Supplementary Information

Extended Materials and Methods

Behavioral tests

General and anxiety-like behaviors were studied in the open field and dark/light box (DLB) tests as previously described [1, 2]. In the open field test, 6- and 9-month-old mice were placed in the center of a white chamber (48 × 33 × 25 cm) for 5 min. General activity, including explored distance, time inactive and percentage of time in the periphery and center of the chamber, was automatically tracked using the ANY-maze system (Panlab Harvard Apparatus). A follow-up test 24 hours later was utilized to assess the memory of these encounters. The dark/light box (DLB) test consisted of a dark compartment (27 × 18 × 27 cm) and a light compartment (27 × 27 × 27 cm), connected by a 7 × 7 cm opening. Mice were placed into the dark area and latency and number of entries to the light area were measured for 5 min. The Morris water maze (MWM; pool: 1.2 m diameter) was performed for five days (6 trials/day; 60 sec/trial) followed by a 24 h probe trial (60 sec). Latencies to target platform, average speed and time percentage in the target quadrant *vs* rest of quadrants (others) were analyzed using ANY-maze software [2]. Experimenters were blind to the genotypes of the mice in all behavioral tests.

Cell-type transcriptional profiling

For gene profiling in excitatory- or parvalbumin (PValb)-positive neurons, we obtained CaMKIIα^{Cre};RiboTag or PValb (PV)^{Cre};RiboTag mice by crossing our mice to CaMKIIα^{Cre} or PValb (PV)^{Cre} mice and RiboTag RPL22 (C57BL/6) mouse, that expresses hemagglutinin (HA)-tagged ribosome-bound mRNAs specifically in Cre-recombinase-expressing cells [3]. Hippocampi of APP or Tau CaMKIIα^{Cre};RiboTag or PValb^{Cre};RiboTag mice (6 months) were lysed and immunoprecipitated (IP) with anti-HA.11 Tag antibody (BioLegend, 901514), and total RNAs from input and IP were extracted using Invitrogen PureLink RNA mini kit (Thermo Fisher Scientific). Purified RNA was

reverse-transcribed and amplified by qRT-PCR. IP/Input ratio of human *APP* and *Tau*, and murine *PDGF*β and *Prpn* genes was calculated by the ΔCt method.

Bulk RNA transcriptional profiling

Bulk RNA-sequencing (RNA-seq) transcriptional profiling was performed in RNA extracted (RNeasy Micro Kit, Qiagen) from fresh hippocampi or hippocampi and BLA (micropunched 1 mm Ø) from frozen brain slices (300 μm) of 6 and 9 month-old females, respectively. cDNA libraries were prepared from 50-100 ng (hippocampi) or 10 ng (amygdalae) RNA using the NEBNext® Ultra™ II RNA Library Prep Kits for Illumina (New England Biolabs). Libraries were sequenced on an Illumina NextSeq 2000 instrument (paired-end 2 x 150 bp for 6 months and 2 x 50 bp for 9 months samples). Around 60 and 30 million reads per sample were obtained for hippocampus and BLA, respectively. Adapter removal and trimming were performed with Trimmomatic (v0.39) and RNA-seq data analyses, including alignment to the reference genome (mm39) and differential expression analysis, were performed using QuasR/Rhisat2 and DESeq2 packages in Bioconductor [4, 5]. Gene ontology (GO) and functional enrichment analyses were performed using enrichR in Bioconductor [6], and EnhancedVolcano and VennDiagram packages were used for illustrating the data.

Biochemical analysis and subcellular fractionation

Hippocampi were lysed in cold-lysis buffer (62.5 mM Tris hydrochloride pH 6.8, 10 % glycerol, 5 % β-mercaptoethanol, 2.3 % sodium dodecyl sulfate (SDS), 5 mM NaF, 100 μM Na_3VO_4, 1 mM EDTA, 1 mM ethylene glycol tetraacetic acid (EGTA), 1 μM okadaic acid and 50 μM cyclosporin A) containing protease and phosphatase inhibitors and boiled [7, 8]. Sucrose gradient fractionation of synaptosomes of individual hippocampi from 6 month-old mice was performed as described [9]. Proteins were resolved on SDS-polyacrylamide gel electrophoresis and immunoblotted with the following antibodies: APP C-terminal fragment (CTF; Sigma, A8717), human Aβ (6E10; BioLegend, SIG-39320), β-actin (Sigma-Aldrich, A1978), β-tubulin (Sigma-Aldrich, T9026), GAPDH (Life Technologies, AM4300), GluN1

(Merck-Millipore, MAB363), Homer1 (Synaptic Systems, 160003), PSD95 (Cell Signaling, 2507), synaptophysin (Sigma-Aldrich, S5768), syntaxin 1A (Santa Cruz sc-12736), pTau (AT8, ThermoFisher MN1020), and tau (D1M9X, Cell Signaling 46687; TG5). Proteins were normalized to GAPDH, β-actin or β-tubulin (total protein) or β-tubulin (synaptic fractions). Chemiluminescent bands were captured and quantified in a linear range using a ChemiDoc MP System and ImageLab 5.2.1 software (Bio-Rad).

Immunohistochemical staining and quantification

For quantification of pTau (AT8 or CP13)- and Aβ intracellular-positive cells and Aβ plaques (6E10) in DAB-stained sections, images were captured using a Nikon Eclipse 80i microscope and processed using ImageJ software. The Colour Deconvolution plugin was used to isolate the DAB channel, and images were converted to 8-bit grayscale and inverted. A standardized threshold, established using negative control sections, was applied to all images to ensure unbiased quantification. Positively stained pTau and Aβ cells per μm^2 and number of Aβ plaques per section (n=3-4 slices/mouse) were manually counted across different brain regions (409.60 x 327.68 μm) using the Cell Counter plugin in ImageJ.

For Aβ42 immunofluorescence staining, deparaffinized coronal brain sections (5 μm) were antigen-retrieved with formic acid (60%, 5 min) before incubated with anti-Aβ42 antibody (MOAB-2, 1:200, Abcam Ab126649). For triple immunofluorescence staining, deparaffined brain sections were treated with citrate buffer (10 mM, pH 6.0) or Tris-EDTA (pH 9.0) in the case of somatostatin staining, and formic acid before incubation with anti-human Aβ antibody (6E10, 1:1000) and blocked using a biotin-conjugated Fab anti-mouse antibody, followed by: 1) mouse pTau (CP13, 1:50) and individual rabbit anti-neuronal markers (pCaMKIIα: Abcam, Ab 32678,1:500; PValb: Abcam, ab11427, 1:500; Somatostatin: Proteintech, 17512-1-AP, 1:50) antibodies, or 2) rabbit anti-Tau (D1M9X; 1:600) and mouse anti-GAD-67 (Abcam, Ab 26116, 1:200) antibodies. Sections were incubated with Cy3-conjugated streptavidin and either AlexaFluor-488/647-conjugated goat anti-mouse or anti-rabbit IgGs (1:400) and Hoechst for 20 min (1:1,0000). For L-glutamate and vGlut1 staining, coronal brain sections (100 μm) from 9-10-month-old mice were CUBIC-cleared for 4 hours, incubated in blocking solution

(PBS, 0.2% gelatin, 0.5% Triton X-100, 5% NGS) for 1.5 hours, and then incubated for 48 h with anti-human Aβ antibody (6E10, 1:1000). Sections were blocked using a biotin-conjugated Fab anti-mouse antibody for one overnight, followed by incubation with: 1) mouse pTau (CP13, 1:50) and either rabbit anti-L-glutamate (Abcam, ab9440, 1:500) or vGlut1 (Proteintech 55491-1-AP, 1:500) antibodies for 48 h. Sections were then incubated with Cy3-conjugated streptavidin and either AlexaFluor-488/647-conjugated goat anti-mouse or anti-rabbit IgGs (1:400) and Hoechst (1:5000). Confocal images (40x; zoom 1) were obtained with a Zeiss Axio Examiner D1 LSM700 laser scanning microscope.

Quantification of GFAP and Iba1 stainings were done in multiple confocal images in ImageJ software. The automated analysis included local thresholding (Phansalkar method, radius: 15 pixels), background subtraction (for Iba1) (rolling ball algorithm, radius: 15 pixels), and noise reduction ("Remove Outliers" function). The "Analyze Particles" function was then applied with size thresholds set to >5 pixels (Iba1) and >1 pixel (GFAP) to obtain the value of Iba1+ and GFAP+ area in each brain subregion, which was then divided by the total brain subregion area (n=4 slices/mouse) as reported [10].

Brain atrophy analysis and colocalization of synaptic proteins by tissue expansion

For brain atrophy, coronal brain sections (200 μm) of 9-10 month-old mice were CUBIC cleared, stained (Hoechst; 1:5000) and confocal imaged with a confocal microscope and quantification was done in multiple slices (n=6/mouse) using ImageJ software. For tissue expansion, frozen brain sections (100 μm) labelled with anti-pTau (CP13, 1:50) and anti-Homer1 (1:300) antibodies, and Hoechst were incubated overnight with Acryloyl-X SE (Thermofisher, A20770) and then with gelling solution (2h, 37º C) as reported [11]. Sections were digested with proteinase K and cleared and expanded with deionized water. Confocal images (20x; zoom 0.5 or 1) were obtained with a Zeiss Axio Examiner D1 LSM700 laser scanning microscope (ImageJ 6.0). Colocalization between Homer 1 and pTau in the hippocampus and BLA of APP/Tau mice was quantified using the Just Another Colocalization Plugin (JACoP) in Image J. After background correction to analyze specifically synaptic Homer 1, Manders' coefficient was used to calculate the fraction of Homer 1 colocalizing with pTau.

Electrophysiological recordings

Electrophysiological measures were performed in 6 month-old mouse brain slices (females) by recording in CA1 hippocampus or lateral amygdala (LA), and whole-cell patch-clamp recordings in the soma of CA1 or amygdalar pyramidal excitatory neurons as described [12-14]. Coronal brain slices (350 μm) were maintained (30-34 ºC) in cerebrospinal fluid (CSF; in mM: 126 NaCl, 3 KCl, 1.25 KH_2PO4, 2 MgSO4, 2 $CaCl_2$, 26 $NaHCO_3$, and 10 glucose (pH 7.2, 300 $mOsmL^{-1}$). Field excitatory postsynaptic potentials (fEPSPs) were recorded in CA1 hippocampus or lateral amygdala (LA) after stimulation (0.2 Hz) of the Schaffer collateral or the thalamic pathway, respectively [12-14]. Basal synaptic transmission was examined by stimulus-response curves by applying 5-10 μA increasing stimulation. In paired-pulse experiments, two consecutive stimuli separated by 40 msec were applied. Data were filtered at 3 kHz and acquired at 10 kHz. Synaptic plasticity was induced by applying a theta burst stimulation (TBS) of 10 bursts of four pulses each (100 Hz, 100 ms duration, 200 ms inter-burst interval; amygdala) or two stimulus trains (100 pulses 100 Hz /train, 20 sec interstimulus; hippocampus). Whole-cell patch-clamp recordings in the soma of CA1 or amygdalar pyramidal excitatory neurons were recorded with a patch-clamp amplifier (Multiclamp 700B). AMPAR- and NMDAR-EPSCs were evoked at 0.2 Hz and recorded in voltage-clamp mode holding the membrane potential at 70 and +40 mV, respectively. All signals were low-pass filtered at 2 kHz, acquired at 10 kHz, digitized, and stored using Digidata 1322A and pCLAMP 10.4 software (Molecular Devices, CA, USA).

Supplementary Table 1. Differentially expressed astrocytic and microglial genes in the hippocampus and basolateral amygdala of 9 month-old APP/Tau mice

Gene symbol	HPC		BLA		Biological function
	Log_2 FC	padj	Log_2 FC	padj	
Astrocytic and reactive astrocytic genes					
***Agt** *	0.380	0.0813	0.462	0.3874	Synaptic function
Aldoc	0.173	0.0105	0.338	0.0004	Glycolytic enzyme
Apoe	0.744	0.0140	0.556	0.0049	Cholesterol metabolism
***Aqp4** *	0.810	0.0050	0.281	0.1415	Water transport
Dbi	0.701	5.43E-07	0.310	0.0562	Synaptic function
Gfap	2.482	6.26E-06	3.081	3.06E-05	Intermediate filament
Id3 [#]	0.602	0.0128	0.244	0.3290	Transcription factor
***Mertk** **	0.165	0.1443	0.255	0.0589	Phagocytosis
Nfatc1	0.459	0.0114	0.322	0.0790	NFAT Transcription factor
***Serpina3n** *	1.655	0.0025	0.942	0.2884	Serine protease inhibitor
Slc1a3	0.235	0.0209	0.181	0.0750	Monocarboxylate transporter
***Sox9** *	0.493	0.0077	0.225	0.2888	Transcription factor
Stat3	0.529	0.0003	0.221	0.0440	Transcription factor
Vim [#]	2.077	2.21E-05	0.545	0.0398	Type III intermediate filament
Xbp1 [#]	-0.153	0.0802	-0.167	0.0759	CNS inflammation
Microglial and DAM genes					
***Aif1 (Iba1)** *	1.121	0.0004	0.251	0.3027	Calcium binding
Axl [#]	0.711	0.0015	0.441	0.0090	Receptor tyrosine kinase
B2m	0.984	0.0017	0.427	0.0753	MHC class II activity
Ccl6	3.736	4.04E-18	2.452	0.0001	Chemokine
Cd33	0.909	0.0002	0.811	0.0112	Negative regulation of cytokine production
Csf1	0.803	9.61E-06	0.469	0.0079	Cytokine
Cst7	5.478	1.26E-14	4.370	1.12E-05	Cysteine protease inhibitor, Immune regulation
Cx3cr1	0.890	0.0002	0.450	0.0049	Fractalkine receptor
Itgax	5.645	1.25E-16	3.480	0.0007	Integrin-mediated cell adhesion
***P2ry12** *	0.280	0.0042	0.131	0.4527	Adenosine signaling
Ptprc (CD45)	1.924	2.28E-07	-1.074	0.0226	Regulation of microglial activation and phagocytosis
Slc16a3	0.910	9.78E-08	0.719	0.0661	Lactate shuttling, microglial-mediated synaptic pruning
***Spp1** *	3.642	8.45E-07	1.299	0.1576	Microglial phagocytosis and synaptic engulfment in AD mice
Trem2	1.849	4.88E-08	1.176	0.0025	Microglial survival and inflammatory responses
Tyrobp	2.139	4.42E-11	1.429	0.0001	Transmembrane adaptor, Trem2 ligand

Expression of selected astrocytic, reactive astrocytic, microglial and DAM genes identified by transcriptomic analysis in the hippocampus (HPC) and/or basolateral amygdala (BLA) of APP/Tau mice compared with non-transgenic (WT) mice. Genes are grouped according to their cellular expression sorted alphabetically with Log_2 fold changes (Log_2 FC) indicating significantly downregulated (< 0) or upregulated (> 0) mRNAs (adjusted *p*-value (padj) < 0.1) in either hippocampus (marked with *) or BLA (marked with **) or in both hippocampus and BLA (not marked). [#]Genes expressed in both astrocytes and microglia. DAM: disease-associated microglia.

Supplementary Table 2. Common differentially expressed AD-related genes in the hippocampus of APP/Tau mice at 6 and 9 months

Biological pathway/gene name	Gene symbol	6 Months		9 Months	
		Log_2 FC	padj	Log_2 FC	padj
Cell signaling					
Inositol polyphosphate-5-phosphatase D	***INPP5D***	0.353	0.0514	0.911	1.76E-07
Rho GTPase activating protein 20	***ARHGAP20***	-0.226	0.0141	-0.338	0.0006
Serine/threonine kinase 32B	***STK32B***	-0.281	0.0387	-0.412	0.0383
Immune response, inflammation					
Clusterin	***CLU***	0.207	0.0144	0.685	0.0015
Triggering receptor expressed on myeloid cells 2	***TREM2***	0.783	0.0146	1.849	4.88E-08
Lipid metabolism					
Aldehyde oxidase 1	***AOX1***	0.390	0.0092	0.605	5.12E-05
Thromboxane A synthase 1	***TBXAS1***	0.761	0.0063	1.116	0.0010
UDP glucuronosyltransferase family 1 member A10	***UGT1A10***	0.481	0.0560	1.562	1.19E-08
UDP glucuronosyltransferase family 1 member A8	***UGT1A8***	0.461	0.0713	1.569	1.15E-08
Synaptic function, ion transport					
Na+/K+ transporting ATPase interacting 2	***NKAIN2***	-0.162	0.0377	-0.145	0.0029
Phosphodiesterase 7B	***PDE7B***	-0.360	0.0153	-0.352	0.0042
Transcriptional regulation					
AHNAK nucleoprotein	***AHNAK***	0.425	0.0355	0.793	0.0072
BCL3 transcription coactivator	***BCL3***	1.528	0.0141	2.499	8.48E-06
CUGBP Elav-like family member 1	***CELF1***	-0.102	0.0531	-0.134	0.0681

Hippocampal expression of GWAS-identified AD-associated genes in APP/Tau female mice shared between 6 and 9 months compared with non-transgenic (WT) mice. Genes are grouped according to their biological pathway sorted alphabetically with Log_2 fold changes (Log_2 FC) indicating significantly downregulated (< 0) or upregulated (> 0) mRNA levels (adjusted *P* value (padj) < 0.1) in both 6 and 9 month-old APP/Tau female mice.

Supplementary Figures

Supplementary Figure 1. Human APP and MAPT/Tau transgenes are expressed in glutamatergic neurons.

A, qRT-PCR analysis showing expression of PDGFβ and hAPP and Prpn and hMAPT/Tau in glutamatergic neurons (CaMKIIα+; black bars) but not parvalbumin interneurons (PV+; white bars) in the hippocampus of APP or Tau CaMKIIαCre RiboTag or PValbCre RiboTag mice, respectively. Log2 fold change (FC)/input values indicate enriched (positive values) or lack of expression (negative values) in the specific cell type. Data represent mean ± SEM. **B,** Confocal microscope images showing localization (yellow) of Aβ/APP (6E10; red) and pTau (Ser202; CP13; magenta) in excitatory pyramidal neurons (CaMKIIα, vGlut1, L-glutamate; green) but not in inhibitory interneurons (GAD-67, parvalbumin, somatostatin, calretinin; green) in the hippocampus of female 9 month-old APP/Tau mice. Bottom images: Aβ is present in some GAD67-postive cells in the BLA of female APP/Tau mice at 9 months as shown in the magnified image. Hoechst staining is depicted in blue. Scale bar: 15 μm.

Supplementary Figure 2. Expression of human mutant APP and Tau in hippocampal excitatory neurons causes hippocampal atrophy in APP/Tau transgenic mice.

A, Biochemical analysis and quantification of human APP fl and β-CTFs (6E10 antibody; top), mouse/human APP fl and CTFs (APP CTF antibody), and phosphorylated tau (AT8) and total tau (D1M9X and TG5 antibodies) in the hippocampus of 6 month-old control (WT, white bars), APP (red bars), Tau (blue bars) and APP/Tau (grey bars) mice. Protein levels are normalized to GAPDH or APP fl. Data represent mean ± SEM. Number of mice (male/female): WT (2/10, white bars/symbols) APP (5/8, red bars/symbols), Tau (0/8, blue bars/symbols) and APP/Tau (3/5), grey bars/symbols). Statistical analysis was determined by one-way ANOVA followed by Tukey's post hoc tests. $*P < 0.05$, $**P < 0.01$, $****P < 0.0001$ *vs* the indicated group. **B,** Confocal microscope images showing intraneuronal Aβ42 staining (MOAB-2 antibody) in the hippocampus of 9 month-old female APP and APP/Tau mice. Scale bar: 20 μm. **C**, Coronal brain sections of 9-10 month-old control (WT) and APP/Tau mice were stained (Hoechst: cyan) and imaged (top), and volume of the dashed regions were quantified (bottom). Scale bar: 75 μm. Data represent mean number ± SEM of region volume (μm^3 x10^6) (n=6 slices/200 μm coronal sections/mouse). Number of mice (male/female): WT (4/5, white bars/symbols) and APP/Tau (3/5, grey bars/symbols). Statistical analysis was determined by unpaired two-tailed Student's t-test or non-parametric Mann-Whitney tests, according to D'Agostino-Pearson omnibus normality test. $**P < 0.01$, $***P < 0.001$, $****P < 0.0001$. mo:molecular layer; po: polymorphic layer; sg: stratum granulosum (granule cell layer); so: stratum oriens; sp: stratum pyramidale (pyramidal layer); sr: stratum radiatum; slm: stratum lacunosum-moleculare.

Supplementary Figure 3. Cerebral Aβ and pTau pathologies in APP, Tau and APP/Tau mice at 9 months of age.

Coronal brain sections of control (WT), APP, Tau and APP/Tau mice at the age of 9 months were stained with anti-human Aβ/APP (6E10; top) or anti-pTau (Ser202, CP13; bottom) antibodies. Representative low and high (insets) magnified images of Aβ-stained neurons in CA1 and CA3 hippocampus, entorhinal cortex (EC) and basolateral amygdala (BLA) are shown. Objective: 20x. Scale bar: 50 μm. The number of Aβ plaques in the indicated region (n=3-4 slices/mouse; n=5 mouse/group) were manually counted in representative brain sections of 9 month-old male APP and APP/Tau mice (right graph).

Supplementary Figure 4. Age-dependent alterations of general behavior in AD transgenic mice.

A, General behavior of mice at 6 months in the open field. Number of mice: control (WT, n= 10; white bars/symbols), APP (n= 10; red bars/symbols), Tau (n= 10; blue bars/symbols) and APP/Tau (n= 9; grey bars/symbols). **B**, Behavior of male (**top**) and female (**bottom**) mice at 9 months of age in the open field. Number of mice (male/female): WT (14/8, white bars/symbols) APP (9/8, red bars/symbols), Tau (10/9, blue bars/symbols) and APP/Tau (7/8, grey bars/symbols). Travelled distance (left), time inactive (middle) and percentage of time in the periphery (P) and center (C) of the box (right) in the experimental groups during days 1 and 2. Statistical analysis was determined by two-way ANOVA followed by Sidak's for day 1 vs day 2 or periphery vs center comparison. $*P < 0.05$, $****P < 0.0001$, *vs* the indicated group or periphery value.

Supplementary Figure 5. Changes of inflammatory and synapse/membrane transporter pathways in APP/Tau hippocampus at 6 and 9 months

A, Venn diagrams illustrating the overlap of upregulated (left) and downregulated (right) genes differentially expressed in the hippocampus of female APP/Tau mice of 6 (n=10) and 9 (n=9) months of age relative to non-transgenic controls (WT) of 6 (n=11) and 9 months (n=11), respectively. Gene set enrichment annotation into Reactome and GO biological processes ranked by gene ratio and adjust *P* value. **B**, Heat maps of GWAS-identified AD-related genes shared in the hippocampus of female APP, Tau and APP/Tau mice at 6 months. The color represents the fold changed compared to the hippocampus of female WT controls.

Bibliography

1. Gimenez-Llort L, Garcia Y, Buccieri K, Revilla S, Sunol C, Cristofol R *et al.* Gender-specific neuroimmunoendocrine response to treadmill exercise in 3xTg-AD mice. *Int J Alzheimers Dis* 2010; **2010:** 128354.

2. España J, Gimenez-Llort L, Valero J, Miñano A, Rabano A, Rodriguez-Alvarez J *et al.* Intraneuronal β-amyloid accumulation in the amygdala enhances fear and anxiety in Alzheimer's disease transgenic mice. *Biol Psychiatry* 2010; **67** (6)**:** 513-521

3. Sanz E, Yang L, Su T, Morris DR, McKnight GS, Amieux PS. Cell-type-specific isolation of ribosome-associated mRNA from complex tissues. *Proc Natl Acad Sci U S A* 2009; **106**(33)**:** 13939-13944.

4. Gaidatzis D, Lerch A, Hahne F, Stadler MB. QuasR: quantification and annotation of short reads in R. *Bioinformatics* 2015; **31**(7)**:** 1130-1132.

5. Love MI, Huber W, Anders S. Moderated estimation of fold change and dispersion for RNA-seq data with DESeq2. *Genome Biol* 2014; **15**(12)**:** 550.

6. Kuleshov MV, Jones MR, Rouillard AD, Fernandez NF, Duan Q, Wang Z *et al.* Enrichr: a comprehensive gene set enrichment analysis web server 2016 update. *Nucleic Acids Res* 2016; **44**(W1)**:** W90-97.

7. Planel E, Yasutake K, Fujita SC, Ishiguro K. Inhibition of protein phosphatase 2A overrides tau protein kinase I/glycogen synthase kinase 3β and cyclin-dependent kinase 5 inhibition and results in tau hyperphosphorylation in the hippocampus of starved mouse. *J Biol Chem* 2001; **276**(36)**:** 34298-34306.

8. Van der Jeugd A, Parra-Damas A, Baeta-Corral R, Soto-Faguas CM, Ahmed T, LaFerla FM *et al.* Reversal of memory and neuropsychiatric symptoms and reduced tau pathology by selenium in 3xTg-AD mice. *Sci Rep* 2018; **8**(1)**:** 6431.

9. Saura CA, Servian-Morilla E, Scholl FG. Presenilin/γ-secretase regulates neurexin processing at synapses. *PLoS ONE* 2011; **6**(4)**:** e19430.

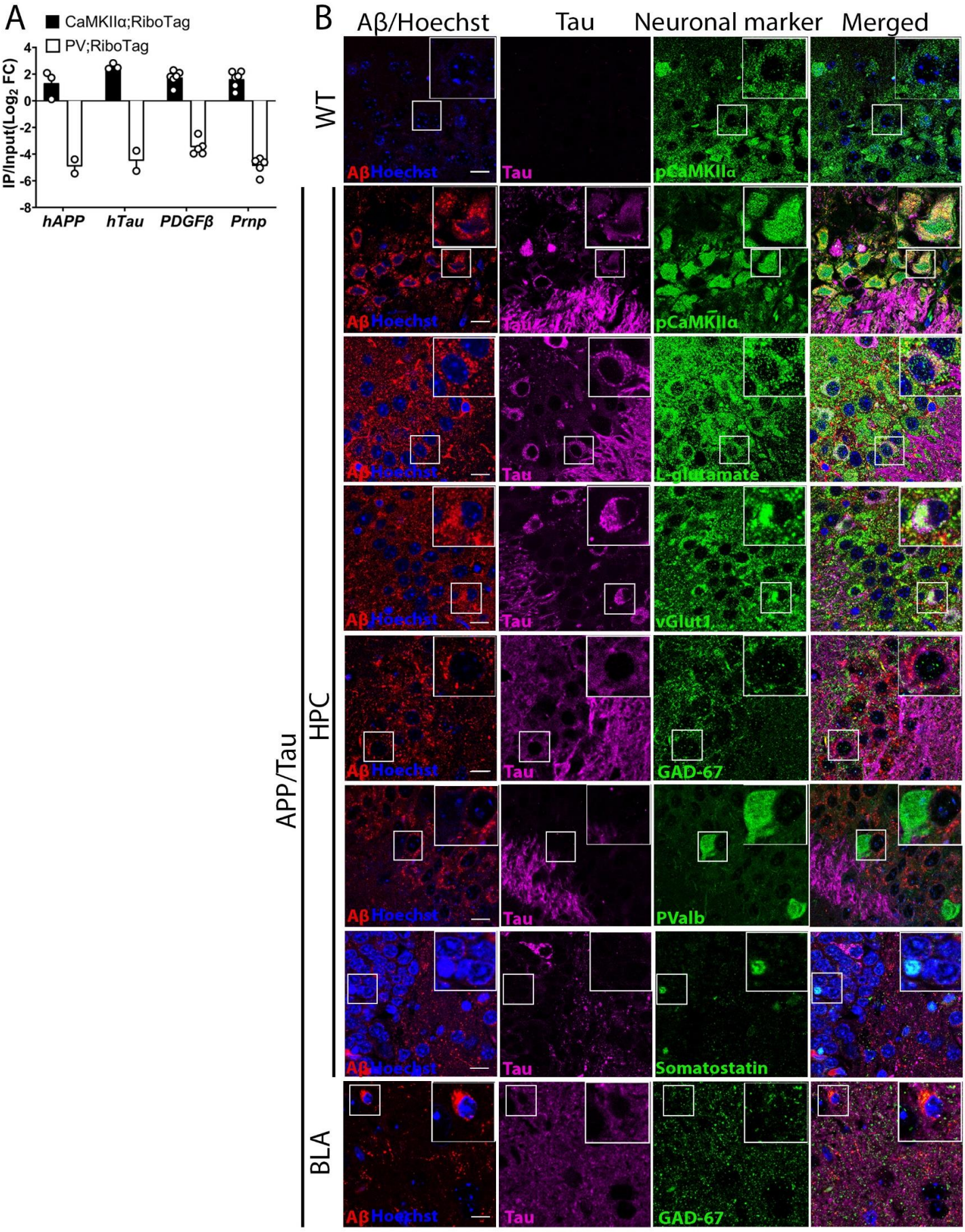
10. Kang J, Watanabe H, Shen J. Protocols for assessing neurodegenerative phenotypes in Alzheimer's mouse models. *STAR Protoc* 2021; **2**(3)**:** 100654.

11. Chen F, Tillberg PW, Boyden ES. Expansion microscopy. *Science* 2015; **347**(6221)**:** 543-548.

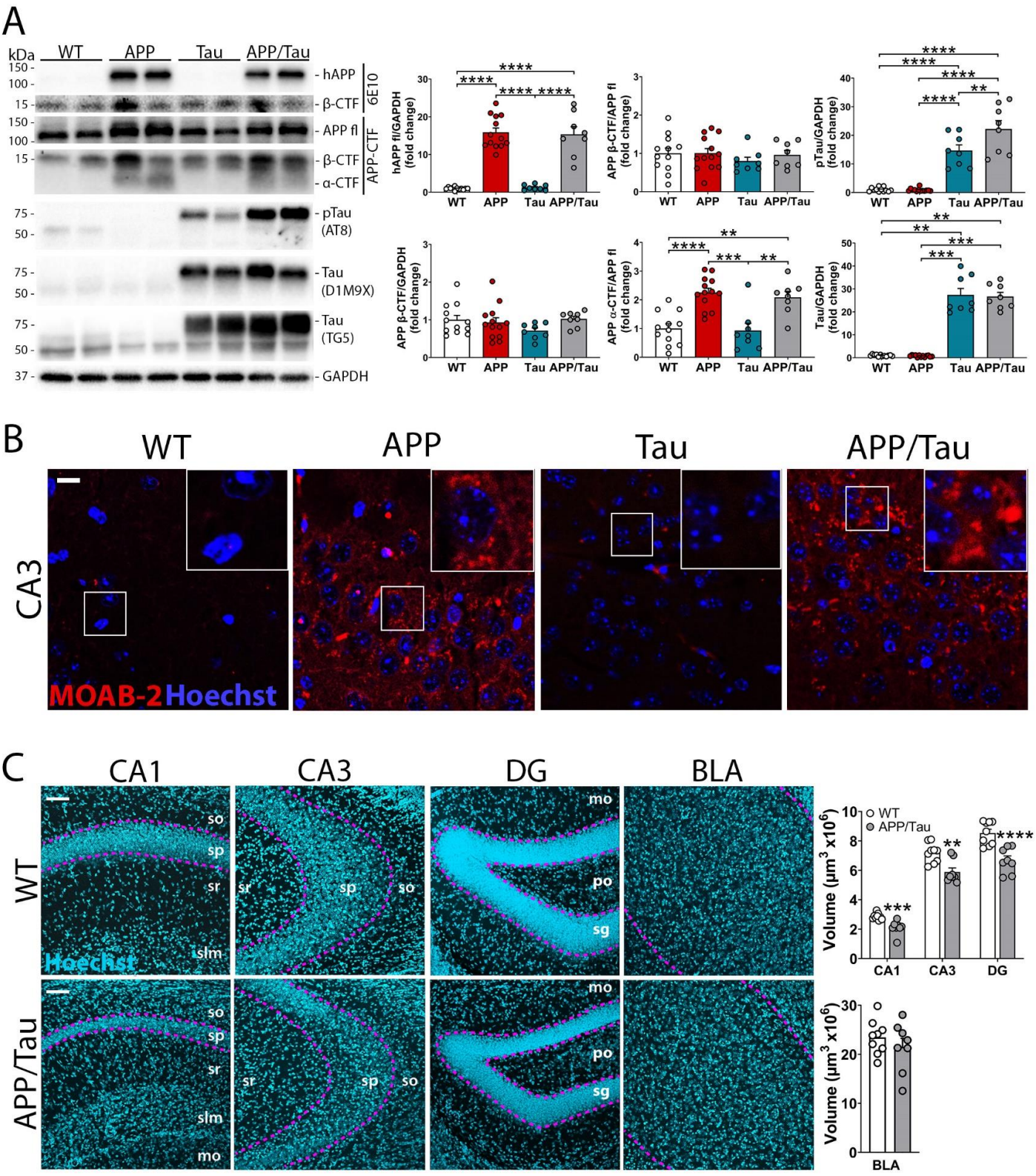
12. Perez-Rodriguez M, Arroyo-Garcia LE, Prius-Mengual J, Andrade-Talavera Y, Armengol JA, Perez-Villegas EM *et al.* Adenosine receptor-mediated developmental loss of spike timing-dependent depression in the hippocampus. *Cereb Cortex* 2018; **29**(8)**:** 3266-3281.

13. Negrete-Diaz JV, Duque-Feria P, Andrade-Talavera Y, Carrion M, Flores G, Rodriguez-Moreno A. Kainate receptor-mediated depression of glutamatergic transmission involving protein kinase A in the lateral amygdala. *J Neurochem* 2012; **121**(1)**:** 36-43.

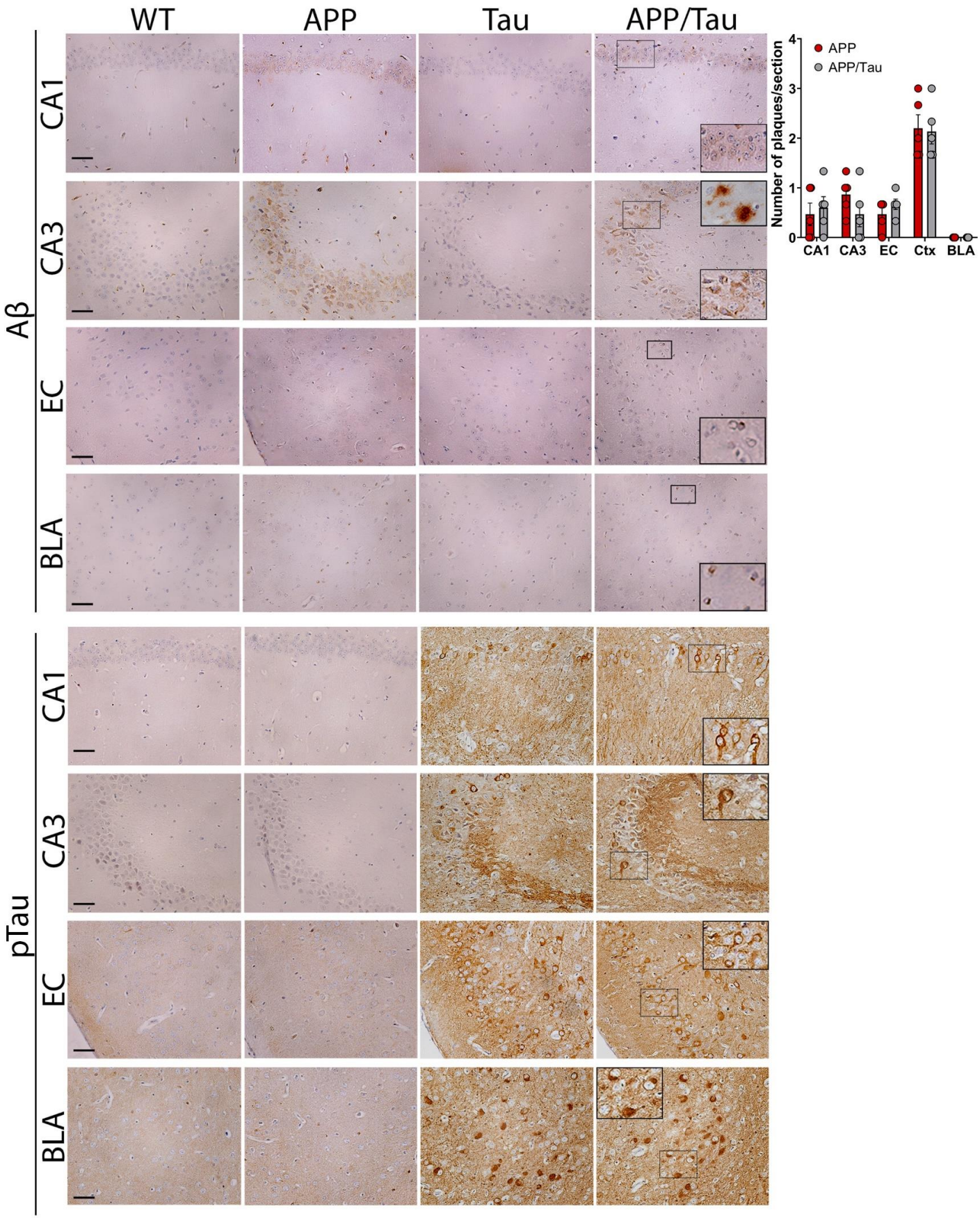
14. Perez-Villegas EM, Perez-Rodriguez M, Negrete-Diaz JV, Ruiz R, Rosa JL, de Toledo GA *et al.* HERC1 Ubiquitin Ligase Is Required for Hippocampal Learning and Memory. *Front Neuroanat* 2020; **14:** 592797.



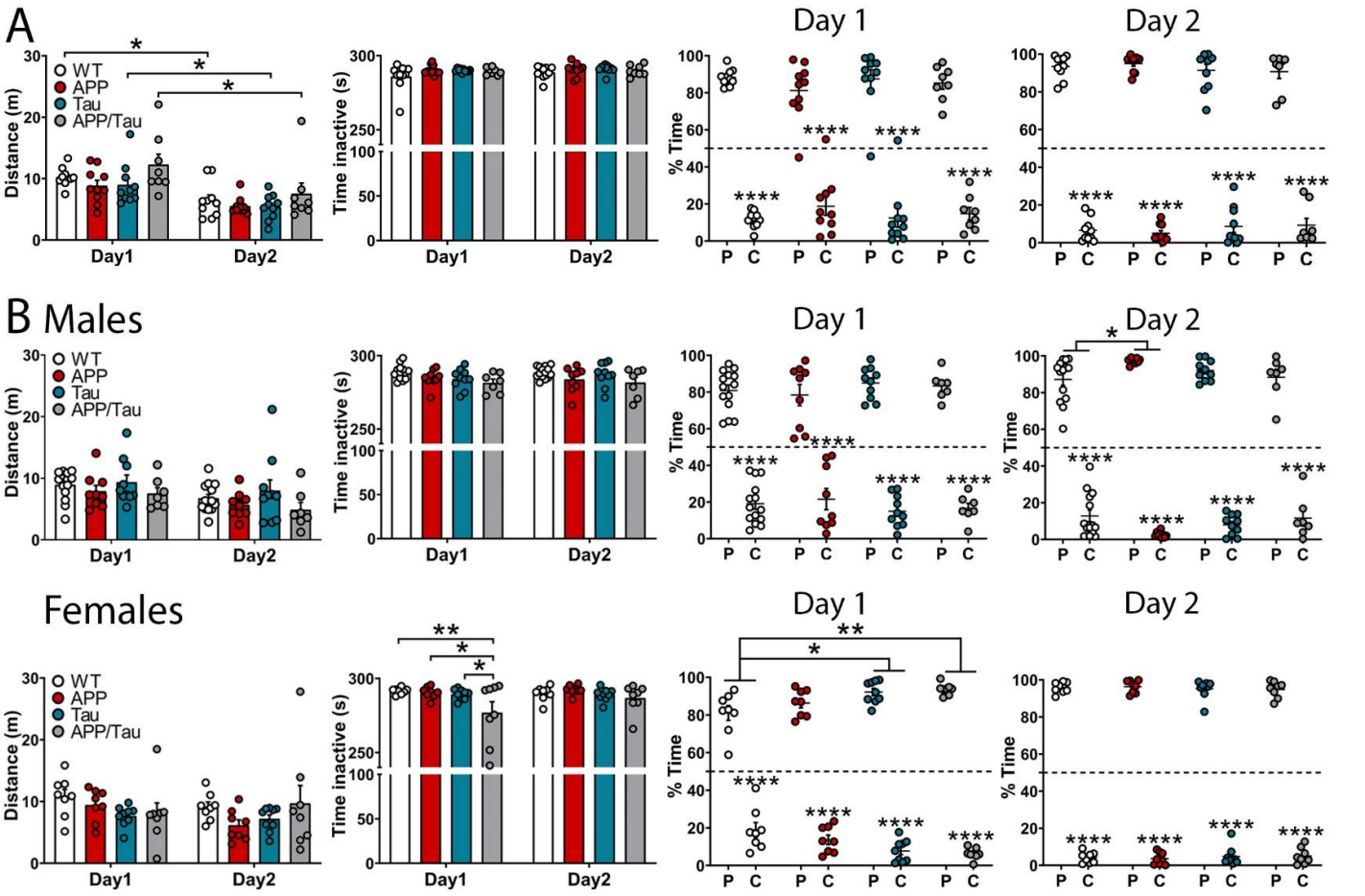
Supplementary Figure 1



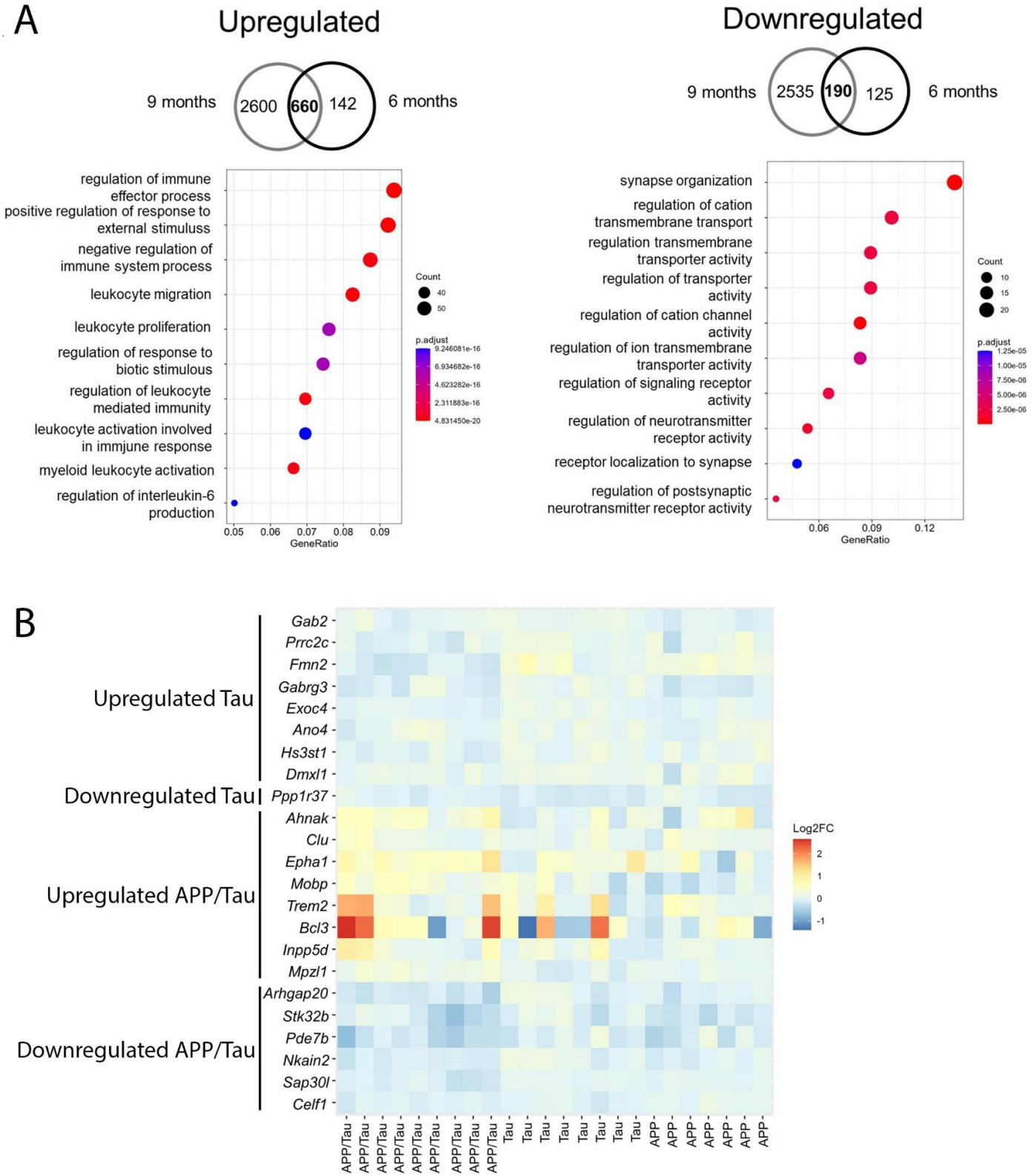
Supplementary Figure 2



Supplementary Figure 3



Supplementary Figure 4



Supplementary Figure 5