

Region-agnostic Staging of Tau Pathology using the PET-only Tau-MaX Pipeline

Christopher A. Brown, MD, PhD¹, Ilya M. Nasrallah, MD, PhD¹, Paul A. Yushkevich, PhD¹, Sandhitsu R. Das, PhD¹, and David A. Wolk, MD¹

¹University of Pennsylvania Contact: Chris Brown, christopher.brown@pennmedicine.upenn.edu



Background

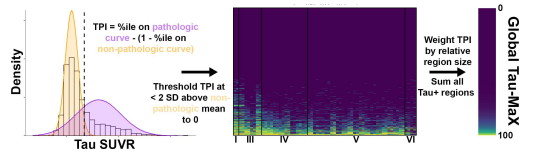
- 2024 AA Workgroup Criteria use combination of spatial extent and magnitude of tau pathology to define biological stages
 - Discrete stages are made up of heterogeneous populations with large overlap between groups
 - Not all individuals may fit within the canonical progression for standard staging
 - Inconsistent approaches to operationalizing criteria, with many opting for spatial extent-only methods
- Objective: Use Tau-MaX to evaluate spatial extent and magnitude along Biological stages and generate continuous Tau Timeline contextualized within AA staging system**

Methods

3019 ¹⁸F-Flortaucipir PET scans from 2173 participants



PHC MRI-free pipeline used to calculate SUVR (Inf. Cereb. Ref) for each cortical ROI in NPDKA parcellation



Gaussian mixture-modelling to convert SUVR to Tau Pathology Index (TPI) and then to Tau-MaX

MTL SUVR	Temp Neocortical SUVR	Global Neocortical SUVR
A < 1.37	< 1.38	< 1.26
B ≥ 1.37	< 1.38	< 1.26
C ≥ 1.38, < 1.75		≥ 1.26, < 1.43
D ≥ 1.75		≥ 1.43

Harrison et al. (HAI 2026) Biological staging system based on AA workgroup criteria

Longitudinal subset to create Tau Timeline

657 PET scans from 251 individuals Staged A-D
Mean 2.62 (2-6) scans over 2.10 ± 1.20 years

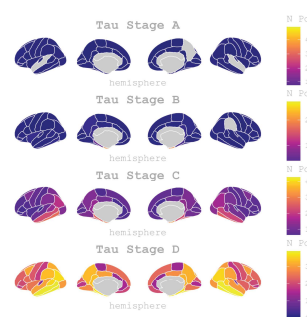
- SILA applied to Tau-MaX with a threshold 1.5 SDs above the mean Tau-MaX in A- participants
- Modeled trajectory used to estimate time from tau onset for all participants

Statistical Analyses

- Mean regional TPI and extent calculated within Tau stages and 1-3 year epochs of tau timeline
- Linear models to compare Tau-MaX and CDR-SB across biological groups controlling for age, sex, and education (CDR-SB analyses)
- Longitudinal linear mixed-effects models with B-spline time term to evaluate CDR-SB change by Tau time (controlling for age, sex, education)

Regional Tau Burden by Stage

A. Tau Extent



B. Tau Magnitude

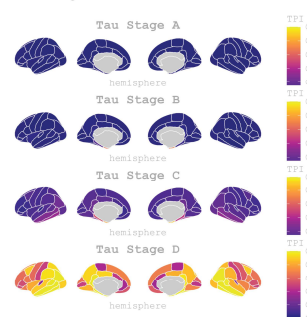


Figure 1. Regional distribution of tau in biological stages. The regional distribution of tau extent (A) and magnitude (B) within each biological stage is shown on a representation of the DKT parcellated brain. A: The number of individuals positive for tau in a given region within each group are shown with warmer colors representing greater positivity. B: The average Tau Pathology Index (TPI) for each region within a stage are shown with warmer colors representing higher TPI

Tau Extent and Magnitude along Tau Timeline

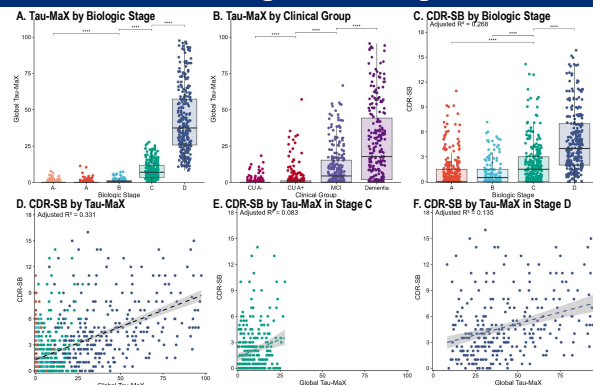


Figure 2. Tau-MaX and CDR-SB across biologic and clinical severity. A-B: Global Tau-MaX is plotted across biological stages (A) and clinical groups (B), demonstrating increasing tau burden with greater biological and clinical severity. Brackets signify groups significantly different from each other after controlling for age and sex. C: Comparison of CDR-SB across biological stages with brackets indicating groups significantly different from each other after controlling for age, sex, and education. D: CDR-SB plotted against Global Tau-MaX with the line representing the linear best-fit across all participants. Points colored by Tau Stage. E-F: CDR-SB is plotted against Global Tau-MaX within stages C (E) and D (F) separately

Progression along Tau Timeline

A. Tau-MaX Trajectory along Tau Timeline

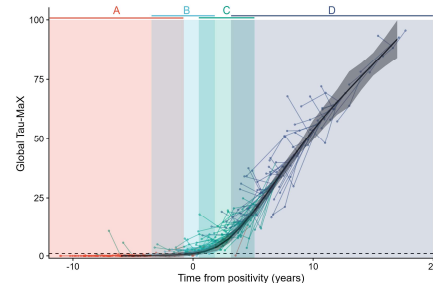
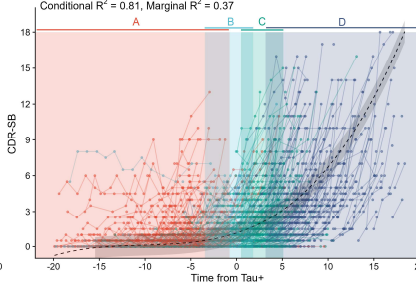


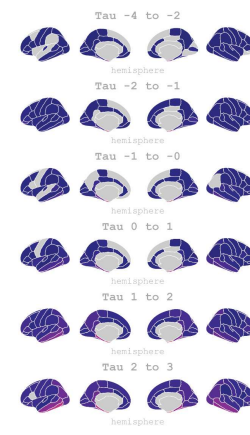
Figure 3. Biological and Clinical Progression on the Tau Timeline. A: Results of the SILA modeling of Tau-MaX. B: Longitudinal change in CDR-SB is plotted against Tau Time with the dashed line representing the best fit using a b-spline with 2 degrees of freedom and the ribbon represents the 95% confidence interval. The conditional R² and marginal R² of the linear mixed-effects model after controlling for age, sex, and education along with a random effect of participant are shown. Both: The shaded boxes represent the mean ± 1.5 standard deviations of tau time for each stage. Points colored by the last Biological Stage observed and thin lines connect data points from the same individual.

B. Longitudinal Change in CDR-SB along Tau Timeline



Tau-MaX and Clinical Impairment by Stage

A. Tau Extent



B. Tau Magnitude



Figure 4. Regional Tau Burden along the Tau Timeline. Tau extent (A) and magnitude (B) are plotted on a representation of the DKT parcellated brain within 1-3 year epochs along the tau timeline. A: The number of individuals positive for tau in a given region within each epoch are shown with warmer colors representing greater positivity. B: The average Tau Pathology Index (TPI) for each region within an epoch are shown with warmer colors representing higher TPI. A-B: Tau Extent follows a Braak-like progression from the MTL to temporal neocortex before spreading posteriorly to parietal associative cortex and then to frontal associative cortex before finally involving primary neocortex later in the disease timeline. Magnitude increases follow a similar pattern but are 1-2 years delayed compared to the corresponding increases in extent.

Conclusions

- Tau-MaX provides a continuous measure of magnitude and extent that captures biological severity along AA working group stages
- The Tau timeline provides a continuous means for assessing tau severity and can be contextualized within AA working group biological stages

Acknowledgements: Data from ADNI, SCAN, NACC, and ADSP-PHC
NIH grants: P30AG072979, K23AG093167
Alzheimer's Association Fred and Barbara Erb Family Foundation AACSF-23-1152241