

## Description of Additional Supplementary Files

File name: Supplementary Dataset 1.

Description: Data tables of differential gene expression using the pseudobulking method for each of the following cell types: astrocytes, CA1-ProS Glut, CA3 Glut, CT/NP SUB Glut, DG Glut, microglia, oligodendrocytes, OPC, Sst/Pvalb Gaba, making the following comparisons: Tau 10 months vs. WT 10 months, Tau 20 months vs. WT 20 months, Tau 20 months vs. Tau 10 months, WT 20 months vs. WT 10 months. Differential expression was processed using DESeq2 using a pseudobulk approach (n=3 animals per group), and Benjamini and Hochberg method was used to generate p-adjusted values. The file name indicates the cell type and comparison groups (ex: de.10.tau.wt.astro.f.xlsx refers to the comparison between tau-10 and wt-10 in astrocytes, with tau-10 being the first group and wt-10 being the second group. A positive avg\_log2FC for a gene would indicate a higher expression in tau-10 in this example; de.20.10.tau.astro.f.xlsx compares tau-20 to tau-10, with a positive avg 2FC indicating a higher expression in tau-20).

File name: Supplementary Dataset 2.

Description: Data tables of differentially expressed gene expression using the NEBULA method (mixed-effect model) for each of the following cell types: astrocytes, CA1-ProS Glut, CA3 Glut, CT/NP SUB Glut, DG Glut, microglia, oligodendrocytes, OPC, Sst/Pvalb Gaba, making the following comparisons: Tau 10 months vs. WT 10 months, Tau 20 months vs. WT 20 months. Differential expression was processed using NEBULA using non-aggregated data grouped by sample ID. More information on the output values can be found on the NEUBLA user guide: <https://github.com/lhe17/nebula>. File names follow the same format as described in Supplementary Dataset 1.

File name: Supplementary Dataset 3.

Description: Data tables of differential gene expression using the Seurat default method for each of the following cell types: astrocytes, CA1-ProS Glut, CA3 Glut, CT/NP SUB Glut, DG Glut, microglia, oligodendrocytes, OPC, Sst/Pvalb Gaba, making the following comparisons: Tau 10 months vs. WT 10 months, Tau 20 months vs. WT 20 months, Tau 20 months vs. Tau 10 months, WT 20 months vs. WT 10 months. Differential expression was processed using non-aggregated data using the Wilcoxon Rank Sum test. Sample level

information is not used in this test. P values were adjusted by Bonferroni correction. File names follow the same format as described in Supplementary Dataset 1.

File name: Supplementary Dataset 4.

Description: Data tables of differential accessibility for each of the following cell types: astrocytes, CA1-ProS Glut, CA3 Glut, CT/NP SUB Glut, DG Glut, microglia, oligodendrocytes, OPC, Sst/Pvalb Gaba, making the following comparisons: Tau 10 months vs. WT 10 months, Tau 20 months vs. WT 20 months, Tau 20 months vs. Tau 10 months, WT 20 months vs. WT 10 months. Differential accessibility was processed using DESeq2 using a pseudobulk approach (n=3 animals per group), and Benjamini and Hochberg method was used to generate p-adjusted values. ClosestFeature function was applied to each peak to identify nearby genes. The file name indicates the cell type and comparison groups (ex: de.10.tau.wt.astro.xlsx refers to the comparison between tau-10 and wt-10 in astrocytes, with tau-10 being the first group and wt-10 being the second group. A positive avg\_log2FC for a gene would indicate higher accessibility in tau-10 in this example; da.20.10.tau.tau.astro.xlsx compares tau-20 to tau-10, with a positive avg\_2FC indicating a higher expression in tau-20).

File name: Supplementary Dataset 5.

Description: Full list of unique and overlapping significant DEG between Tau and WT in the longitudinal aging analysis, as shown in the Venn Diagrams in Supplementary Fig. 23. Comparisons were made between Tau 20-mo vs. Tau 10-mo and WT 20-mo vs. WT 10-mo, and the upregulated and downregulated genes that are specific to Tau, specific to WT, or in common are listed for each of the major cell types. The full DE tables, including log2fc and p-values, are found in Supplementary Dataset 3.

File name: Supplementary Dataset 6.

Description: Numerical source data for bar graphs for Figure 2, Figure 4, Supplementary Figure 14 and 21 are in the corresponding tabs.