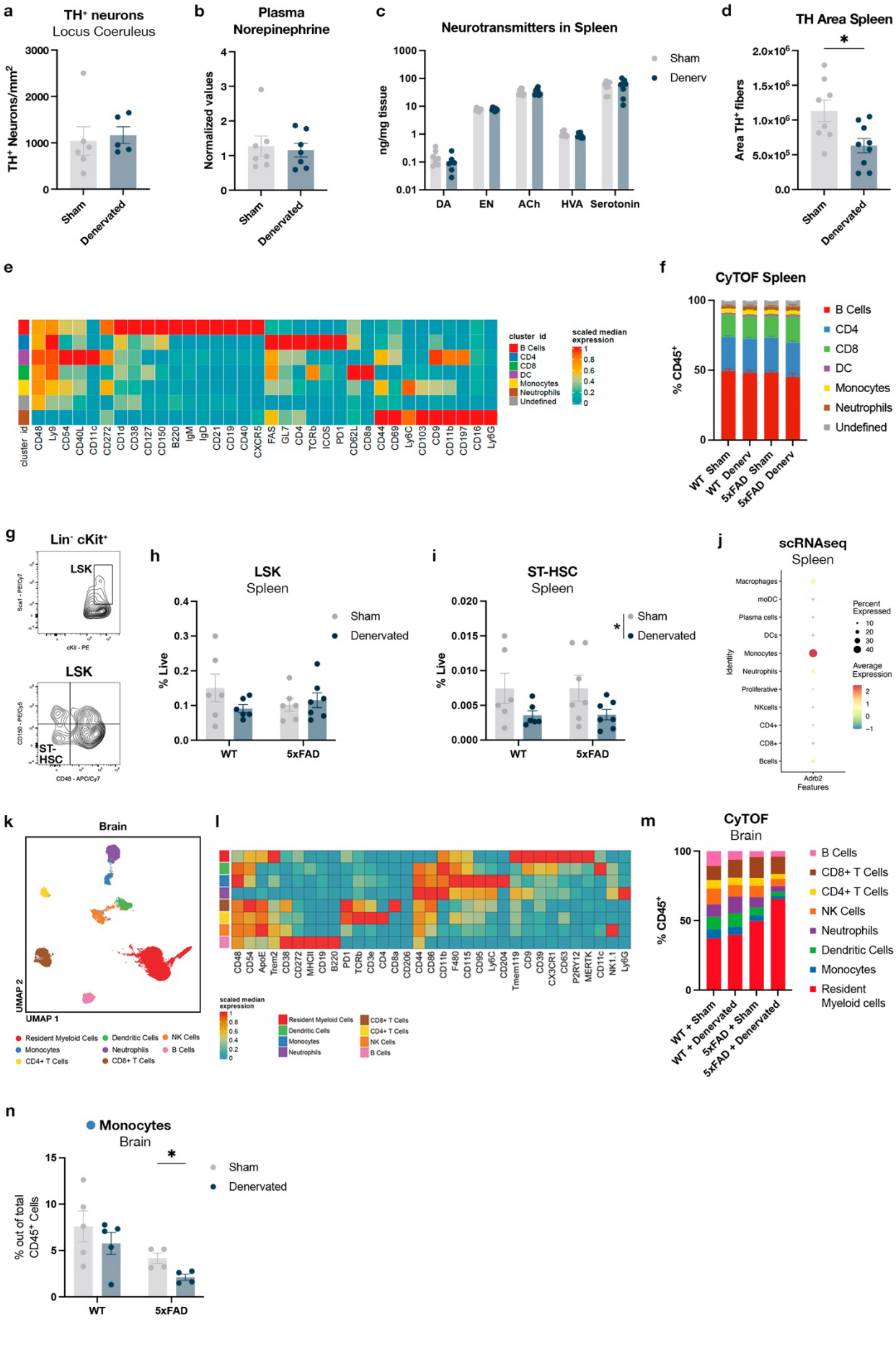
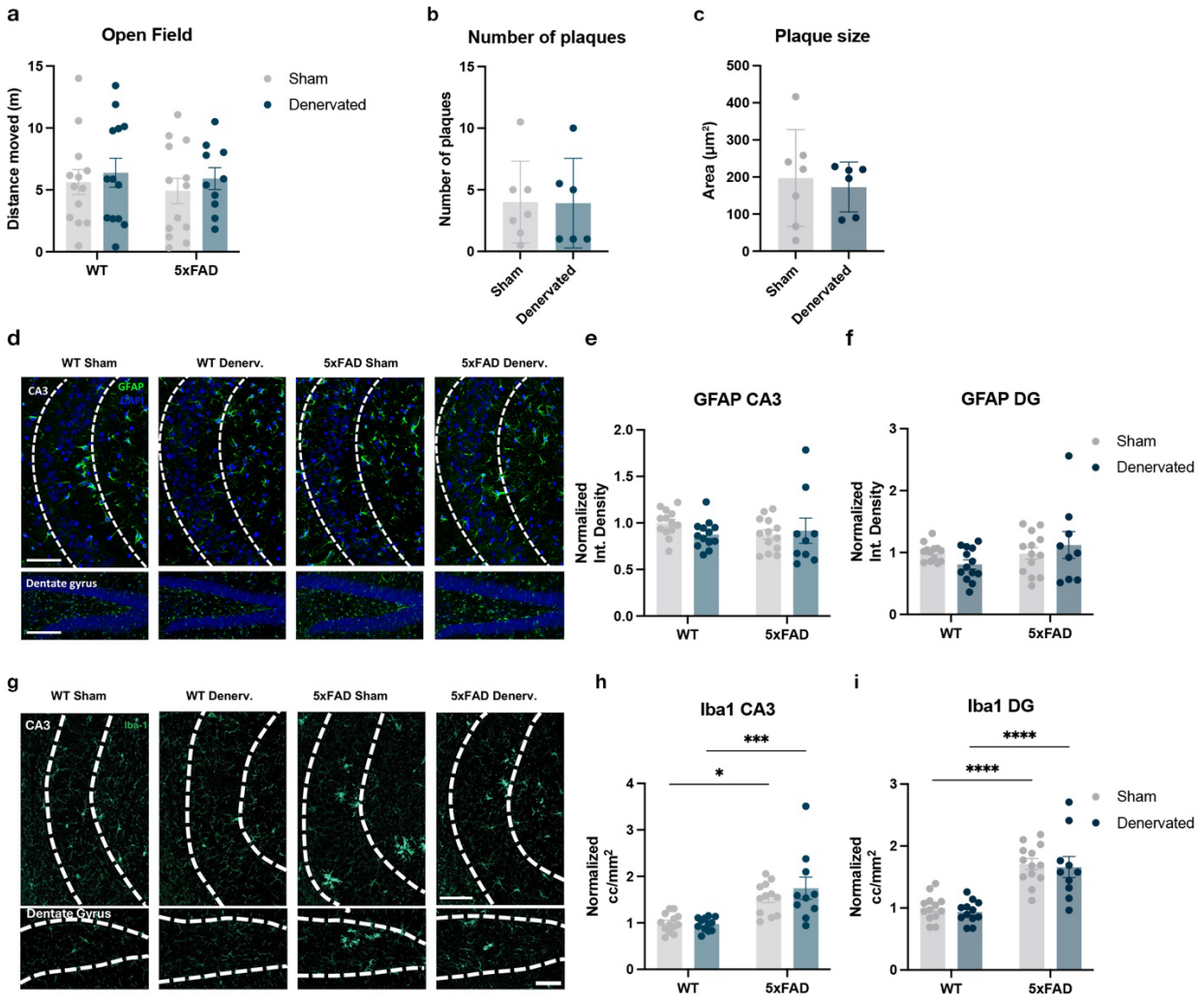
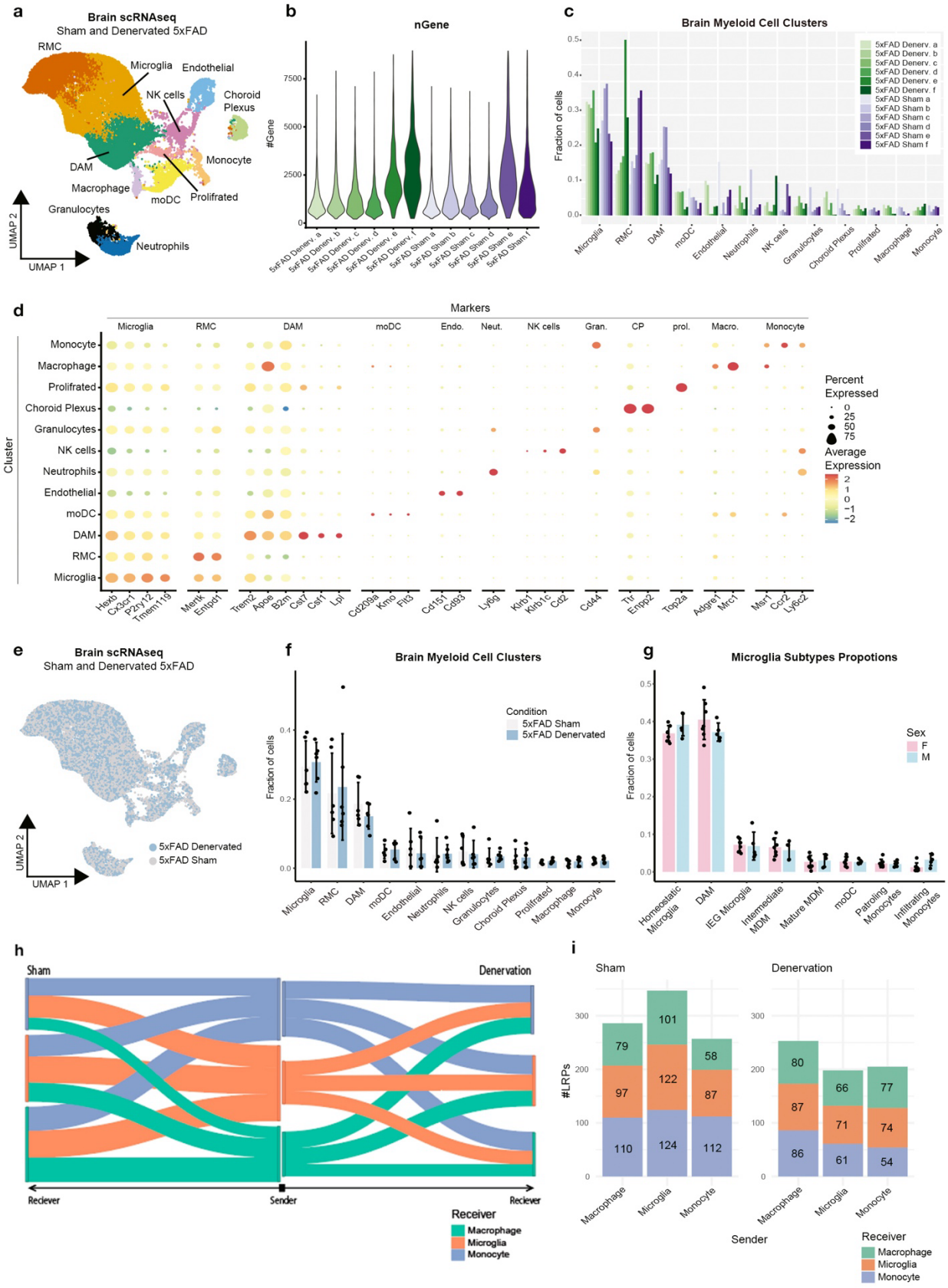

a
TH+ neurons
Locus Coeruleus
TH+ Neurons/mm2
3000
2000
1000
0
Sham
Denervated
b
Plasma
Norepinephrine
Normalized values
4
3
2
1
0
Sham
Denervated
c
Neurotransmitters in Spleen
ng/mg tissue
1000
100
10
1
0.1
0.01
DA
EN
ACh
HVA
Serotonin
Sham
Denerv
d
TH Area Spleen
Area TH+ fibers
2.0x10^6
1.5x10^6
1.0x10^6
5.0x10^5
0.0
*
Sham
Denervated
e
cluster id
B Cells
CD4
CD8
DC
Monocytes
Neutrophils
Undefined
scaled median expression
1
0.8
0.6
0.4
0.2
0
CD48
Ly9
CD54
CD40L
CD11c
CD272
CD1d
CD38
CD127
CD150
B220
IgM
IgD
CD21
CD19
CD40
CXCR5
FAS
GL7
CD4
TCRb
ICOS
PD1
CD62L
CD8a
CD44
CD69
Ly6C
CD103
CD9
CD11b
CD197
CD16
Ly6G
f
CyTOF Spleen
% CD45+
100
50
0
B Cells
CD4
CD8
DC
Monocytes
Neutrophils
Undefined
WT Sham
WT Denerv
5xFAD Sham
5xFAD Denerv
g
Lin- cKit+
LSK
Sca1 - PE/Cy7
cKit - PE
LSK
CD150 - PE/Cy5
ST-HSC
CD48 - APC/Cy7
h
LSK
Spleen
% Live
0.4
0.3
0.2
0.1
0.0
Sham
Denervated
WT
5xFAD
i
ST-HSC
Spleen
% Live
0.020
0.015
0.010
0.005
0.000
*
Sham
Denervated
WT
5xFAD
j
scRNAseq
Spleen
Macrophages
moDC
Plasma cells
DCs
Monocytes
Neutrophils
Proliferative
NKcells
CD4+
CD8+
Bcells
Identity
Adrb2
Features
Percent Expressed
10
20
30
40
Average Expression
2
1
0
−1
k
Brain
UMAP 2
UMAP 1
Resident Myeloid Cells
Dendritic Cells
NK Cells
Monocytes
Neutrophils
B Cells
CD4+ T Cells
CD8+ T Cells
l
scaled median expression
1
0.8
0.6
0.4
0.2
0
Resident Myeloid Cells
Dendritic Cells
Monocytes
Neutrophils
CD8+ T Cells
CD4+ T Cells
NK Cells
B Cells
CD48
CD54
ApoE
Trem2
CD38
CD272
MHCII
CD19
B220
PD1
TCRb
CD3e
CD4
CD8a
CD206
CD44
CD86
CD11b
F480
CD115
CD95
Ly6C
CD204
Tmem119
CD9
CD39
CX3CR1
CD63
P2RY12
MERTK
CD11c
NK1.1
Ly6G
m
CyTOF
Brain
% CD45+
100
50
0
B Cells
CD8+ T Cells
CD4+ T Cells
NK Cells
Neutrophils
Dendritic Cells
Monocytes
Resident Myeloid cells
WT + Sham
WT + Denervated
5xFAD + Sham
5xFAD + Denervated
n
Monocytes
Brain
% out of total CD45+ Cells
15
10
5
0
*
Sham
Denervated
WT
5xFAD

Supplementary Fig. 1: Spleen denervation in the 5xFAD mouse model causes alterations in extramedullary hematopoiesis and increases monocyte homing to the brain. a, Quantification of TH^+ neurons in the locus coeruleus of denervated animals compared to sham-operated mice (Sham, N = 3M/3F; Denervated, N = 2M/3F). **b**, Levels of systemic circulating norepinephrine in the plasma of sham-operated and denervated mice (Sham, N = 4M/3F; Denervated, N = 4M/3F). **c**, Levels of neurotransmitters detected in the spleen of denervated animals compared to sham operated mice (Sham, N = 4M/4F; Denervated, N = 4M/4F). DA, dopamine; EN, epinephrine; ACh, acetylcholine; HVA, homovanillic acid. **d**, Quantification of tyrosine hydroxylase (TH) by immunofluorescence in the spleen of sham and denervated animals (Sham, N = 4M/4F; Denervated, N = 4M/5F). **e**, Heatmap with scaled marker expression values detected by mass cytometry (CyTOF) in the spleen of sham-operated or denervated WT or 5xFAD animals. **f**, Proportions of different immune cell subsets detected by CyTOF in the spleen of sham-operated or denervated WT or 5xFAD animals (WT-Sham, N = 6M/6F; WT-Denerv, N = 6M/6F; 5xFAD-Sham, N = 5M/7F; 5xFAD-Denerv, N = 4M/5F). **g**, Flow cytometry gating strategy of HSPC subsets in the spleen of 5xFAD mice. **h**, Abundance of $Lin^-Sca1^+cKit^+$ (LSK) hematopoietic progenitors in the spleen of sham-operated or denervated WT or 5xFAD mice (WT-Sham, N = 4M/2F; WT-Denerv, N = 3M/3F; 5xFAD-Sham, N = 3M/3F; 5xFAD-Denerv, N = 4M/3F). **i**, Short-term hematopoietic stem cells (ST-HSC) in the spleen in WT or 5xFAD animals after denervation, compared to sham-operated animals (WT-Sham, N = 4M/2F; WT-Denerv, N = 3M/3F; 5xFAD-Sham, N = 3M/3F; 5xFAD-Denerv, N = 4M/3F). **j**, Dot-plot showing the scaled expression of the *Adrb2* gene in the different cell types found in the spleen by single-cell RNAseq. **k**, Dimensional reduction by UMAP of mass cytometry (CyTOF) data of immune cells in the brain of sham or denervated WT and 5xFAD mice. **l**, Heatmap showing the scaled signal of markers studied by CyTOF to annotate clusters of immune cells. **m**, Proportion of the different immune cell types detected in the brains of WT and 5xFAD mice that were denervated or sham-operated. **n**, Proportion of infiltrating monocytes in the brain as determined by CyTOF (WT-Sham, N = 5M; WT-Denerv, N = 5M; 5xFAD-Sham, N = 4M; 5xFAD-Denerv, N = 4M). Unpaired t-test or two-way ANOVA followed by Sidak's multiple comparisons test. In all panels, data are represented as mean ±SEM. *$p < 0.05$.

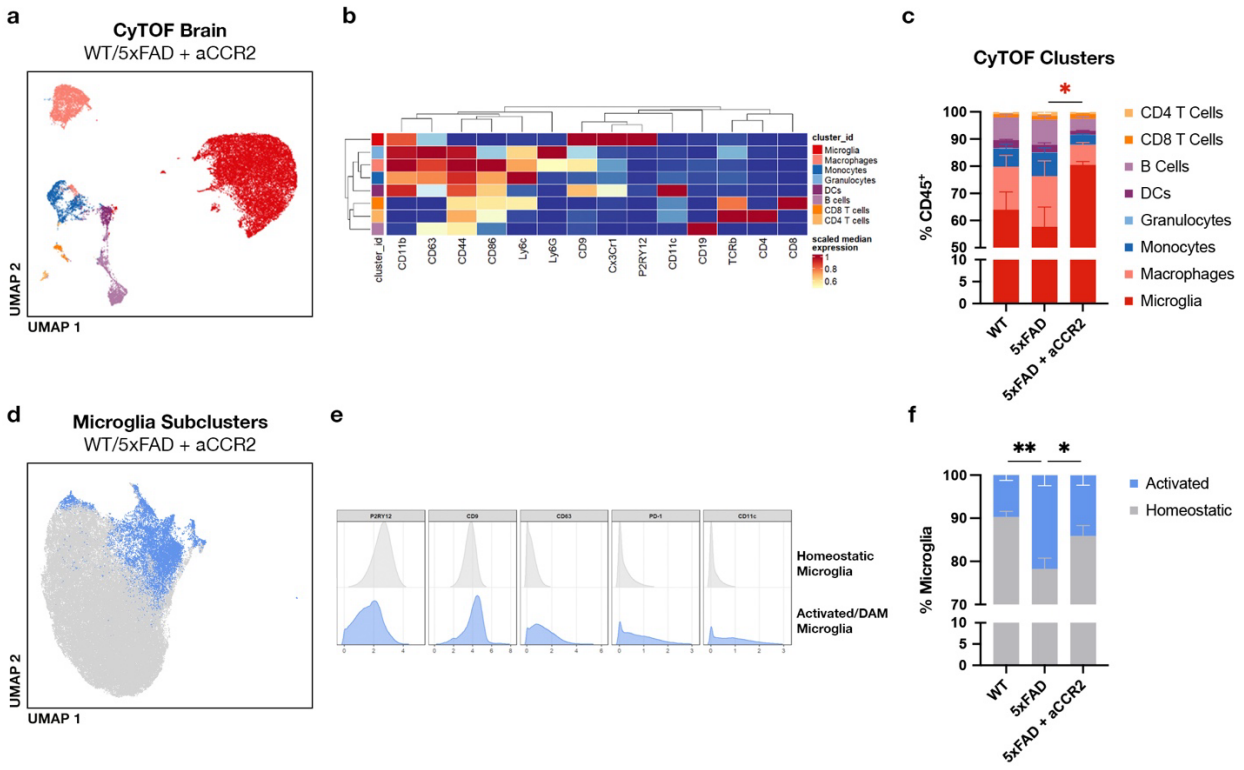


Supplementary Fig. 2: Denervation of the spleen does not affect amyloid deposition, astrogliosis or microgliosis in the 5xFAD model. a, Distance moved during 20 minutes in the open field test (WT-Sham, N = 9M/9F; WT-Denerv, N = 9M/8F; 5xFAD-Sham, N = 8M/9F; 5xFAD-Denerv, N = 7M/8F). **b**, Number of plaques in the hippocampus of sham-operated or denervated 5xFAD animals (5xFAD-Sham, N = 4M/3F; 5xFAD-Denerv, N = 3M/3F). **c**, Plaque size in the hippocampus of sham-operated or denervated 5xFAD animals (5xFAD-Sham, N = 4M/3F; 5xFAD-Denerv, N = 3M/3F). **d**, Representative images of GFAP immunolabeling in the CA3 and the dentate gyrus in the hippocampus of sham-operated or denervated WT or 5xFAD mice. Scale bar: 100 µm. **e**, Quantification of the GFAP intensity in the CA3 of sham-operated or denervated WT and 5xFAD animals (WT-Sham, N = 6M/7F; WT-Denerv, N = 7M/6F; 5xFAD-Sham, N = 6M/7F; 5xFAD-Denerv, N = 5M/4F). **f**, Quantification of the GFAP intensity in the DG of sham-operated or denervated WT and 5xFAD animals (WT-Sham, N = 6M/7F; WT-

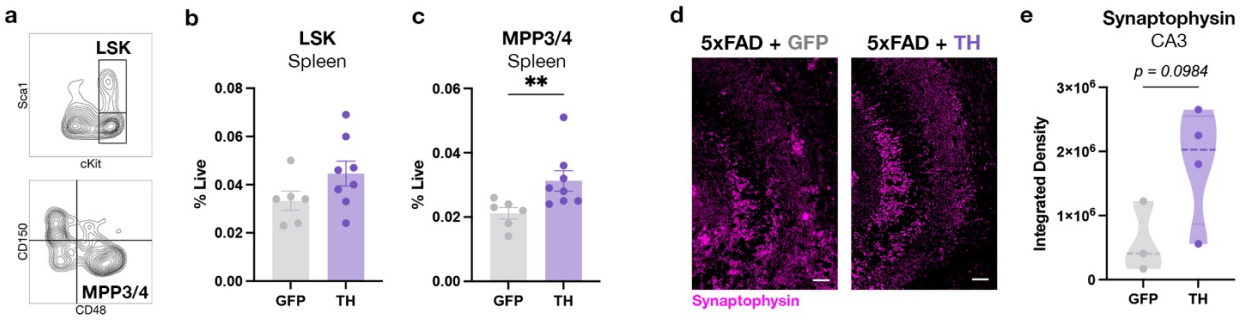
Denerv, N = 7M/6F; 5xFAD-Sham, N = 6M/7F; 5xFAD-Denerv, N = 5M/4F). **g**, Representative images of Iba1 immunostaining in the CA3 and the dentate gyrus in the hippocampus of sham-operated or denervated WT and 5xFAD mice. Scale bar: 100 μm. **h**, Quantification of the normalized Iba1 counts in the CA3 of sham-operated or denervated WT or 5xFAD animals (WT-Sham, N = 6M/7F; WT-Denerv, N = 6M/6F; 5xFAD-Sham, N = 5M/7F; 5xFAD-Denerv, N = 5M/5F). **i**, Quantification of the normalized Iba1 counts in the DG of sham-operated or denervated WT or 5xFAD animals (WT-Sham, N = 6M/7F; WT-Denerv, N = 6M/6F; 5xFAD-Sham, N = 5M/7F; 5xFAD-Denerv, N = 5M/5F). Unpaired t-test or two-way ANOVA followed by Sidak's multiple comparisons test. In all panels, data are represented as mean ±SEM. *$p < 0.05$, ***$p < 0.001$.


a
Brain scRNAseq
Sham and Denervated 5xFAD
RMC
Microglia
Endothelial
NK cells
Choroid Plexus
Monocyte
DAM
Macrophage
moDC
Prolifrated
Granulocytes
Neutrophils
UMAP 2
UMAP 1
b
nGene
#Gene
5xFAD Denerv. a
5xFAD Denerv. b
5xFAD Denerv. c
5xFAD Denerv. d
5xFAD Denerv. e
5xFAD Denerv. f
5xFAD Sham a
5xFAD Sham b
5xFAD Sham c
5xFAD Sham d
5xFAD Sham e
5xFAD Sham f
c
Brain Myeloid Cell Clusters
Fraction of cells
Microglia
RMC
DAM
moDC
Endothelial
Neutrophils
NK cells
Granulocytes
Choroid Plexus
Prolifrated
Macrophage
Monocyte
d
Markers
Cluster
Percent Expressed
Average Expression
e
Brain scRNAseq
Sham and Denervated 5xFAD
5xFAD Denervated
5xFAD Sham
f
Brain Myeloid Cell Clusters
Condition
5xFAD Sham
5xFAD Denervated
g
Microglia Subtypes Propotions
Sex
F
M
Homeostatic Microglia
IEG Microglia
Intermediate MDM
Mature MDM
Patroling Monocytes
Infiltrating Monocytes
h
Sham
Denervation
Reciever
Sender
Receiver
Macrophage
Microglia
Monocyte
i
Sham
Denervation
#LRPs
Sender
Receiver
Macrophage
Microglia
Monocyte

Supplementary Fig. 3: Denervation of the spleen remodels monocyte-microglia communication in the brains of 5xFAD mice. a, UMAP embedding of 34,198 single-cell RNA profiles from whole brain- myeloid cells from sham-operated or denervated 5-month-old 5XFAD mice. **b**, Number of genes across samples. Violin plot showing the distribution of the number of transcripts (unique UMIs) detected per mouse. **c**, Bar plot of the proportions of all cell types recognized in the myeloid cell-enriched dataset across samples. **d**, Marker genes used for annotation of the clusters. **e**, UMAP embedding of 34,198 single-cell RNA profiles from whole brain- myeloid cells from sham-operated or denervated 5-month-old 5XFAD mice, color-coded by treatment. **f**, Bar plot of the proportions of brain-myeloid cell types across the two conditions: sham-operated and denervated. **g**, Bar plot of the proportions of brain-myeloid cell types across sex: Male and Female. **h**, Number of statistically significant LRPs between pairs of cell types (color-coded) across experimental groups out of top 25% ranked LRPs of the MultiNicheNet analysis (score>0.653). **i**, Differential ligand-receptor pairs (LRPs) across experimental groups out of top-ranked LRPs of the MultiNicheNet analysis (score>0. 653).



Supplementary Fig. 4: Blockade of the CCR2-CCL2 axis reduces monocyte homing to the brain and microglial activation. a, UMAP dimensional reduction of CD45^{+} cells from the brains of WT and 5xFAD mice treated with anti-CCR2 blocking antibody. **b**, Heatmap showing immune markers used in the CyTOF analysis to annotate the immune clusters. **c**, Immune cell proportions in the brains of WT and 5xFAD mice treated with anti-CCR2 (WT, N = 3M/3F; 5xFAD, N = 3M/4F; 5xFAD + aCCR2, N = 3M/3F). **d**, Subclustering of microglial cells from the brains of WT and 5xFAD mice treated with anti-CCR2. Clusters of activated microglia are highlighted in blue. **e**, Histograms showing the expression of different activation and homeostatic microglial markers in the two annotated subpopulations. **f**, Proportions of activated or homeostatic microglia in the brains of WT and 5xFAD mice treated with anti-CCR2 (WT, N = 3M/3F; 5xFAD, N = 3M/4F; 5xFAD + aCCR2, N = 3M/3F). One-way ANOVA followed by Dunnett's multiple comparisons test. Data are represented as mean ±SEM. *$p < 0.05$, **$p < 0.01$



Supplementary Fig. 5: Tyrosine hydroxylase overexpression in the spleen promotes extramedullary hematopoiesis and synaptic recovery in the 5xFAD model. a, Flow cytometry gating strategy of HSPC subsets in the spleen of 5xFAD mice. **b**, Abundance of $Lin^{-}Sca1^{+}cKit^{+}$ (LSK) hematopoietic progenitors in the spleen of 5xFAD mice overexpressing GFP or tyrosine hydroxylase (TH) (5xFAD-GFP, N = 3M/3F; 5xFAD-TH, N = 3M/5F). **c**, Multipotent progenitors with lymphoid and myeloid potential (MPP3/4) in the spleen of 5xFAD mice overexpressing GFP or TH (5xFAD-GFP, N = 3M/3F; 5xFAD-TH, N = 3M/5F). **d**, Representative images of synaptophysin staining in the CA3 region of the hippocampus of 5xFAD mice overexpressing GFP or TH. Scale bar: 50 µm. e, Synaptophysin quantification in the CA3 region of the hippocampus of 5xFAD mice overexpressing GFP or TH (5xFAD-GFP, N = 3F; 5xFAD-TH, N = 5F). Unpaired t-test. In all panels, data are represented as mean ±SEM. **p < 0.01.

Supplementary Table 1: Flow Cytometry antibodies

Antigen	Fluorophore	Clone	Supplier	Ref. No.	Dilution
CD117 (cKit)	PE	2B8	BioLegend	105808	1/200
CD11b	PE	M1/70	BioLegend	101207	1/500
CD11b	FITC	M1/70	BioLegend	101206	1/500
CD150	PE-Cy5	TC15-12F12.2	BioLegend	115912	1/200
CD44	APC	IM7	BioLegend	103011	1/200
CD45	BV421	30-F11	BioLegend	103134	1/200
CD48	APC-Cy7	HM48-1	BioLegend	103432	1/200
Lineage Cocktail	Biotin	---	Miltenyi Biotec	130-092-613	1/20
Ly-6C	PE-Dazzle	HK1.4	BioLegend	128044	1/200
Ly-6G	APC	1A8	BioLegend	127613	1/500
Ly-6A/E (Sca-1)	PE-Cy7	D7	BioLegend	108114	1/200
Streptavidin	FITC	---	BioLegend	405202	1/200
TCRbeta	APC-Cy7	H57-597	BioLegend	109220	1/200

Supplementary Table 2: CyTOF pannel (all concentrations were used in 1:100)

Marker	Metal Tag	Clone
CD45	89Y	30-F11
CD4	116Cd	RM4-5
Ly6G	141Pr	1A8
CD39	142Nd	24DMS1
TCRβ	143Nd	H57-397
CD11b	148Nd	M1/70
CD19	149Sm	6D5
Ly6C	150Nd	HK1.4
MERTK	151Eu	2B10C42
TMEM119	152Sm	106-6
TREM2	153Eu	237920
CD272 (BTLA)	156Gd	6F7
CD9	158Gd	KMC8
PD-1	159Tb	J43
P2RY12	160Gd	S16007D
CD54 (ICAM-1)	163Dy	YN1/1.7.4
CX3CR1	164Dy	SA011F11
ApoE	165Ho	WUE-4
CD204 (MSR1)	167Er	1F8c33
CD8	168Er	53-6.7
CD206 (MRC1)	169Tm	C068C2
CD44	171Yb	IM7
CD86	172Yb	GL1
CD38	175Lu	90
CD11c	209Bi	N418