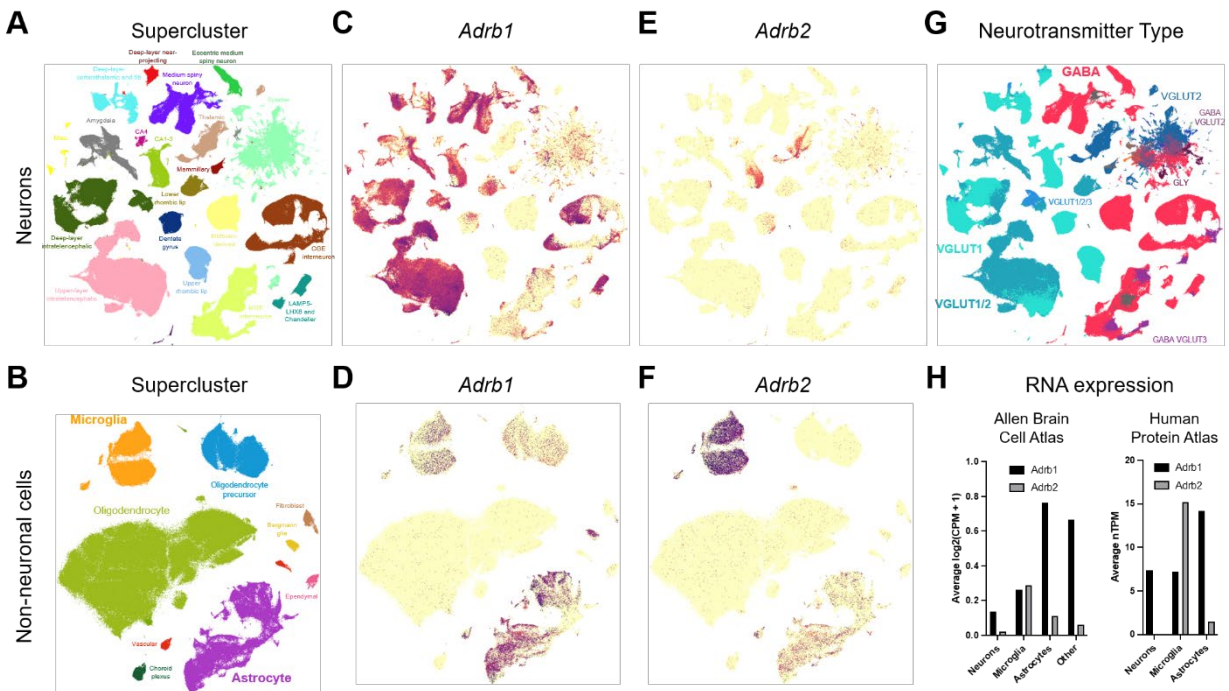
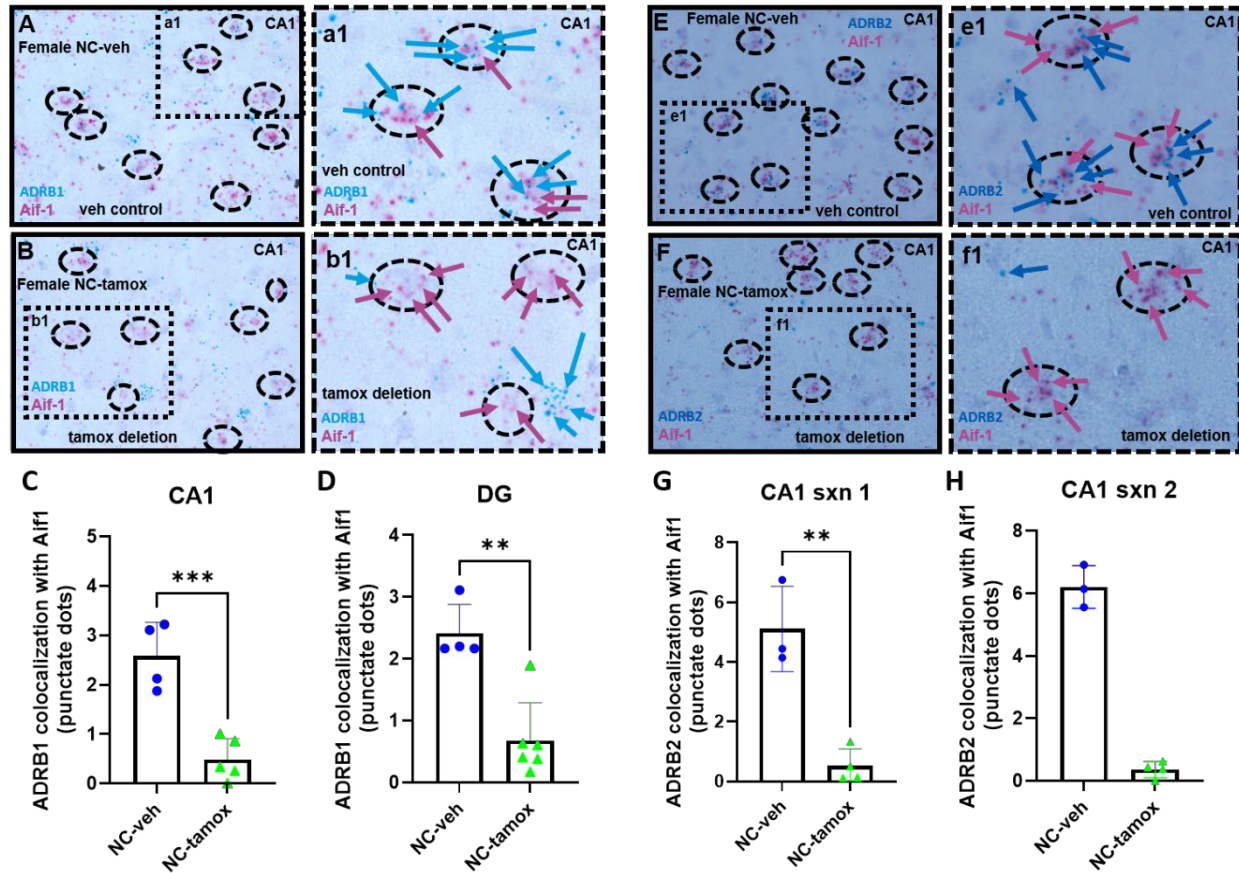


Supplemental Figures

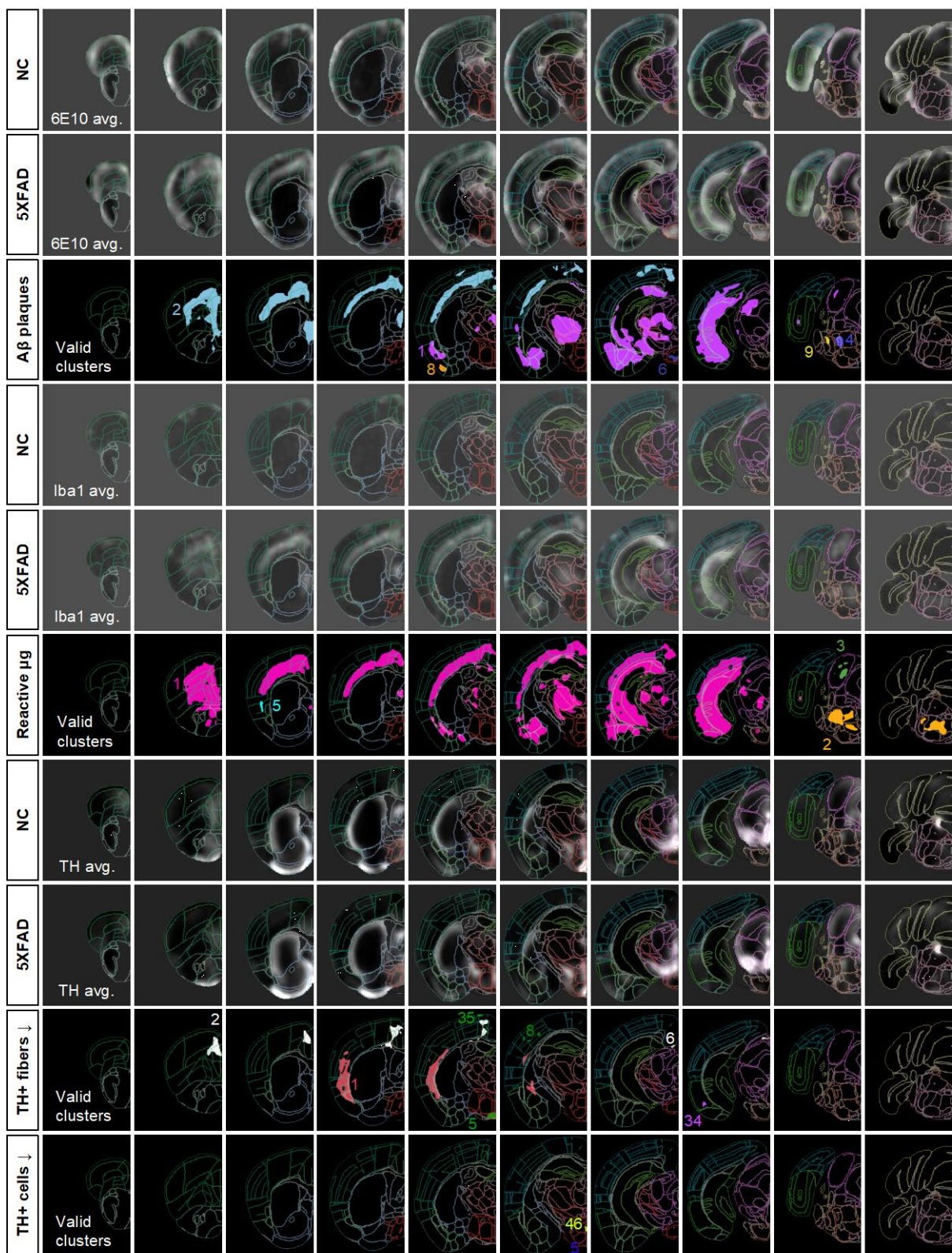


Supplemental Figure S1. Expression of *Adrb1* and *Adrb2* across neuronal and non-neuronal cell types in the adult human brain, visualized using single-cell RNA-sequencing data from the Allen Brain Cell Atlas (portal.brain-map.org/atlas-and-data/bkp/abc-atlas) (Siletti et al., 2023). **A-B)** tSNE plots showing superclusters of major cell types for **(A)** neurons and **(B)** non-neuronal cells. **C-F)** tSNE plots indicating the expression of *Adrb1* **(C-D)** and *Adrb2* **(E-F)** across neuronal **(C, E)** and non-neuronal **(D, F)** cell types. Expression intensity is color-coded, with darker colors representing higher expression levels. **G)** Neurotransmitter type classification of neuronal clusters, highlighting cell types expressing markers for neurotransmitters such as GABA and glutamate (e.g., VGLUT1, VGLUT2). The data were retrieved from the Allen Brain Cell Atlas(1) (Siletti et al. 2023). **H)** Using this data and data from the Human Protein Atlas (www.proteinatlas.org)(2) (Karlsson et al., 2021), we quantified the average expression of *Adrb1* and *Adrb2* across broad cell-type categories. CPM = counts per million. nTPM = normalized transcripts per million.

1. Siletti K, Hodge R, Mossi Albiach A, Lee KW, Ding SL, Hu L, et al. Transcriptomic diversity of cell types across the adult human brain. *Science*. 2023;382(6667):eadd7046.
2. Karlsson M, Zhang C, Mear L, Zhong W, Digre A, Katona B, et al. A single-cell type transcriptomics map of human tissues. *Sci Adv*. 2021;7(31).

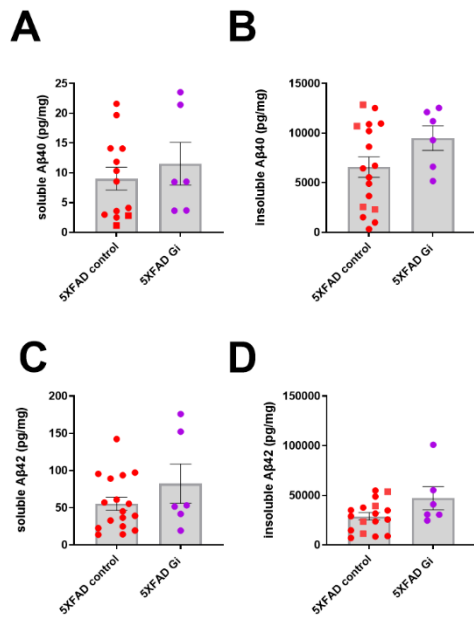


Supplemental Figure S2. RNAscope quantification of colocalization of *adrb1* and *adrb2* expression with allograft inflammatory factor 1 (*aif1*; also known as ionized calcium binding adapter molecule 1; *iba1*) expression in microglia. **A and B**) Representative images of RNAscope dual labelling of *aif1* (red) and *adrb1* (green). Dashed ovals indicate area around *aif1* clusters as approximation of microglial cell bodies for quantification of *adrb1* puncta. **A1 and B1**) Higher magnification representation of the dashed rectangular areas in **A** and **B** with colored arrows indicating representative punctate label. Green arrows indicate *adrb1* puncta. Red arrows indicate *aif1* puncta. **C and D**) Quantification of average number of *adrb1* puncta within each *aif1*-positive cluster. **E and F**) Representative images of RNAscope dual labelling of *aif1* (red) and *adrb2* (green). Dashed ovals indicate area around *aif1* clusters as approximation of microglial cell bodies for quantification of *adrb2* puncta. **E1 and F1**) Higher magnification representation of the dashed rectangular areas in **E** and **F** with colored arrows indicating representative punctate label. Green arrows indicate *adrb2* puncta. Red arrows indicate *aif1* puncta. **G and H**) Quantification of average number of *adrb2* puncta within each *aif1*-positive cluster.

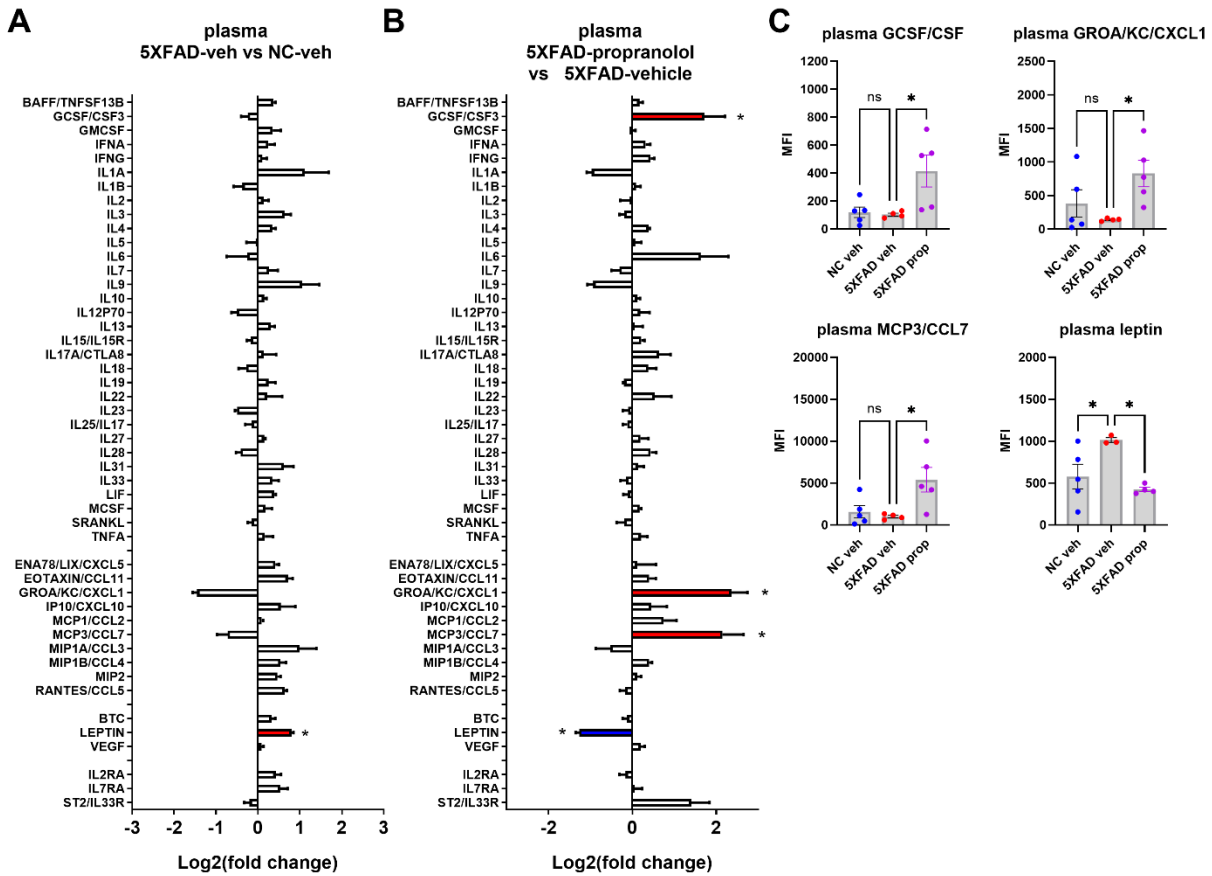


Supplemental Figure S3. Coronal slices showing averaged immunofluorescence and valid clusters.

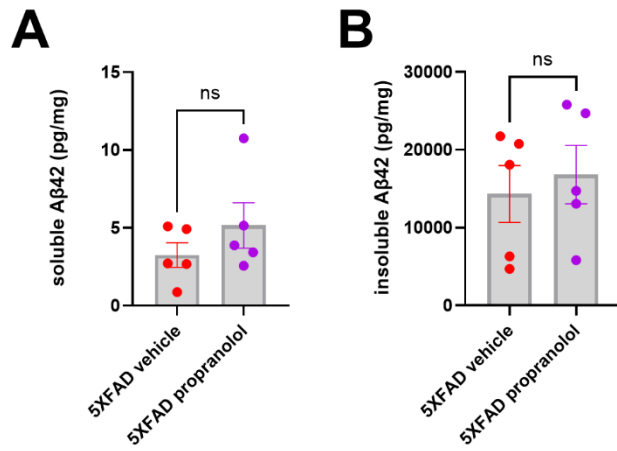
Brains from aged 5XFAD (6.5 months) and non-carrier (NC) control mice were immunostained, cleared, imaged in 3D with LSM and analyzed with UNRAVEL. Immunofluorescence labeling was preprocessed to minimize autofluorescence and non-specific staining. This involved rolling ball background subtraction (pixel radius of 20) to remove autofluorescence. Non-specific staining from the mouse 6E10 antibody was zeroed out with an Ilastik-based segmentation of capillaries and the brain's surfaces. Likewise, signal from reactive and aggregated microglia was isolated by segmenting them and zeroing out other voxels. No mask was used for TH labeling. Autofluorescence images were registered with an iDISCO+/LSFM-specific average template brain aligned to the CCFv3 Allen brain atlas. Transformation matrices from this were used to warp the preprocessed immunofluorescence images to atlas space for voxel-wise statistics. Each brain was z-scored and smoothed. Images for each immunolabel and group were averaged (avg.) together. Images were visualized with FSLeves. The display range was set to -0.3 – 1 for 6E10, -0.3 – 0.8 for reactive microglia, and -0.3 – 2 for TH. Valid clusters were randomly colored and their IDs are shown. Detailed info on each cluster is available in **Supplementary Table S10**. The images were overlaid with a semi-transparent wireframe version of the Allen brain atlas.



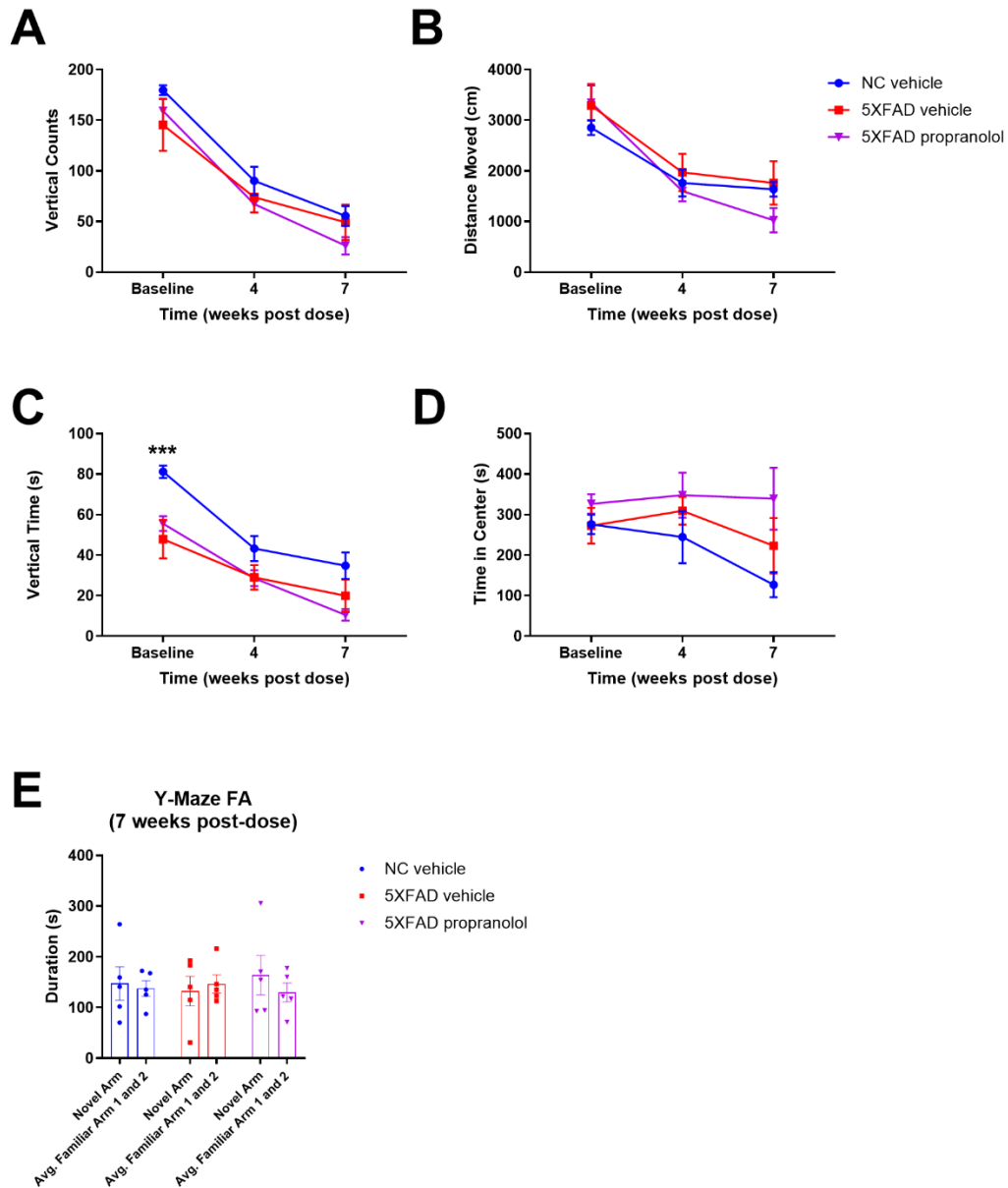
Supplemental Figure S4. No effects of chemogenetic inhibition of locus coeruleus noradrenergic neurons were detected on cortical tissue concentrations of amyloid beta. Bar graphs depict brain concentrations of soluble and insoluble **A,B)** Aβ40 and **C,D)** Aβ42 in female 5XFAD control mice and 5XFAD mice with chemogenetic inhibition (Gi) of the locus coeruleus.



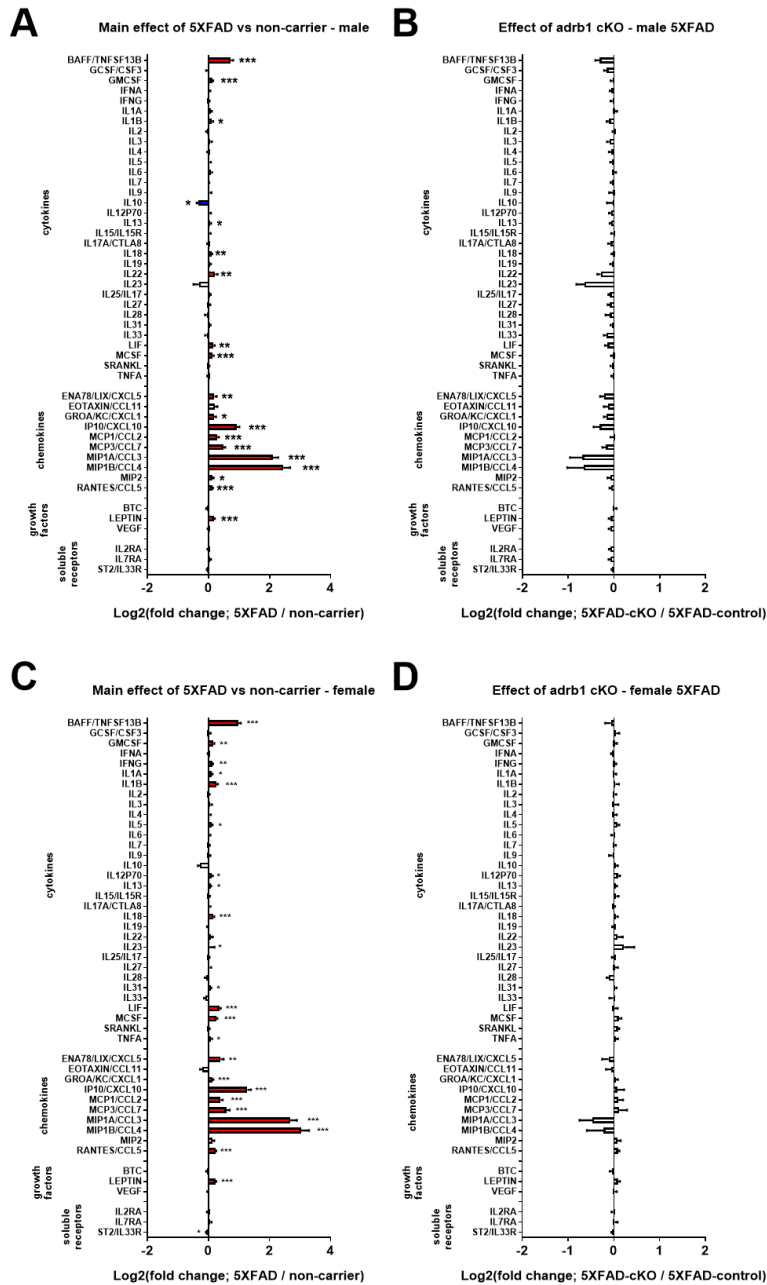
Supplemental Figure S5. Pharmacological inhibition of beta-adrenergic receptors with propranolol potentiates systemic inflammation and attenuates leptin in the 5XFAD mouse model of amyloidosis. Log2-fold change graphs depict effects of **A**) 5XFAD (5XFAD-veh/non-carrier (NC)-veh); n=5) in vehicle-treated mice and **B**) propranolol (5XFAD-prop/5XFAD-veh; n=6) in 5XFAD mice. **C**) Bar graphs indicate raw data from proteins affected by propranolol, as indicated in panel **B**. *p < 0.05; Sidak's post-hoc comparison of means following one-way ANOVA.



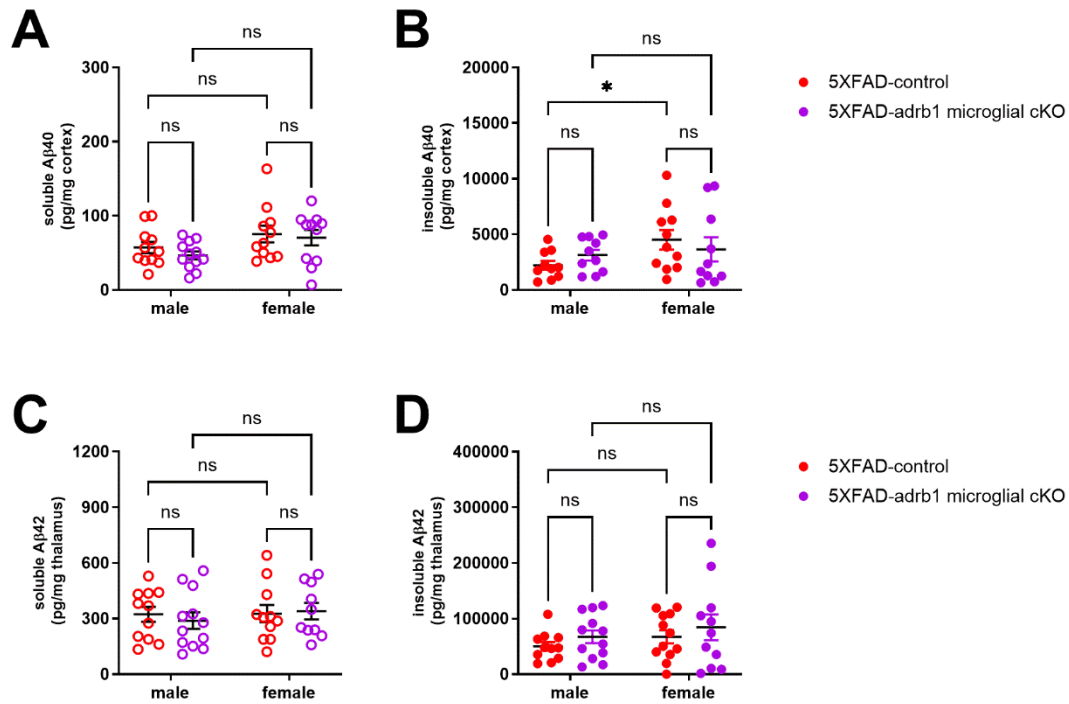
Supplemental Figure S6. No effects of propranolol were detected on frontal cortex concentrations of amyloid beta in 5XFAD mice. Bar graphs depict brain concentrations of **A)** soluble and **B)** insoluble A β 42.



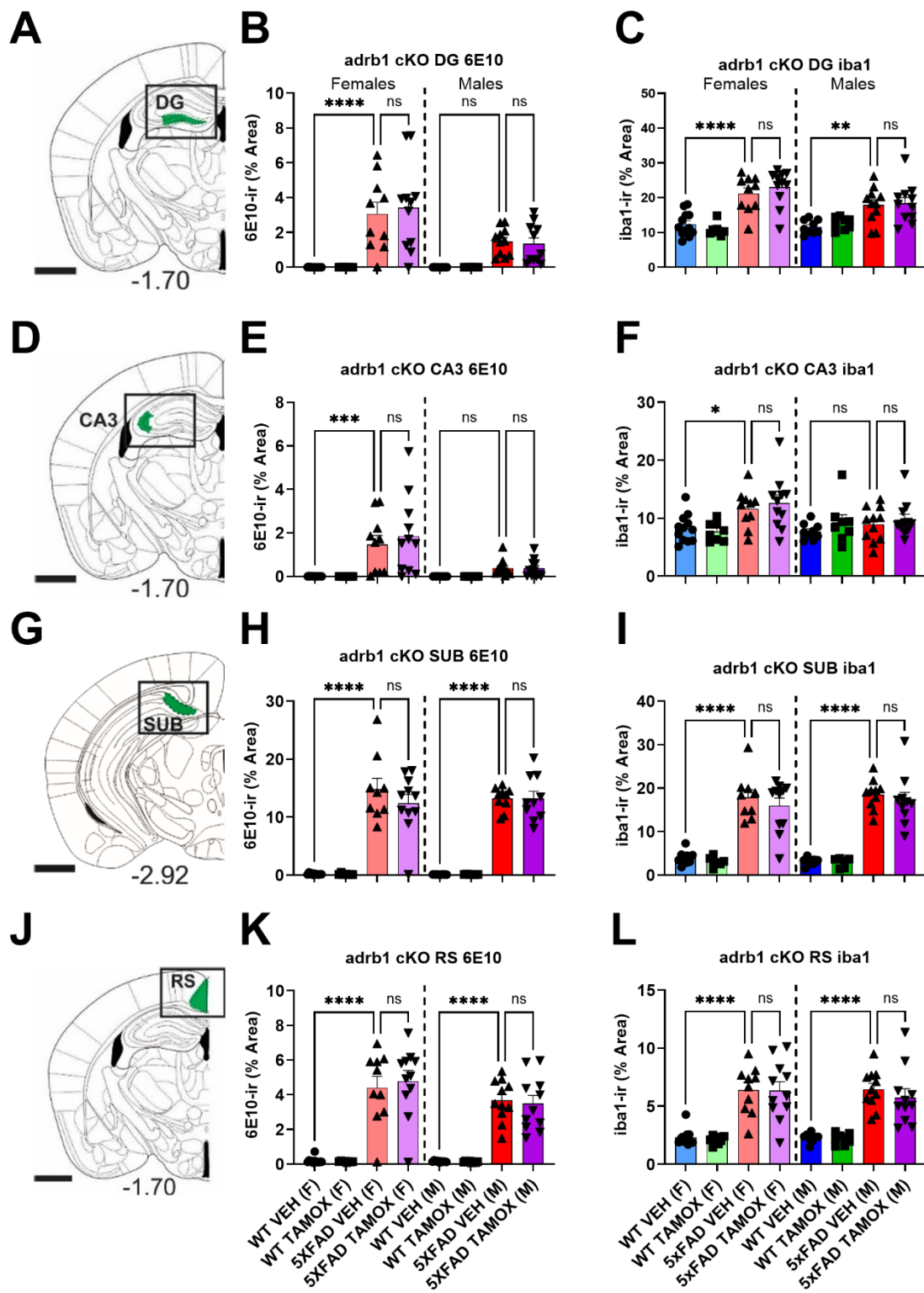
Supplemental Figure S7. Propranolol did not affect behavior in the activity chamber (**A-D**) or Y-maze (**E**) in 5XFAD mice. **A-D**) Line graphs depict Vertical Counts, Distance Moved, Vertical Time, and Time in the Center for the Activity Chamber assay. At baseline, 5XFAD mice showed less vertical time than non-carrier controls. **E**) Bar graphs depict duration in novel versus familiar arms after 7 weeks of dosing with propranolol. *** $p < 0.001$ for non-carrier-vehicle vs 5XFAD-vehicle Dunnett's post-hoc following two-way ANOVA.



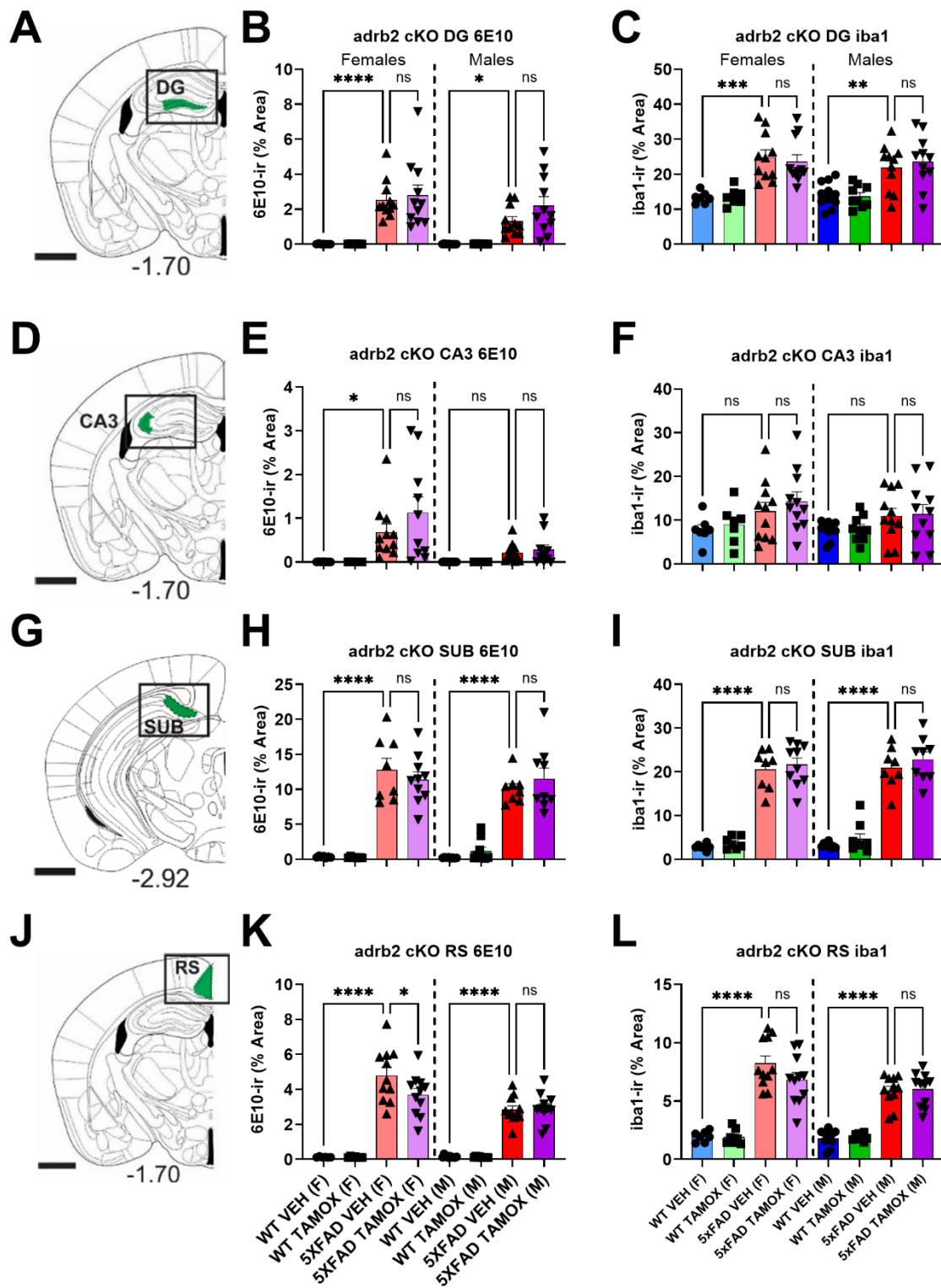
Supplemental Figure S8. Effects of conditional knockout of *adrb1* in microglia in 5XFAD and non-carrier mice. Log2-fold graphs show fold changes across a panel of immune-related markers in response to **A)** 5XFAD in male mice and **B)** *adrb1* cKO in male 5XFAD mice. Likewise, log2-fold graphs show immune regulation from **H)** 5XFAD in female mice and **I)** *adrb1* cKO in female 5XFAD mice. For **A,C)** * indicates the main effects. For **B,D)** * indicates post-hoc Sidak's comparison of means following two-way ANOVA (5XFAD x *adrb1* cKO). **p* < 0.05, ***p* < 0.01, ****p* < 0.001, *****p* < 0.0001.



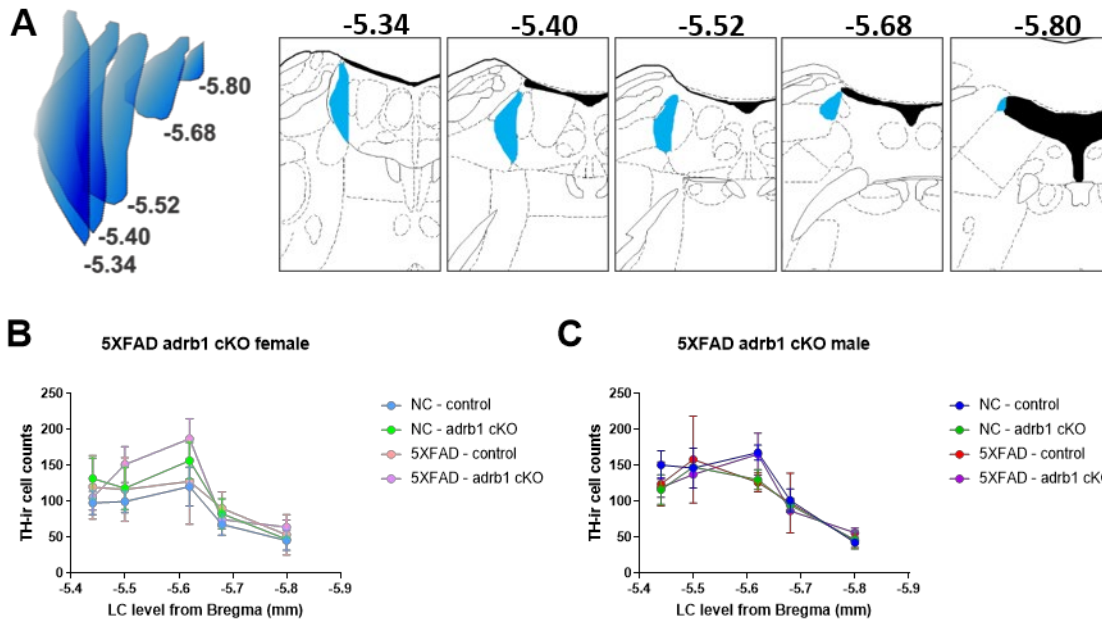
Supplemental Figure S9. No effects of conditional KO of adrb1 were detected on brain tissue concentrations of amyloid beta in 5XFAD mice. Bar graphs depict brain concentrations of soluble and insoluble **A,B** A β 40 (cortex) and **C,D** A β 42 (thalamus). * $p < 0.05$; Sidak's post-hoc comparison of means following two-way ANOVA (sex x adrb1 cKO).



Supplemental Figure S10. Conditional knockdown of adrb1 in mouse microglia did not increase 6E10 or iba1 immunoreactivity (ir) in 5XFAD mice. Bar graphs depict 6E10-ir or iba1-ir in the dentate gyrus (DG), CA3 region of the hippocampus, subiculum (SUB), or retrosplenial cortex (RS). * $p < .05$, ** $p < 0.01$, *** $p < 0.001$, **** $p < 0.0001$; Sidak's post-hoc comparison of means following two-way ANOVA (5XFAD x adrb1 cKO) for each sex.



Supplemental Figure S11. Conditional knockdown of adrb2 in mouse microglia did not increase 6E10 or iba1 immunoreactivity (ir) in 5XFAD mice. Bar graphs depict 6E10-ir or iba1-ir in the dentate gyrus (DG), CA3 region of the hippocampus, subiculum (SUB), or retrosplenial cortex (RS). * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, **** $p < 0.0001$; Sidak's post-hoc comparison of means following two-way ANOVA (5XFAD x adrb2 cKO) for each sex.



Supplemental Figure S12. Conditional knockdown of *adrb1* in mouse microglia does not alter LC neuronal cell counts. **A)** Schematic representation of the rostrocaudal extent of locus coeruleus regional cell quantification with atlas plates. Numbers indicate mm from bregma. Line graphs depict the quantification of LC TH-immunoreactive neurons across the rostrocaudal extent of the LC in **B)** female and **C)** male mice.