

Can we untangle the molecular origins of Tau pathology using spatial transcriptomics?

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- 5HT/glut neurons of the DRN differentially express ion-channel genes in hTau mice and in post-mortem AD. hTau 5HT/glut neurons are more excitable, which increases pTau accumulation, and may drive deficits in social interaction behaviors. In parallel, human 5HT/glut neurons are especially vulnerable to tau pathology.
- Which comes first, pTau or changes in gene expression? Future studies combining spatial transcriptomics, ephys, and purpose-built *de novo* animal models will answer this question.

**Introduction**

Persons with Alzheimer’s disease (AD) exhibit social withdrawal and changes in mood prior to cognitive decline. These may be driven by pathological changes in the serotonergic (5-HT) nuclei, particularly the dorsal raphe nucleus (DRN). Using Visium Spatial Gene Expression, we previously determined that the DRN of hTau mice (transgenic model for early AD, Khan 2023) differentially expresses ion-channel genes (Kolling 2025), which regulate the electrical activity of neurons. Hyper-phosphorylated Tau (pTau) disrupts neuronal excitability, which may exacerbate its spread.

References

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