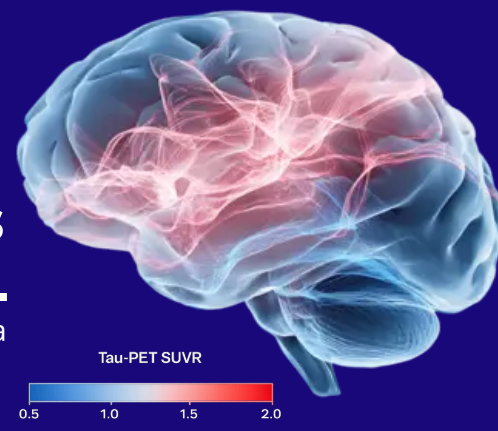




# Shannon Entropy of Tau-PET Spreading Patterns Predict Alzheimer's Disease Progression in Amyloid-Positive APOE4 Carriers



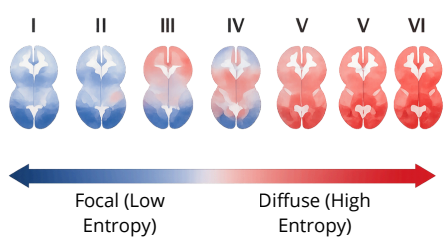
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## 1 Introduction

Tau-PET reveals substantial heterogeneity in tau distribution in Alzheimer's disease (AD). Discrete subtypes have been proposed, but a continuous and clinically interpretable metric is lacking.

We applied Shannon entropy to quantify tau dispersion across Braak regions and examined associations with cognition, longitudinal tau accumulation, amyloid status, and APOE genotype.

### Braak Regions (bilateral averages)



### Shannon Entropy (Normalized)

$$H = \frac{\sum_{i=1}^6 p_i \log_2(p_i)}{\log_2(6)}$$

Range: [0, 1]  
Lower = focal  
Higher = diffuse

## 2 Methodology

931 ADNI participants (1,570 scans)  
<sup>18</sup>F-AV-1451 tau-PET (UC Berkeley pipeline)

Six bilateral Braak-stage regions (I–VI) SUVR composites

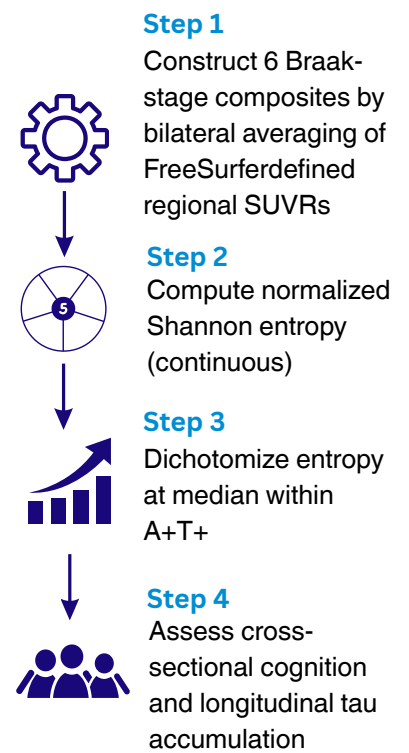
Shannon entropy of regional distribution normalized by  $\log_2(6) \rightarrow [0, 1]$

Temporally matched to tau-PET ( $\pm 180$  days; n=869)

A+ (amyloid positive): CSF A $\beta$ 2 <976 pg/mL (n=403) T+ (high tau): upper tertile of composite SUVR (>1.22)

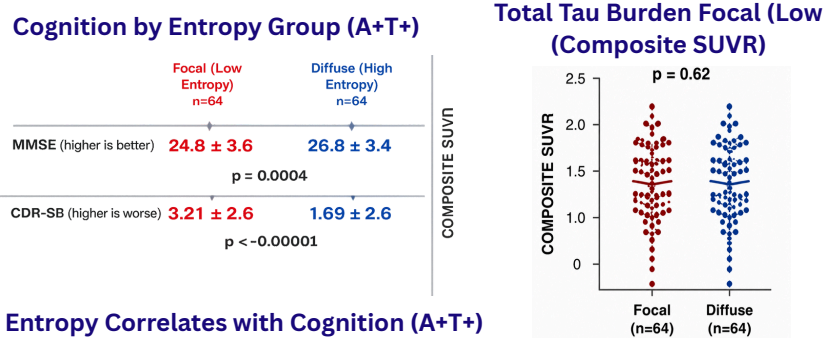
A+T+ (amyloid-positive, tau-positive): n=128. Entropy dichotomized at median within A+T+ Longitudinal A+ with follow-up  $\geq 1.5$  y: n=112 (mean follow-up 3.07 $\pm$ 1.03 years) A–T+ (amyloid-negative, tau-positive): n=21

### Analytical Workflow

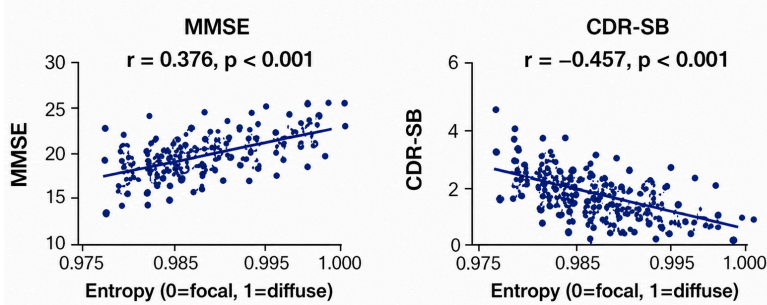


## 3 Results

### FOCAL (LOW ENTROPY) PATTERNS ARE ASSOCIATED WITH WORSE COGNITION DESPITE SIMILAR TOTAL TAU BURDEN (A+T+ PARTICIPANTS)

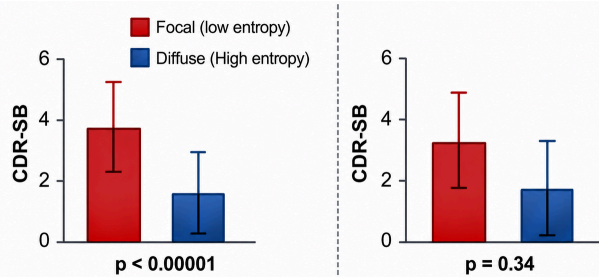


### Entropy Correlates with Cognition (A+T+)



### COGNITIVE IMPACT OF ENTROPY IS APOE4-DEPENDENT (PRIMARY RESULT)

#### CDR-SB by Entropy Group Within Genotype (A+T+)

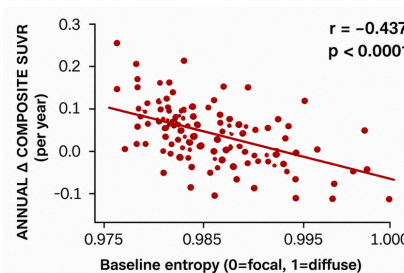


★ **Focal vs. diffuse differences in cognition occur despite similar total tau burden, and this effect is present only in APOE4 carriers.**

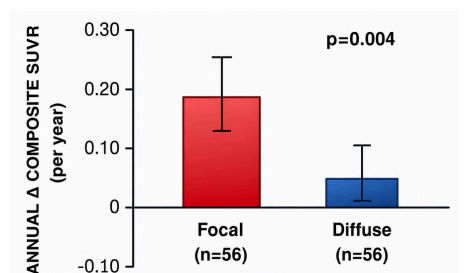
## 4 Results (Longitudinal)

### LOWER BASELINE ENTROPY PREDICTS FASTER TAU ACCUMULATION IN AMYLOID-POSITIVE PARTICIPANTS

#### Correlation: Baseline Entropy vs. Annual Tau Accumulation (A+)



#### Annual Tau Accumulation by Entropy Group (A+)



★ **Group-level: Focal patterns show significantly greater tau accumulation than diffuse patterns in amyloid-positive participants.**

No association in amyloid-negative participants  
r = 0.06, p = 0.82

## 5 Results (Amyloid-Negative, Tau-Positive)

A–T+ Participants (n=21)



Preserved Cognition

MMSE and CDR-SB within normal to mildly impaired ranges

Lower APOE4 frequency



28.6% in A–T+ vs. 71.9% in A+T+ p = 0.0003

## 7 References

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★ Entropy could capture clinically meaningful heterogeneity in tau spread. In amyloid-positive APOE4 carriers, focal tau patterns may forecast worse outcomes—earlier.

## 6 Conclusions

- Shannon entropy may provide a concise and robust measure of tau-PET spatial heterogeneity.
- Focal tau patterns could identify amyloid-positive APOE4 carriers with greater clinical impairment and faster tau accumulation—despite similar total tau burden.
- Preserved cognition in A–T+ participants and lower APOE4 frequency support the amyloid-dependent clinical impact of tau.
- Entropy may improve patient stratification for disease monitoring and therapeutic trials.