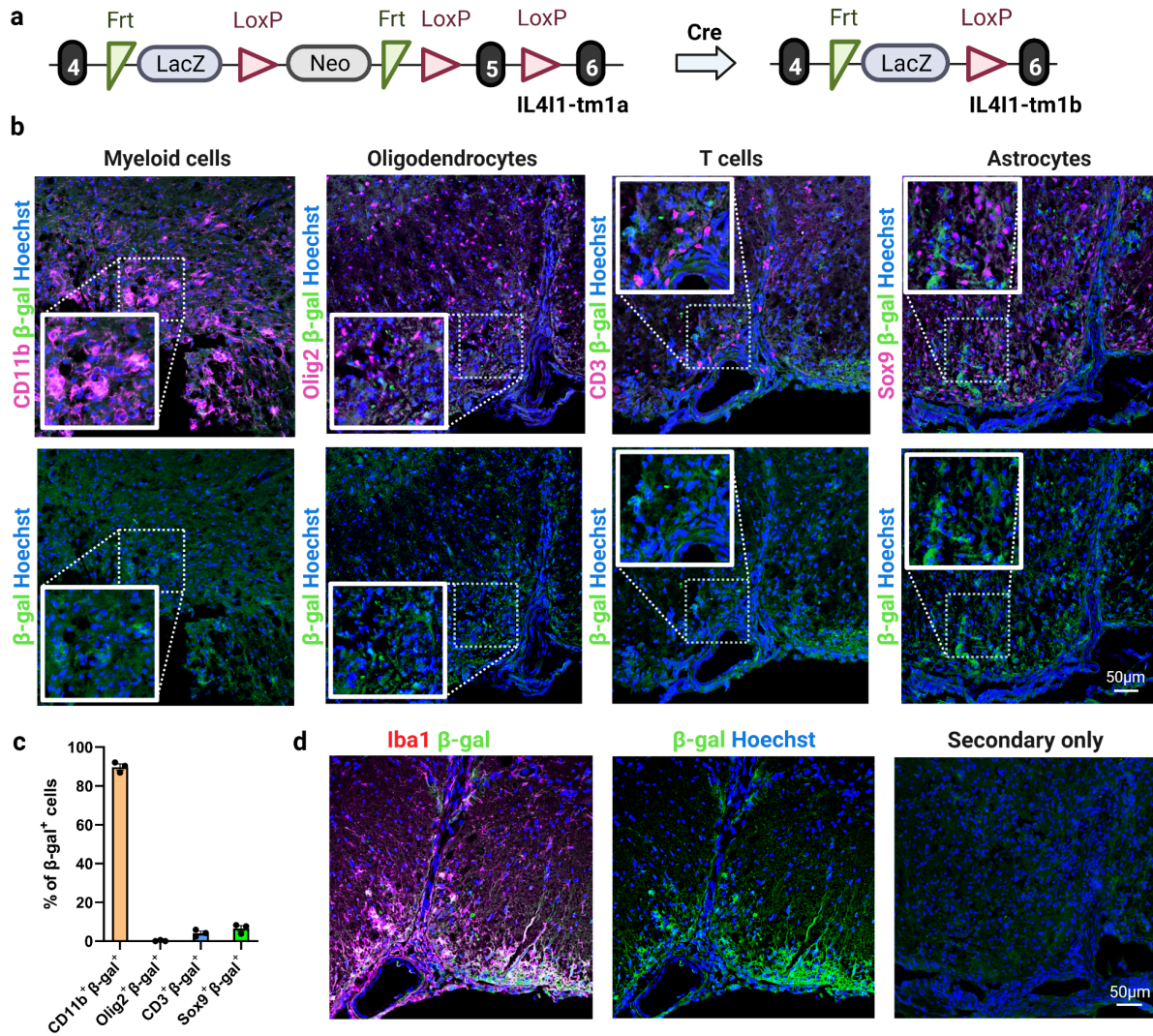


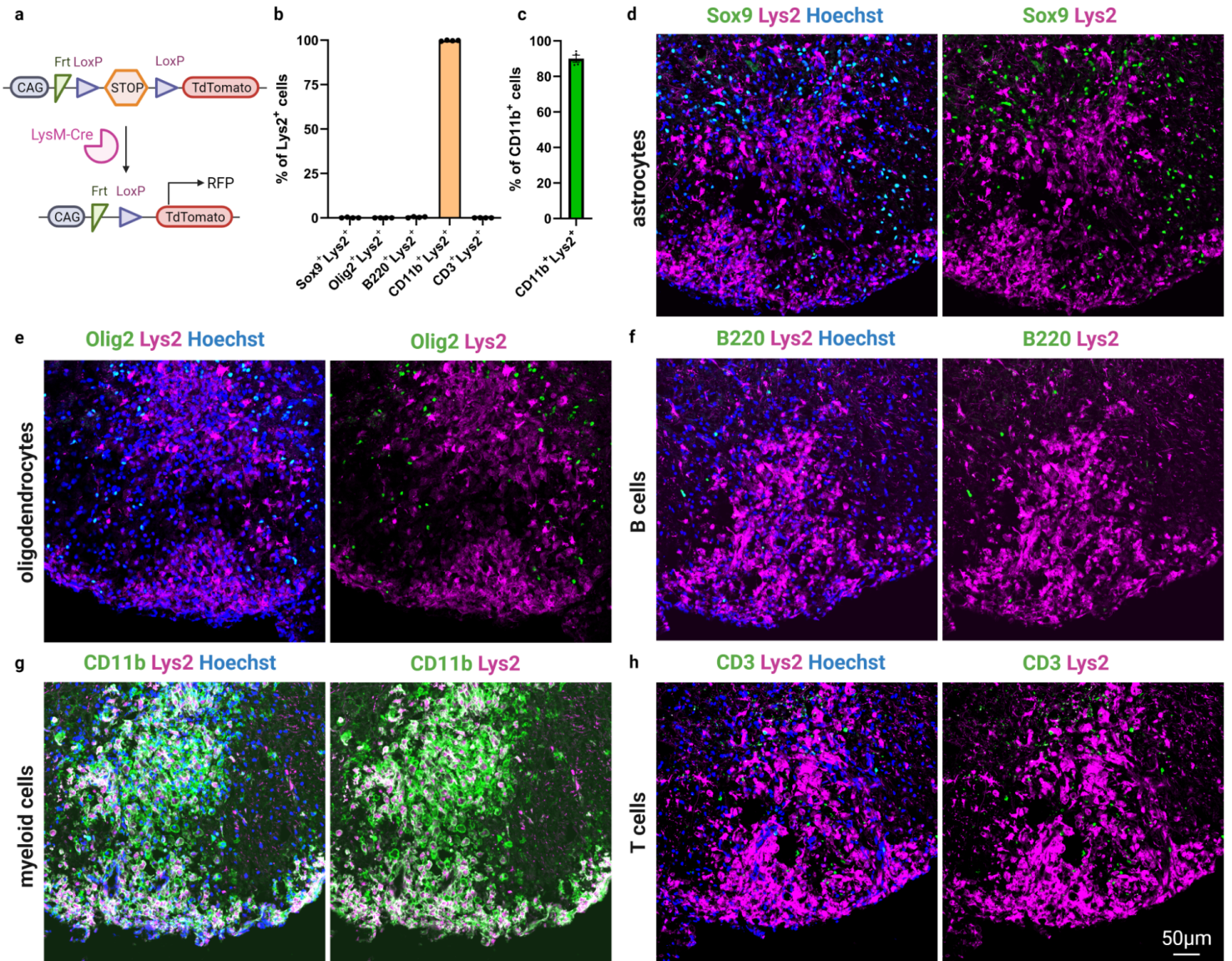
SUPPLEMENTARY FIGURES



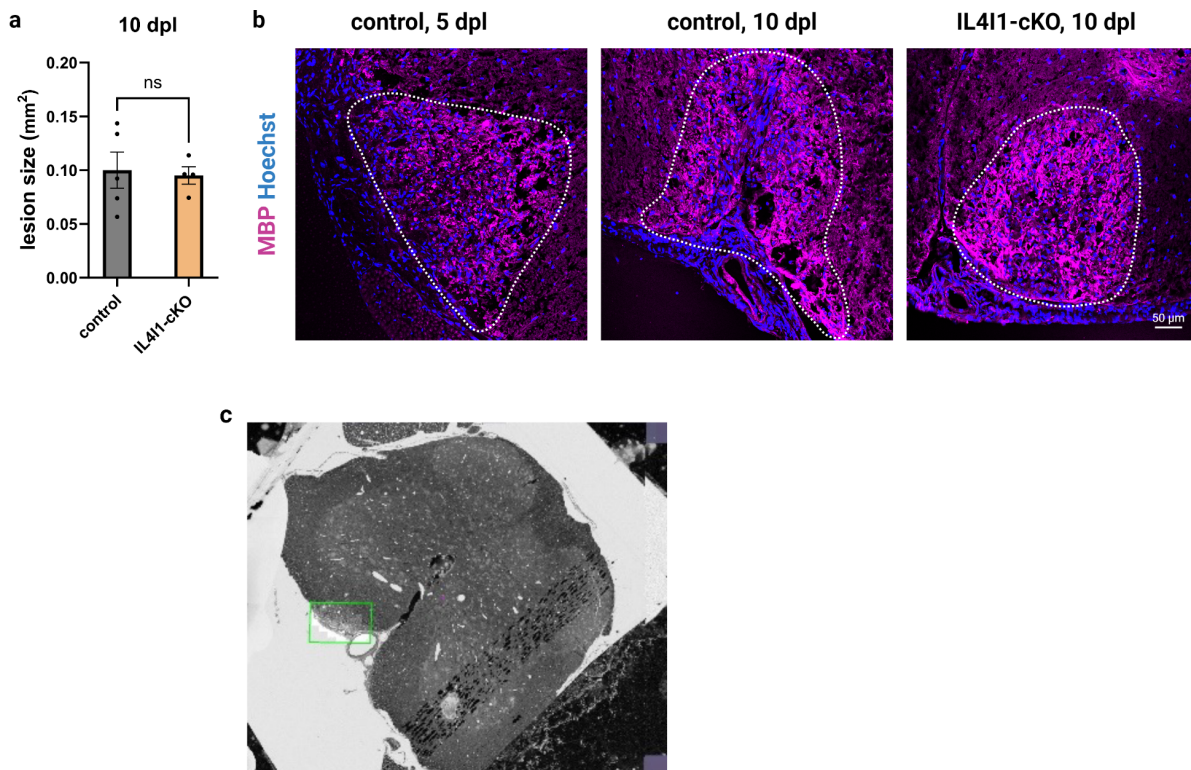
Supplementary Figure 1. IL411 expression pattern in demyelinated lesions. a, Schematic of generating IL411-tm1b reporter line. **b,** Representative images for immunostaining of *Il4i1*^{tm1b/+} mouse lesions for LacZ reporter (β -gal), CD11b, Olig2, CD3, and Sox9. **c,** Quantification for CD11b⁺ β -gal⁺ myeloid cells, Olig2⁺ β -gal⁺ oligodendrocytes, CD3⁺ β -gal⁺ T cells, and Sox9⁺ β -gal⁺ astrocytes over all IL411-expressing (β -gal⁺) cells in lesions (n=3 mice). **d,** Representative images of

immunostaining for LacZ reporter (β -gal), myeloid cells marker (Iba1), and secondary-only control in *I4i1^{tm1b/+}* mouse lesions. Bars represent the means with SEM.

The scale bar represents 50 μ m.

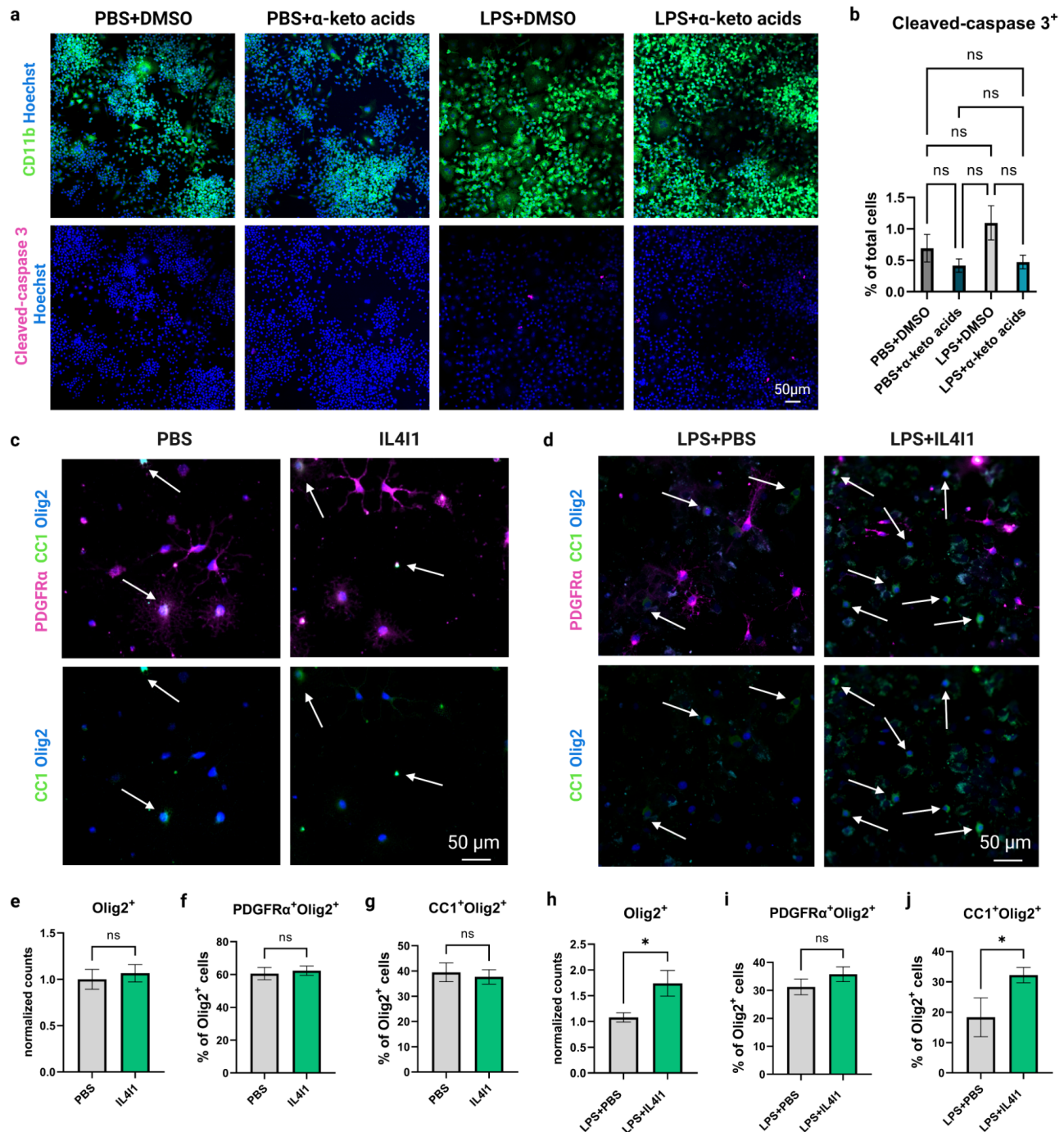


Supplementary Figure. 2. Characterization of LysM-Cre expression. **a**, Schematic of crossing LysM-Cre line with a ROSA reporter line, where Cre recombinase removes the stop codon and leads to the expression of endogenous red fluorescent protein (RFP). **b**, Quantification for Sox9⁺Lys2⁺ astrocytes, Olig2⁺Lys2⁺ oligodendrocytes, B220⁺Lys2⁺ B cells, CD11b⁺Lys2⁺ myeloid cells, and CD3⁺Lys2⁺ T cells over all Lys2⁺ cells in lesions (n=4 mice). Bars represent the mean with SEM. **c**, Quantification for CD11b⁺Lys2⁺ cells over all CD11b⁺ cells. **d-h**, Representative images for endogenous RFP that represents Lys2 expression, and immunostaining of Sox9, Olig2, B220, CD11b, and CD3. The scale bar = 50 μm.



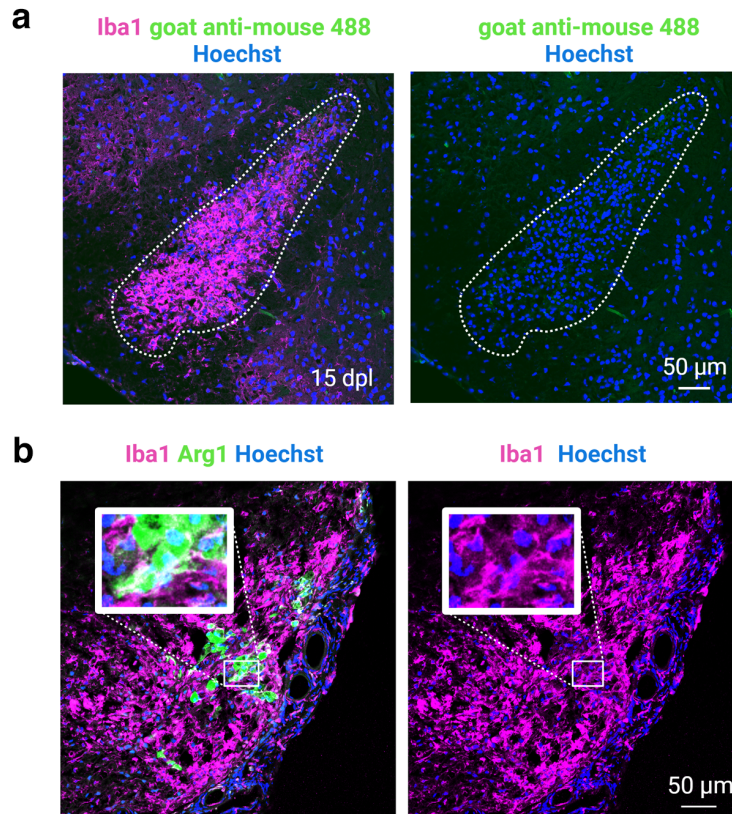
Supplementary Figure 3. Demyelinated lesion size of IL411-cKO and control mice.

a, Quantification of the demyelinated lesion sizes in IL411-cKO and control mice at 10 dpl (n=4-5 mice, unpaired t-test). **b**, Representative images of MBP immunostaining in control animals at 5 dpl, which display more punctate and disconnected staining, indicative of myelin fragments, and in control and IL411-cKO mice at 10 dpl, which display smooth and connected staining, indicative of newly generated myelin. The scale bar = 50 μ m. **c**, Representative low magnification image of a spinal cord section containing a focal lesion (green outline) under SEM. Once a lesion has been identified, the lesion is then imaged at high magnification. Bars represent the means with SEM. Each point represents an individual mouse. ns=non-significant.

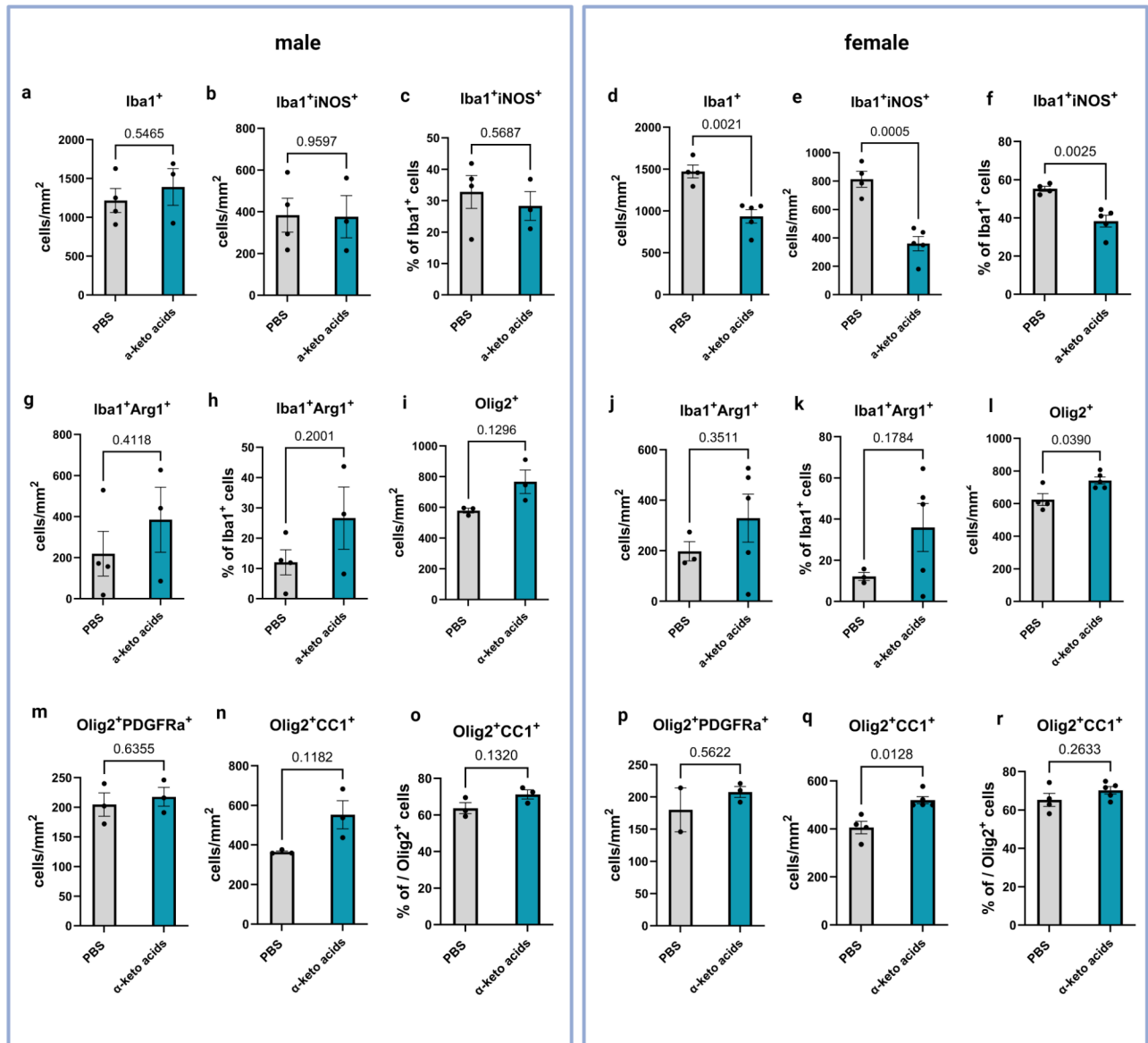


Supplementary Figure. 4. Viability test on AKAs-treated myeloid cells, and effect of IL411 on oligodendrocyte and mixed glial cultures. a, Representative image of

immunostaining for myeloid cells (CD11b⁺) and apoptosis (cleaved-caspase 3⁺) in RAW 264.7 cells treated with PBS+DMSO, PBS+AKAs, LPS+DMSO, and LPS+AKAs. **b**, Quantification of immunostaining for cleaved-caspase 3⁺ cells over total cells (n=10 fields of view from two rounds of independent studies, Tukey's multiple comparisons test). **c**, Representative image of PDFGR α , CC1, and Olig2 staining in PBS or IL4I1-treated OPC cultures. **d**, Representative image of PDFGR α , CC1, and Olig2 staining in PBS or IL4I1-treated mixed glial cultures under LPS stimulation. **e-g**, Quantification of Olig2⁺ oligodendrocyte lineage cells (e), and the percentage of Olig2⁺PDGFR α ⁺ immature oligodendrocytes (f) and Olig2⁺CC1⁺ mature oligodendrocytes (g) overall oligodendrocyte lineage cells. (n=15-19 fields of view from two independent studies, unpaired t-test.) **h-j**, Quantification of Olig2⁺ oligodendrocyte lineage cells (h), and the percentage of Olig2⁺PDGFR α ⁺ immature oligodendrocytes (i) and Olig2⁺CC1⁺ mature oligodendrocytes (j) over all Olig2⁺ cells (n=5-19 fields of view from two independent studies, unpaired t-test). Arrows pointing at CC1⁺Olig2⁺ cells. The scale bar = 50 μ m. Bars represent the means with SEM. *P < 0.05; ns=not significant.



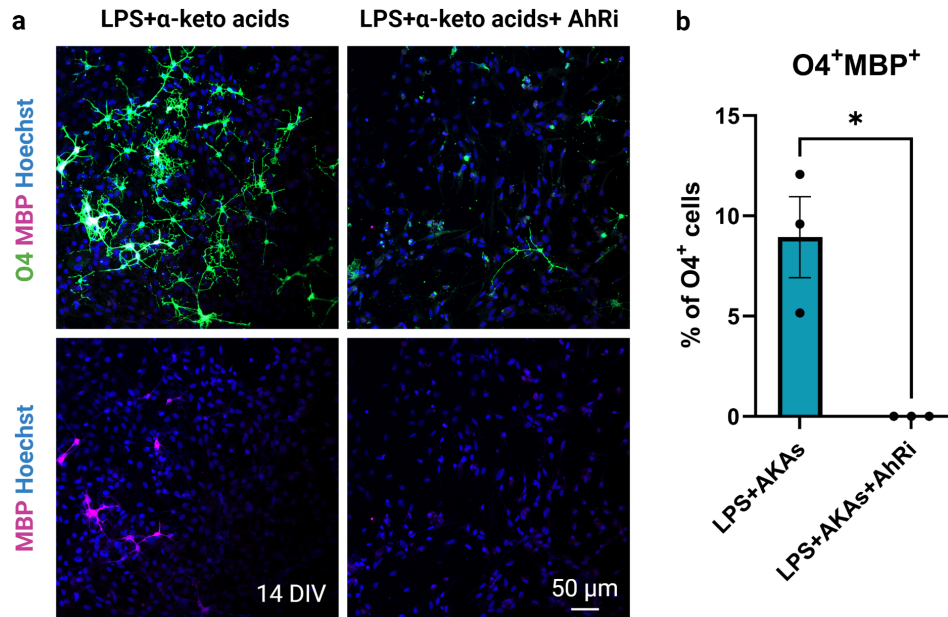
Supplementary Figure 5. iNOS and Arg1 staining of lesions. a, Image of secondary antibody-only control for iNOS staining. **b,** High-magnification representative image of Arg1 and Iba1 staining. The scale bar = 50 μ m.



Supplementary Figure 6. The effect of AKAs on male and female lesioned mice.

a-f, Quantification of Iba1⁺ myeloid cells and Iba1⁺iNOS⁺ inflammatory myeloid cells in lesions from PBS or AKAs-treated male (n=3-4) and female mice (n=4-5, unpaired t-test). **g-l**, Quantification of Iba1⁺Arg1⁺ pro-regenerative myeloid cells and Olig2⁺ oligodendrocyte lineage cells in lesions from PBS or AKAs-treated male (n=3-4) and

female mice (n=3-5, unpaired t-test). **m-r**, Quantification of Olig2⁺PDGFR α ⁺ OPCs, and Olig2⁺CC1⁺ mature oligodendrocytes in lesions from PBS or AKAs-treated male (n=3) and female mice (n=2-5 mice, unpaired t-test). Bars represent the means with SEM. Each point represents an individual value.



Supplementary Figure 7. AhR inhibitor treatment of mixed glial culture. a-b, Representative images, and quantification of O4⁺MBP⁺ mature oligodendrocyte in mixed glial culture under LPS stimulation and AKAs treatment with or without AhR inhibitor (AhRi). The scale bar = 50 μ m. *P < 0.05.