



Neural Excitability Precedes Tau Pathology and Cognitive Decline in Alzheimer's Disease

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INTRODUCTION

Alzheimer's disease (AD) is associated with amyloid- β and tau accumulation and early neural circuit dysfunction. The aperiodic spectral slope reflects neural excitability, but its temporal relationship to AD pathology is unknown. We used event-based modeling (EBM) to define its trajectory relative to amyloid and tau accumulation.

METHODS

Magnetoencephalography (MEG): Resting-state MEG was acquired from amyloid-positive AD participants (n=64) and cognitively normal controls (n=66).

Amyloid-PET and tau-PET: Centiloids (n=42) and medial temporal tau (n=29) from PET were estimated for AD.

Structural MRI: Parahippocampal gyrus (PHG) volume was estimated for all AD and control subjects as a measure of atrophy.

Global Cognition: Mini-Mental State Examination (MMSE) was acquired for all AD and control subjects

Demographics	AD (n=64)
Age-yr	63.5 $\pm$ 9.1
Female sex- no (%)	40 (62.5)
MMSE	22.7 $\pm$ 4.9
CDR	0.8 $\pm$ 0.45
Centiloid (n=42)	99.4 $\pm$ 28.4
Tau (n=29)	2.4 $\pm$ 0.69

Aperiodic Slope

Spectral slope was estimated from the 15-50Hz frequency range using the IRASA method.

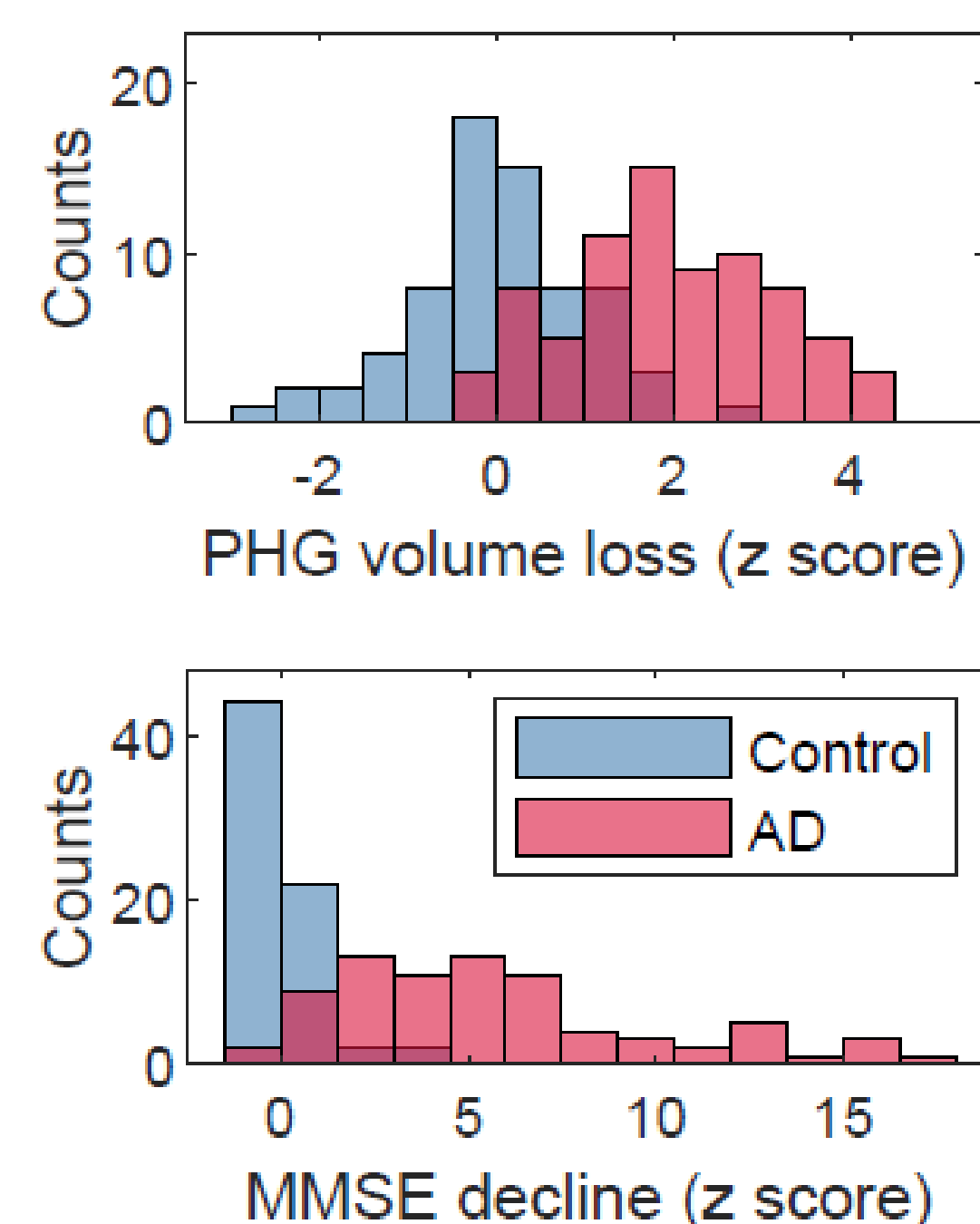
Event-based Model (EBM)

Z-scored PHG volume loss and MMSE were included in the model to get seven stages.

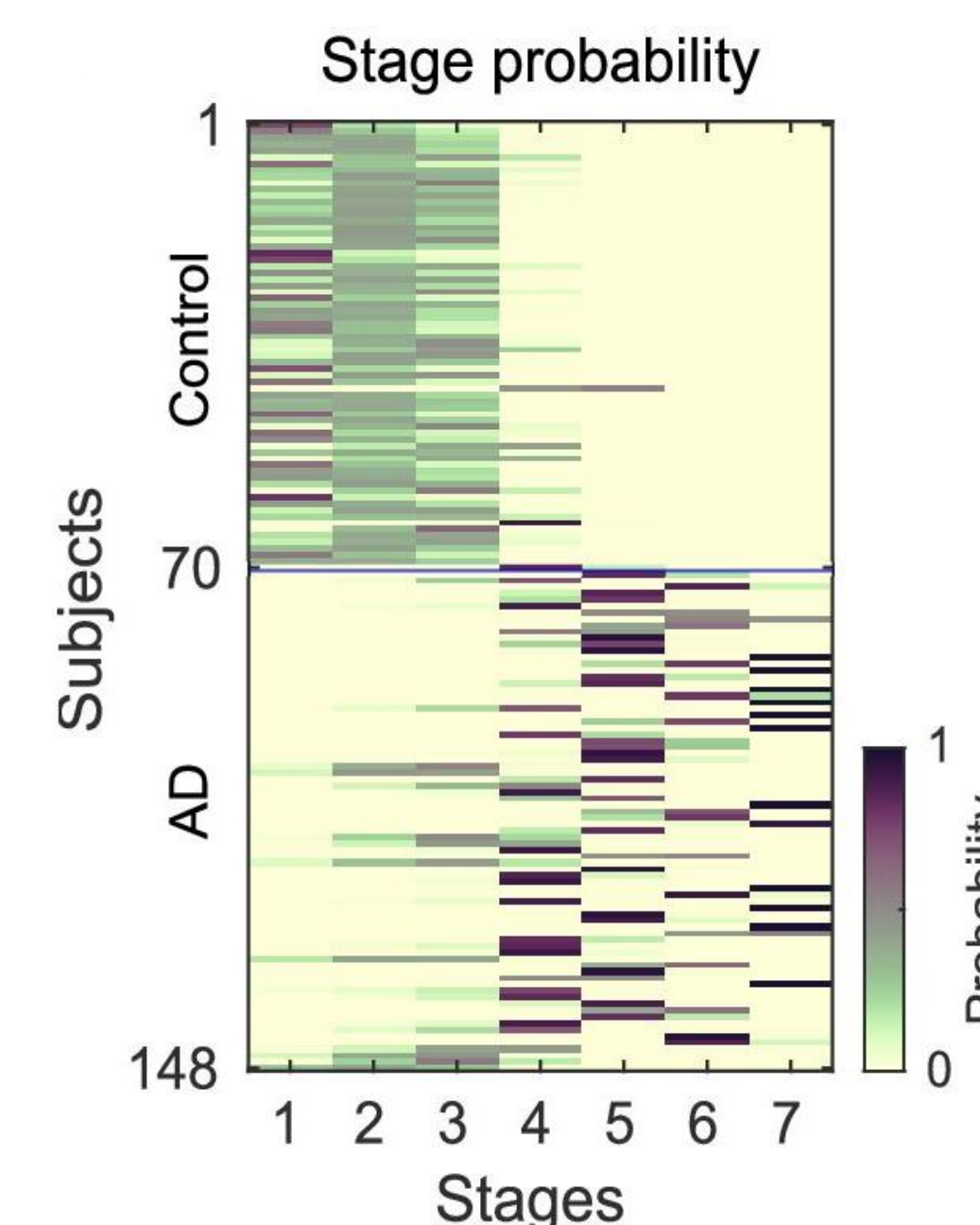
RESULTS

Aperiodic slope progressively flattens with advancing disease stage, which is inferred as abnormal excitability. Abnormal excitability emerged early in the disease course, following amyloid accumulation but preceding tau pathology and measurable cognitive decline.

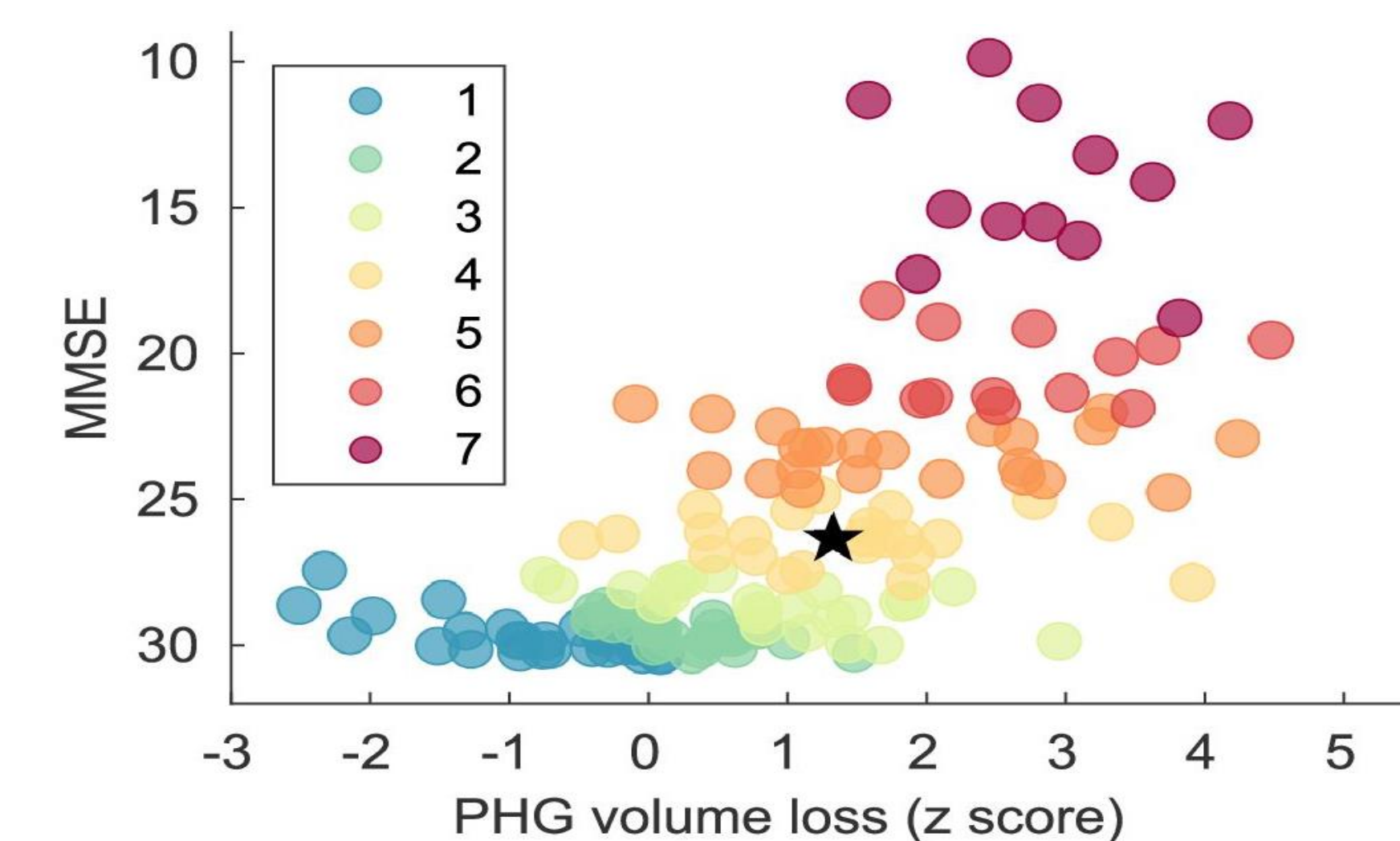
Histogram of PHG volume loss and MMSE



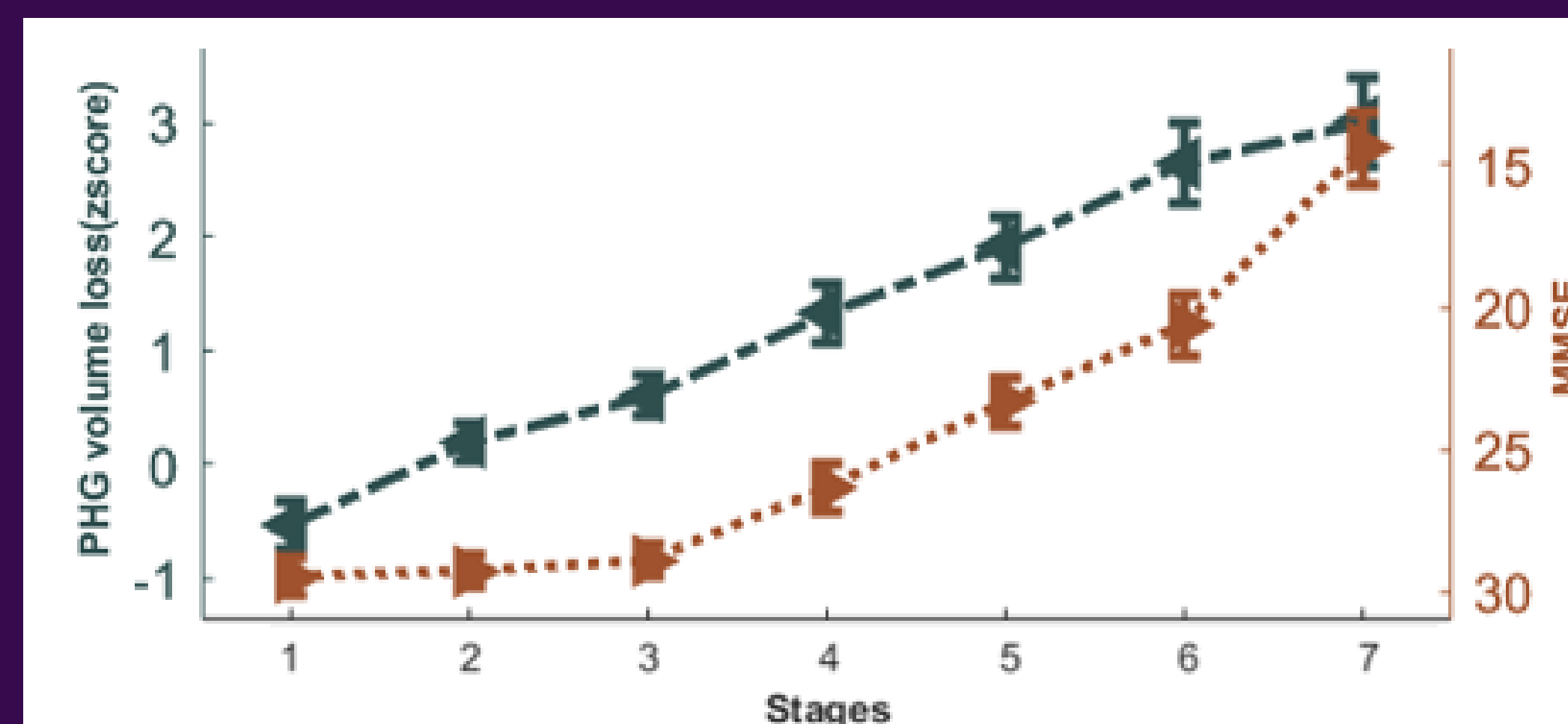
Posterior probabilities, $p_j(k)$, that a subject j belongs to a stage k



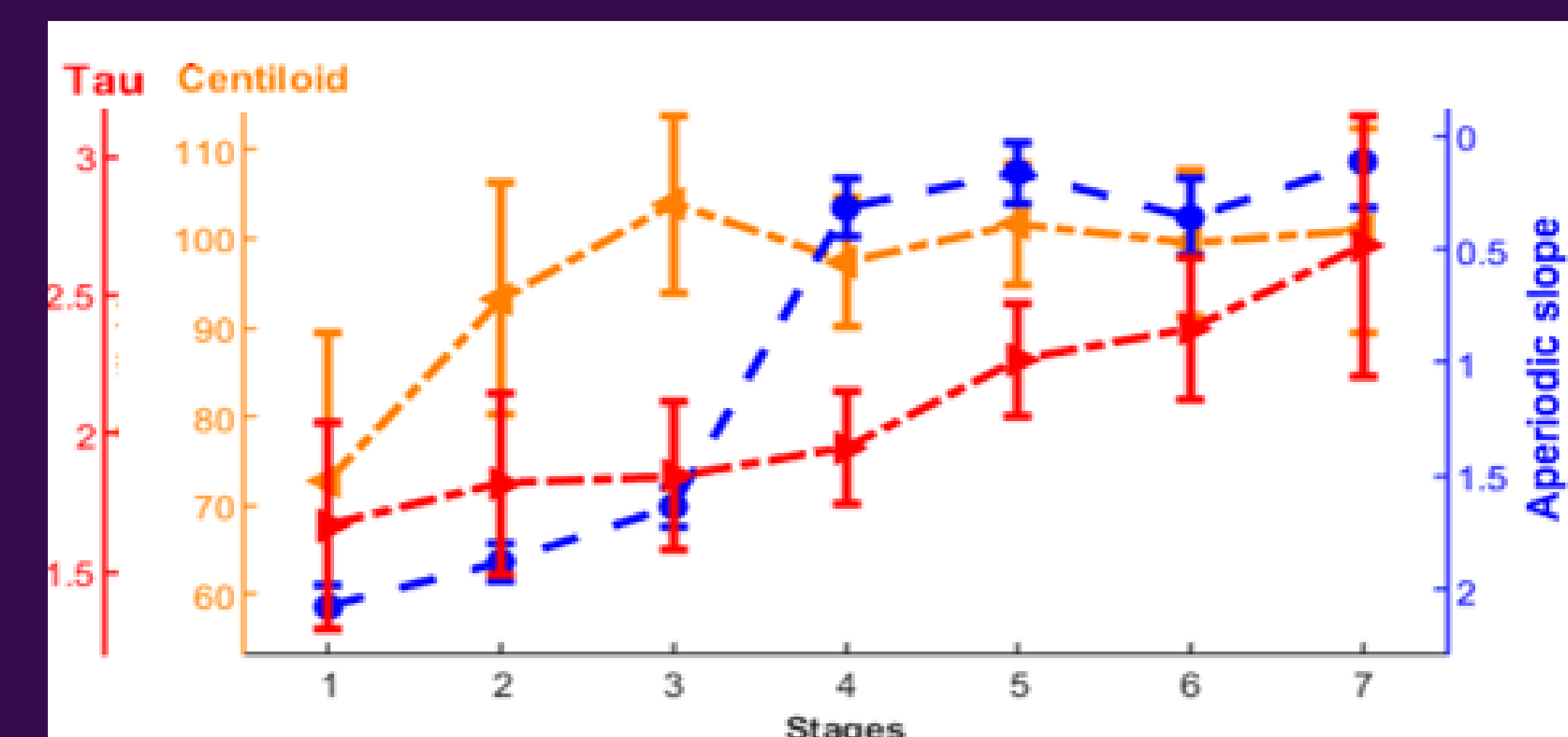
Distribution of the stages in the space spanned by PHG volume loss and MMSE score.



Atrophy-cognition EBM staging of AD progression



Amyloid, Tau, and Aperiodic slope profiles as a function of Atrophy-cognition EBM staging



CONCLUSIONS

The alignment of electrophysiological, molecular, and clinical changes along a common temporal staging provides mechanistic insight into how circuit-level dysfunction relates to molecular pathology.