Tau-induced Hyperexcitability Of Locus Coeruleus Neurons Drives Behavioral Changes In A Mouse Model Of Alzheimer's Disease

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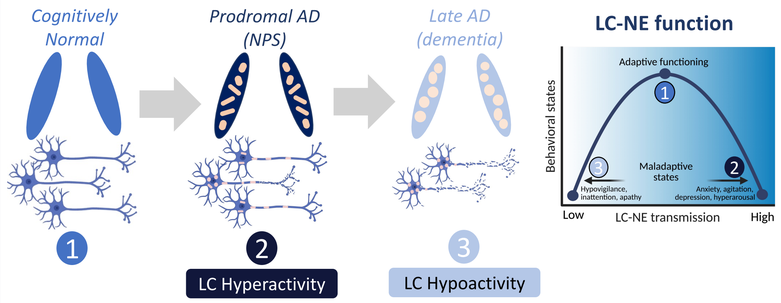
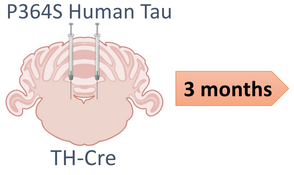
Background

- Early stages of Alzheimer's disease (AD) are characterized by neuropsychiatric symptoms (NPS) such as anxiety, apathy, compulsivity, and sleep disturbances, which manifest years before cognitive deficits.
- It has been hypothesized that dysregulation of the locus coeruleus-norepinephrine (LC-NE) system contributes to these symptoms because:
- LC is the first site where hyperphosphorylated 'pretangle' tau can be detected in the human brain.
- NE influences physiological processes such as mood, stress responses, and arousal.
- Clinical studies show correlations between LC dysfunction and NPS; however, ***a causal relationship between early tau accumulation in the LC and the manifestations of prodromal behaviors remains to be resolved.***
- Here, we developed a **translationally-relevant tau mouse model** that recapitulates the '*LC first*' phenomena commonly observed in humans.

Proposed Model: LC-NE Dysregulation over Disease Continuum



Experimental Design & Methods

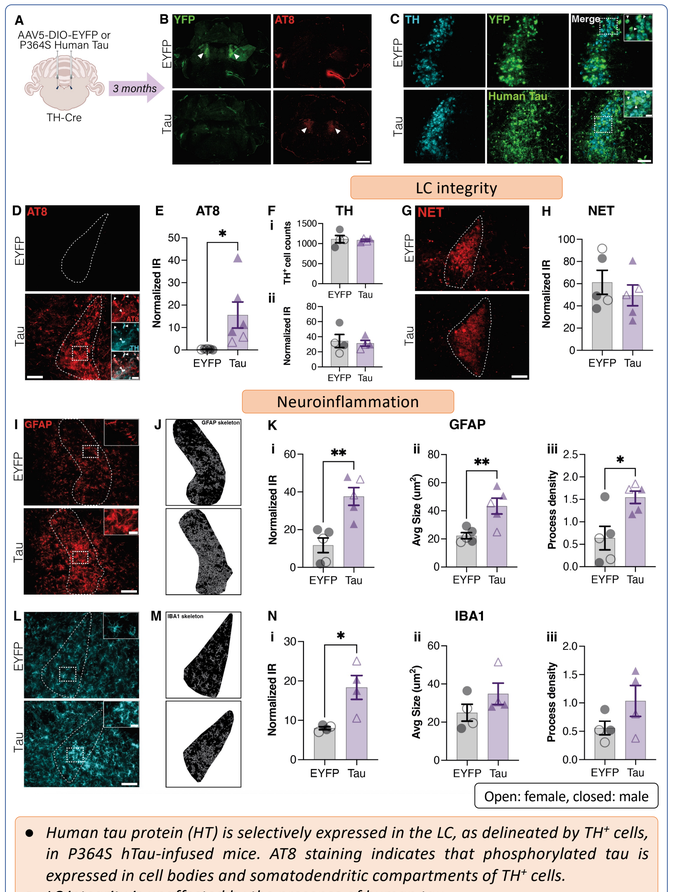


Behavior	Pathology
• Anxiety • Compulsivity • Novelty responses • Sleep • Associative Memory	• Immunofluorescence: tau pathology, LC integrity, neuroinflammatory responses • Slice electrophysiology • Translating Ribosome Affinity Purification (**TRAP**) • Cell type-specific in vivo biotinylation of proteins (**CIBOP**)

- **Subjects**: Adult male and female tyrosine hydroxylase (TH)-Cre mice aged 2-3 months received intra-LC infusions of a Cre-dependent adeno-associated virus (AAV) expressing EYFP or P364S mutant human tau (n=10-14/group).
- **Behavioral tests**: novelty-suppressed feeding (anxiety), nestlet shredding (compulsivity), fear conditioning (association memory). For sleep studies, 24-hour EEG/EMG recordings were performed, scored for behavioral states (REM, non-REM, wakefulness) and analyzed for sleep spindles.
- **Immunofluorescence (IF)**: Human Tau (HT1) and AT8 (Ser202/Thr205) antibodies to assess tau pathology, Tyrosine Hydroxylase (TH) and NE transporter (NET) to evaluate LC integrity and innervation density, gliosis markers such as Glial Fibrillary Acidic Protein (GFAP) and Ionized calcium binding adaptor molecule 1 (Iba1). 20x Images were acquired on Keyence BZ-X700 microscope and analyzed on FIJI/ImageJ software.
- **Slice electrophysiology:** Brains were sectioned horizontally into 220 µm slices, LC was identified as the cell body-dense area rostral to the fourth ventricle and medial to the motor neurons of the mesencephalic tract. Loose cell-attached recordings of spontaneous firing were made at 34 C using a sodium-HEPES based pipette solution.
- **Omics-based studies for TRAP and CIBOP:** These methods have been previously described (Korukonda et al., 2026)
- **Statistical Analysis:** All data are reported as mean ± SEM ($p < 0.05$). IF and electrophysiology were compared between EYFP and Tau groups using a two-tailed unpaired t-test (or Welch t-test when variance assumptions were violated) or multiple unpaired t-test for DG IF analysis (corrected for multiple comparisons with Holm-Sidak method) or Mann-Whitney U test, as determined in GraphPad Prism 10. For behavioral assessments, a two-way ANOVA was used with factors such as treatment, location/time where appropriate. Post-hoc tests were performed using Sidak's comparisons. Outliers were identified and removed with Grubb's test.

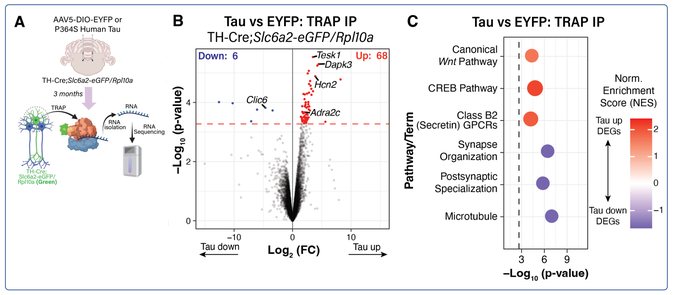
Results

P364S hTau induces hyperphosphorylated tau (pTau) expression and neuroinflammatory responses in the LC

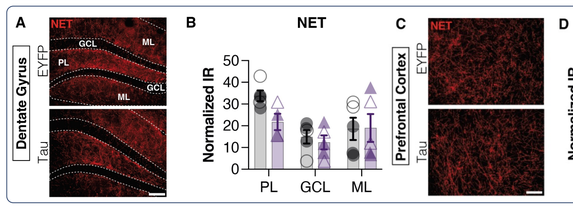


- *Human tau protein (HT) is selectively expressed in the LC, as delineated by TH⁺ cells, in P364S hTau-infused mice. AT8 staining indicates that phosphorylated tau is expressed in cell bodies and somatodendritic compartments of TH⁺ cells.*
- *LC integrity is unaffected by the presence of human tau.*
- *Tau pathology triggers discernable neuroinflammatory responses in P364S hTau-infused mice.*

Tau induces alterations to the LC translatome

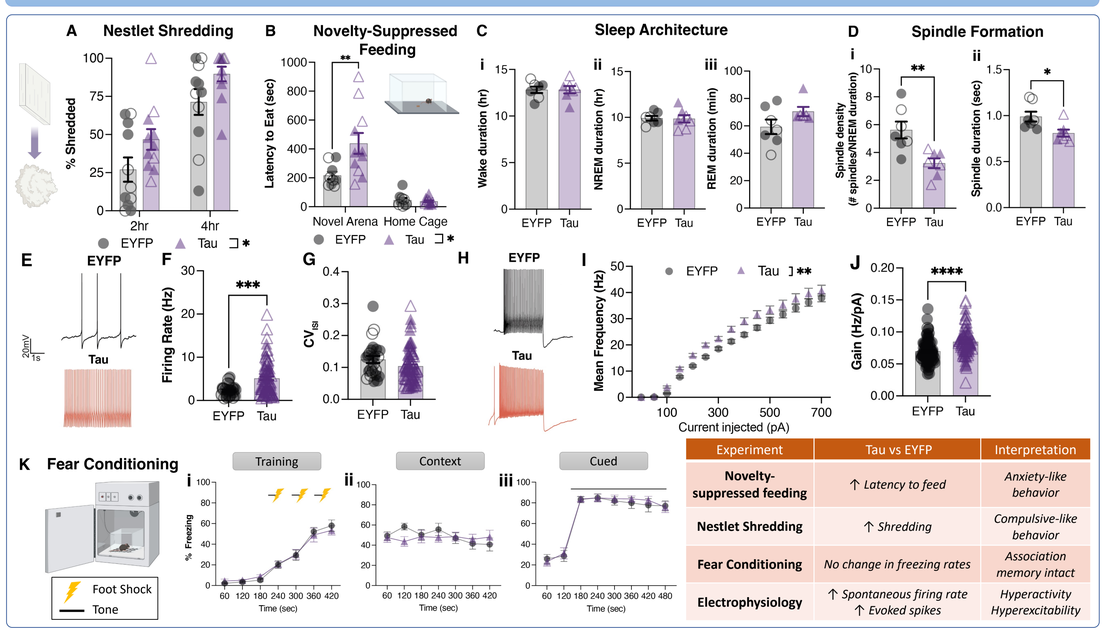


LC tau pathology does not affect NE terminal density or spread in projection regions



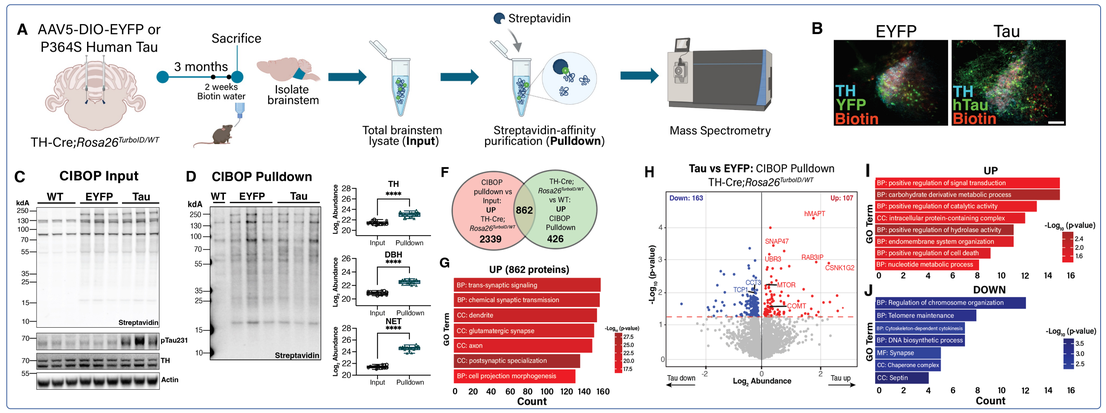
- *NET terminal density is unaffected by the LC-specific pTau.*
- *No evidence of pTau in the PFC or hippocampus.*

pTau drives anxiety-like behaviors, reduces sleep spindles, and provokes LC hyperactivity

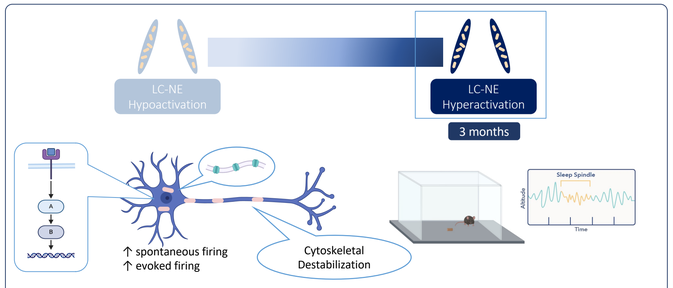


Experiment	Tau vs EYFP	Interpretation
Novelty-suppressed feeding	↑ *Latency to feed*	*Anxiety-like behavior*
Nestlet Shredding	↑ *Shredding*	*Compulsive-like behavior*
Fear Conditioning	*No change in freezing rates*	*Association memory intact*
Electrophysiology	↑ *Spontaneous firing rate* ↑ *Evoked spikes*	*Hyperactivity* *Hyperexcitability*

CIBOP for LC-NE proteome reveals modest changes in response to pathogenic tau



Conclusions: Working Model



- Developed a translationally-relevant mouse model that recapitulates tau pathology during early stages of AD.
- Expressing P364S human tau in the LC contributes to behavioral disturbances, implicating LC-NE hyperactivity in mediating symptoms relevant to AD.

Next steps & Future Directions

- Employ fiber photometry in the LC and key projection regions to assess if excessive LC-NE release accompanies electrophysiological hyperactivity and anxiogenic behaviors in real-time.
- Validation of pTau-associated molecular changes identified through the omics analyses (i.e., Hcn2, Clic6 or those involved in metabolism and proteostasis)
- For more information, please refer to the Biorxiv preprint:

Relevant References

- Korukonda, A., Weinshenker, D. (2026). A new hope: locus coeruleus-norepinephrine system at the nexus of neuropsychiatric symptoms. *Mol Psychiatry*, https://doi.org/10.1038/s41380-026-03696-z.
- Chalermpalanupap, T. et al. (2018). Locus Coeruleus Ablation Exacerbates Cognitive Deficits, Neuropathology, and Lethality in P301S Tau Transgenic Mice. *The Journal of neuroscience*, *38*(1), 74–92.
- Kelberman, M.A. et al. (2023). Age-dependent dysregulation of locus coeruleus firing in a transgenic rat model of Alzheimer's disease. *Neurobiology of aging*, 125, 98–108.
- Braak, H. et al. (2011). Stages of the Pathologic Process in Alzheimer Disease: Age Categories From 1 to 100 Years, *Journal of Neuropathology & Experimental Neurology*, *70*(11), 960–969.
- Weinshenker D. (2018). Long Road to Ruin: Noradrenergic Dysfunction in Neurodegenerative Disease. *Trends in Neurosciences*, *41*(4), 211–223.
- Cassidy, C.M. et al. (2022). Association of locus coeruleus integrity with Braak stage and neuropsychiatric symptom severity in Alzheimer's disease. *Neuropsychopharmacology,* 47, 1128–1136.

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