

Sex and Life Experience Converge on Hippocampal Transcriptomic Responses in a Locus Coeruleus Pretangle Tau Model



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BACKGROUND & RATIONALE

Locus coeruleus (LC) neurons are among the earliest sites to develop pretangle tau pathology in humans. However, how life experiences interact with early LC tau pathology to influence Alzheimer's disease (AD) initiation and progression, and whether these effects differ between males and females, remains poorly understood. Using a rat model that recapitulates the human origin of pretangle tau by selectively expressing pseudophosphorylated tau in LC noradrenergic neurons of TH-Cre rats, we investigated how early- and late-life stress and environmental enrichment shape hippocampal transcriptomic responses, with the goal of identifying the earliest molecular events underlying AD pathogenesis.

MODEL & EXPERIMENTAL DESIGN

- Animal Model:** Pseudophosphorylated human tau (htauE14) was selectively expressed in LC noradrenergic neurons of male and female TH-Cre rats.
- Life-Course Interventions:** Rats were exposed to early-life stress (eSTR), early-life enrichment (eER), late-life enrichment (ISTR), late-life stress (IER), or standard housing conditions (cGFP and cE14).
- Transcriptomic Profiling:** Hippocampal single-nucleus RNA sequencing (snRNA-seq) was utilized to profile complex transcriptomic alterations.

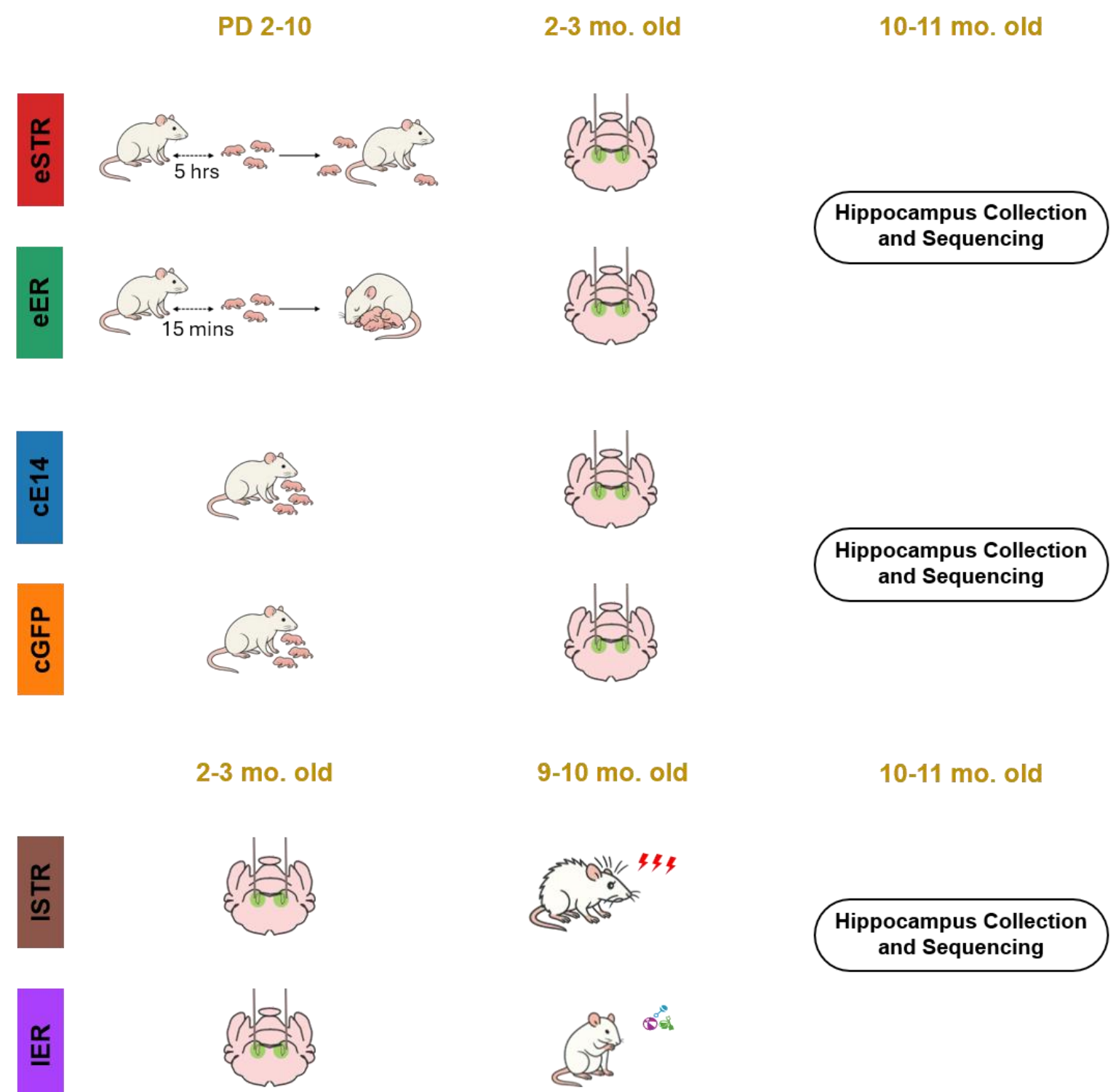
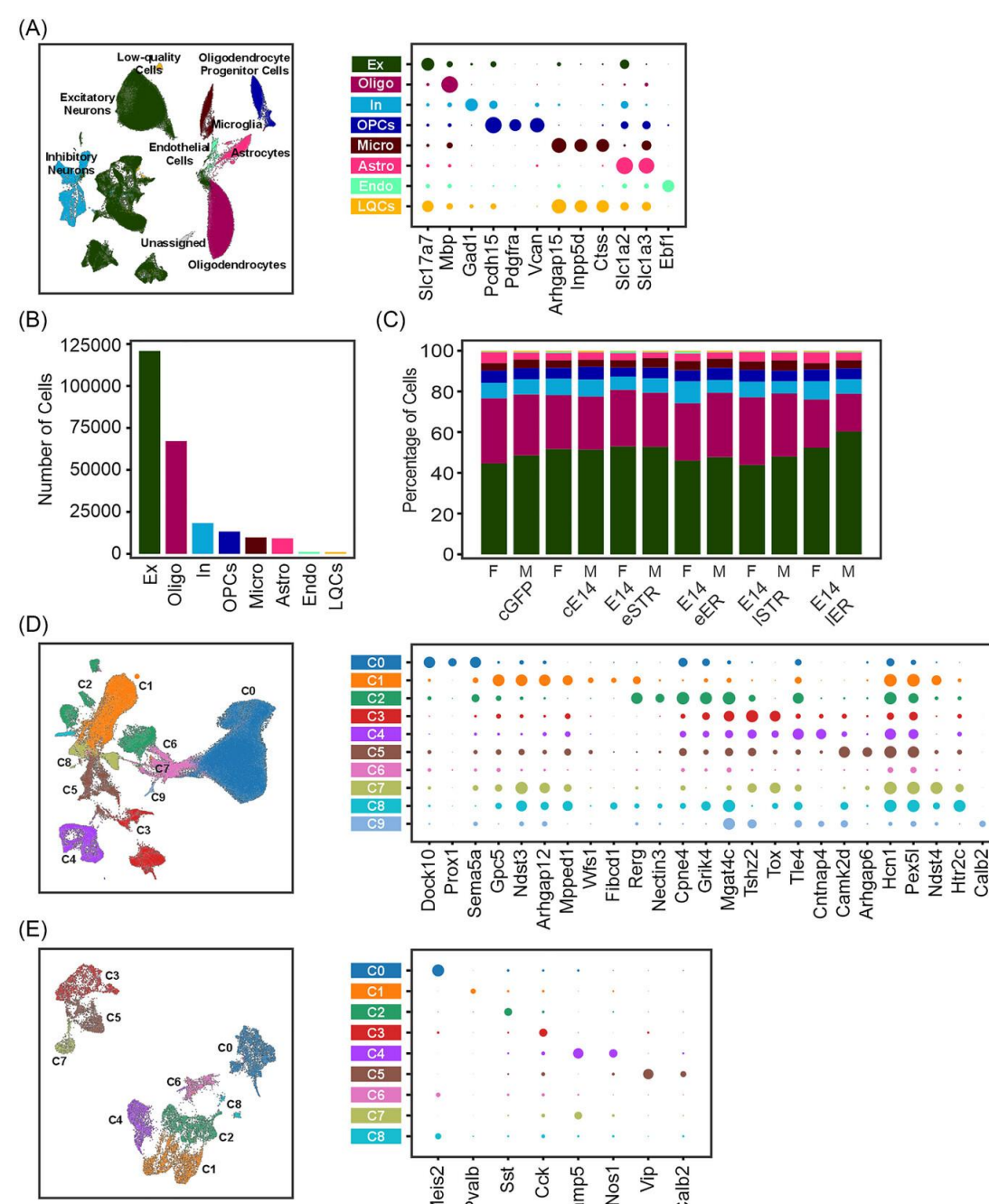


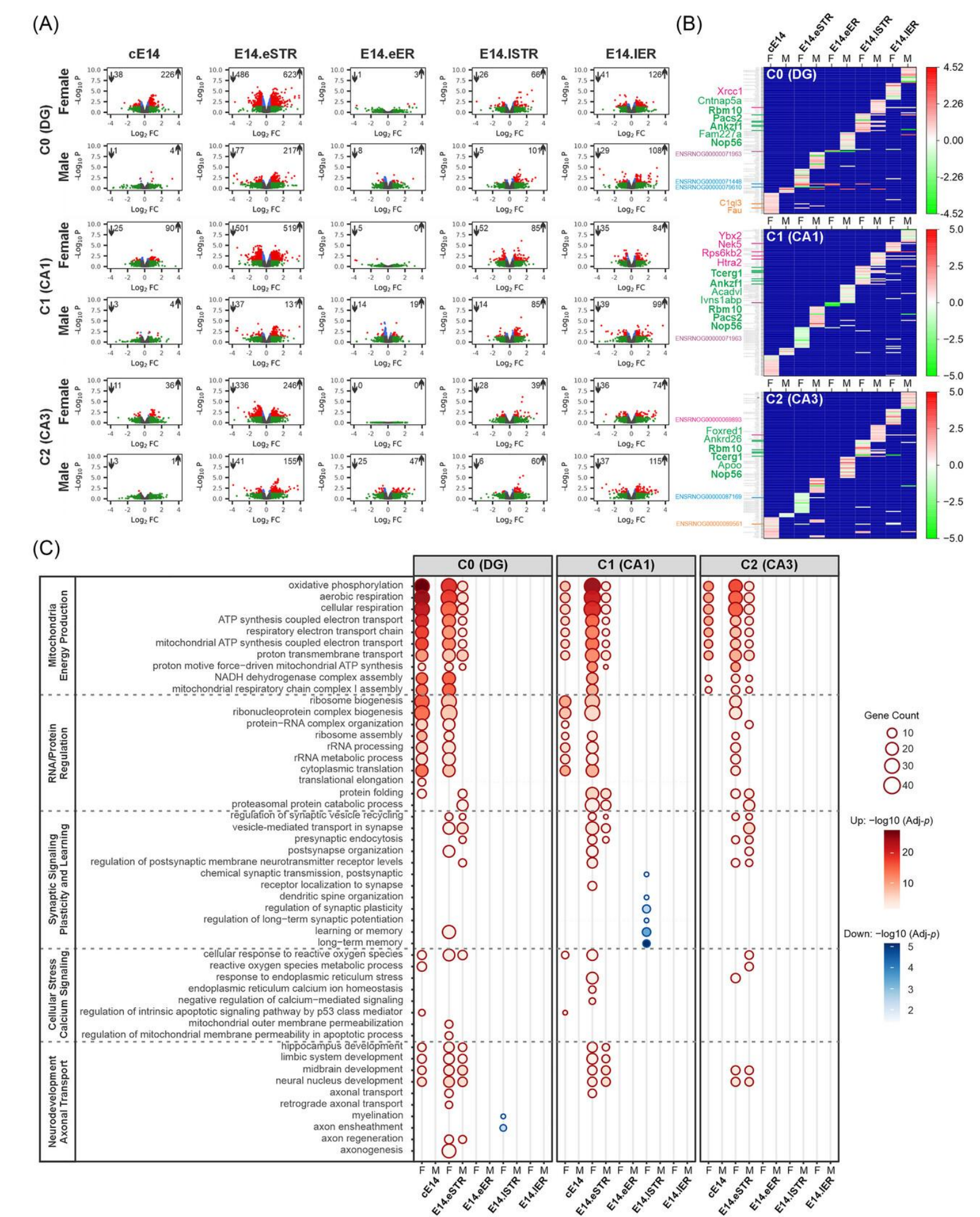
Figure 1. Environmental manipulation using stress and enrichment paradigms.

CELL TYPE ATLAS: HIPPOCAMPUS

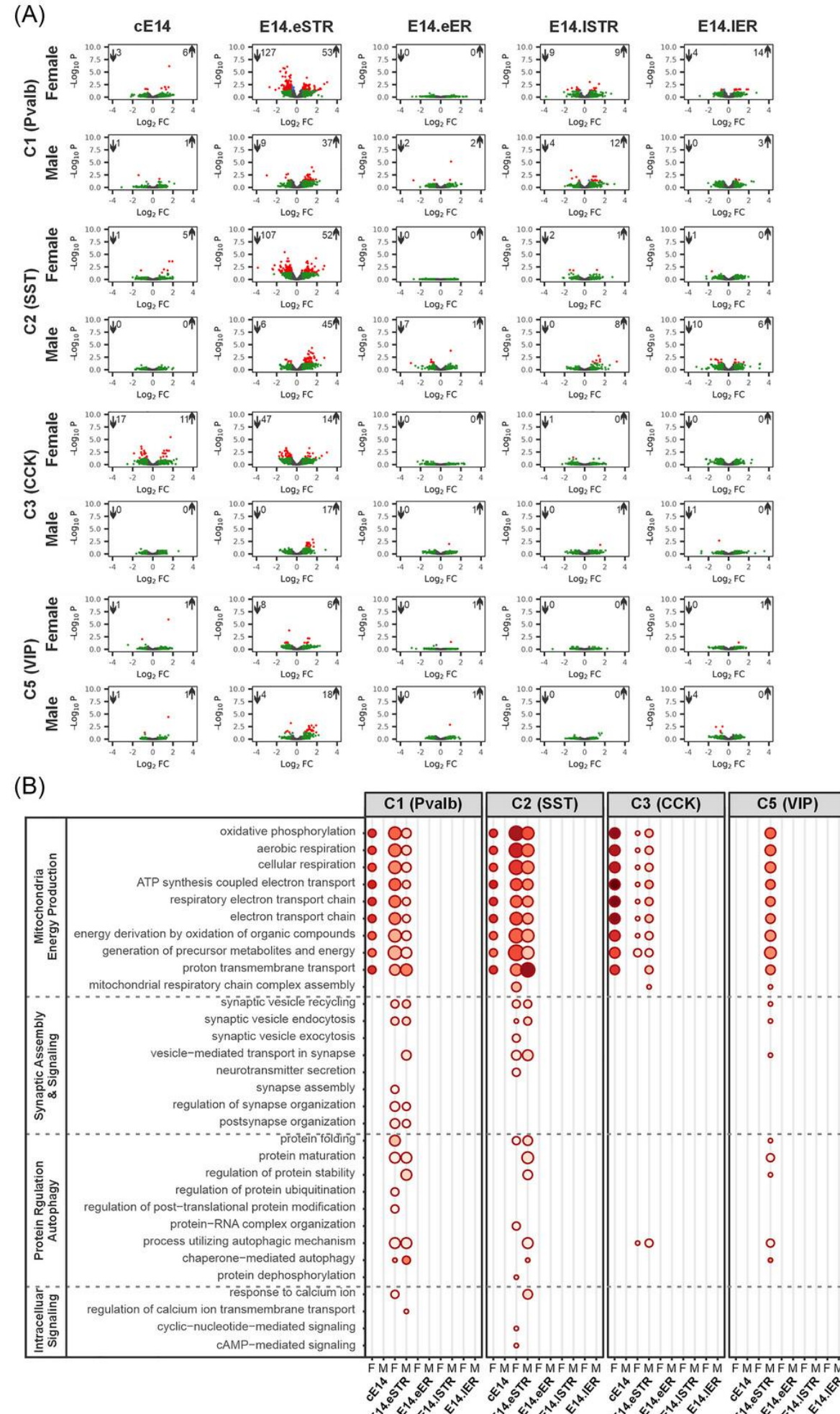


Figures 2. hippocampal cell types classification. (A) Clustering identified 7 major cell types (UMAP) based on marker expression (Dot plots). (B) Histogram shows nuclei counts per cell type. (C) Stacked bar plot displays cell-type proportions across groups. (D-E) UMAP and dot plots further identify 10 excitatory (Ex) and 9 inhibitory (In) neuronal subclusters.

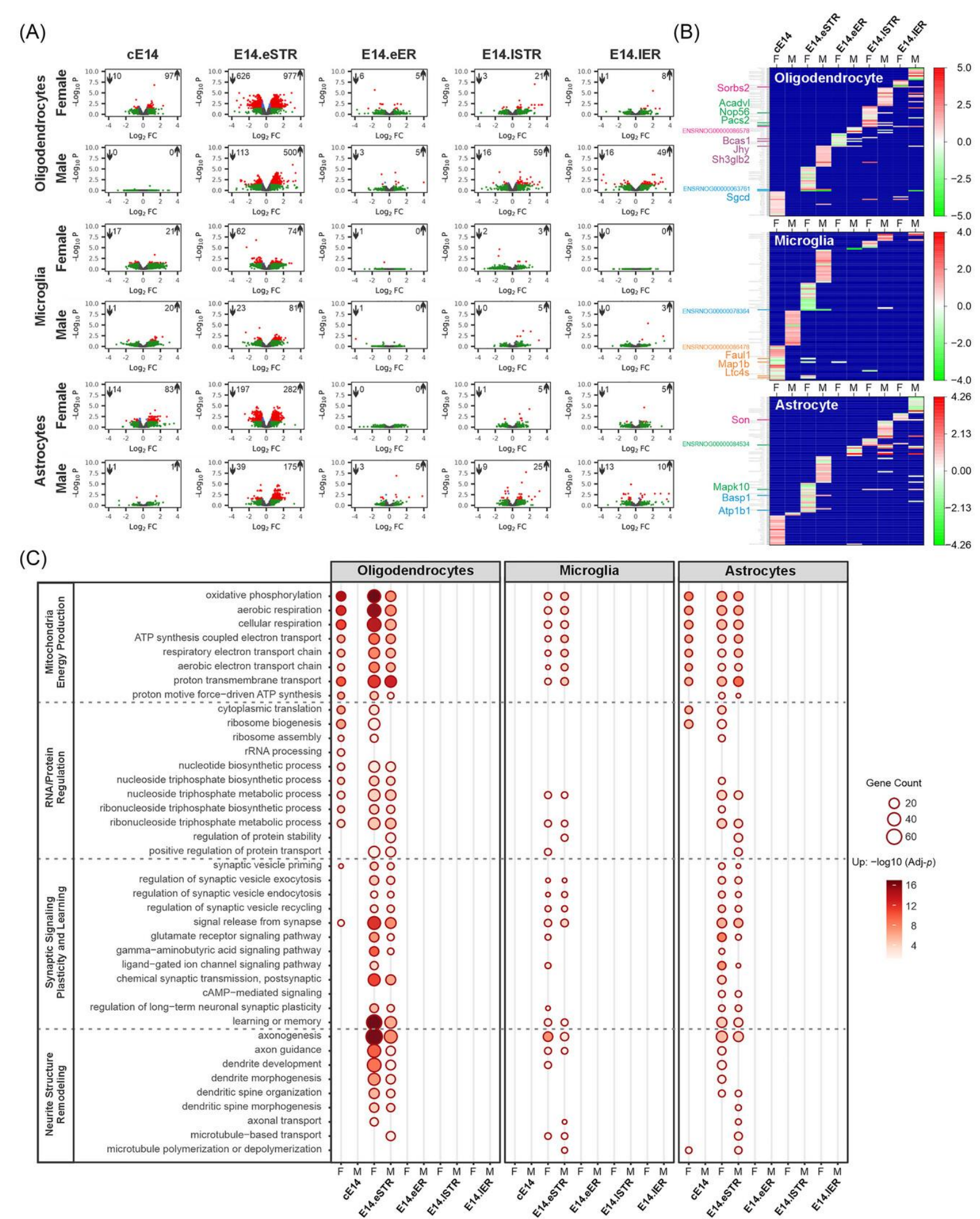
SEX- AND EXPERIENCE-DEPENDENT TRANSCRIPTOMIC REMODELING



Figures 3. Environmental effects on gene expression in excitatory neuron subtypes. (A) Volcano plots show DEGs in DG (C0), CA1 (C1), and CA3 (C2) neurons across 5 groups relative to cGFP. Red = significant (Adj-p < 0.05, |log2FC| > 0.5); blue = Adj-p < 0.05; green = non-significant. Arrows indicate up/downregulated gene counts. (B) Dot plots show the top GO terms enriched in DEGs from DG (C0), CA1 (C1), and CA3 (C2).



Figures 4. Environmental effects on gene expression in inhibitory neuron subtypes. (A) Volcano plots show DEGs in Pvalb (C1), SST (C2), CCK (C3) and VIP (C5) neurons across 5 groups relative to cGFP. (B) Dot plots show the top GO terms enriched in DEGs for each subtype.



Figures 5. Environmental effects on gene expression in non-neuronal cell types. (A) Volcano plots show DEGs in oligodendrocytes, microglia, and astrocytes across 5 groups relative to cGFP. (B) Dot plots show the top GO terms enriched in DEGs for each cell type.

KEY FINDINGS

- Cell-Type Specificity:** Hippocampal snRNA-seq revealed highly distinct, sex- and cell-type-specific transcriptional responses to distant LC tau pathology.
- Sex-Specific effects:** htauE14 induced robust transcriptional changes in the DG, CA1, and CA3 of females, preferentially affecting metabolic and synaptic pathways, whereas males showed mild transcriptomic alterations.
- Early-Life Modulation:** Environmental exposures drove distinct transcriptomic signatures. The transcriptional effects of tau pathology were amplified by early stress but stabilized by early enrichment. Specifically, early stress further disrupted mitochondrial and synaptic programs, whereas early enrichment conferred transcriptional stability.
- Late-Life Modulation:** In contrast, late-life experiences primarily recruited homeostatic regulatory programs.

ACKNOWLEDGEMENTS



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