importance, NPS are highly heterogeneous and often overlap across symptom domains, limiting the ability of traditional clustering methods to identify meaningful behavioral phenotypes.⁵ Topological Data Analysis (TDA) is a machine learning framework capable of identifying intrinsic structures in complex, nonlinear datasets without assuming predefined geometric relationships.⁴ In this study, we applied TDA to Neuropsychiatric Inventory (NPI)² data from the Alzheimer's Disease Neuroimaging Initiative (ADNI)³ to identify data-driven neuropsychiatric pathways in symptomatic AD patients.

METHODS



ADNI Cohort

Study Population

- Primary etiological AD diagnosis
- NPI data available for ≥ 10 of 12 domains
- Most recent visit included



NPI Assessments
(12 Domains)

Data Preparation

- NPI scores z-score standardized
- Cutoff: total NPI score 24
- 402 symptomatic AD patients
- Missing scores imputed (domain medians)



Topological Data Analysis

- Persistent homology (Ripser)
- Mapper algorithm (KeplerMapper)
- UMAP projection



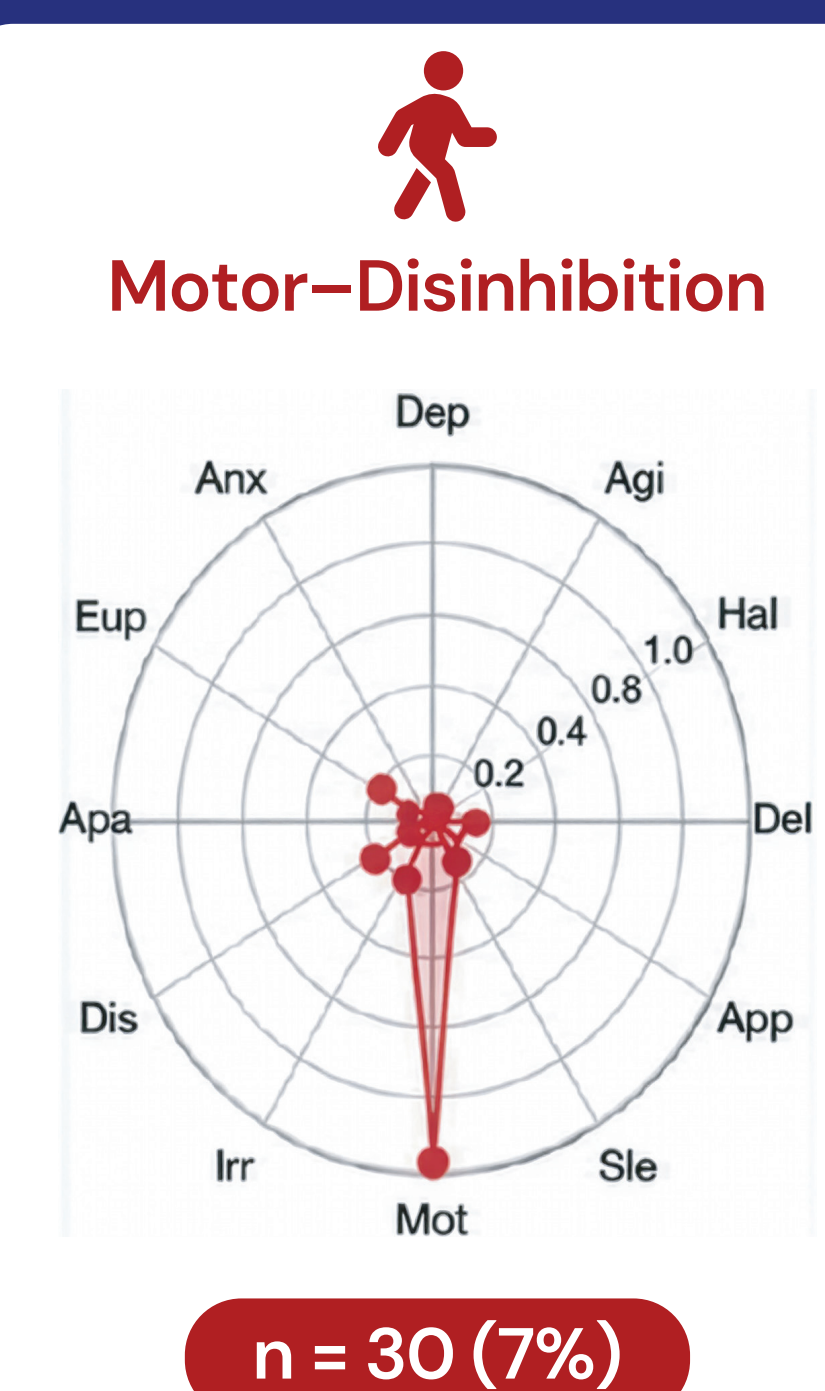
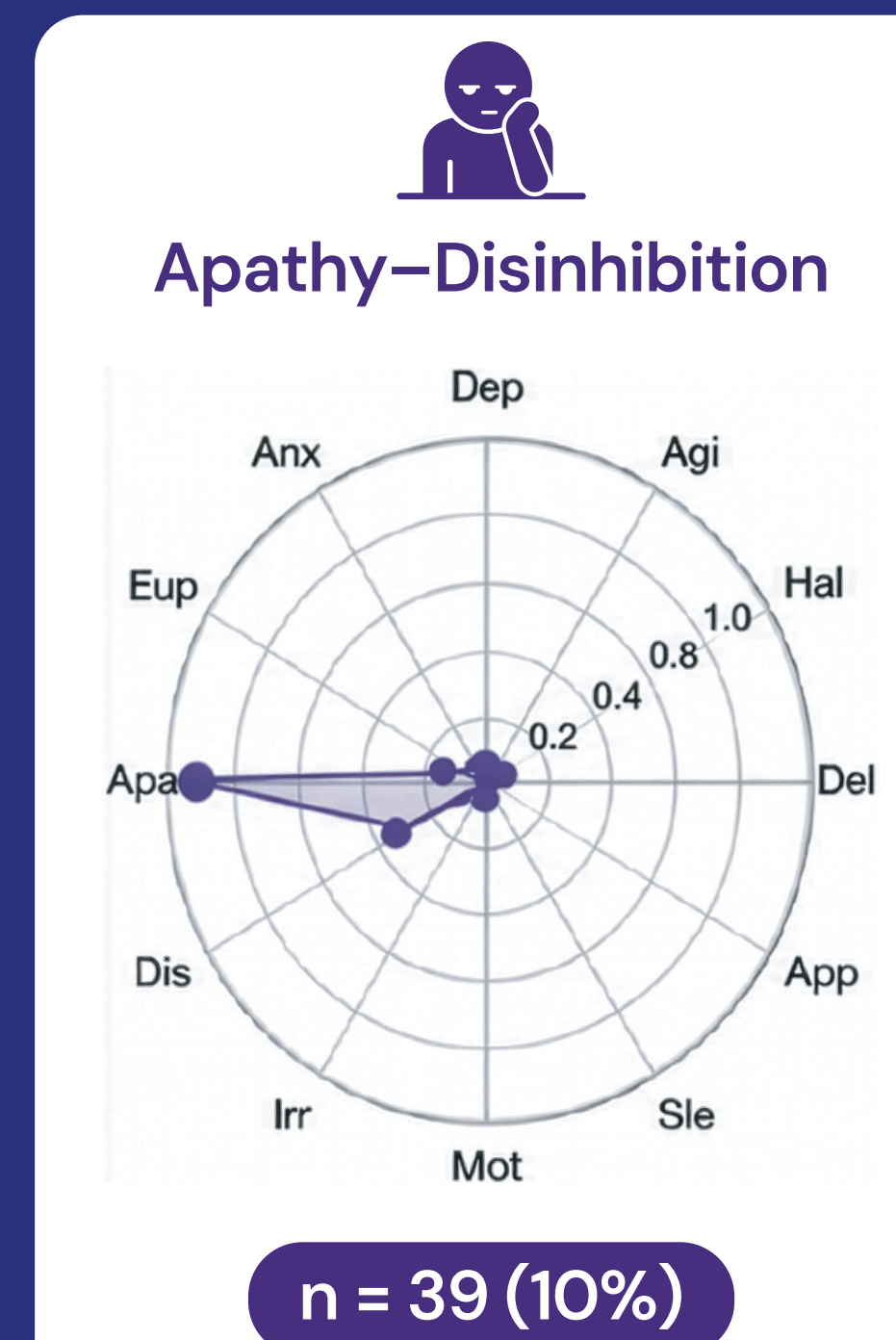
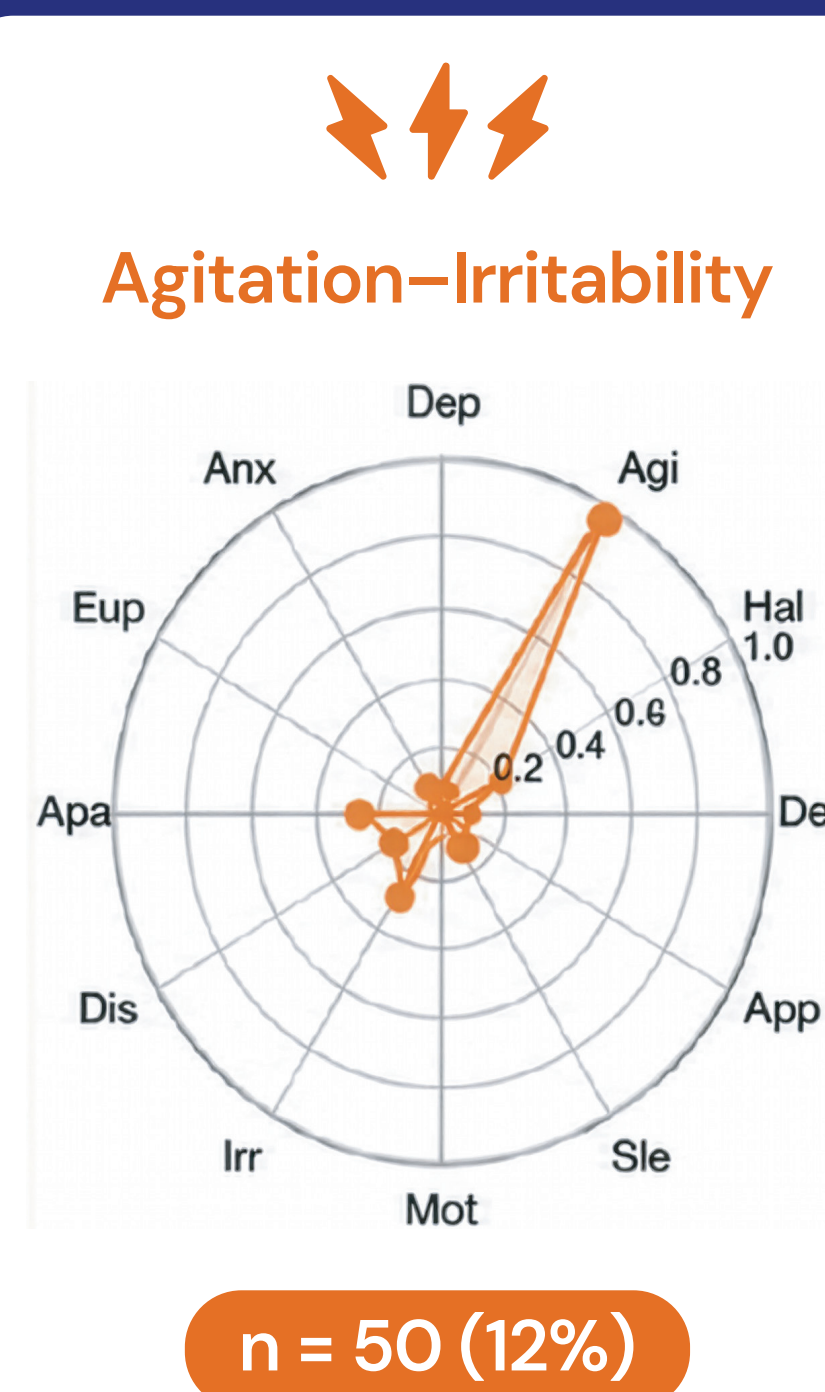
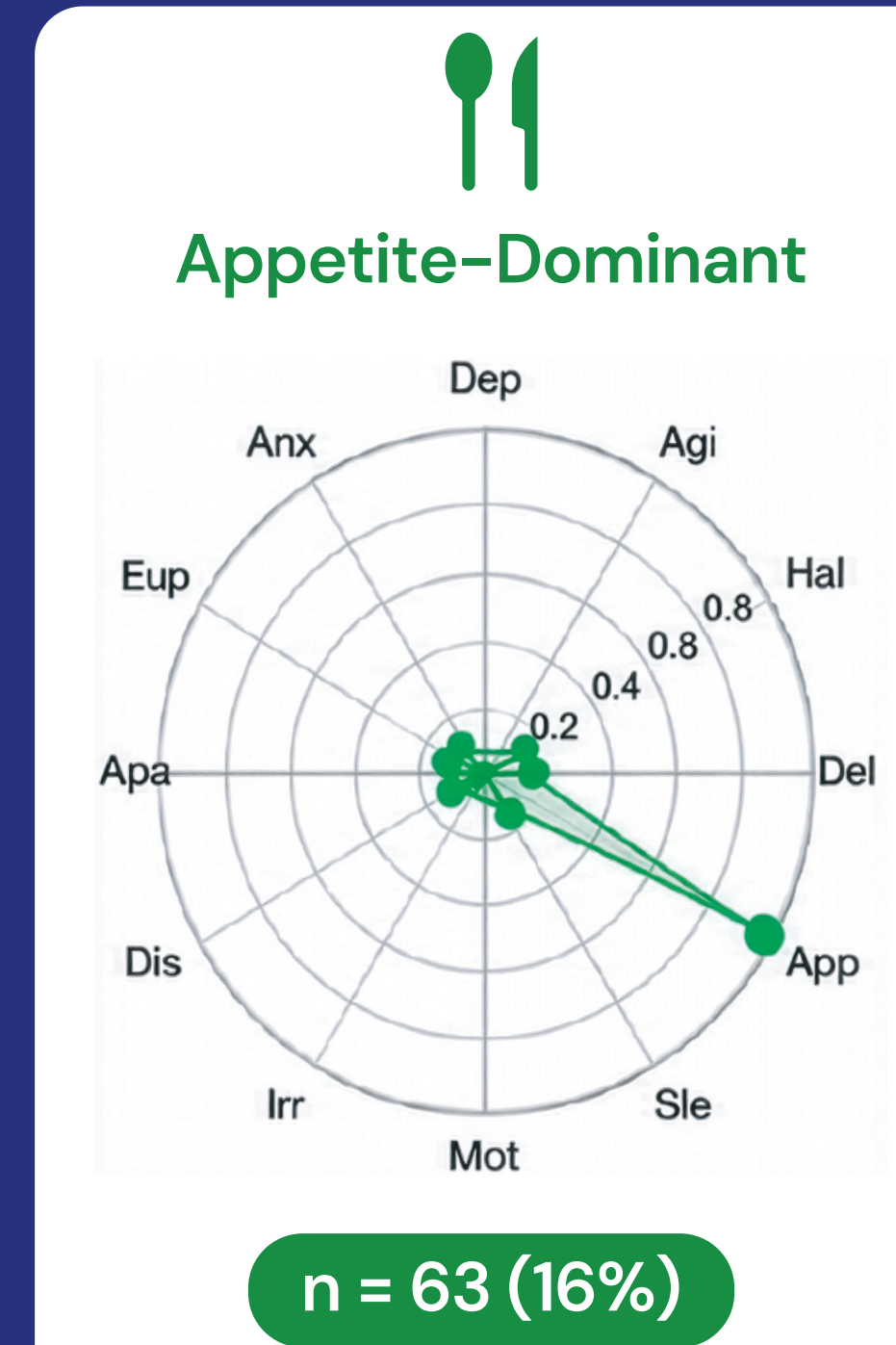
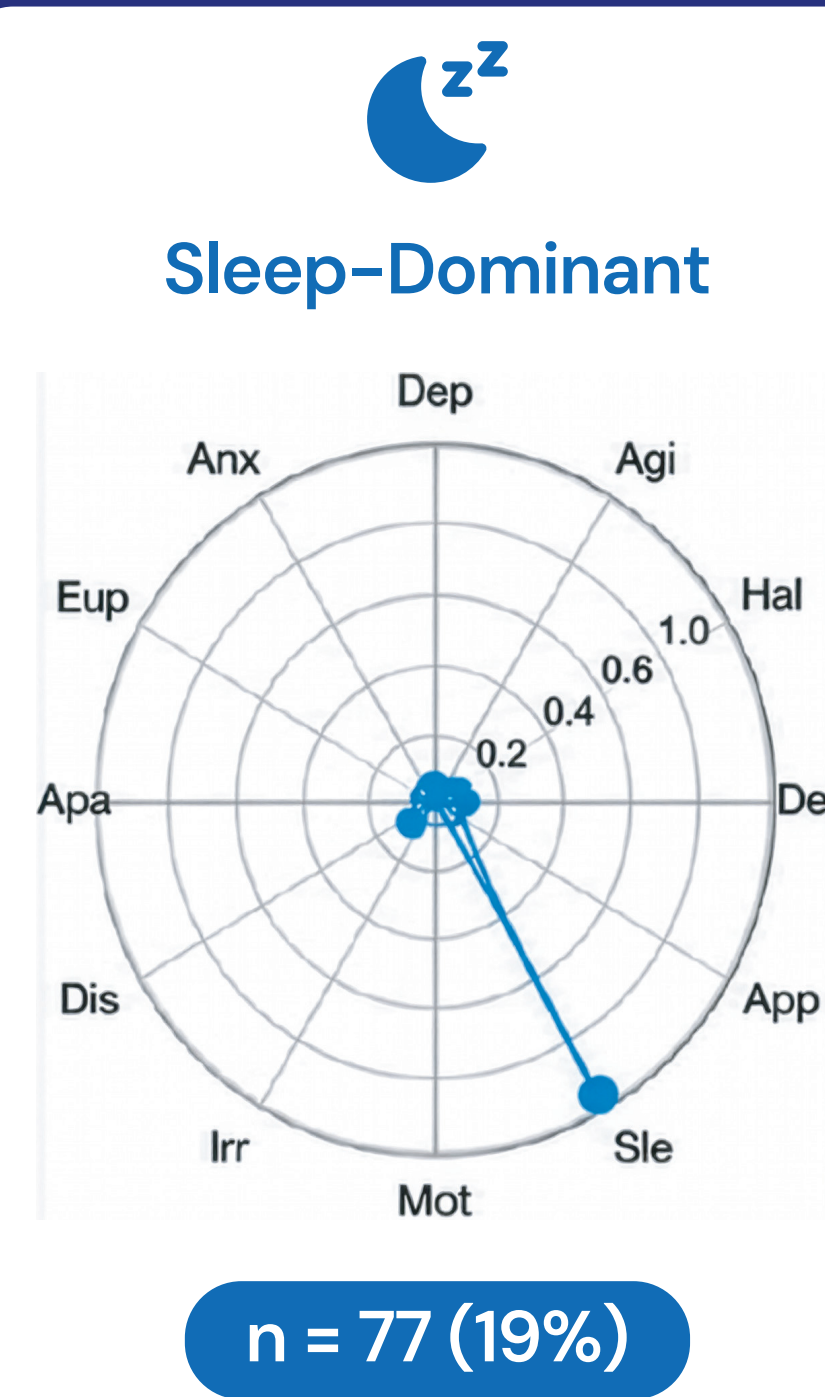
Statistical Validation

- ANOVA, permutation testing, effect size estimation



TDA Pipeline

RESULTS



Radar profiles of five neuropsychiatric pathways in Alzheimer's disease (symptomatic AD patients, N=402). Each radar chart shows the normalized NPI profile for one pathway. Axes represent 12 NPI domains. Abbreviations: Del=Delusions, Hal=Hallucinations, Agi=Agitation, Dep=Depression, Anx=Anxiety, Eup=Euphoria, Apa=Apathy, Dis=Disinhibition, Irr=Irritability, Mot=Motor, Sle=Sleep, App=Appetite.

Data-driven TDA identified eight distinct neuropsychiatric pathways, of which five were most clinically relevant. All pathways demonstrated statistically distinct NPI profiles (ANOVA $p < 0.001$ for 8/12 domains; permutation test $p < 0.001$; effect size $\eta^2 = 0.30$). All pairwise comparisons remained significant after Bonferroni correction ($p < 0.001$).



DISCUSSION AND CONCLUSION

- Topological Data Analysis identified five phenotypically distinct and clinically recognizable neuropsychiatric pathways in Alzheimer's disease through an entirely data-driven framework.
- TDA captured nonlinear, multidimensional symptom interactions that conventional clustering approaches miss.
- Identified symptom constellations align with previously reported NPS co-occurrence networks, supporting the phenotypic plausibility of the structures.
- Findings support pathway-based stratification to improve patient characterization, optimize clinical trial design, and guide personalized therapeutic strategies in Alzheimer's disease.

DISCLOSURE OF FUNDING

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SCAN ME

TAKE-HOME MESSAGE

Topological Data Analysis uncovers phenotypically distinct and clinically recognizable neuropsychiatric subtypes in Alzheimer's disease that may improve precision stratification and targeted therapeutic approaches.