



Cognitive Organization Breaks Down in Aging and Alzheimer's Disease

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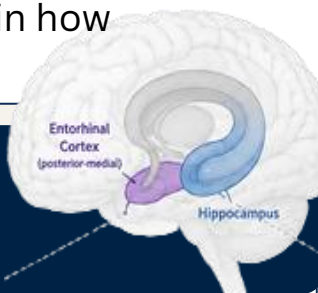
RUB

Key takeaway: A topology-based index reveals entorhinal-anchored cognitive disorganization that predicts clinical progression.

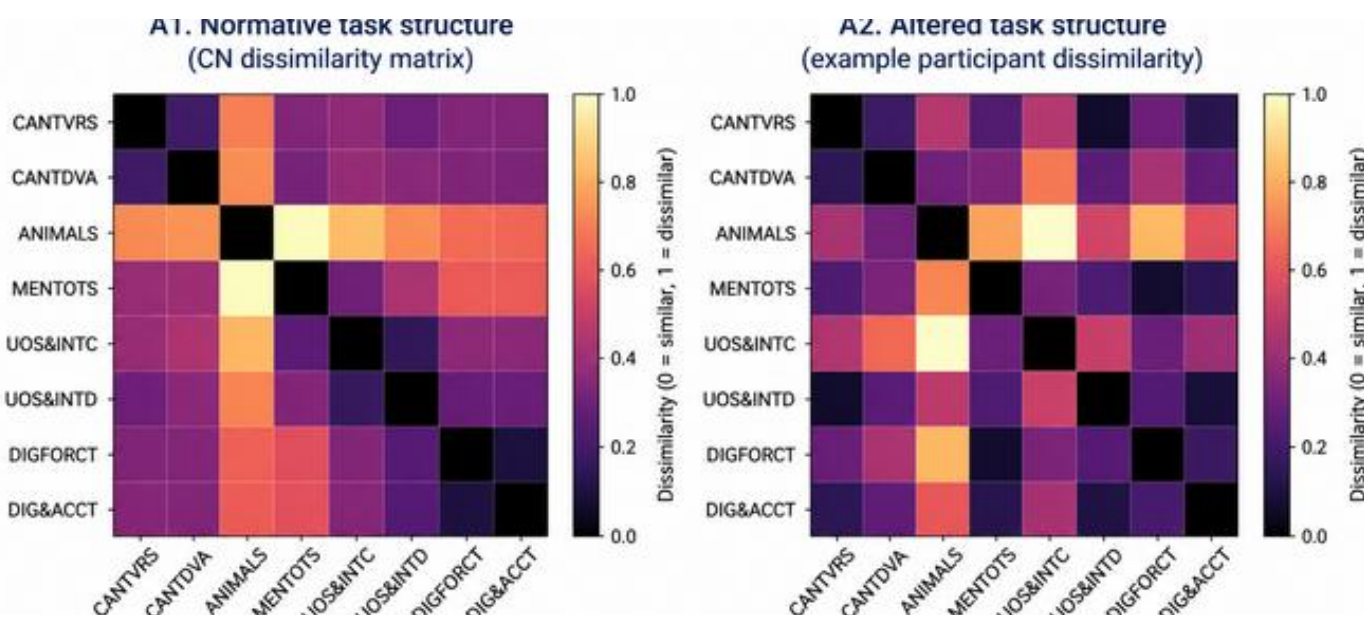
BACKGROUND & MOTIVATION

INTRODUCTION

The entorhinal cortex (EC) is affected early in Alzheimer's disease, but clinical cognition is usually measured as isolated test performance. We asked whether disease progression also reflects disruption in how cognitive domains are organized



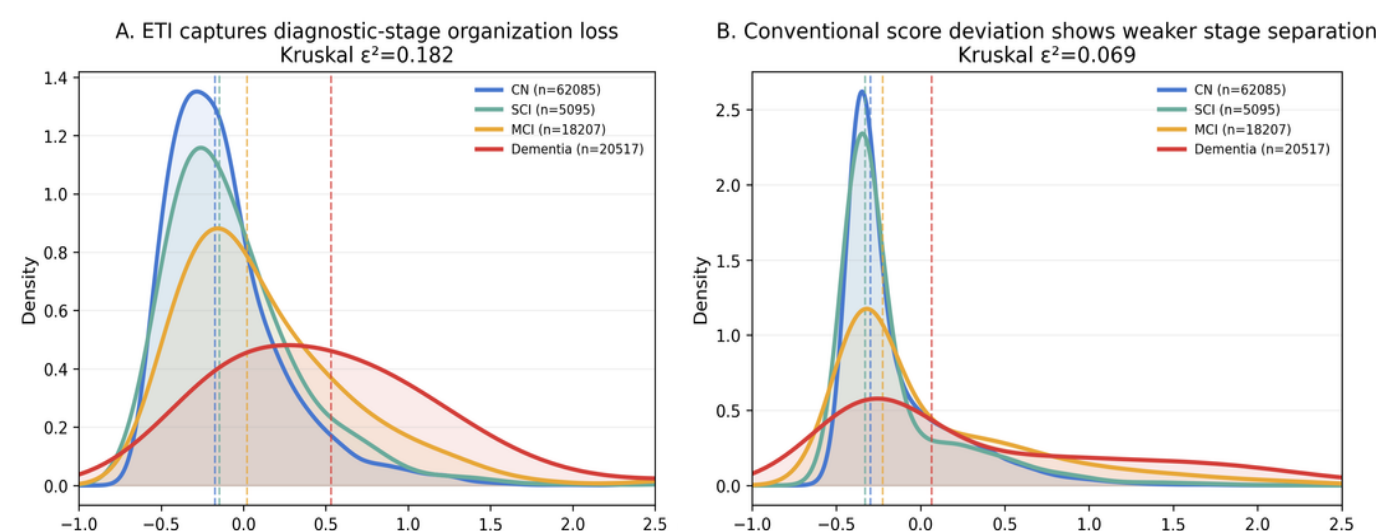
STANDARD SCORES MISS COGNITIVE ORGANIZATION



Task-task dissimilarity matrices.

Cognitively normal participants show organized task relationships, whereas high ETI participants with AD show disrupted cross-domain structure.

ORGANIZATION ≠ IMPAIRMENT — A DISTINCT DIMENSION



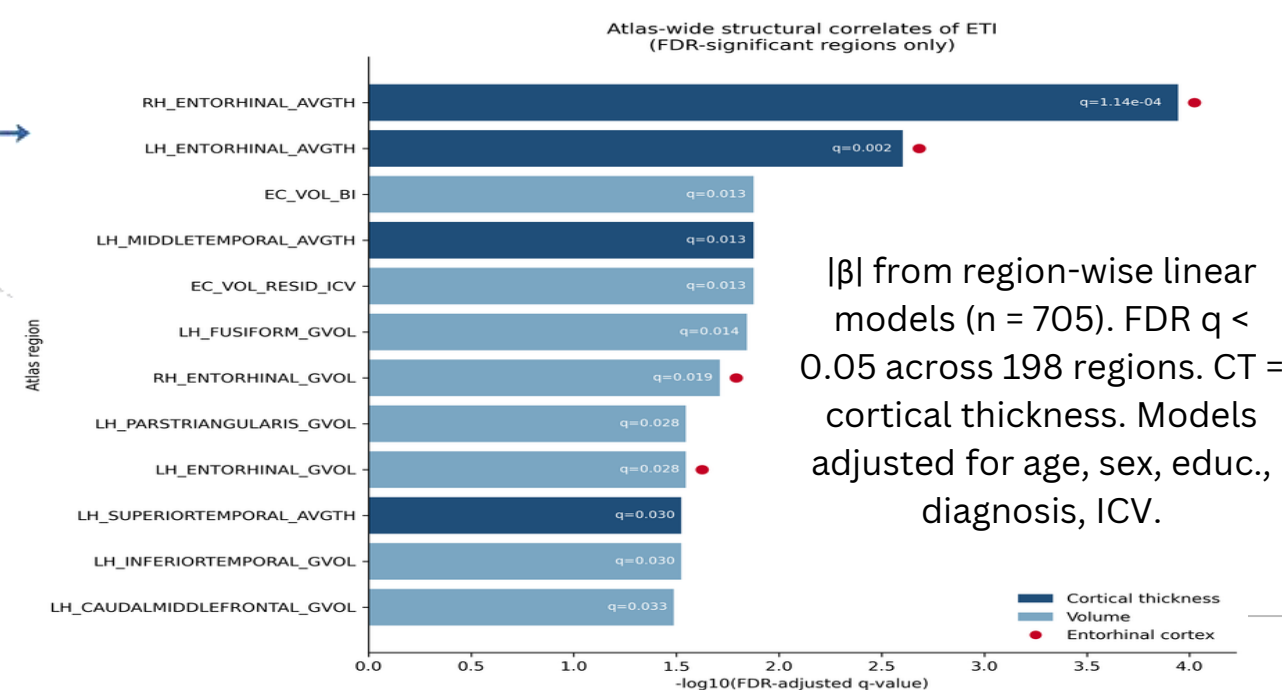
Conventional models quantify deviation in raw scores. ETI quantifies deviation in cross-domain task relationships.

ETI and dcore-based deviation showed partial but non-redundant overlap (Pearson $r = 0.54$; Spearman $\rho = 0.23$)

METHODS & SAMPLE

ENTORHINAL-ANCHORED DISORGANIZATION

ETI associations localized most strongly to bilateral entorhinal cortex, with additional posterior-medial and lateral temporal effects.



$|b|$ from region-wise linear models ($n = 705$). FDR $q < 0.05$ across 198 regions. CT = cortical thickness. Models adjusted for age, sex, educ., diagnosis, ICV.

LARGE-SCALE NACC COHORT — ADRC MULTI-SITE

Structural MRI from FreeSurfer-processed T1-weighted scans linked within ± 365 days of ETI baseline visit.

105,904 total participants with ETI computed

61,006

Cognitively normal

5,410

Subjective cognitive impairment

19,432

Mild cognitive impairment

20,056

Dementia

CN $\rightarrow$ MCI / Dementia $n = 8,490$

Low ETI

~7%

Mid ETI

~12%

High ETI

~22%

1.026

95% CI 1.013–1.040

HR: CN $\rightarrow$ MCI/DEM

MCI $\rightarrow$ Dementia $n = 3,635$

Low ETI

~15%

Mid ETI

~27%

High ETI

~43%

1.026

95% CI 1.019–1.034

HR: MCI $\rightarrow$ DEM

ETI stratified 3-year conversion risk, and improved prognostic performance beyond Trail Making Test Part B alone.

RESULTS

FUNCTIONAL OUTCOMES — EC + PMN, NOT HIPPOCAMPUS

EC + PMN retained across outcomes; hippocampal volume attenuated jointly.



EC and PMN retained independent associations across outcomes. Hippocampal volume did not improve joint models. All models adjusted for age, sex, education, diagnosis, APOE $\epsilon 4$. *** $p < 0.001$, ** $p < 0.01$. Ordinal logistic regression used for FAQ travel item.

TAKE-HOME

- 1 Cognitive decline reflects breakdown in cross-domain organization, not only loss of performance.
- 2 Disorganization is preferentially anchored to entorhinal cortex integrity, with additional posterior-medial network contributions.
- 3 ETI independently predicts clinical progression beyond conventional neuropsychological measures.

KEY REFERENCES

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