

TOWARD BETTER ALZHEIMER'S MODELING: A NOVEL AMYLOID-BETA/TAU CO-PATHOLOGY MOUSE MODEL

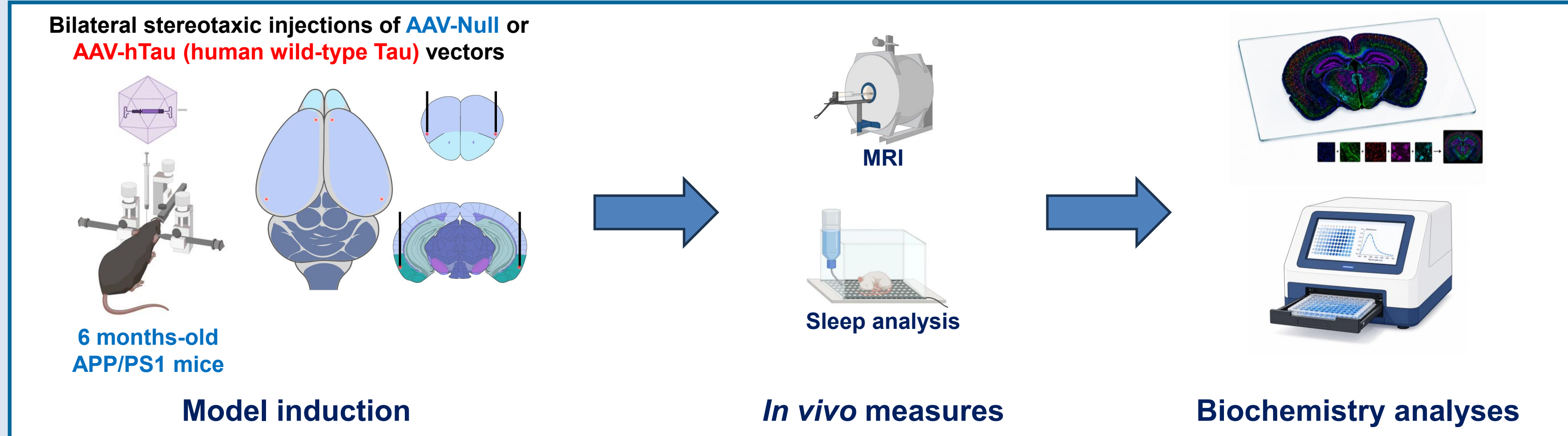
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Introduction

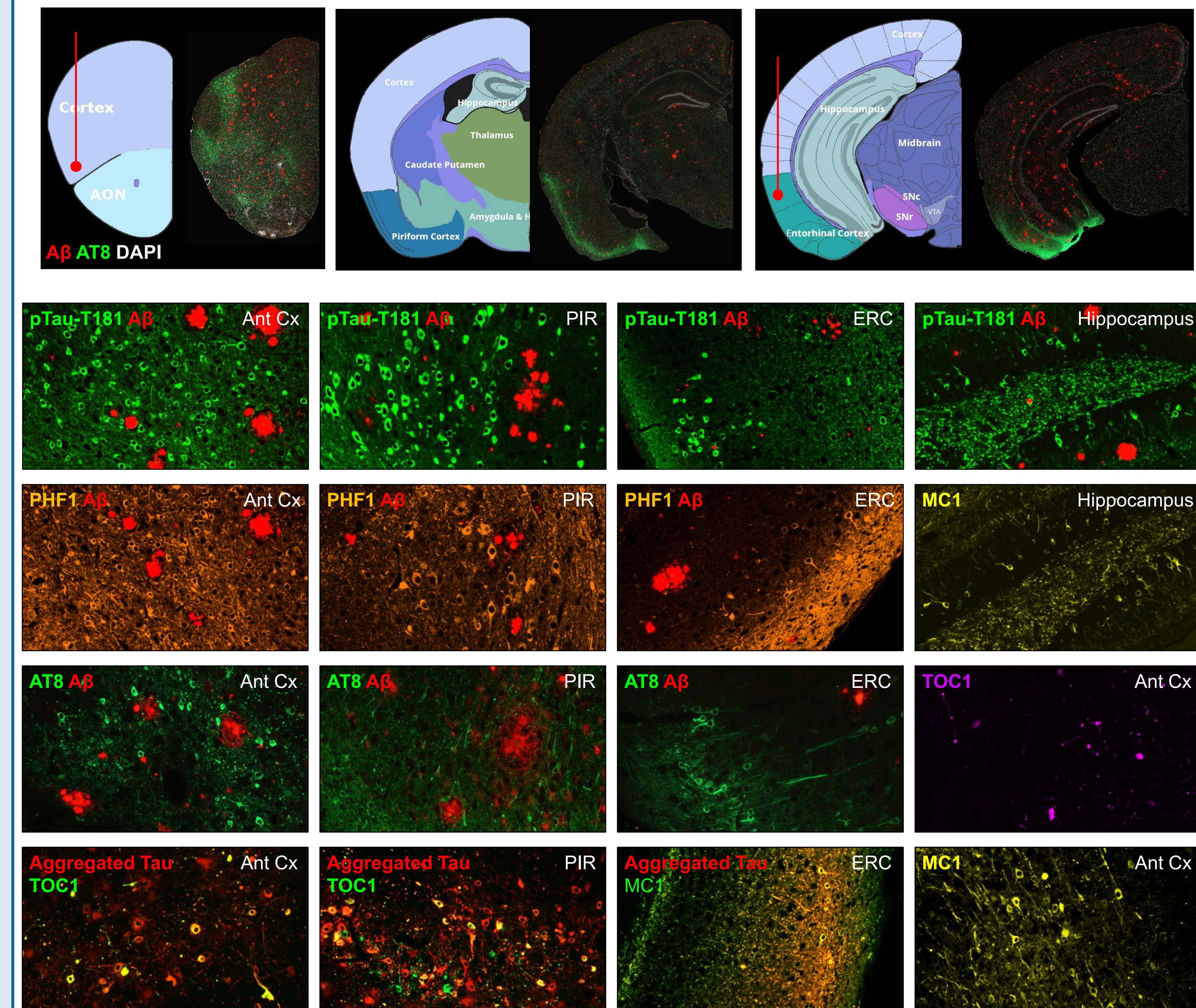
- Refining animal models is essential for capturing the complexity of human neurodegenerative diseases and improving outcomes for drug development.
- Alzheimer's disease is marked by the presence of both amyloid- β plaques and tau neurofibrillary tangles. However, traditional animal models typically show pathology associated with one or the other, leading to an incomplete characterization of the disease.
- We have developed a novel mouse model of Alzheimer's disease that recapitulates both amyloid- β and tau pathologies and demonstrates features that can be measured using "translational biomarkers".

Methods



Results

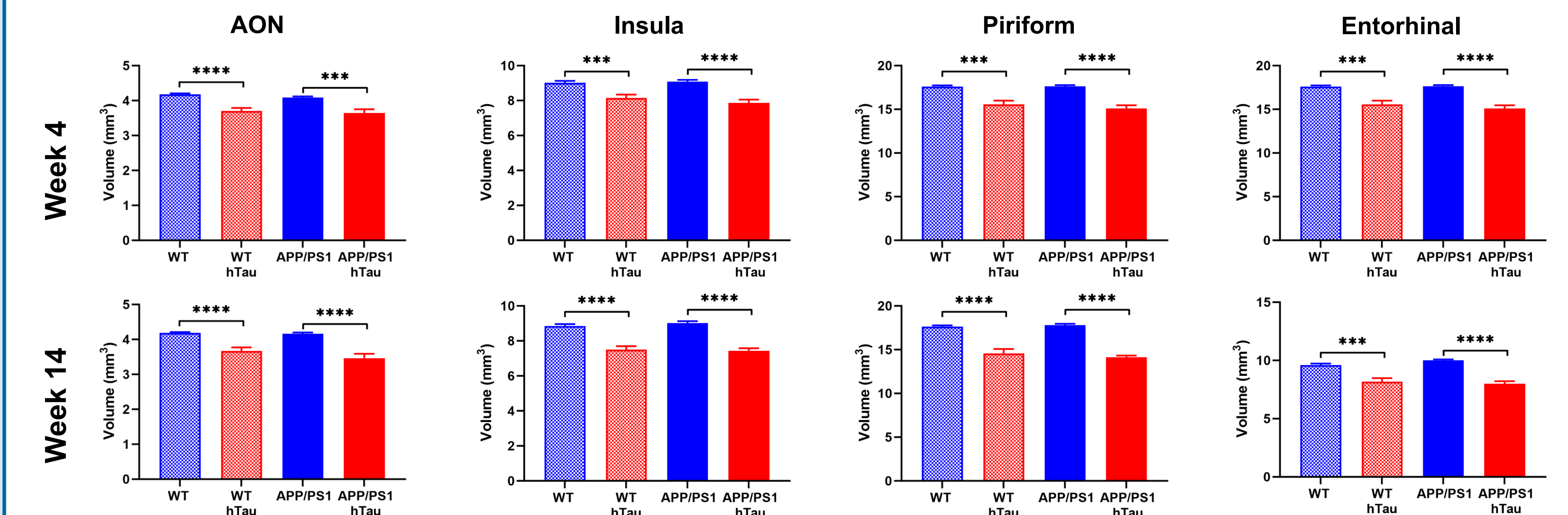
Amyloid- β and Tau Co-Pathology



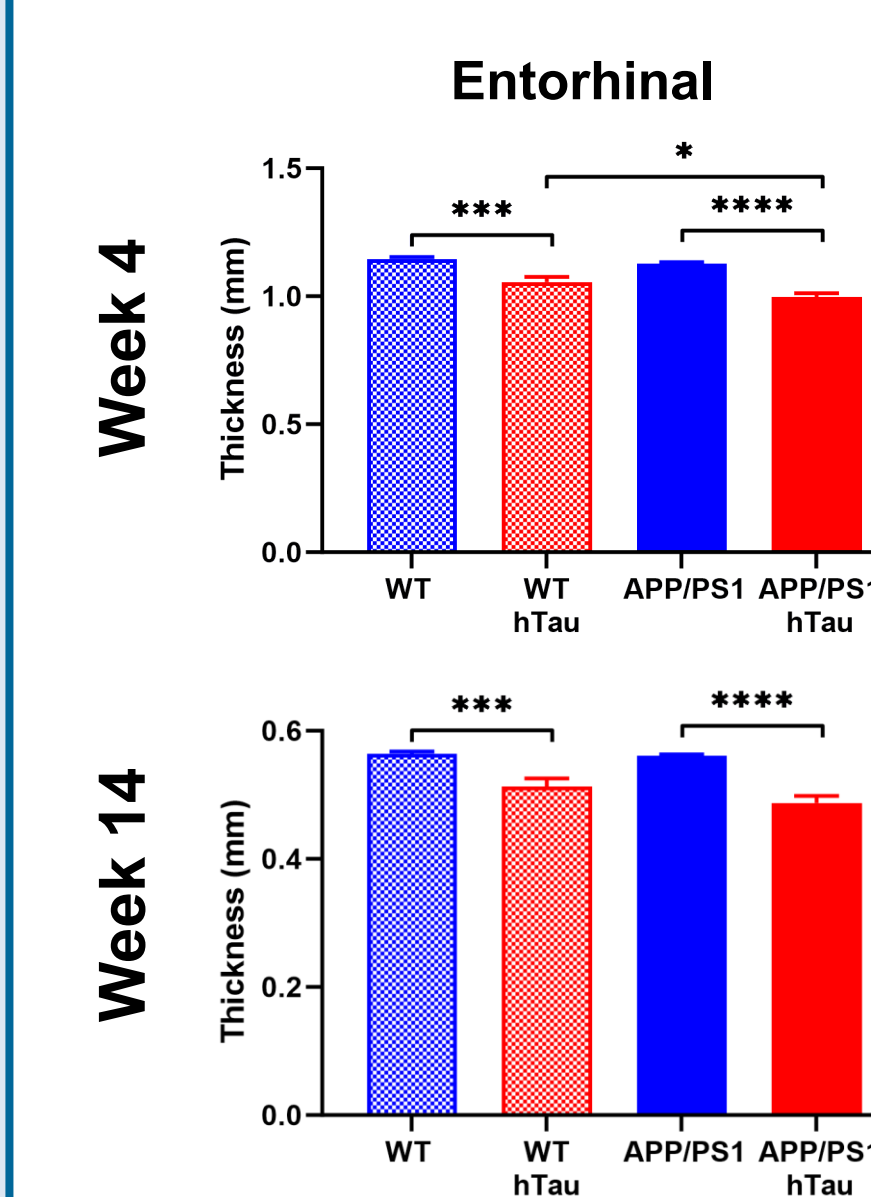
Coronal tissue sections from APP/PS1/hTau mouse brain demonstrate Tau accumulation and pathological Tau species, shown by AT8 (pTau-S202/T205), MC1 (conformationally altered Tau), pTau-T181, PHF1 (pTau-S396/404), TOC1 (Tau oligomers) and aggregated Tau immunostaining, in the neuronal soma and processes, as well as fibrillar amyloid- β in plaques and cerebrovascular pathology. Tau accumulation was observed both near and beyond the injection sites. Note the extensive level of pTau in the piriform and entorhinal cortical regions. No immunoreactivity was observed in WT brains. *Ant Cx*: anterior cortex; *PIR*: piriform cortex; *ERC*: entorhinal cortex.

Early Neurodegeneration

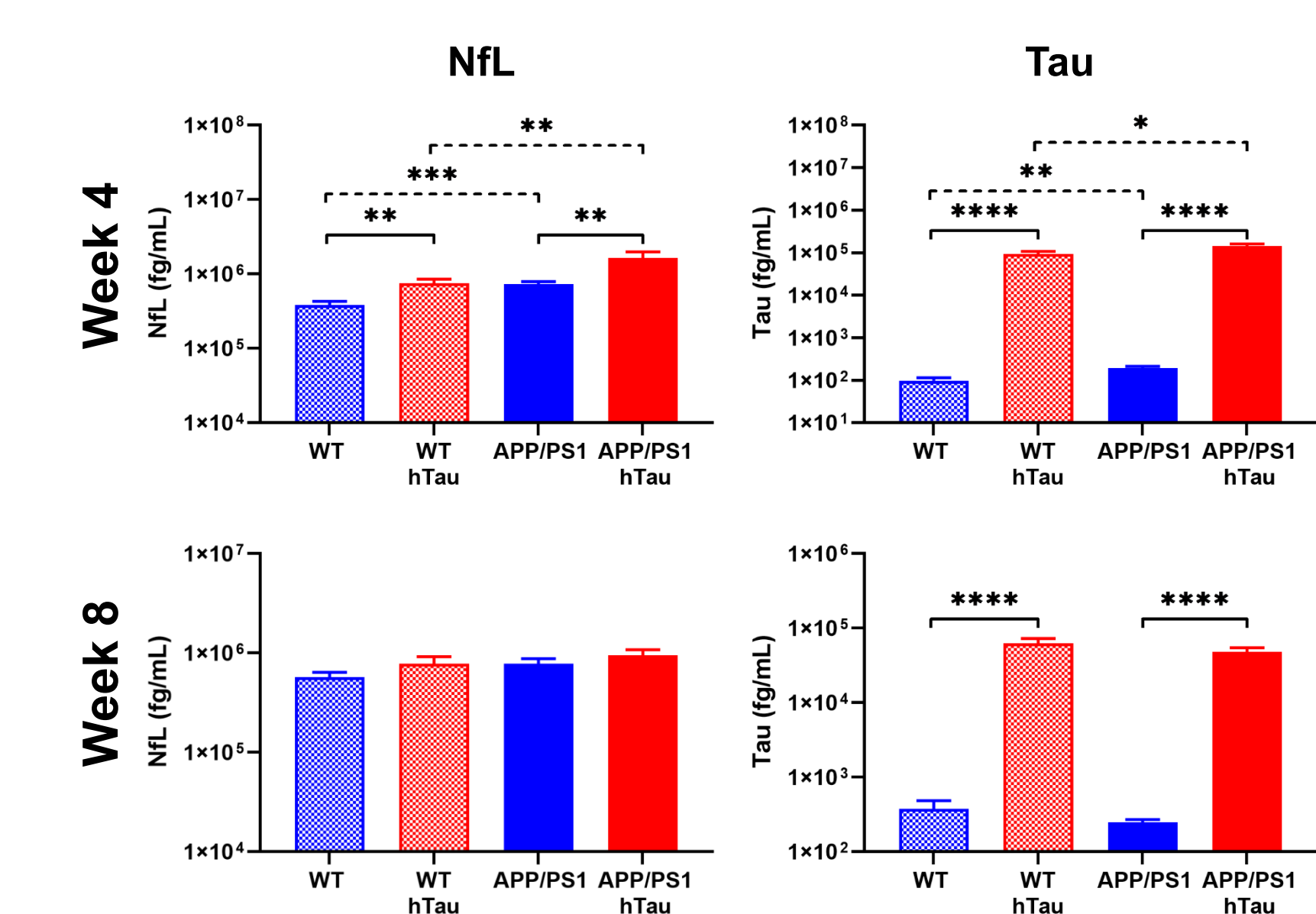
A. Regional Volumes



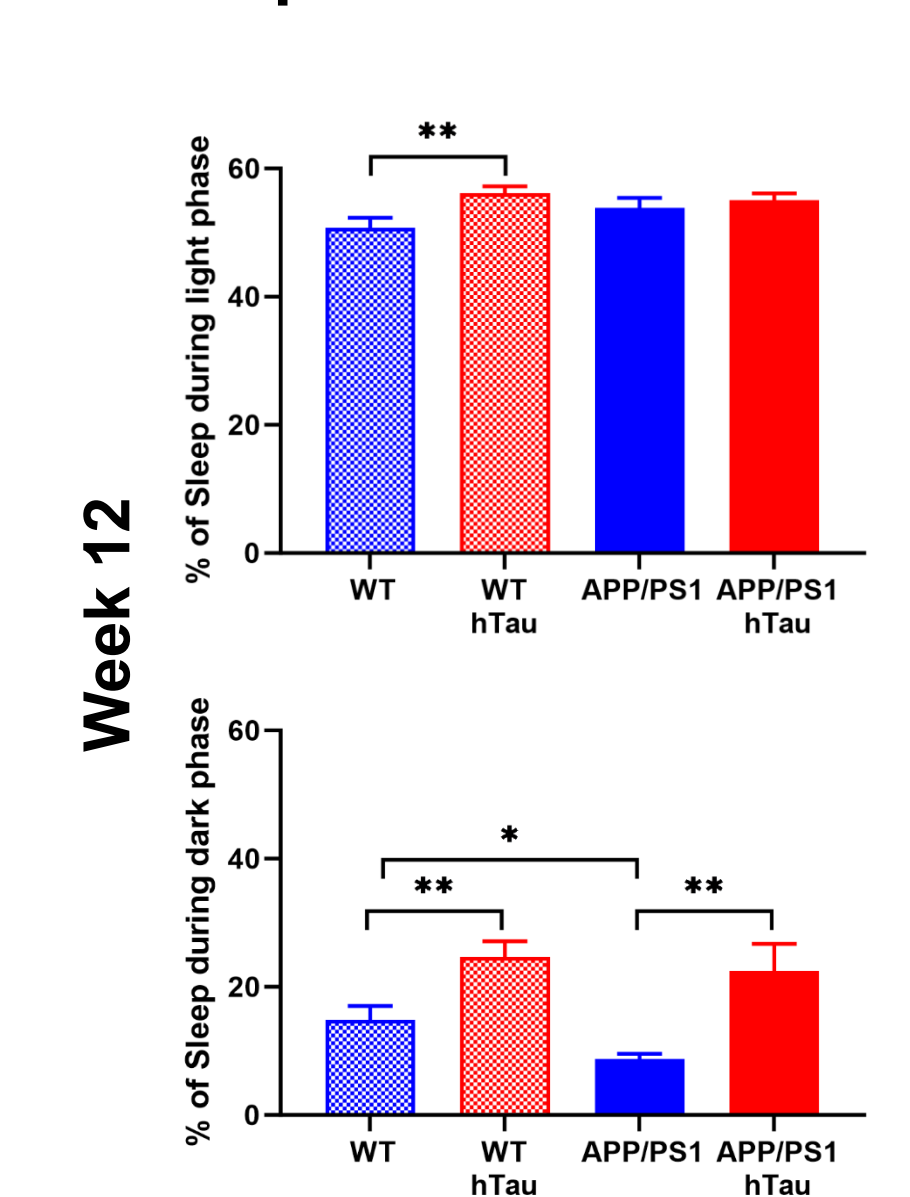
B. Cortical Thickness



C. Plasma Biomarkers



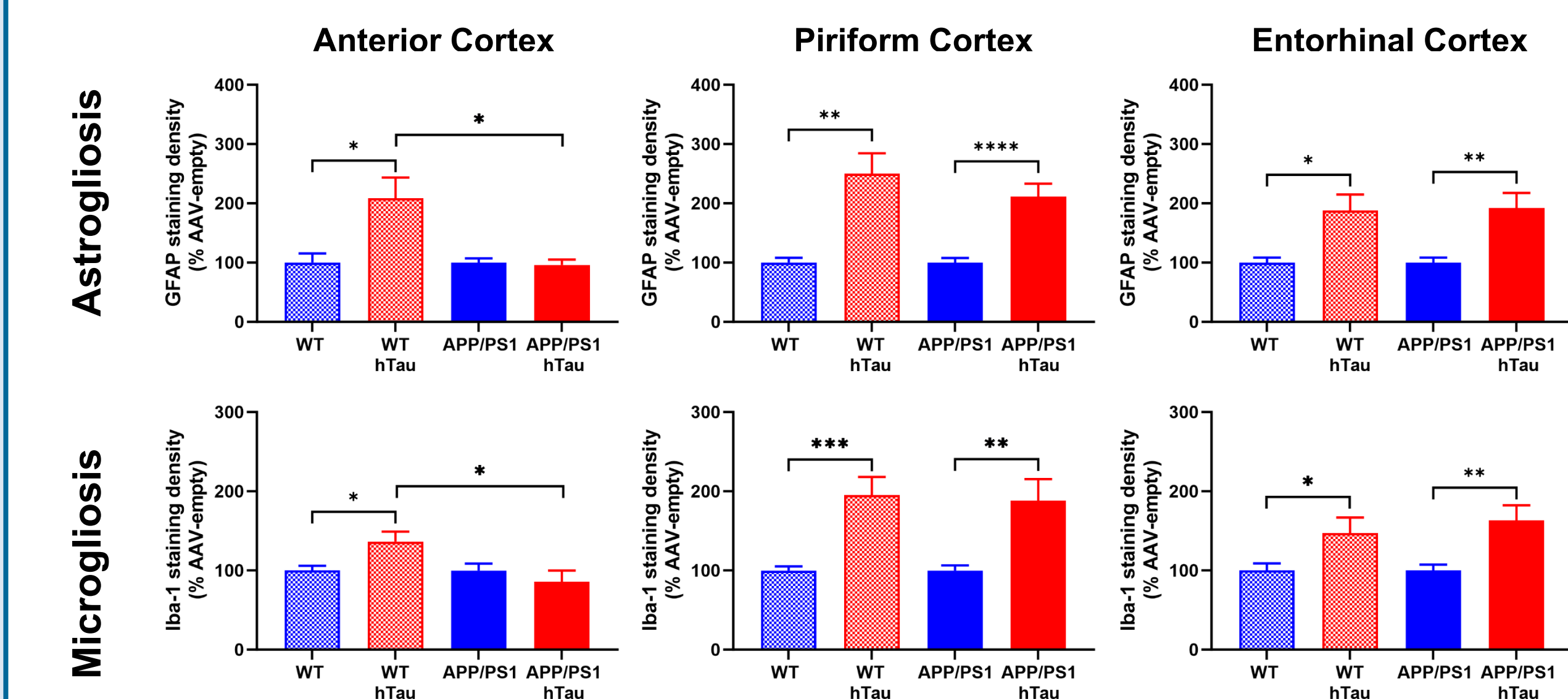
D. Sleep Disturbances



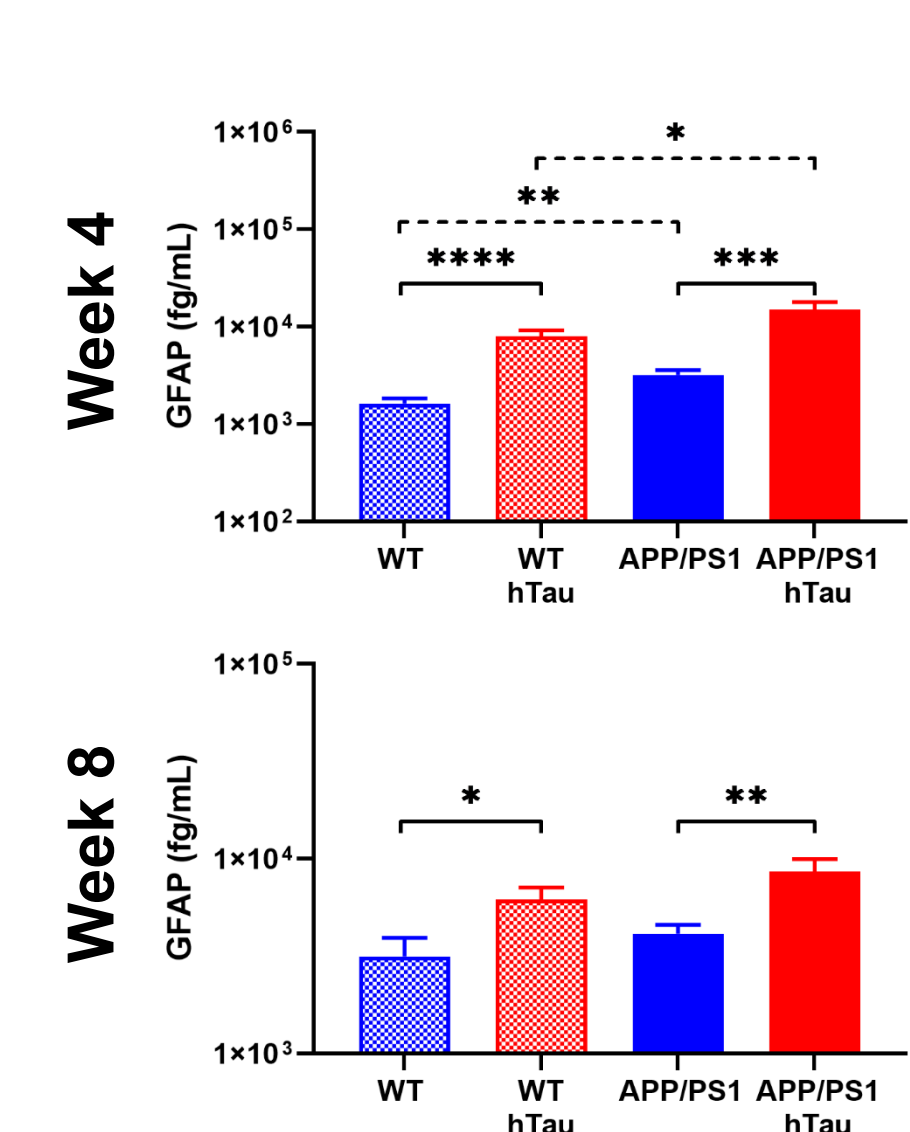
Injection of AAV-Tau induced highly significant (A) reductions of regional volumes and (B) cortical thickness in both WT and APP/PS1 animals, (C) increased NfL and Tau plasma levels, and (D) sleep disturbances characterized by an increased percentage of sleep. Note that APP/PS1 mice without AAV-Tau injections do not show any brain atrophy compared to WT mice. Interestingly, reduced cortical thickness and increased NfL and Tau plasma levels were observed in the APP/PS1/hTau mice compared the WT/hTau mice, suggesting a potential modulatory role of amyloid- β (Mean $\pm$ SEM; t-test; *p<0.05, **p<0.01, ***p<0.001, ****p<0.0001).

Neuroinflammation

A. Quantitative Immunofluorescence



B. Plasma GFAP



Significant neuroinflammation in AAV-hTau injected mice, marked by (A) an increase in astrogliosis (GFAP) and microgliosis (Iba-1), especially in the piriform cortex and entorhinal cortex, where extensive Tau pathology was observed, associated with (B) increased plasma GFAP levels (Mean $\pm$ SEM; t-test; *p<0.05, **p<0.01, ***p<0.001, ****p<0.0001).

Conclusion

This novel amyloid- β and tau co-pathology mouse model recapitulates several features of Alzheimer's disease, such as sleep disturbances, extensive amyloid- β pathology, accumulation of pathological Tau in cell bodies and processes, neuroinflammation in areas of extensive co-pathology, and brain atrophy especially in regions typically affected by the disease. With quantifiable in-life and post-mortem translational biomarkers, the APP/PS1/hTau mice model can serve as a useful model for preclinical evaluation of disease-modifying therapeutics for Alzheimer's disease.