Evaluation of Quantitative Measurements of Tau Pathology with Semi-Quantitative Ratings and Age

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Introduction: Tau Pathology Is a Hallmark of AD

- Tau pathology, a hallmark of Alzheimer's Disease (AD), is typically assessed semi-quantitatively, with regional ratings of severity and a global Braak Stage of 0 to 6
- Quantitative digital neuropathology provides an alternative to Braak staging or regional semi-quantitative ratings by measuring a wider range of variability in pathology and type of inclusion (tangles, threads, astrocytic tau, etc.)

Aim: What is the Utility of Quantitative Pathology Measurements Beyond Conventional Ratings?

- We examined a **quantitative tau pathology method** on 6µm tissue stained with phosphorylated tau PHF1
- We compared these measurements with semi-quantitative pathology ratings, age at death, and the presence of TDP-43 and alpha-synuclein co-pathologies. **We hypothesized that quantitative measurements would show high agreement with semi-quantitative ratings** in the same region, and **that within high Braak stage patients, quantitative measurements of tau pathology would decrease with age at death** and **increase with higher co-pathology ratings.**

Methods: Generated Quantitative Maps for Tangle and Thread Pathology

- A **machine learning method** (Yushkevich et al., 2021, Sadaghiani et al., 2022) trained on 20µm AT8-stained whole slide images **generated summary measures of tangle and thread pathology for each slide** from **215 patients** with **AD continuum neuropathological diagnoses**
- Up to 14 regions were sampled in each patient, including amygdala, angular gyrus, anterior cingulate, dentate nucleus, hippocampus, lentiform nucleus, medulla, middle frontal cortex (MFC), occipital cortex, orbital frontal cortex (OFC), pons, substantia nigra (SN), superior temporal cortex, and thalamus
- A subset of slides also had semi-quantitative ratings by pathologists available in the same region, which were compared to the quantitative measurements
  - Quantitative amygdala slide measurements were compared to semi-quantitative ratings in amygdala (AMYG), and entorhinal cortex (EC), and quantitative hippocampus slide measurements were compared to semi-quantitative ratings in dentate gyrus (DG), entorhinal cortex (EC), and Ca/Subiculum (CS)

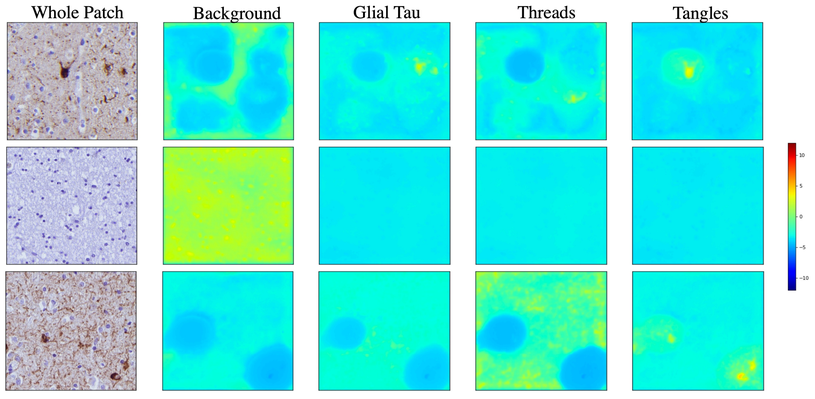

Figure 1: Sample activation maps: Patches sampled from 6µm PHF1-stained whole-slide images (WSI) and corresponding activation maps generated by the deep learning weakly supervised segmentation model WildCat. High values (yellow/red color) in the activation map are regions of the patch where the model detects evidence of a given class (e.g., tangles). A summary tangle score for a WSI is generated by sampling 200 patches across the WSI, excluding background; computing the 99th percentile of the tangle activation map in each patch; and computing the 90th percentile of this measure across the 200 sampled patches; similarly for the summary thread score. To the right, a legend for Wildcat model activation values is provided. Up to 14 regions were sampled in each patient for this analysis, with an average of 10.52 regions sampled per patient.

Results: Quantitative Measurements Show High Overall Agreement with Corresponding Semi-Quantitative Ratings

- **Quantitative measurements of tau tangles** (left columns) and **threads** (right columns**) largely agree with semi-quantitative ratings by pathologists** ranging from 0 (none) to 3+ (severe) in the same region

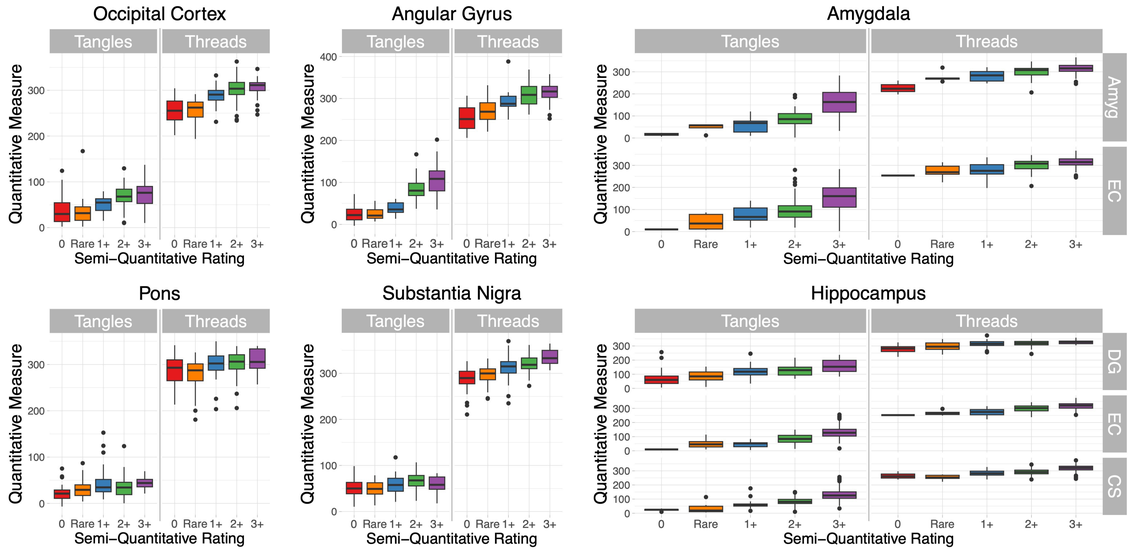

Figure 2: Semi-quantitative tau rating comparisons with quantitative measurements in the same region: Plots showing the relationship between semi-quantitative pathology ratings (i.e., 0-3 reflecting none, rare, mild, moderate, severe) from neuropathologists compared to quantitative tangle and thread measurements generated using WildCat in a subset of regions where both ratings were available, specifically, two cortical regions (the occipital cortex and angular gyrus), two subcortical regions (the pons and substantia nigra), and two regions important in AD pathology (the amygdala and hippocampus). AMYG = Amygdala, EC = Entorhinal Cortex, DG = Dentate Gyrus, CS = cornu ammonis / subiculum

Summary / Conclusions

- Quantitative measurements of tau pathology largely agree with semi-quantitative ratings by pathologists in the same region
- Even within high Braak stage patients, quantitative measurements of tau pathology can offer additional prediction for variables such as age at death and the amount of TDP43 co-pathology
- A limitation of this study, to be addressed in future work, is that a global measurement of pathology across the slide was used, without anatomical specificity
- **Quantitative pathology measurements agree with current standards and provide additional, clinically relevant information beyond Braak staging**

References and Support

Yushkevich, P. A., Muñoz López, M., Iñiguez de Onzoño Martin, M. M., Ittyerah, R., Lim, S., Ravikumar, S., ... & Insausti, R. (2021). Three-dimensional mapping of neurofibrillary tangle burden in the human medial temporal lobe. *Brain*, *144*(9), 2784-2797.

Sadaghiani, S., Trotman, W., Lim, S. A., Chung, E., Ittyerah, R., Ravikumar, S., ... & Yushkevich, P. A. (2023). Associations of phosphorylated tau pathology with whole-hemisphere ex vivo morphometry in 7 tesla MRI. Alzheimer's & Dementia, 19(6), 2355-2364.

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Results: Quantitative Measurements Can Offer Additional Information Beyond Braak Stage in High Braak Stage Patients

- In 150 patients with **high Braak stages (V/VI)**, summary measures of tangle and thread pathology in each region were correlated **with age at death**, **TDP43 severity**, and **alpha-synuclein severity**
- Significant associations (shown here in Figure 3) were found between **age at death and tangles in MFC, OFC, and thalamus**, between **age at death and threads in OFC**, and between **TDP-43 severity score and tangles in SN.**

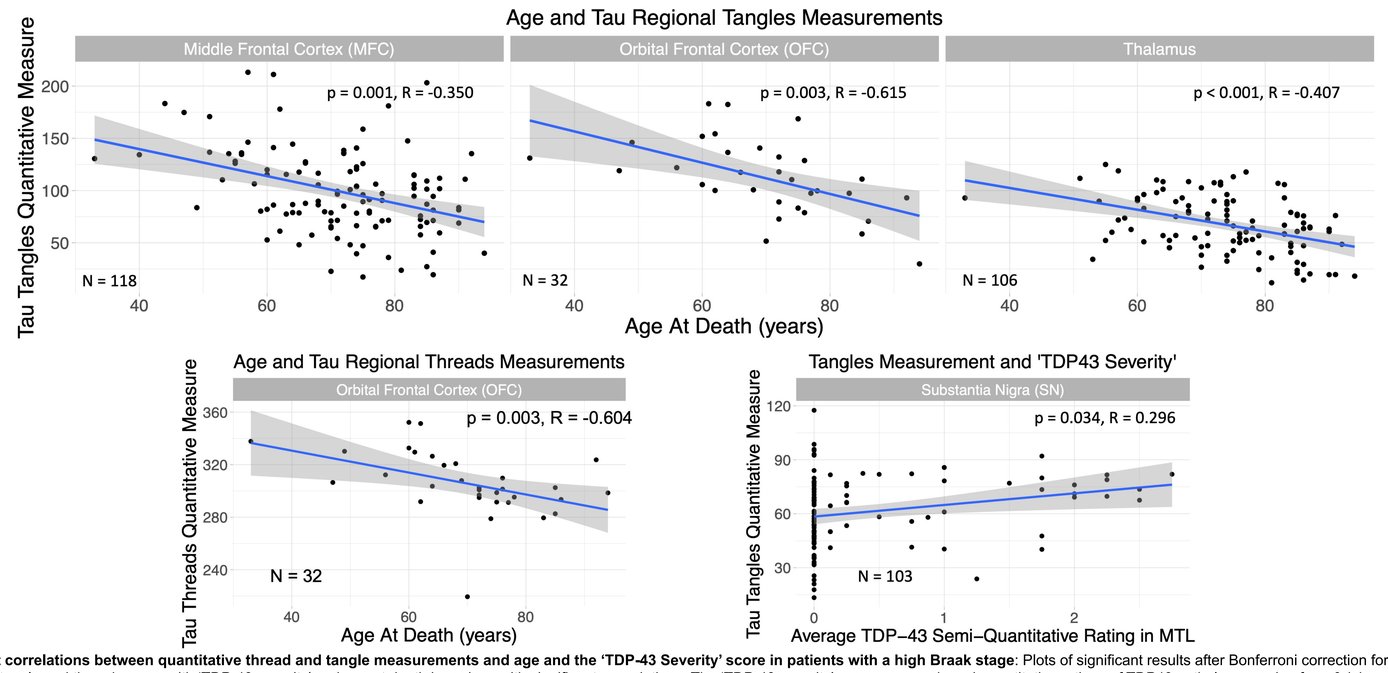

Figure 3: Significant correlations between quantitative thread and tangle measurements and age and the 'TDP-43 Severity' score in patients with a high Braak stage: Plots of significant results after Bonferroni correction for Spearman correlations between tangle and thread scores with 'TDP-43 severity' and age at death in regions with significant associations. The 'TDP-43 severity' score averaged semi-quantitative ratings of TDP43 pathology ranging from 0 (absent) to 3+ (severe) in medial temporal lobe (MTL) regions, a key site for pathology in LATE-NC (Limbic-predominant Age-related TDP-43 Encephalopathy Neuropathological Change) including the amygdala, entorhinal cortex, dentate gyrus, and combined region of cornu ammonis (CA) subfields and subiculum. The 'alpha-synuclein severity' score averaged semi-quantitative ratings of alpha-synuclein pathology ranging from 0 (absent) to 3+ (severe) in regions it commonly accumulates, including the amygdala, cornu ammonis (CA) subfields and subiculum region, cingulate gyrus, midbrain, and substantia nigra. The number of patients for each region varied and is given in the bottom left of each plot.

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