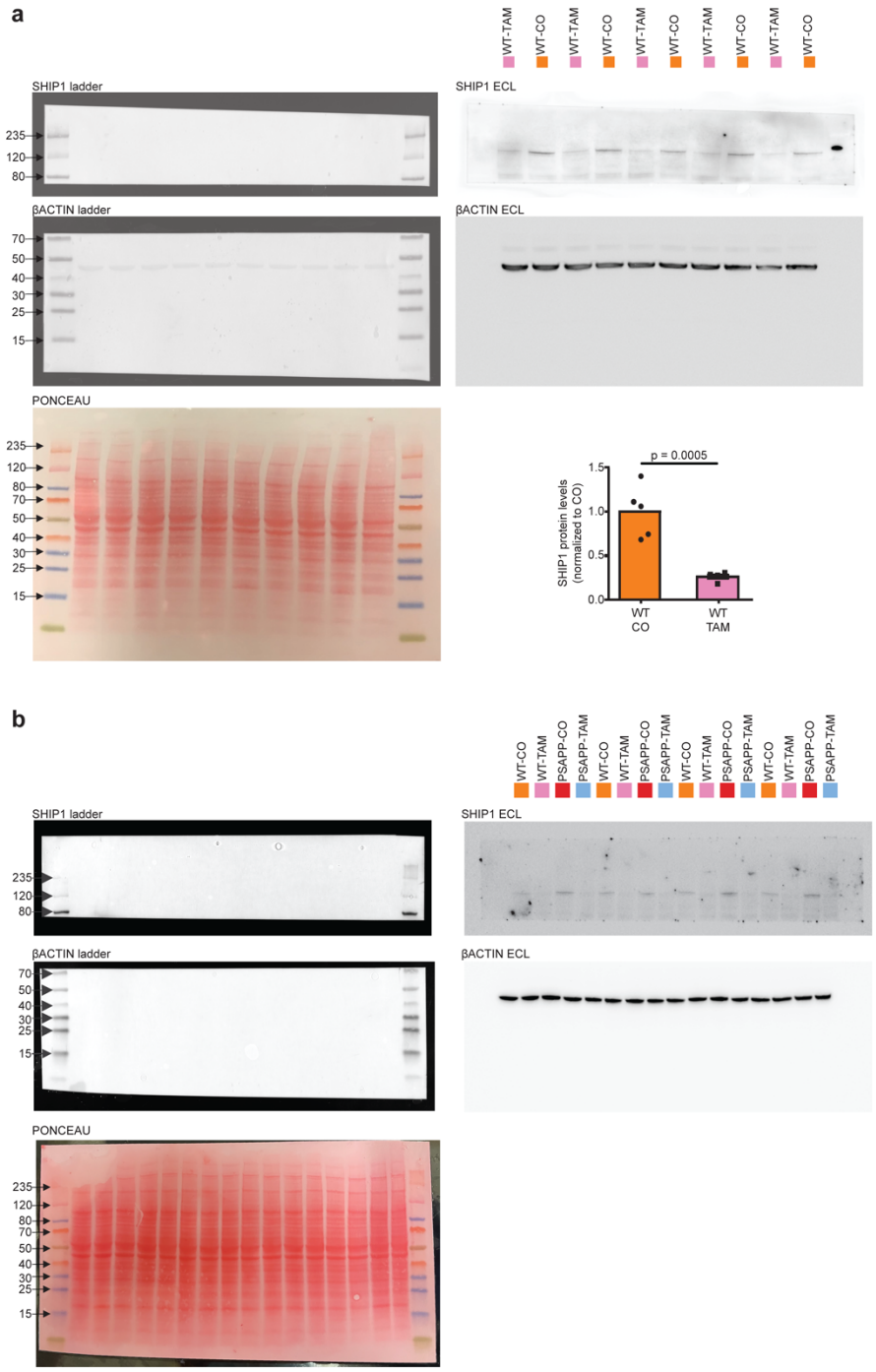
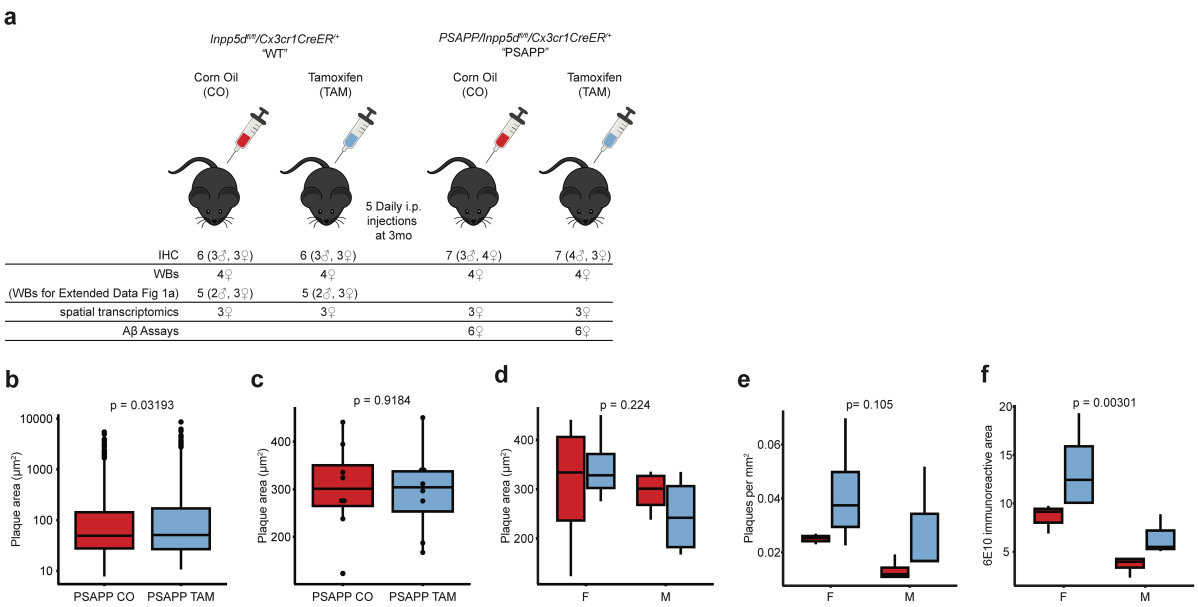
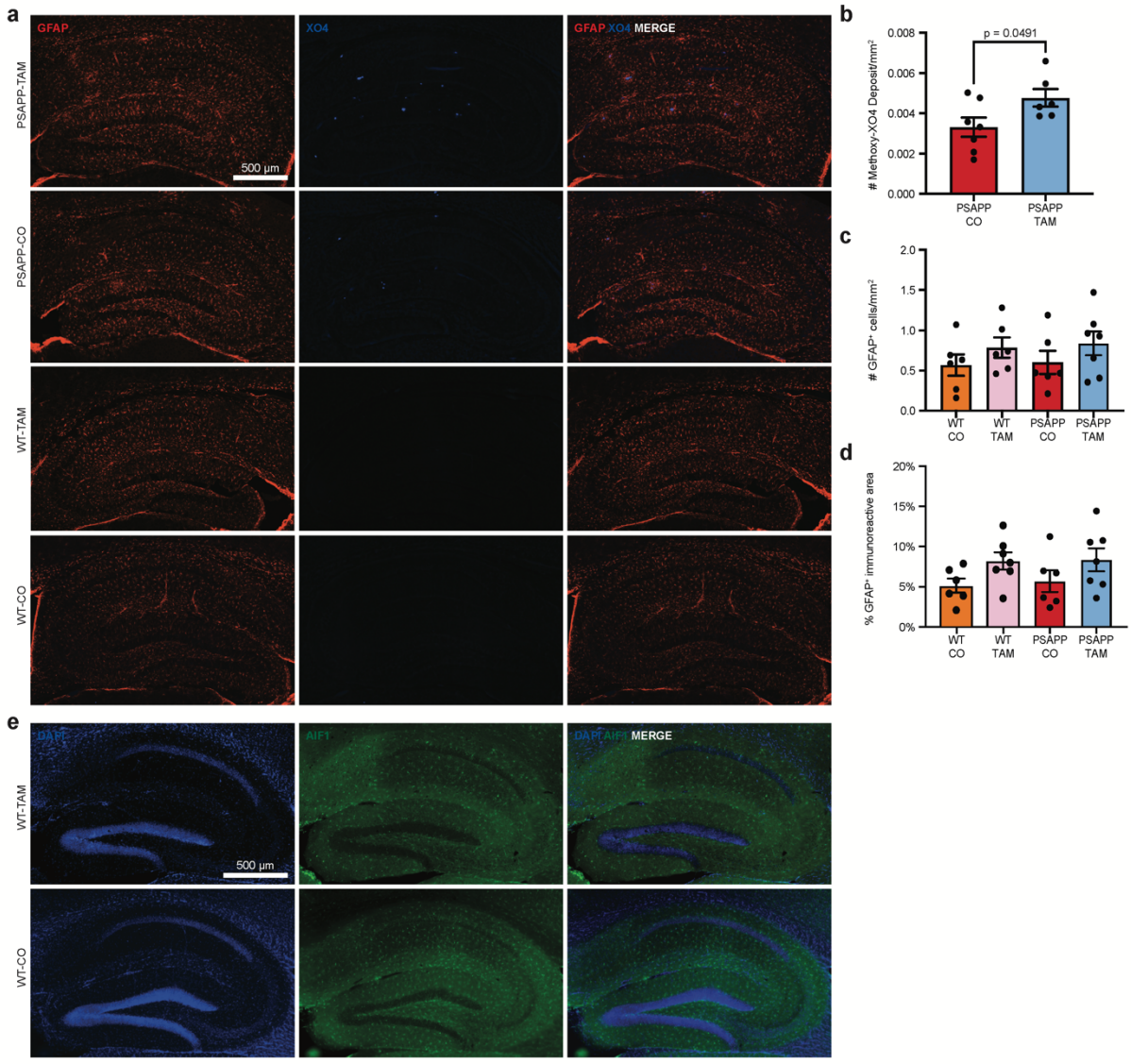


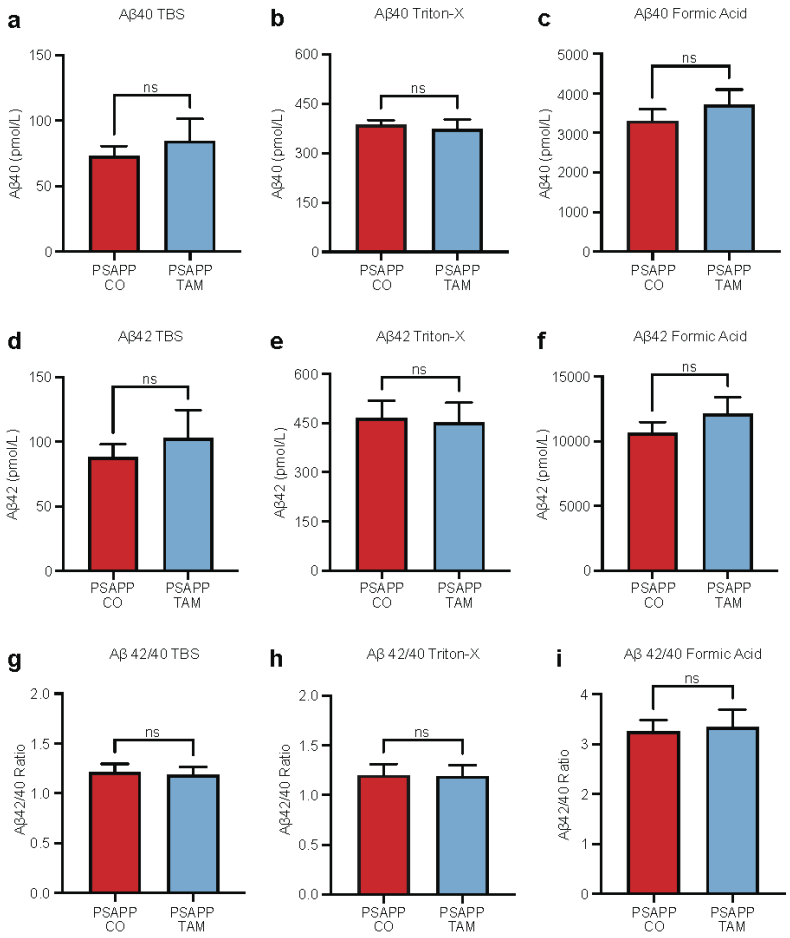
Supplementary Fig. 1. Full western blot images for anti-SHIP1 and anti-β-actin and Ponceau S from animals at (**a**) 4 months of age, i.e. 1 month after tamoxifen administration and (**b**) 6.5 months of age associated with Fig. 1b-c.



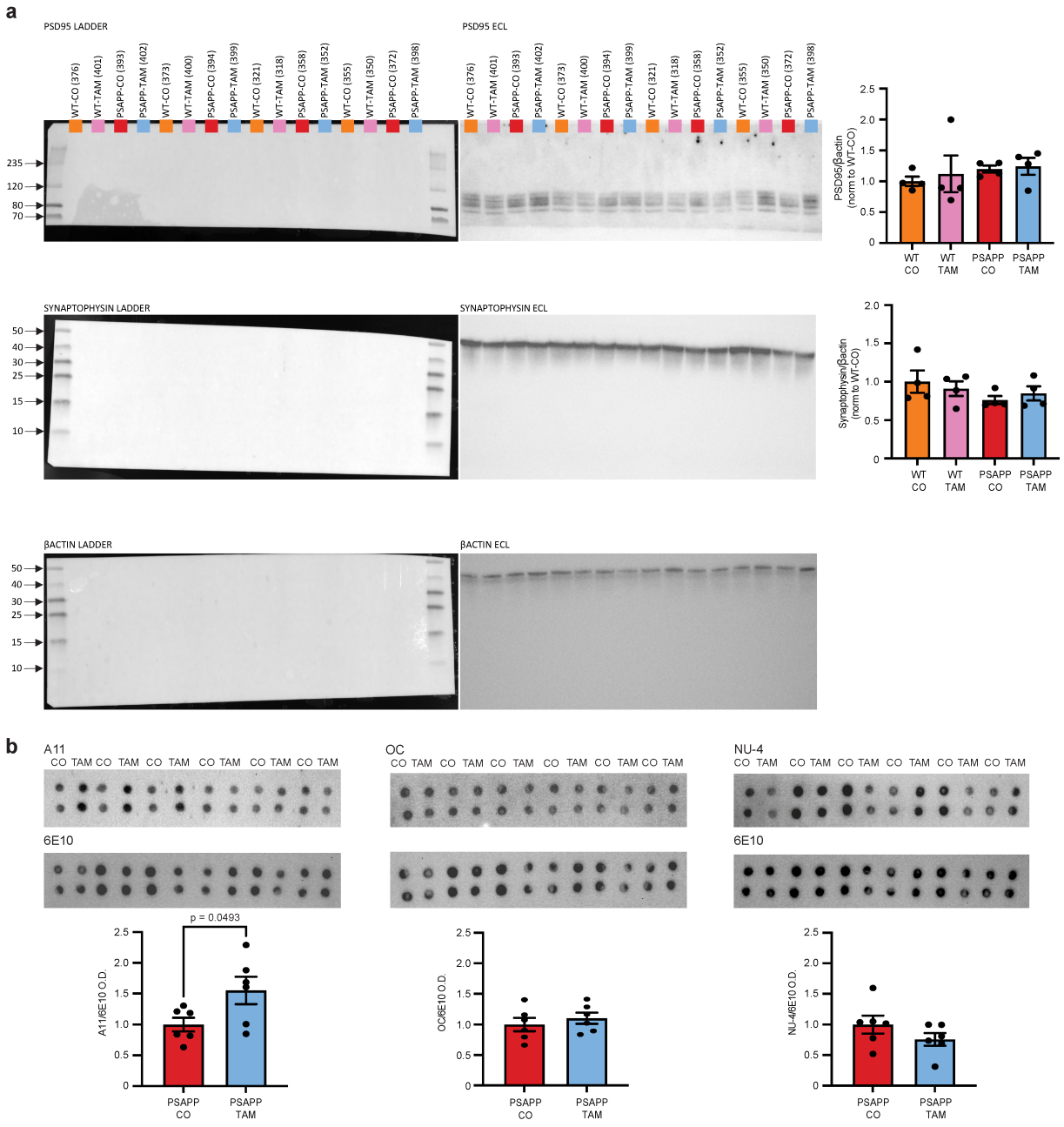
Supplementary Fig. 2. a) Top: Schematic showing the animal models used for microglia-specific ablation of *Inpp5d* and corn oil vs tamoxifen conditions. Bottom: Table of animal numbers and sex used across the different experiments. **b)** Plaque area (μm^2) of PSAPP-CO and PSAPP-TAM mice from 8 animals per group shown for each plaque (1077 plaques in PSAPP-CO and 1306 plaques in PSAPP-TAM; center line represents the median, dots represent outliers). **c)** Similar to (**a**) but summarized for each animal (n=8 animals per group, dots represent animals). **d)** Plaque area (μm^2) of PSAPP-CO and PSAPP-TAM mice from 8 animals per group split by sex (n=4 PSAPP-CO female, n=4 PSAPP-CO male, n=4 PSAPP-TAM female, n=4 PSAPP-TAM male). **e)** Number of plaques per mm^2 of PSAPP-CO and PSAPP-TAM mice split by sex (n=3 PSAPP-CO female, n=4 PSAPP-CO male, n=4 PSAPP-TAM female, n=3 PSAPP-TAM male). **f)** 6E10 immunoreactive area (6E10+ area (μm^2) per area of hippocampus (mm^2) of PSAPP-CO and PSAPP-TAM mice split by sex (n=3 PSAPP-CO female, n=4 PSAPP-CO male, n=4 PSAPP-TAM female, n=3 PSAPP-TAM male). P-values were calculated as follows: for **b** and **c**, unpaired t-tests; for **d-f**, one-way ANOVA on the effect of sex on plaque size.



Supplementary Fig. 3. a) Representative images from 6 month old PSAPP-TAM, PSAPP-CO, WT-TAM and WT-CO mice stained with anti-GFAP (astrocytes, red) or XO4 (plaques, blue). Scale bar = 500 µm. **b)** Number of XO4-positive deposits in the hippocampus of male and female PSAPP-TAM and PSAPP-CO mice. **c)** Quantification of number of $GFAP^+$ astrocytes and **d)** area of $GFAP^+$ immunostaining in hippocampus from PSAPP-TAM, PSAPP-CO, WT-TAM and WT-CO mice (n = 7-8 mice per group). **e)** Representative images from 6 month old WT-TAM and WT-CO mice immunostained with 6E10 (amyloid, red) or anti-IBA1 (myeloid cells, green). Scale bar = 500 µm.

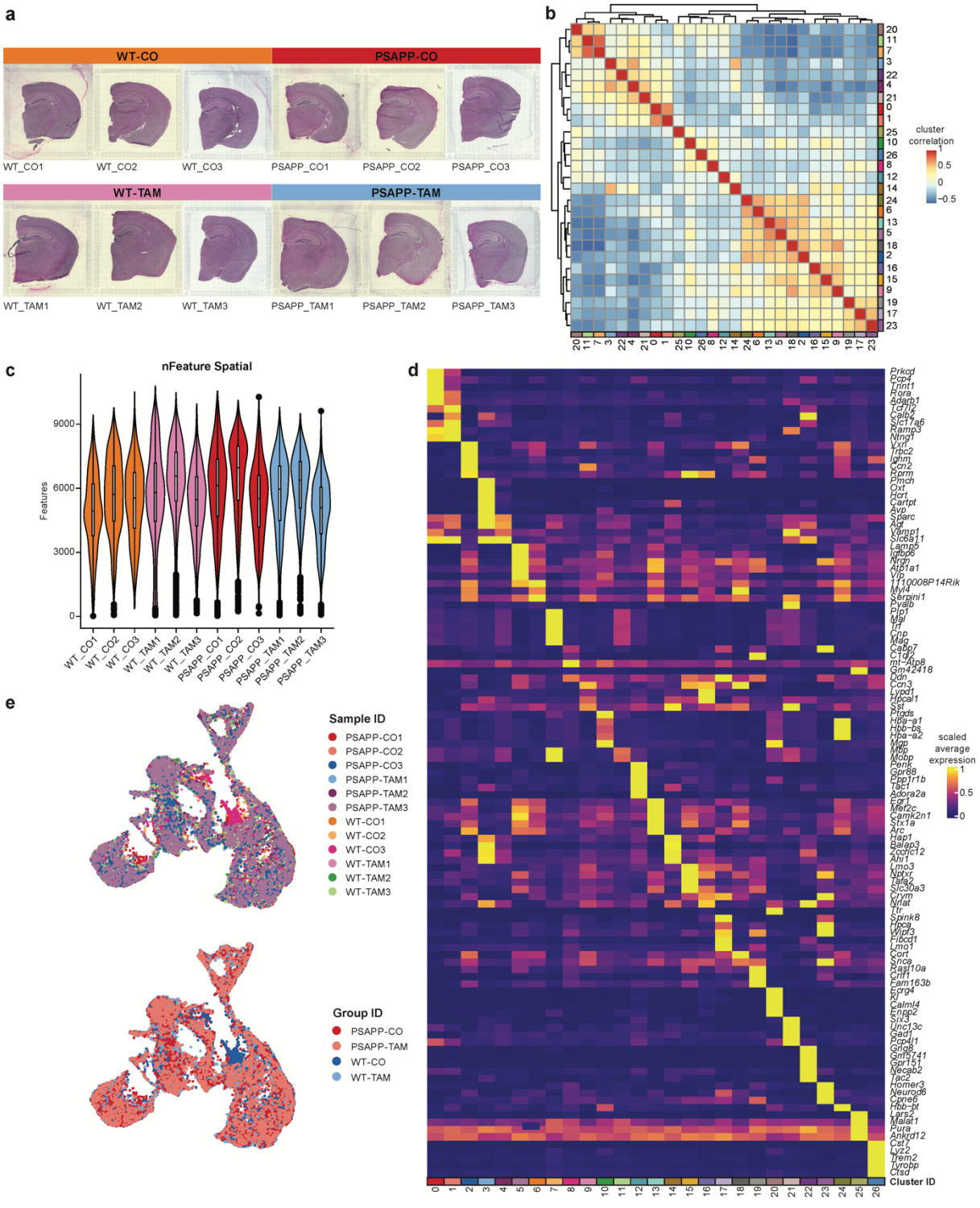


Supplementary Fig. 4. Tissues from hippocampus and posterior cortex from female PSAPP-CO and PSAPP-TAM mice were processed via serial extraction to produce fractions of TBS-, Triton-X and formic acid soluble Aβ. Levels of Aβ40 (**a-c**) and Aβ42 (**d-f**) were determined from each fraction via ELISA. The Aβ42/40 ratio was calculated for each fraction (**g-i**). n=6 per group. ns: not significant. Data presented as mean ± SEM. P-values for all were calculated using a t-test.



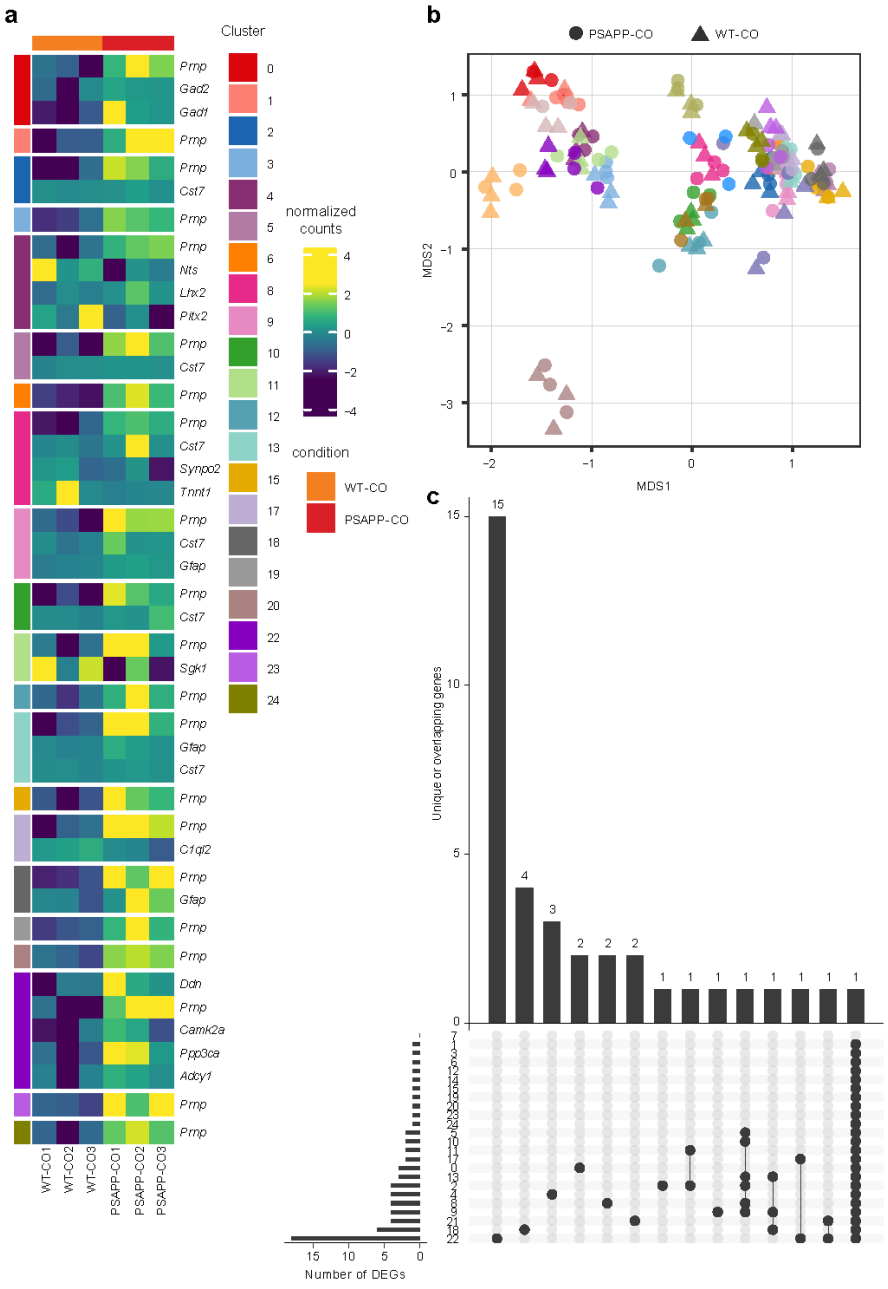
Supplementary Fig. 5. a) Western blot of hippocampal tissue from 6 month female WT-CO, WT-TAM, PSAPP-CO and PSAPP-TAM mice for synaptic markers PSD95 and synaptophysin normalized to β-actin. Quantification is shown at right. **b)** TBS-soluble fractions from PSAPP-CO and PSAPP-TAM mice were spotted for dot-immunobinding assays using conformational Aβ antibodies: anti-A11 for pre-fibrillar oligomers (left); anti-OC for fibrillar oligomers and fibrils (middle); and anti-NU-4 for oligomers (right). Blots were normalized to total Aβ-like

immunoreactivity using anti-APP/Aβ antibody 6E10. Quantification and results of statistical analysis are shown at the bottom of the panel. P-values for all were calculated using a t-test.

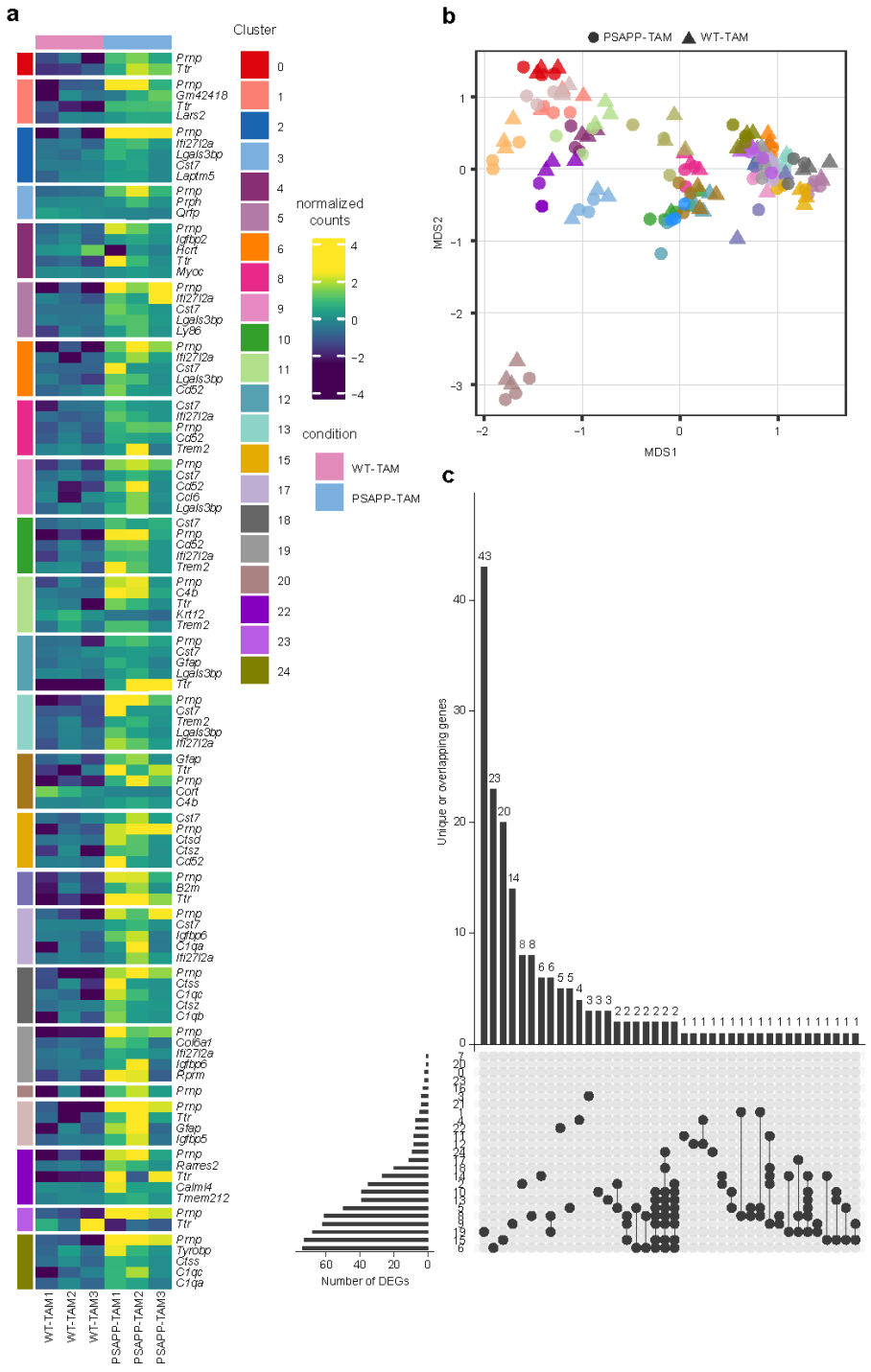


Supplementary Fig. 6. a) Hematoxylin and eosin (H&E) stain of the 12 brain sections used for Visium spatial transcriptomics. **b)** Correlation matrix as calculated with *CIDER* shows correlation

of transcriptomic cluster identities. **c)** Violin Plot showing the number of features per spot for each sample. **d)** Heatmap showing the average expression of the top 5 genes enriched within each cluster normalized to their maximal expression. **e)** UMAPs of the Visium spots grouped by sample ID (top) and group ID (bottom).

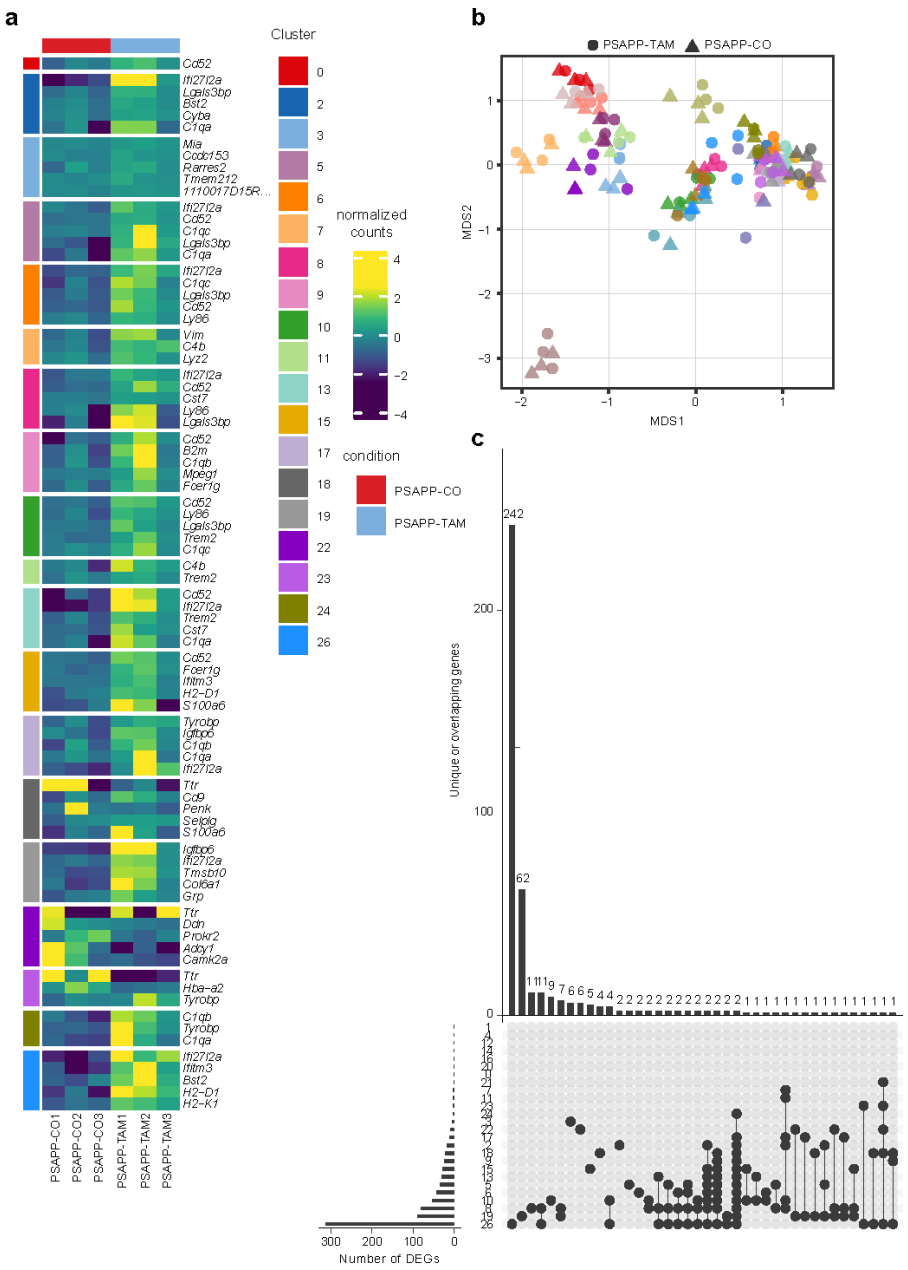


Supplementary Fig. 7. a) Heatmap showing cluster-resolved DEGs as calculated using *edgeR* on sum of counts within the *muscat* package when comparing WT-CO to PSAPP-CO. **b)** Multidimensional scaling (MDS) plot showing effect of PSAPP on gene expression across all clusters and all samples. **c)** UpSet plot showing unique and overlapping DEGs with l2f > |1|. Note that Cluster 26 is only present in PSAPP mice and is therefore excluded by *edgeR*.

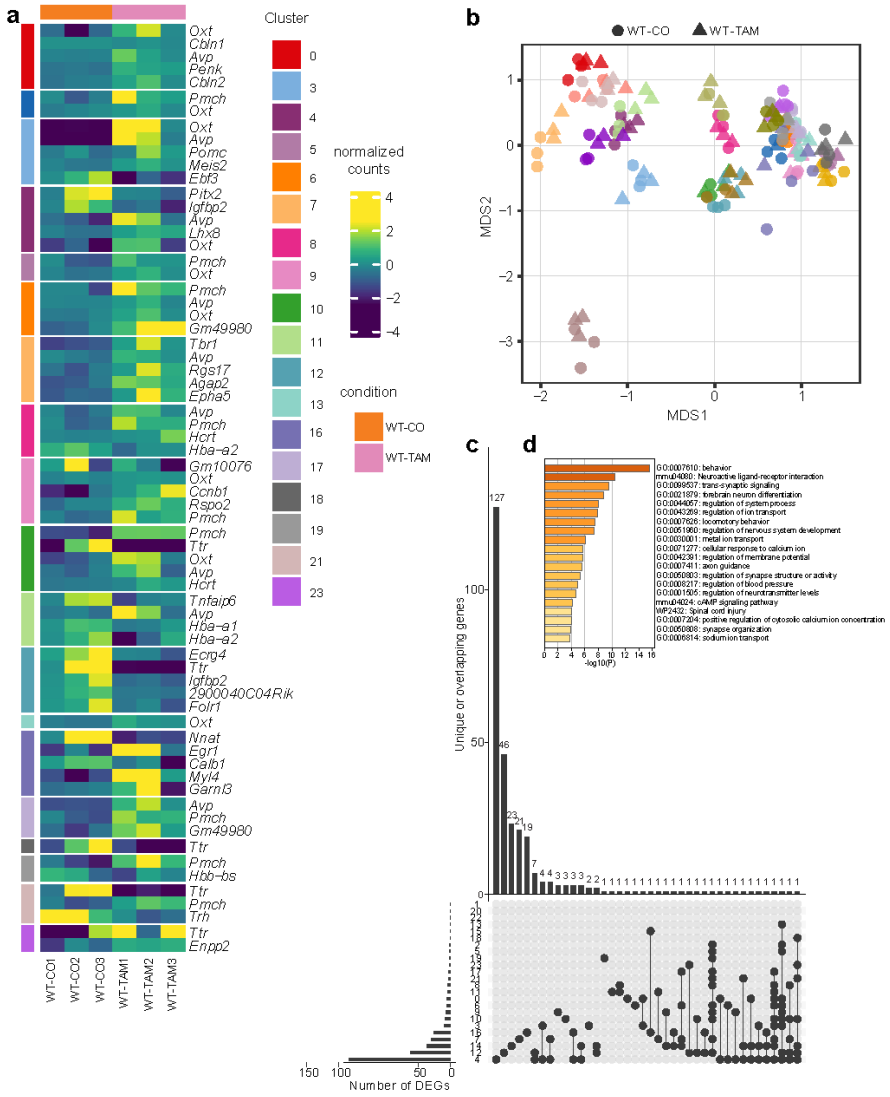


Supplementary Fig. 8. a) Heatmap showing cluster-resolved DEGs as calculated using *edgeR* on sum of counts within the *muscat* package when comparing WT-TAM to PSAPP-TAM. **b)** MDS plot showing effect of PSAPP-TAM on gene expression across all clusters and all samples. **c)**

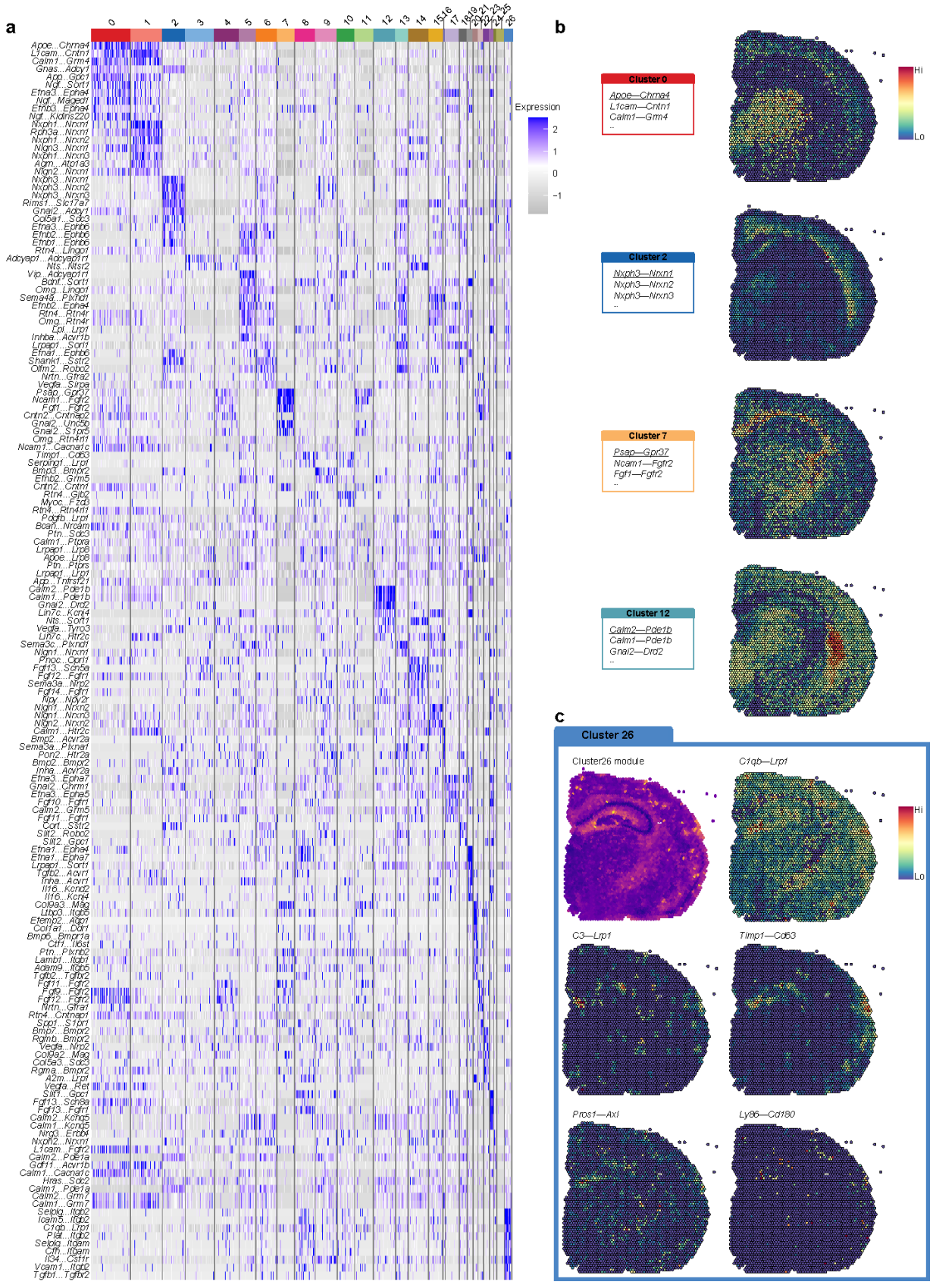
UpSet plot showing unique and overlapping DEGs with l2f > |1|. Note that Cluster 26 is only present in PSAPP mice and is therefore excluded by *edgeR*.



Supplementary Fig. 9. a) Heatmap showing cluster-resolved DEGs as calculated using *edgeR* on sum of counts within the *muscat* package when comparing PSAPP-TAM to PSAPP-CO. **b)** MDS plot showing effect of PSAPP-TAM on gene expression across all clusters and all samples. **c)** UpSet plot showing unique and overlapping DEGs with l2f > |1|.



Supplementary Fig. 10. a) Heatmap showing cluster-resolved DEGs as calculated using *edgeR* on sum of counts within the *muscat* package when comparing WT-CO to WT-TAM. **b)** MDS plot showing effect of WT-TAM on gene expression across all clusters and all samples. **c)** UpSet plot showing unique and overlapping DEGs with l2f > |1|. **d)** GO term analysis on all DEGs l2f > 1 shows absence of any interferon-induced gene programs following tamoxifen administration.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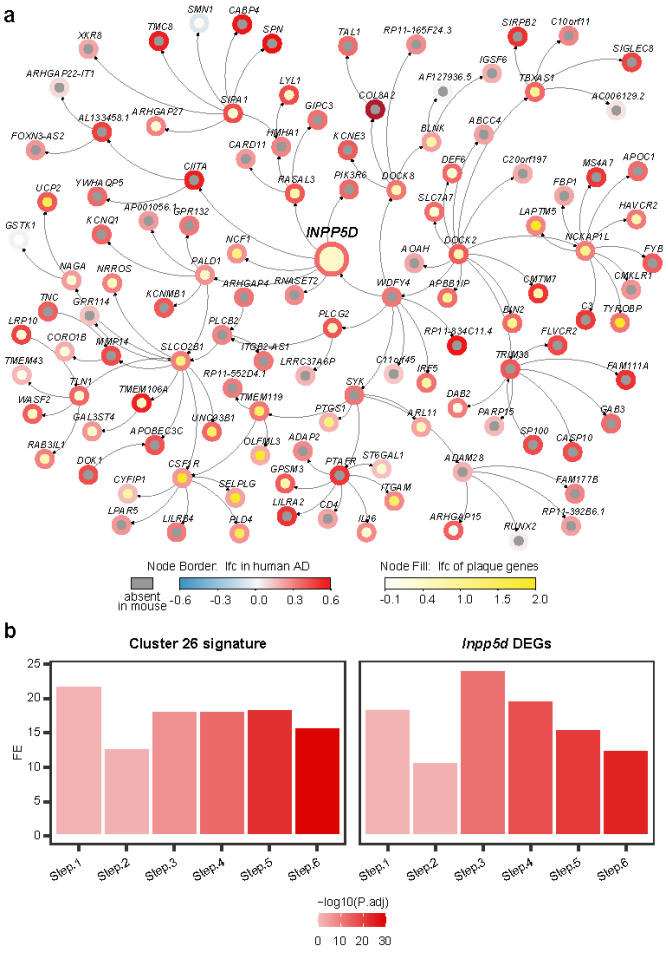
L1cam—Cntn1
Calm1—Grm4
Cluster 2
Nxph3—Nrxn1
Nxph3—Nrxn2
Nxph3—Nrxn3
Cluster 7
Psap—Gpr37
Ncam1—Fgfr2
Fgf1—Fgfr2
Cluster 12
Calm2—Pde1b
Calm1—Pde1b
Gnai2—Drd2
Hi
Lo
c
Cluster 26
Cluster26 module
C1qb—Lrp1
C3—Lrp1
Timp1—Cd63
Pros1—Axl
Ly86—Cd180

Supplementary Fig. 11. a) Heatmap of receptor-ligand pairs enriched in each of the 27 clusters identified using *NICHES* [31]. **b)** Examples of cluster-enriched receptor-ligand pairs show receptor-ligand pairs can express along anatomical regions (see Fig. 2c for comparison). **c)** *NICHES* on Cluster 26 highlights enrichment of receptor-ligand pairs involved in inflammation and phagocytosis.



Supplementary Fig. 12. a) Network showing the gene expression change in human AD and Cluster 26 from *Inpp5d* knockdown mice within the neighborhood of 4 steps of *INPP5D*. Node border paint denotes the $\log_2$ fold-change (lfc) in human AD brains compared to control brains. Node fill paint denotes the $\log_2$ fold-change caused by *Inpp5d* in mice, with grey color denoting absence in mouse data. **b)** Barplot showing enrichment of Cluster 26 signature and *Inpp5d* knockdown DEGs in the network neighborhood of *INPP5D* in human AD network. X-axis denotes the neighborhood at step 1-6 from *INPP5D*. Y-axis denotes the fold-enrichment (FE). Color gradient of the bars denote the *P* value significance of the enrichment.