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Analysis of molecular characteristics linked with P301S tauopathy in the Locus Coeruleus by single-cell and single-nucleus transcriptomic profiling

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Circadian disruption has been associated with the onset and progression of various neurodegenerative diseases, including Frontotemporal Dementia (FTD). Tauopathy is a pathological condition characterized by the aggregation of abnormally hyperphosphorylated tau protein. In MAPT mutation–based FTD models, tau accumulation in the locus coeruleus (LC) precedes cortical pathology, highlighting the LC as a key region to study tauopathy.

In this study, we used the P301S Tau transgenic mouse model, which expresses the pathogenic MAPT P301S mutation identified in FTD patients, to examine circadian phase (day/night)-dependent molecular changes associated with tau pathology in the LC. We performed single-cell RNA sequencing (scRNA-seq) and single-nucleus RNA sequencing (snRNA-seq) on LC-enriched brain regions from three-month-old and six-month-old P301S mice, ages that reflect early and advanced tau pathology.

In total, 171,014 cells were captured by scRNA-seq and 34,498 by snRNA-seq. After doublet removal and quality filtering, 38,043 cells from scRNA-seq and 25,348 cells from snRNA-seq were retained for analysis. Cell-type annotation revealed underrepresentation of neurons in 3-month-ScRNA seq data. At this stage, no major transcriptional differences were detected between control and P301STau mice. By six months, however, tau-associated oligodendrocyte clusters emerged showing circadian phase different transcriptional differences. To trace trajectory of oligodendrocyte dysfunction we integrated three- and six-month datasets. Anchoring-based SCTransform normalization followed by Harmony integration enabled robust alignment major glial and neuronal populations. Ongoing analyses are focused on identifying the altered biological processes and gene expression changes in oligodendrocytes that underlie the progression of tauopathy.