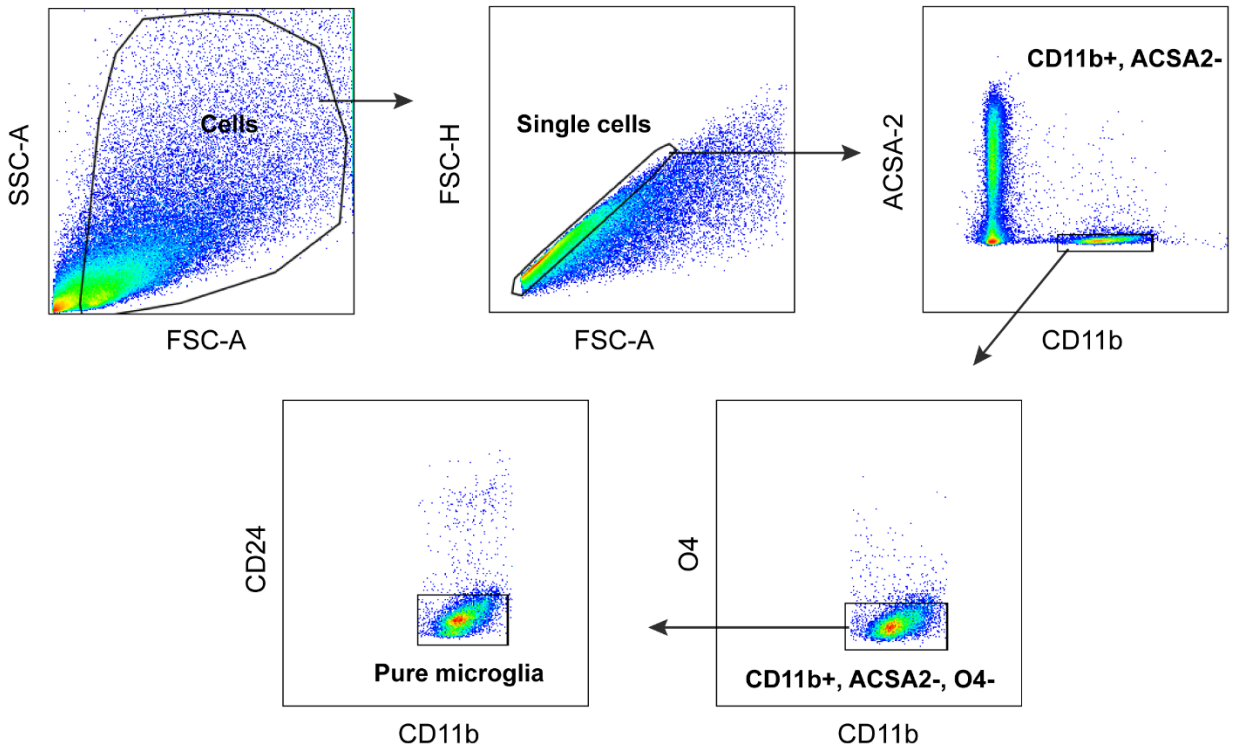

Figure S1. Scheme for FACS sorting of microglia from mouse brains, Related to Figure 3

Microglia are gated from the single cell population as CD11b+/ACSA2-/O4-/CD24- cells to exclude potential contamination of astrocytes (ACSA2+), oligodendrocytes (O4+), blood myeloid cells (CD24+) and neurons (CD24+).

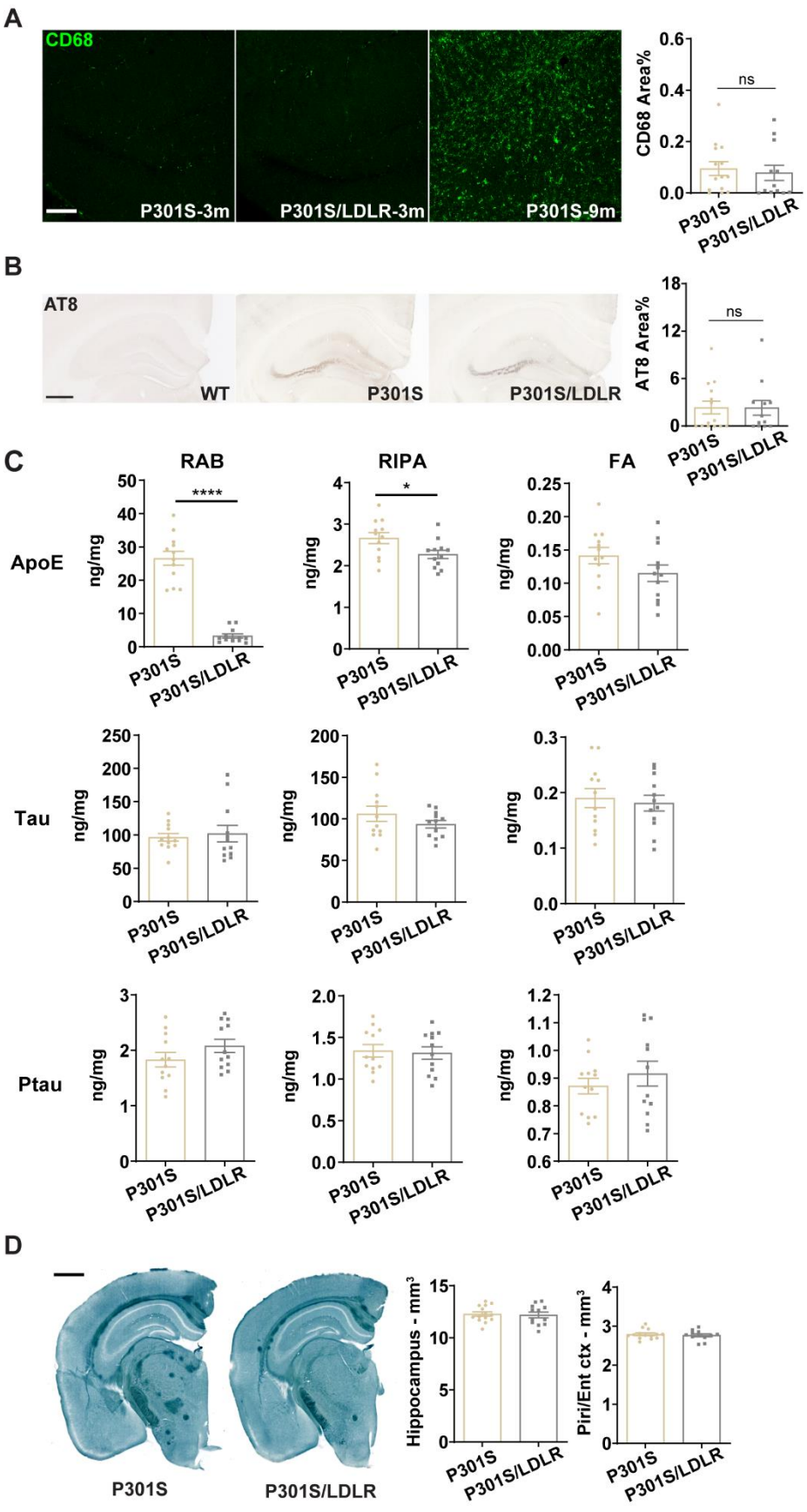
A
CD68
P301S-3m
P301S/LDLR-3m
P301S-9m
CD68 Area%
ns
P301S
P301S/LDLR
B
AT8
WT
P301S
P301S/LDLR
AT8 Area%
ns
C
RAB
RIPA
FA
ApoE
Tau
Ptau
ng/mg
****
*
D
P301S
P301S/LDLR
Hippocampus - mm³
Piri/Ent ctx - mm³

Figure S2. LDLR OX does not affect tau pathology and brain volume at 3-month of age prior to microglial activation, Related to Figure 1

(A) Immunofluorescent staining and quantification of CD68 in the hippocampus of 3-month P301S and P301S/LDLR mice (n=12-14). A 9-month P301S sample was used as a positive control. Scale bar: 100µm.

(B) Left: Representative images of AT8 staining in the hippocampus of 3-month old WT, P301S and P301S/LDLR mice. P301S and P301S/LDLR mice show an early type1 ptau pattern in mossy fibers whereas WT mice do not show any AT8+ signal. Right: Quantification of AT8+ area% (n=12-14). Scale bar: 500µm.

(C) ELISA measurement of apoE, human tau, and p-tau levels in RAB, RIPA and 70% FA fractions respectively for 3-month P301S and P301S/LDLR mouse posterior cortical lysates (n=12).

(D) Sudan Black staining and brain volume quantification of 3-month P301S and P301S/LDLR mice (n=12-14). Scale bar: 1mm.

Data expressed as mean ± SEM. *p<0.05, ****p<0.0001. Mann-Whitney test (two-sided) in (A) and (B). Student's t-test (two-sided) in (C) and (D).

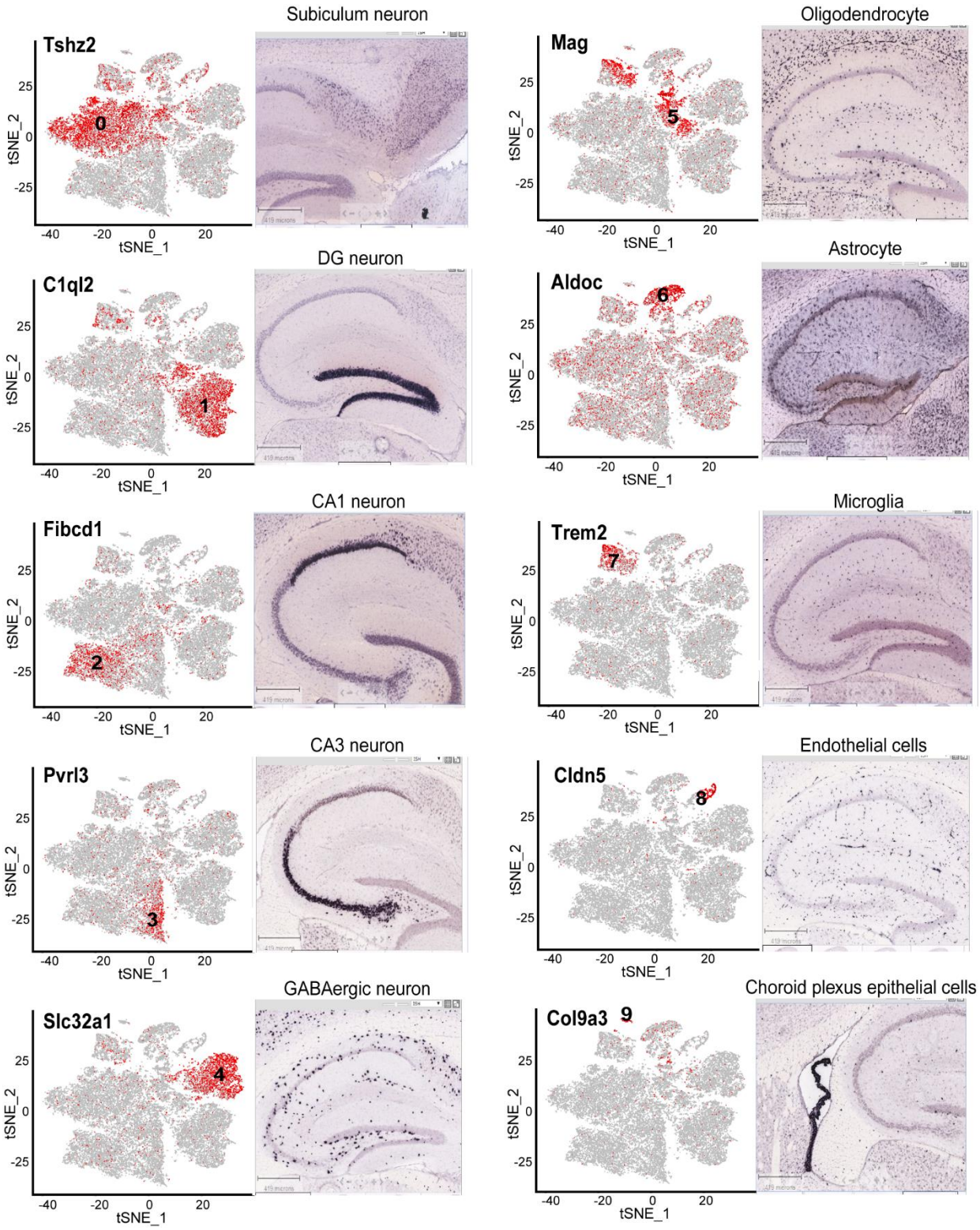
Subiculum neuron
Tshz2
0
Oligodendrocyte
Mag
5
DG neuron
C1ql2
1
Astrocyte
Aldoc
6
CA1 neuron
Fibcd1
2
Microglia
Trem2
7
CA3 neuron
Pvrl3
3
Endothelial cells
Cldn5
8
GABAergic neuron
Slc32a1
4
Choroid plexus epithelial cells
Col9a3
9
tSNE_1
tSNE_2
-40
-20
0
20
25
0
-25

Figure S3. Brain cell types determined by cell type-specific markers in snRNAseq, Related to Figure 4

RNA in situ hybridization data in Allen brain atlas showing spatial locations and morphological properties of each cell cluster marker gene from Figure 4B. This information was used to determine cell identity.

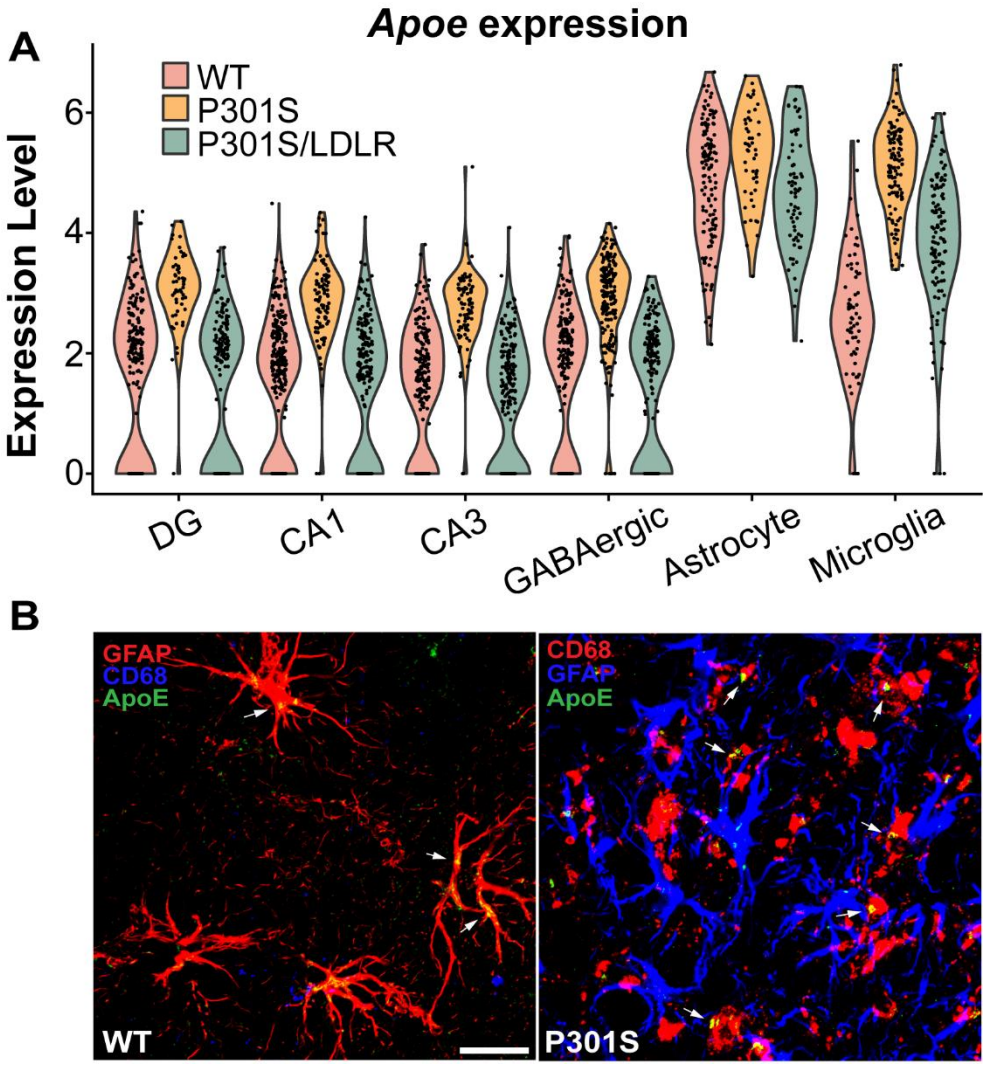

Figure S4. *Apoe* expression is upregulated uniquely in microglia over other brain cell types in tau-associated neurodegeneration, Related to Figure 4

(A) Violin plot showing *Apoe* expression in major brain cell types of 9-month WT, P301S, and P301S/LDLR mice. Expression level on the Y-axis is the normalized, natural log-transformed gene count. *Apoe* expression in neurons under physiological condition is likely background noise.

(B) Co-staining of apoE with astrocytes (GFAP) and activated microglia (CD68) in 9-month WT and P301S mice. Scale bar: 20μm.

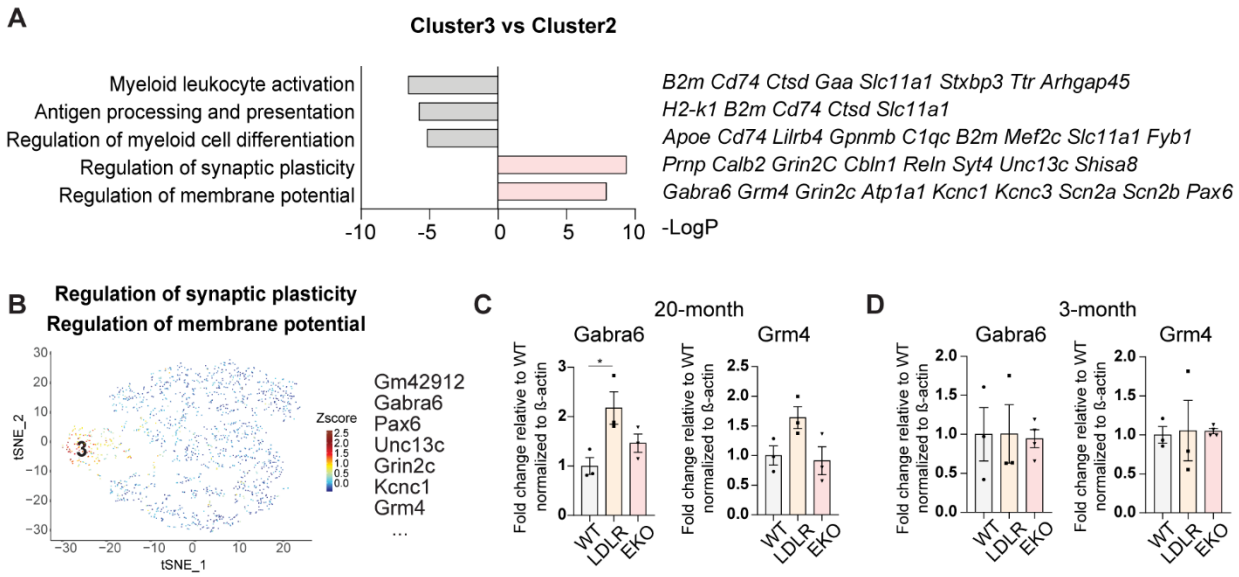

Figure S5. LDLR-associated microglia upregulate genes encoding subsets of ion channels and neurotransmitter receptors and downregulate microglial activation pathways, Related to Figure 5

(A) Top upregulated and downregulated pathways with featured genes in LDLR-associated microglia (cluster 3) compared to DAM microglia (cluster 2).

(B) tSNE plot showing top enriched genes and pathways in LDLR-associated microglia (cluster 3).

(C, D) qPCR for top upregulated genes in cluster 3 (*Gabra6, Grm4*) in microglia acutely isolated from 20-month (C) and 3-month (D) WT, LDLR and EKO mouse brains (n=3).

Data expressed as mean ± SEM, One-way ANOVA with Tukey's post hoc test, two-sided for all quantifications. *p<0.05.

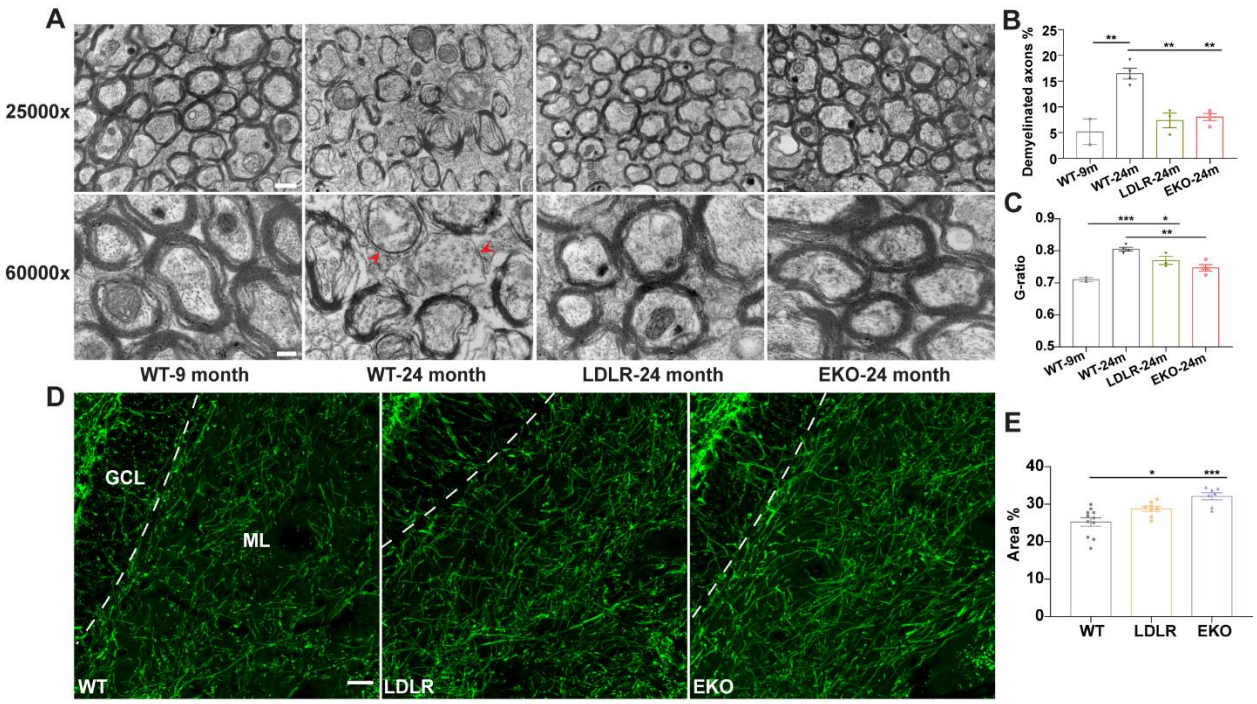

Figure S6. ApoE-deficiency and LDLR-OX preserve myelin integrity in aging, Related to Figure 7

(A) EM images of corpus callosum in posterior brain regions of 9-month WT, 24-month WT, 24-month LDLR, and 24-month EKO mice. Upper row: 25000X magnification, scale bar: 600nm; Lower row: 60000X magnification, scale bar: 200nm. Arrowheads point to axons with myelin damage.

(B, C) Quantification of axonal G-ratio and the percentage of demyelinated axons (myelin layer ≤ 2) in EM images (n=2-4).

(D, E) MBP staining and quantification of MBP covered area in DG molecular layer of 24-month mice (n=7-11). Mixed sex. Left of dash line: GCL (granule cell layer); right of dash line: ML (molecular layer); scale bar: 25μm.

Data expressed as mean ± SEM, One-way ANOVA with Tukey's post hoc test, two-sided for all quantifications. *p<0.05, **p<0.01, ***p<0.001.