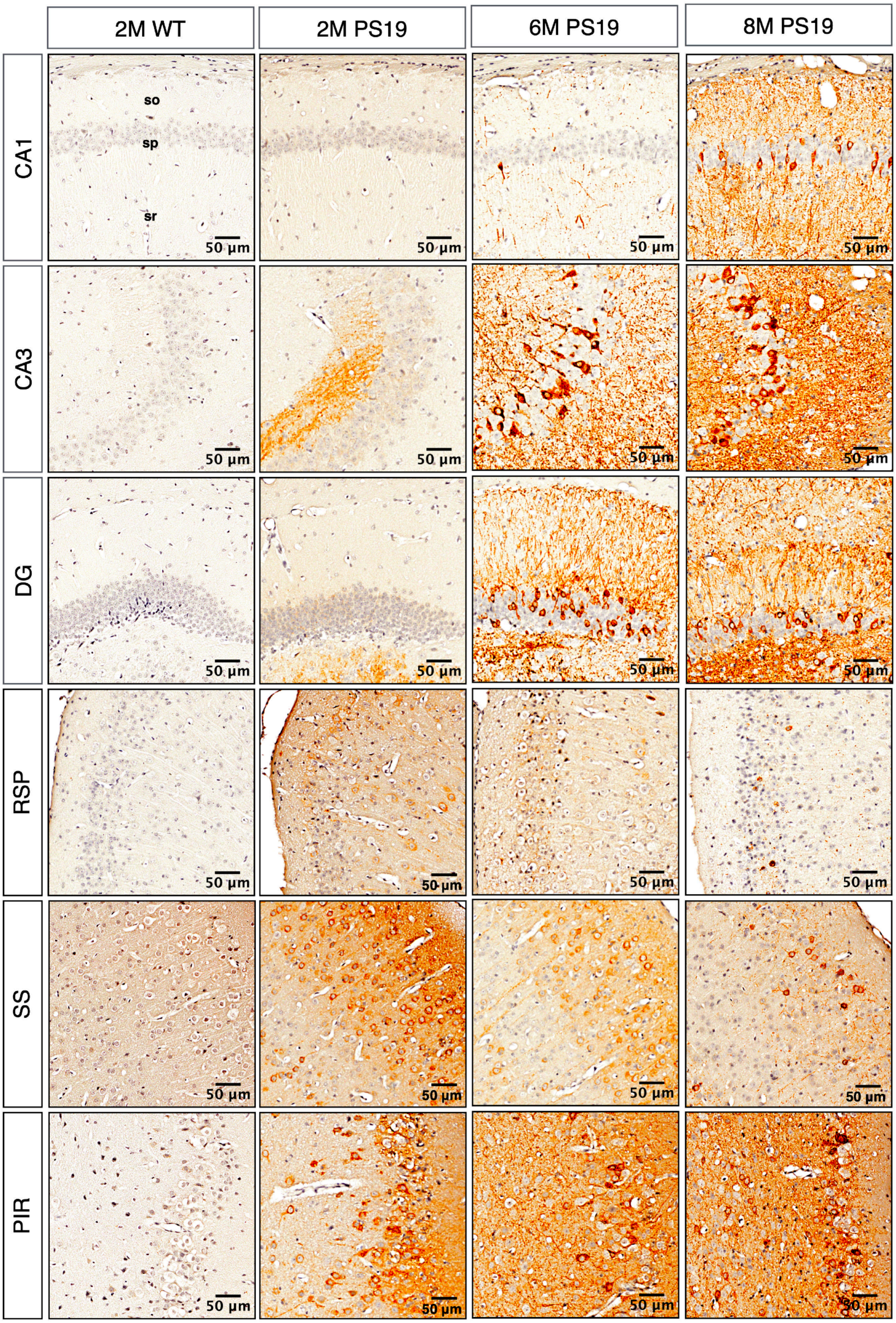
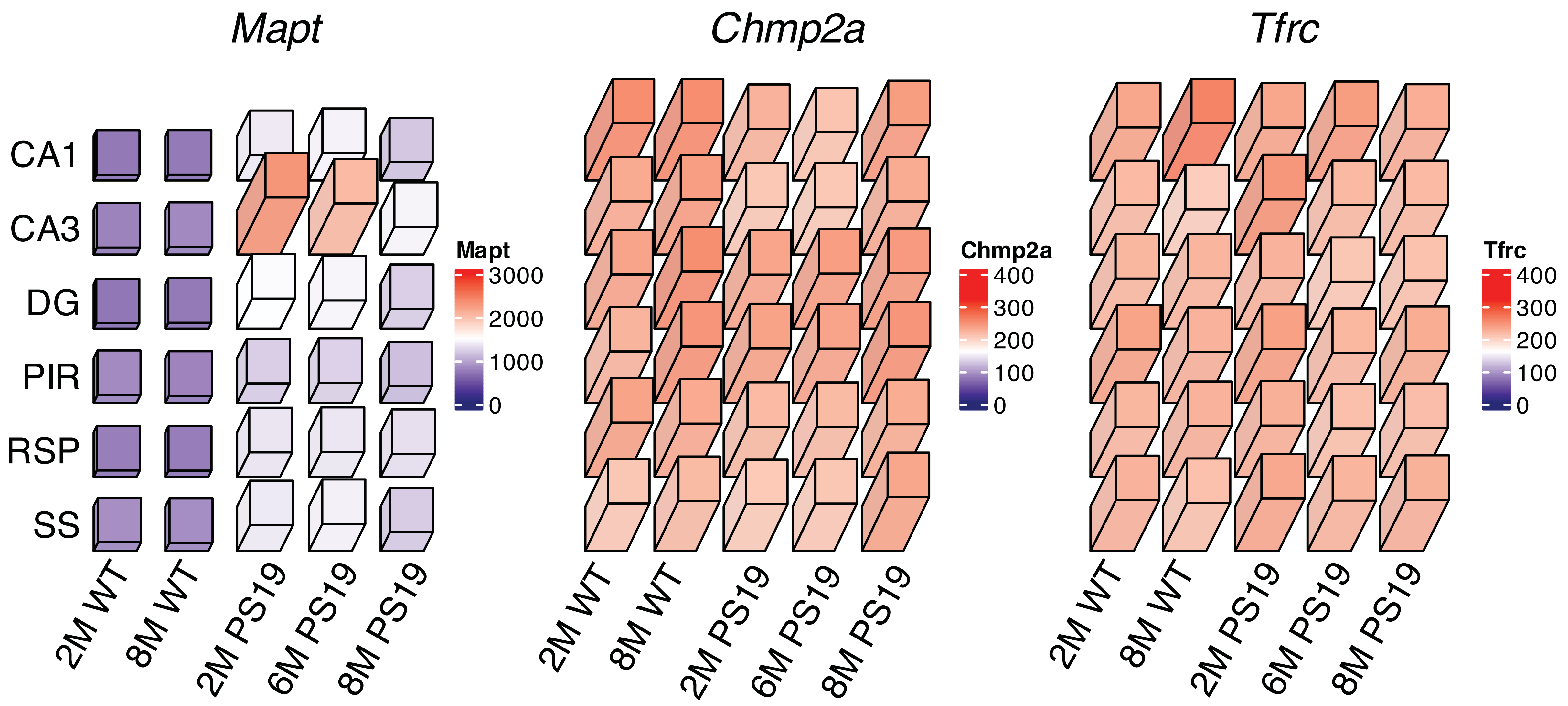
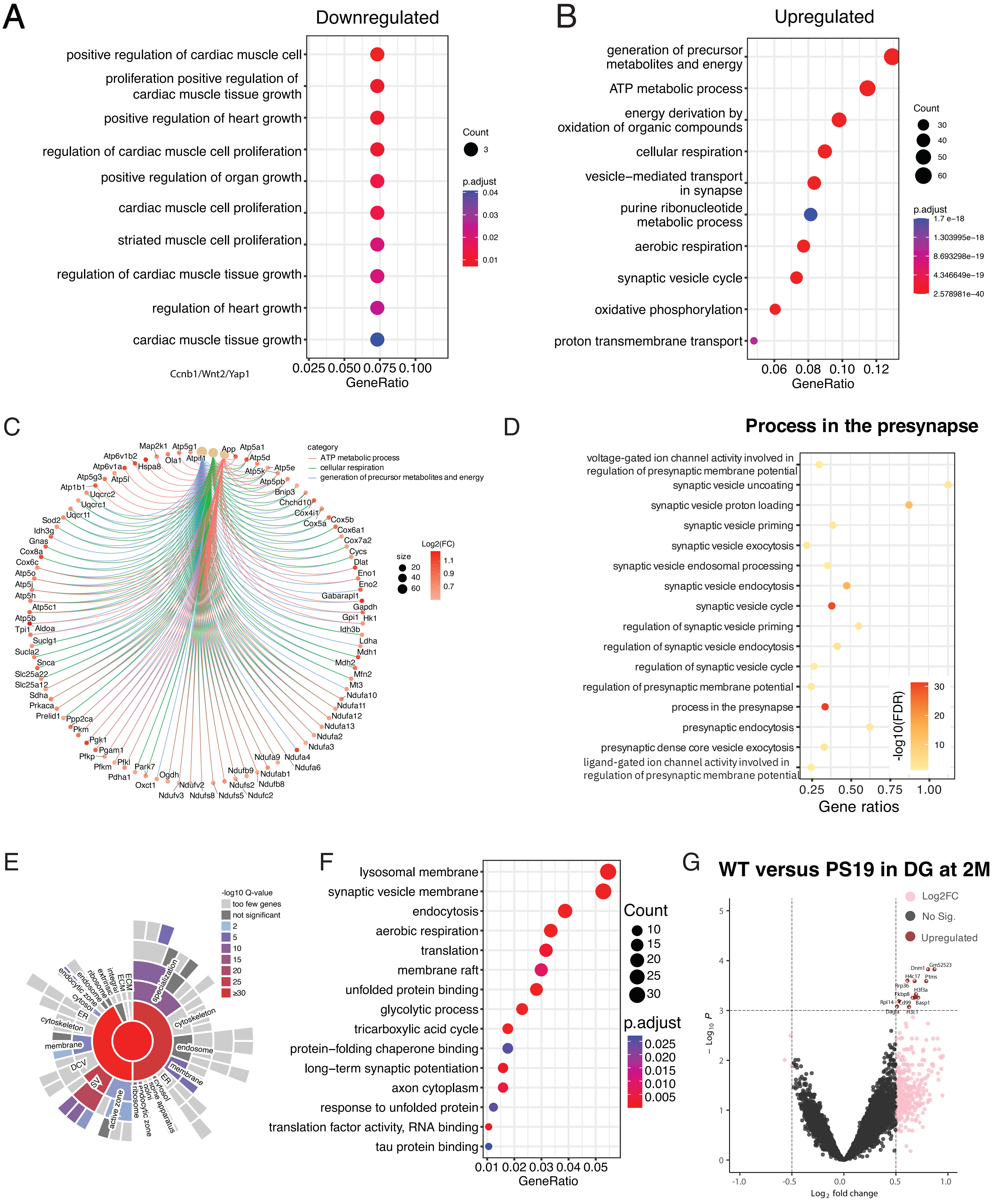


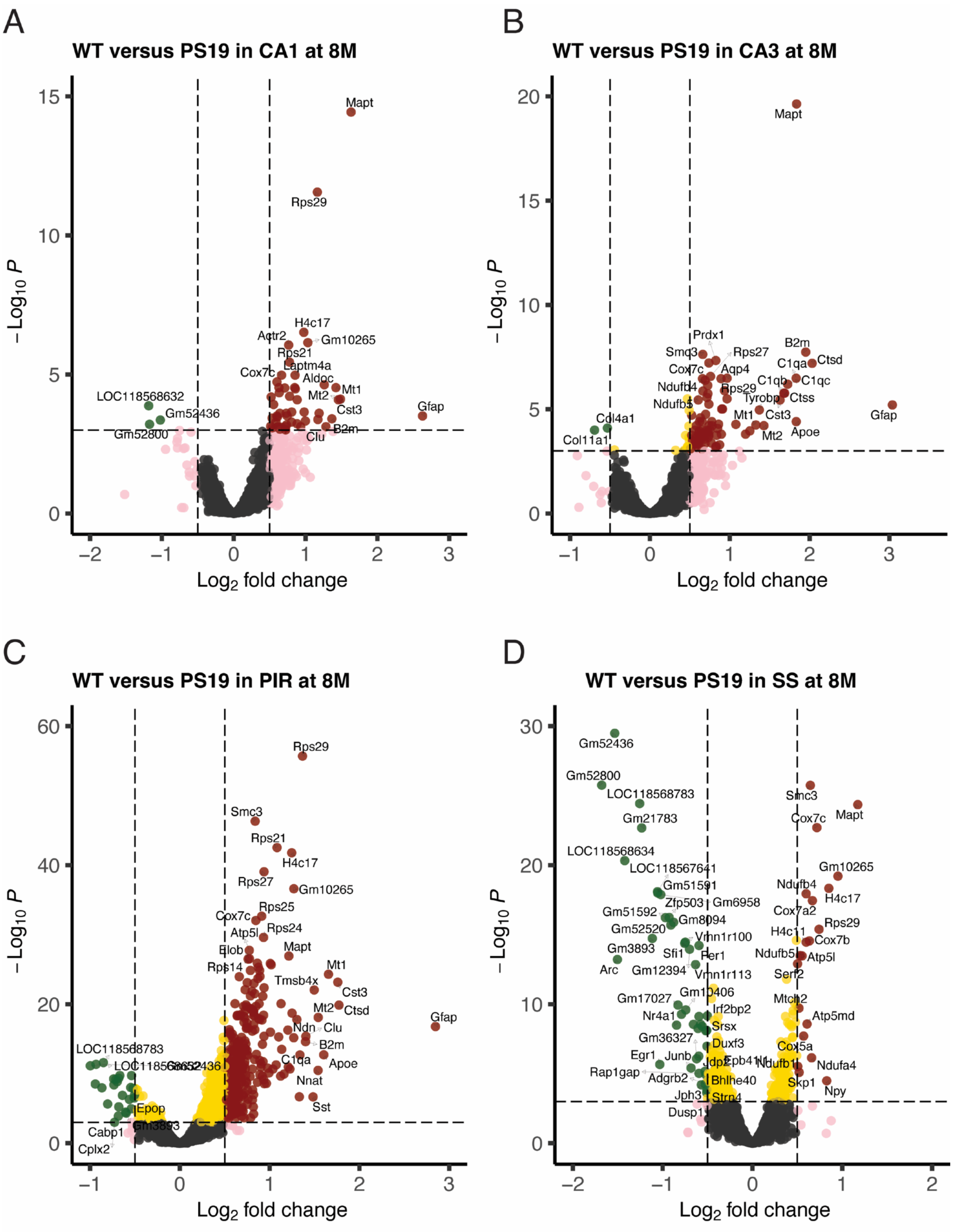
Supplementary Fig. 1: p-tau (pSer202/pThr205) levels by mAb AT8 staining. Immunohistochemical analysis of p-tau (pSer202/pThr205) levels in the male PS19 mice at 2, 6, and 8 months of age, analyzed by mAb AT8 staining. CA1, CA3, and DG from the hippocampus and RSP, SS, and PIR from the cortex. Scale bar, 500 µm.



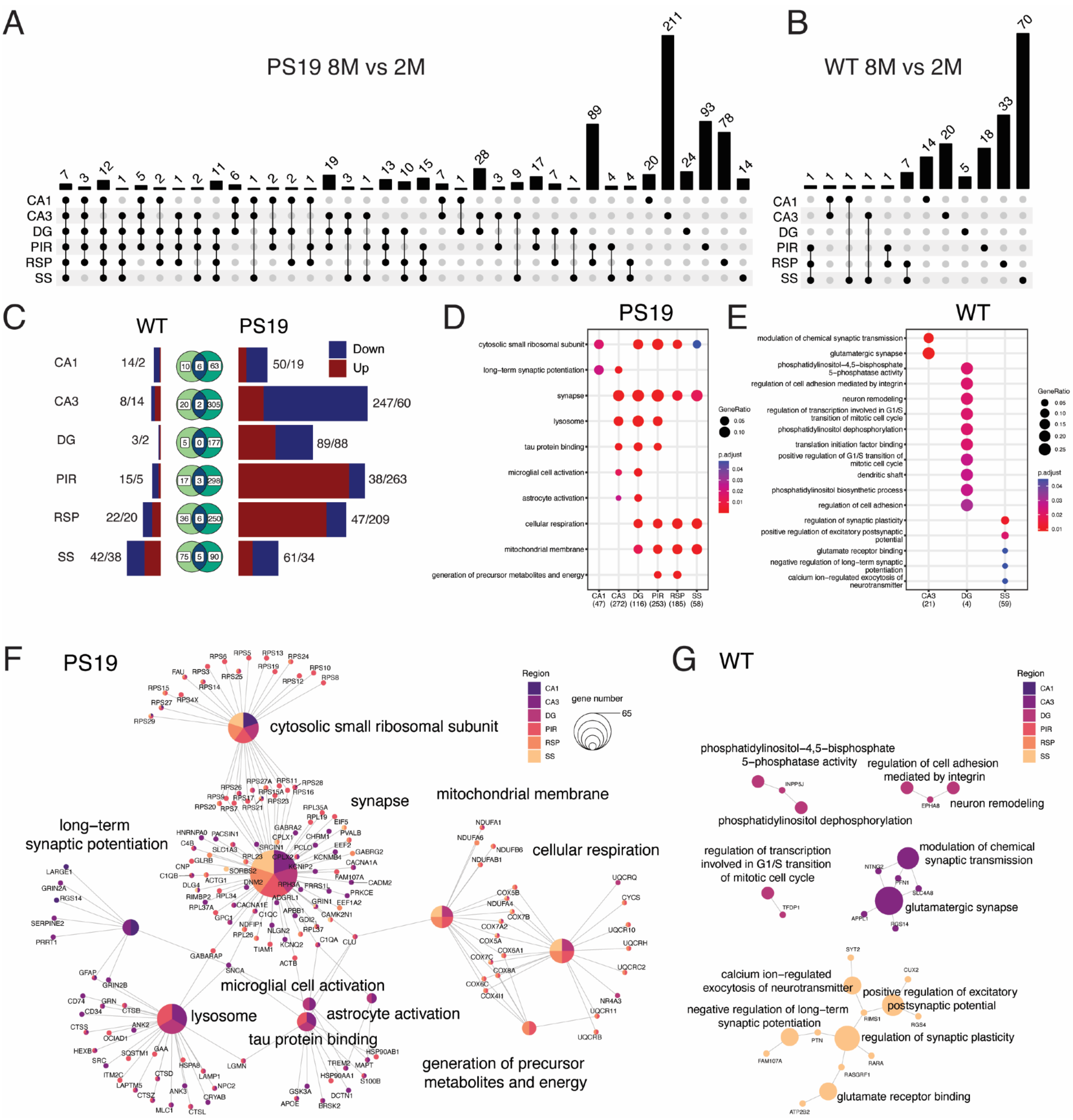
Supplementary Fig. 2: MAPT/*Mapt* mRNA levels. The normalized mRNA counts of MAPT/*Mapt* and housekeeping genes (*Chmp2a* and *Tfrc*) are shown as 3D heatmaps.



Supplementary Fig. 3: Transcriptomic changes in the hippocampus at 2 months of age. Functional annotation (GO biological processes) corresponding to downregulated (A) and upregulated DEGs (B) in the CA3 region of 2-month-old PS19 compared to WT mice. The gene count in each GO term is shown as the size of the circle. Red and blue colors indicate the *p* values. (C) Three gene sets of selected GO terms from upregulated DEGs in Fig. S2B. (D) SYNGO terms in Fig. 2E. (E) SYNGO (Synaptic Gene Ontologies) Cellular Component terms from the 658 DEGs in CA3 are illustrated in the sunburst plot. (F) The dot plot presents the top 15 terms from Fig. 2G. The size of the circle represents the gene count in each GO term. Red and blue colors indicate the adjusted *p* values. (G) Volcano plot depicting the differentially expressed genes between PS19 and WT in the DG region at 2 months of age. Color-coded symbols indicate the fold change and *p* values relative to the thresholds. Red: $p < 0.01$, and log2 (fold change) > 0.5; Pink: $p > 0.01$, and |log2 (fold change) | > 1; $p > 0.01$, and | log2 (fold change) | < 0.5.



Supplementary Fig. 4: Transcriptomic changes in the CA1, CA3, PIR, and SS regions at 8 months. The volcano plots illustrate the DEGs between PS19 and WT in CA1 (A), CA3 (B), PIR (C), and SS (D) at 8 months of age. Color-coded symbols indicate the fold change and p values relative to the thresholds. Green: $p < 0.01$, and log2 (fold change) < -0.5; Red: $p < 0.01$, and log2 (fold change) > 0.5; Pink: $p > 0.01$, and |log2 (fold change) | > 1; Gold: $p < 0.01$, and |log2 (fold change) | < 0.5; Grey: $p > 0.01$, and | log2 (fold change) | < 0.5.



Supplementary Fig. 5: Spatiotemporal transcriptomic signatures between 2-month-old *vs.* 8-month-old mice (A) The UpSet plot displays the DEGs between 2-month-old and 8-month-old PS19 mice across all six regions sampled. (B) The UpSet plot illustrates the DEGs between 2-month-old and 8-month-old WT mice in all six regions. (C) The bar plots on the left and right sides depict the counts of up-regulated and down-regulated DEGs from the six regions of WT and PS19 mice, respectively. The Venn diagrams in the center shows the number of shared DEGs from aging WT and PS19 animals for each region. (D) The dot heatmap represents the gene ontology analysis results for the DEGs between 2-month-old and 8-month-old PS19 mice across all six regions. The gene ratio in each GO term is indicated by the size of the circle. Red and blue colors represent the *p* values. (E) The dot heatmap represents the gene ontology analysis results for the DEGs between 2-month-old and 8-month-old WT mice in the CA3, DG, and SS regions. The gene ratio in each GO term is indicated by the size of the circle. Red and blue colors represent the *p* values. (F) Gene network visualization for the GO results on DEGs from aging PS19. The colors of the center node indicate the regions where the enriched pathway terms appeared, and the node size represents the number of genes associated with the term. (G) Gene network visualization for the GO results on DEGs from aging WT.