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Introduction

Alzheimer's disease (AD) is characterized by **individual heterogeneity** in disease onset and progression.

Variability across individuals **not predicted/fully explained by AD proteinopathy** (e.g., amyloid- β , tau) $\rightarrow$ challenge for disease prognosis and patient stratification.

While proteinopathies accumulate over the course of the disease, **neurophysiological changes emerge in the earliest stages of cognitive impairment**^{1,2,3}, positioning them as candidates to predict prognosis from disease onset.

Methods

N=47 A β -positive patients with mild cognitive impairment (MCI) had full clinical evaluation, Clinical Dementia Rating Sum of Boxes (CDR-SB) scores, and resting-state magnetoencephalography (MEG) imaging. Patients were followed over periods of 0.4-15.4 years, with repeated CDR-SB.

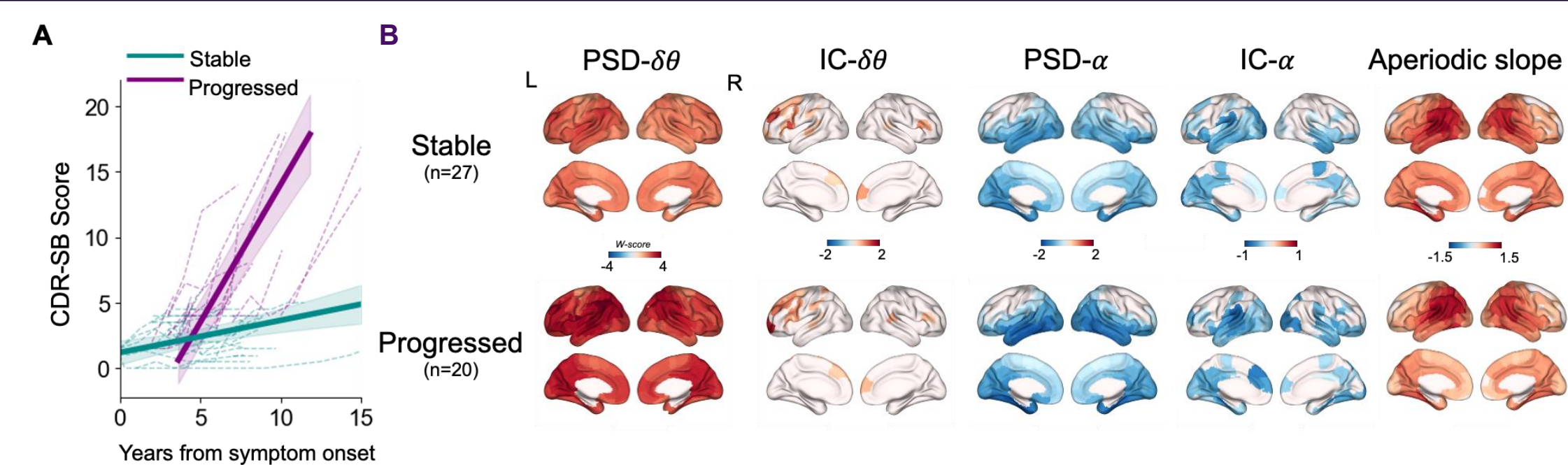
We assessed MCI-stage neurophysiology: **power spectral density (PSD)** and **imaginary coherence (IC)** in delta-theta ($\delta\theta$, 2-8Hz) and alpha (α , 8-12Hz), and **aperiodic spectral slope**.

We tested the relationship of MCI-stage neurophysiology with two primary outcomes: 1) conversion from MCI to dementia (reaching CDR-SB score ≥ 4.5), and 2) rate of disease progression (slope of CDR-SB change).

References: 1) Palop JJ, Mucke L. Network abnormalities and interneuron dysfunction in Alzheimer disease. Nat Rev Neurosci 2016;17:777-92. 2) Bloom GS. Amyloid- β and Tau: The Trigger and Bullet in Alzheimer Disease Pathogenesis. JAMA Neurol 2014;71:505-8 3) Ranasinghe KG, Kudo K, Casaletto K, Rojas-Martinez JC, Syed F, Vossel K, et al. Neurophysiological signatures of aging: compensatory and compromised neural mechanisms. Brain Commun 2025:fcaf131.

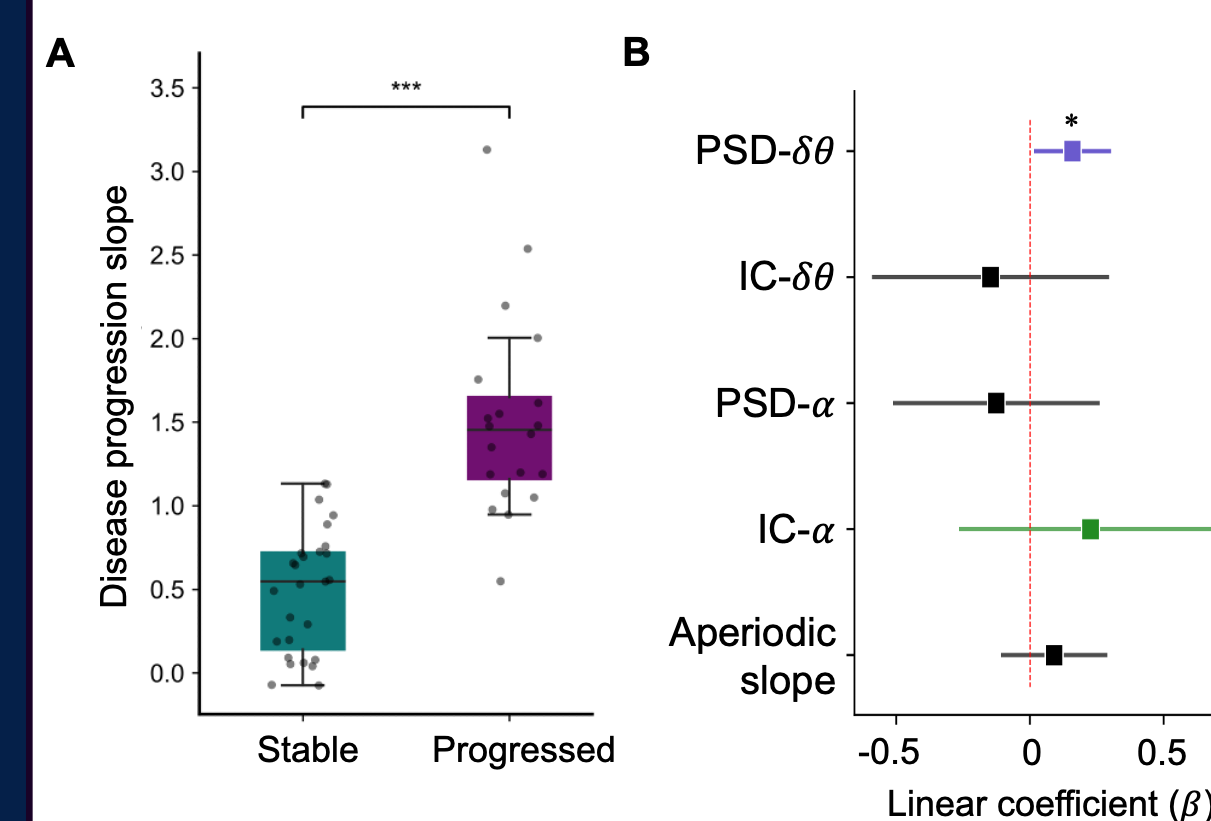
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Neurophysiology



(A) MCI patient disease trajectories categorized as "Stable" or "Progressed" based on annual rate of CDR-SB score change. (B) Neurophysiology (MEG) W-scores (difference from controls).

PSD- $\delta\theta$ predicts rate of disease progression

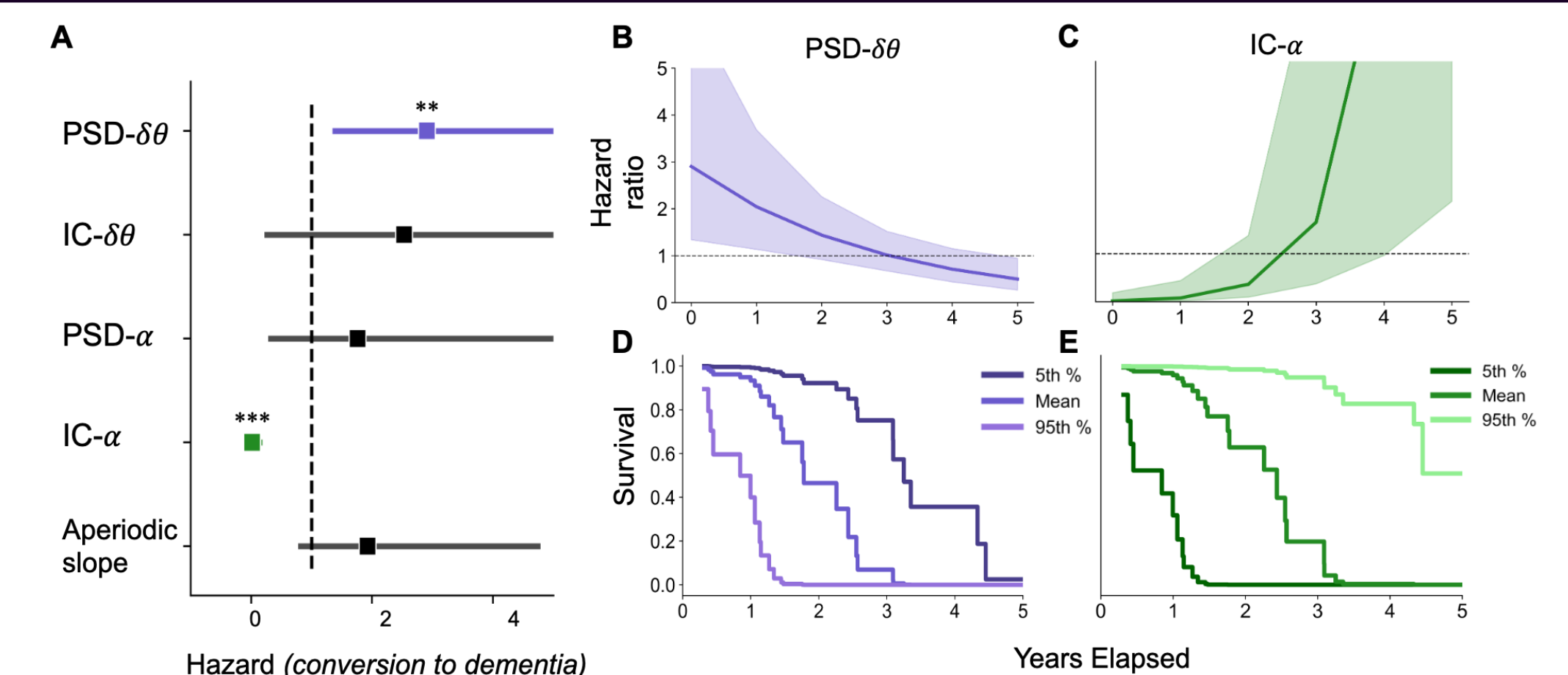


Mixed-effects regression of CDR-SB $\rightarrow$ individual slopes of disease progression. (A) Slopes by progression group. (B) Second linear regression predicted slope using MCI-stage neurophysiology.

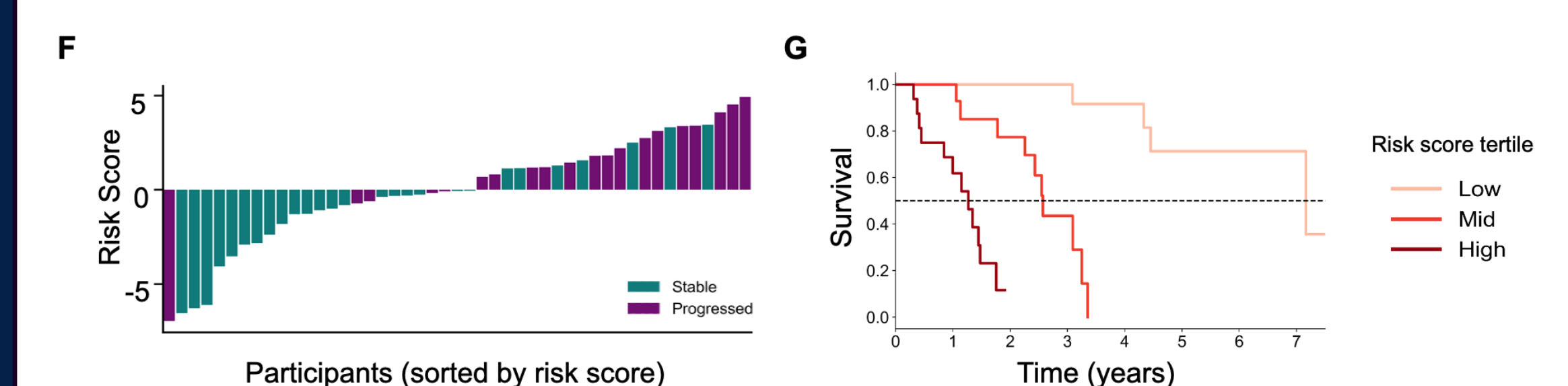
Conclusions

- Neurophysiology changes at MCI predict features of future dementia risk.
- MCI-stage **increases in delta-theta band PSD** associated with **higher hazard of dementia conversion and faster disease progression**.
- MCI-stage **reduction in alpha band IC** associated with **higher hazard of dementia conversion**.

PSD- $\delta\theta$, IC- α predict dementia conversion



Cox modeling of main (A) and linear time interaction effects revealed higher PSD- $\delta\theta$ and lower IC- α each predicted higher hazard of conversion to dementia in the near term, with each effect reducing over time (B-E).



Cox model risk scores show concordance with independent "Progressed" vs. "Stable" grouping (F) and strong dementia risk stratification (G).

Increased hazard rate of dementia for

MCI-stage neurophysiology:

↑ **spectral power in $\delta\theta$ (2-8Hz)**

↓ **coherence in α (8-12Hz)**

