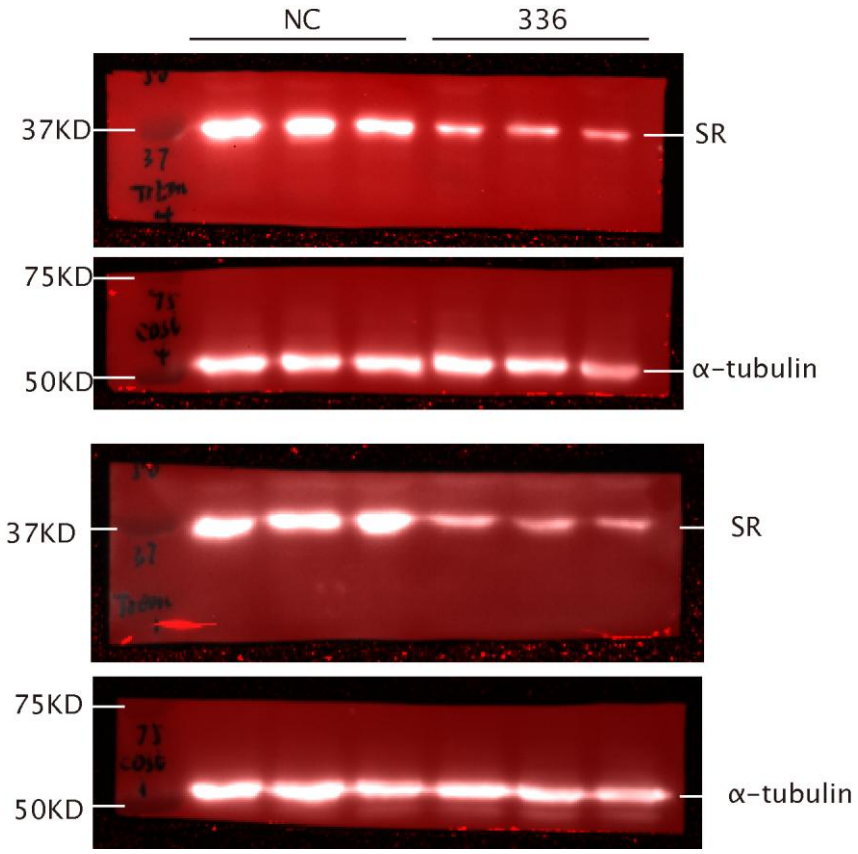
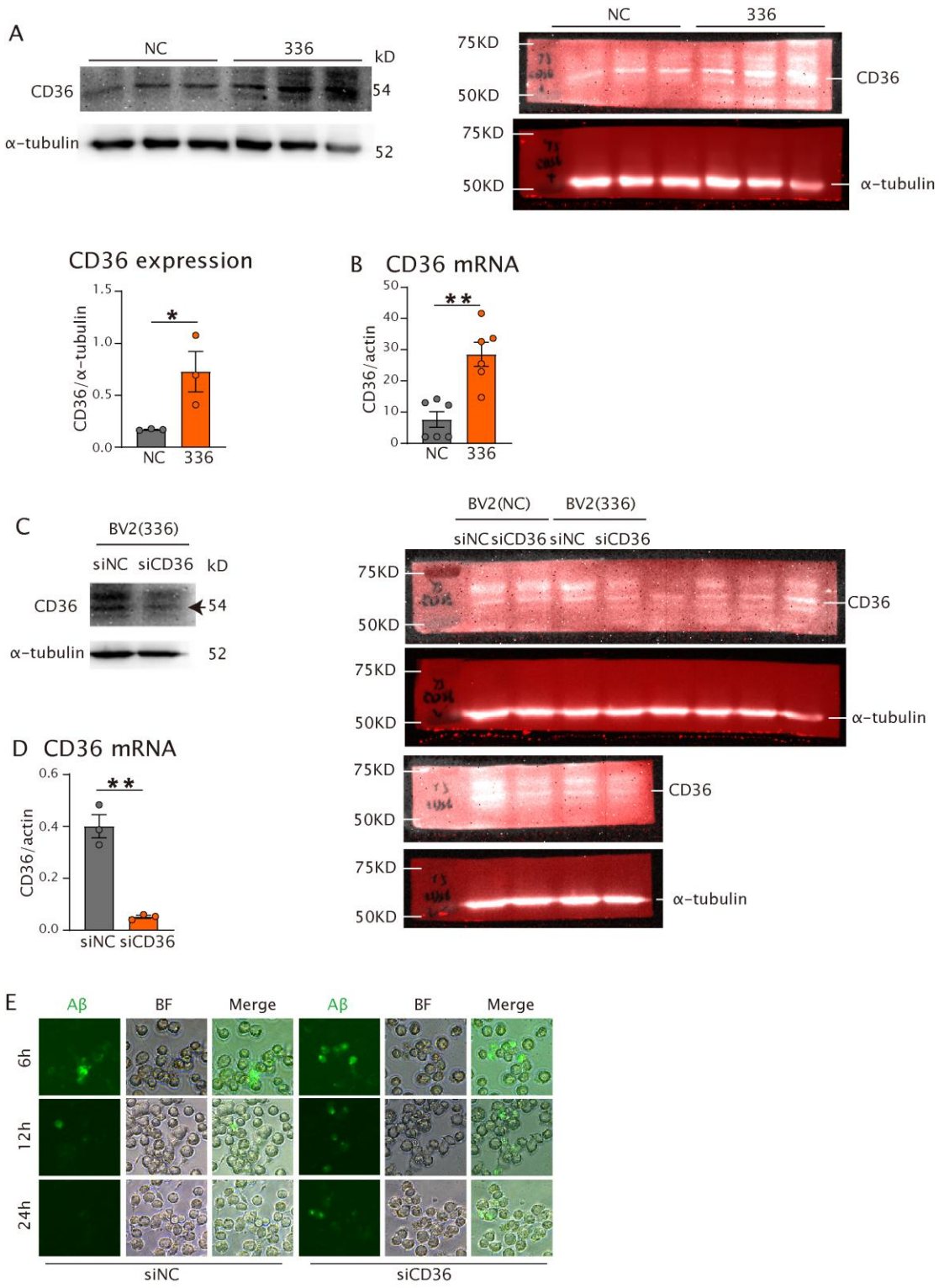
**Supplemental Figures**




**Supplemental Figure 1. Original uncropped gel for Figure 1A.** The images were acquired with Flurochem E (2016064100, Proteinsimple, Inc).

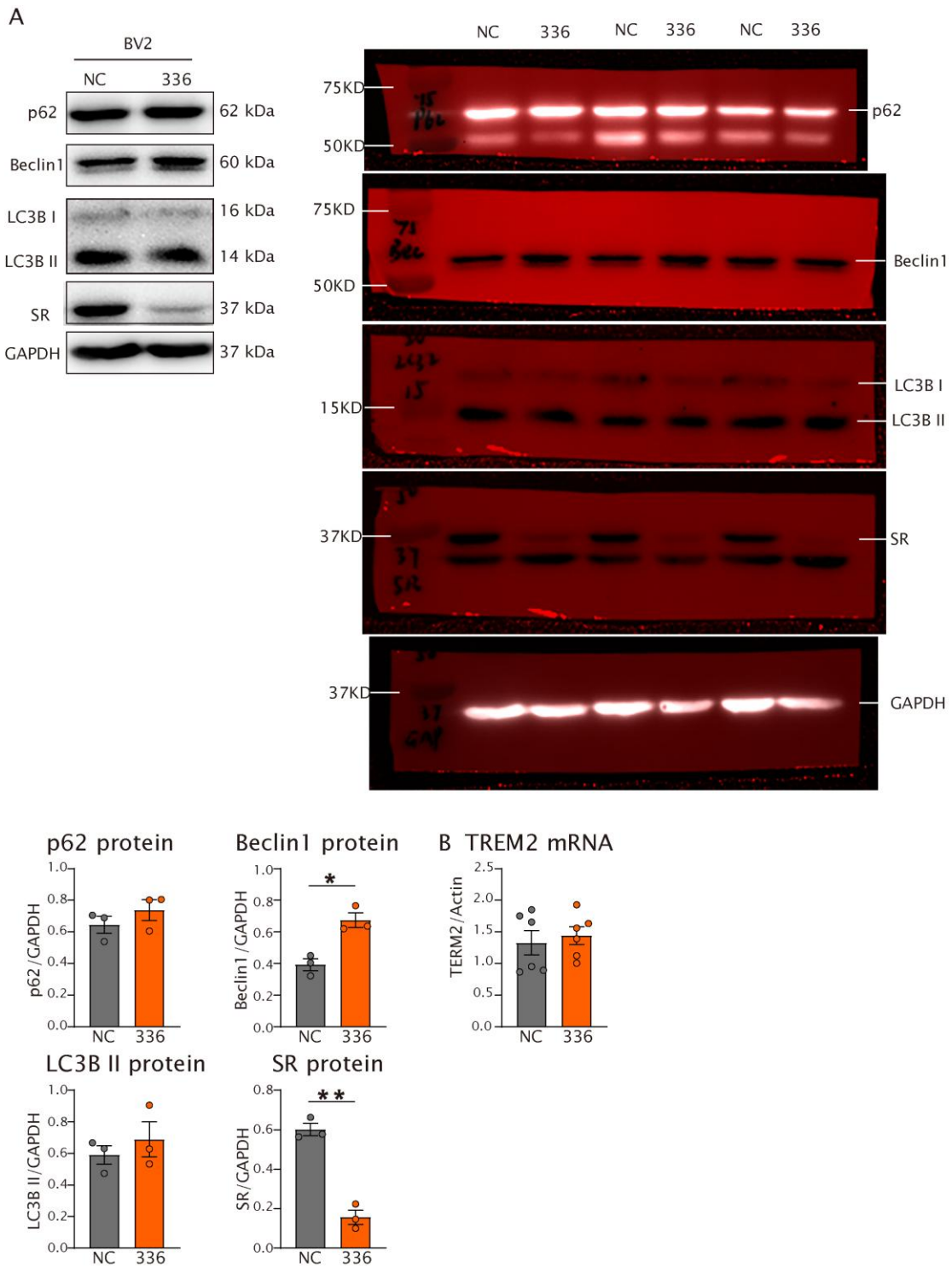



**Supplemental Figure 2. Stable knockdown of *Srr* in microglia increased Aβ phagocytosis, which was not dependent on CD36.**

(**A**) The homogenates from BV2 (NC) and BV2 (336) (n=3 for each) were subjected to western blot analyses for CD36. Original uncropped blots are provided alongside. The images were acquired with Flurochem E (2016064100, Proteinsimple, Inc). Student's *t* test was used to compare the protein levels of CD36; t[4]=2.874, p=0.045.

(**B**) RNA was extracted from BV2 (NC) and BV2 (336) (n=6 for each) and subjected to RT-qPCR analyses for the mRNA levels of CD36. Mann-Whitney U test was used for comparison; p=0.002.
(**C**) BV2 (NC) and BV2 (336) (D) were transfected with scrambled RNA or CD36-specific siRNA and subjected to western blot analyses for CD36. Typical images were indicated. Original uncropped blots are provided alongside. N=3 for each. Additional blots are results from different sets of siRNA (unremarked).
(**D**) The cells from C were also subjected to RT-qPCR analyses for CD36 (n=3 for each), and Mann-Whitney U test was used for comparison; p=0.002.
(**E**) BV2 (NC) and BV2 (336) were transfected with scrambled RNA or CD36-specific siRNA and incubated with Aβ-FITC for 6–24 h. Images were captured using LEICA DMi8 microscope system with a 10× objective.

Error bars denote the variability of the data.

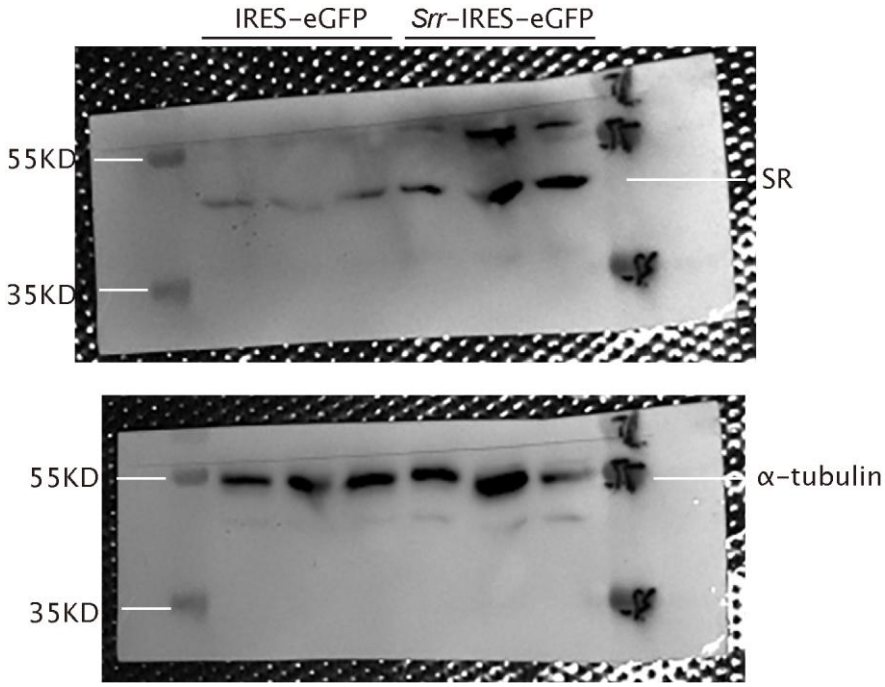



**Supplemental Figure 3. Stable knockdown of *Srr* in microglia altered Beclin1 protein levels and did not alter TRM2 mRNA levels.**

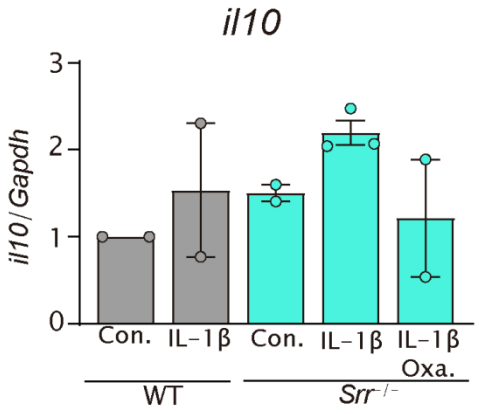
(**A**) The homogenates from BV2 (NC) and BV2 (336) (n=3 for each) were subjected to western blot analyses for p62, Beclin1, and LC3BII. Original uncropped blots are provided alongside. The images were acquired with Flurochem E (2016064100, Proteinsimple, Inc). Mann-Whitney U test was used to compare the protein levels of

p62; p=0.400. Student's *t* test was used to compare the protein levels of Beclin1; t[4]=4.758, p=0.009; LC3BII, p=0.480; and SR, t[4]=9.382, p=0.001.
(**B**) RNA was extracted from BV2 (NC) and BV2 (336) (n=6 for each) and subjected to RT-qPCR analyses for the mRNA levels of TREM2. Student's *t* test was used to compare the mRNA levels of TREM2; t[10]=0.470, p=0.648.

Error bars denote the variability of the data.



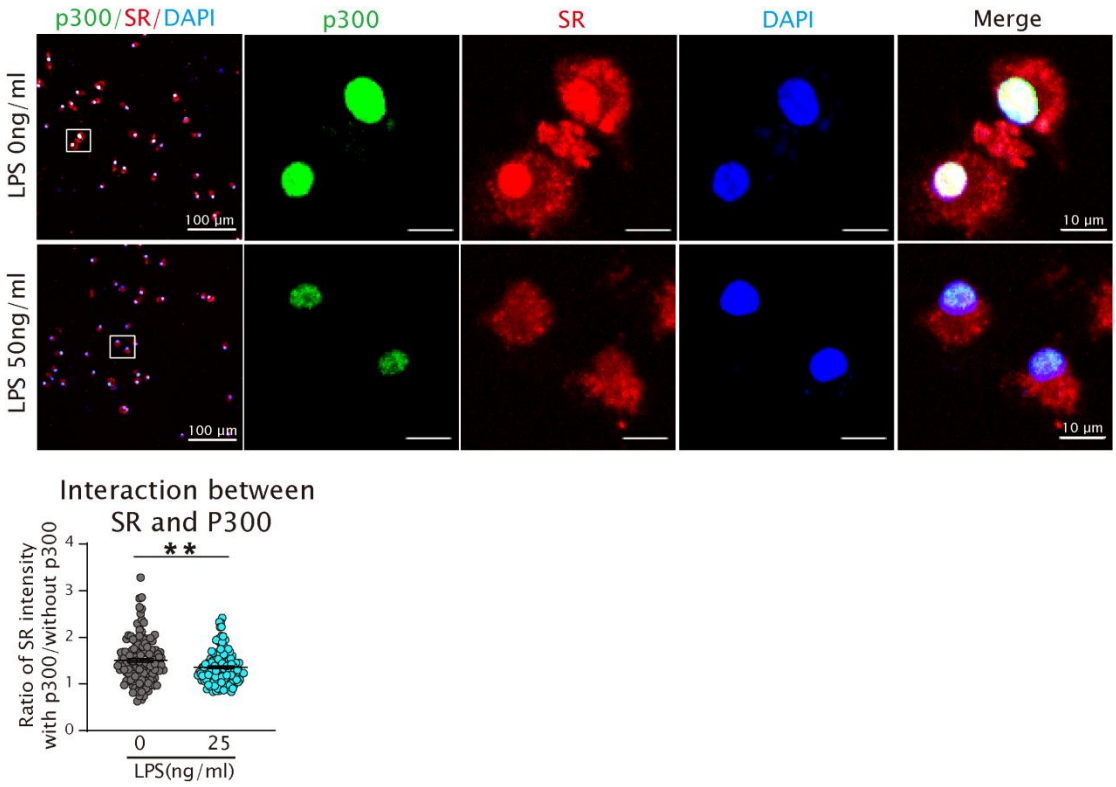

**Supplementary Figure 4. Original uncropped gels for Figure 1D.** The images were acquired with Fluorchem E (2022386901, Proteinsimple, Inc).




**Supplemental Figure 5. IL-1β treatment induced a trend increase of *Il10* mRNA, albeit without significant difference.**

*Srr*$^{-/-}$ and WT primary microglial cultures were pre-treated with an LDHA inhibitor oxamate (Oxa., 10 mM) for 4 h, then treated with IL-1 β (10 ng/mL) for 24 h. Two independent cell cultures were used.

Error bars denote the variability of the data.



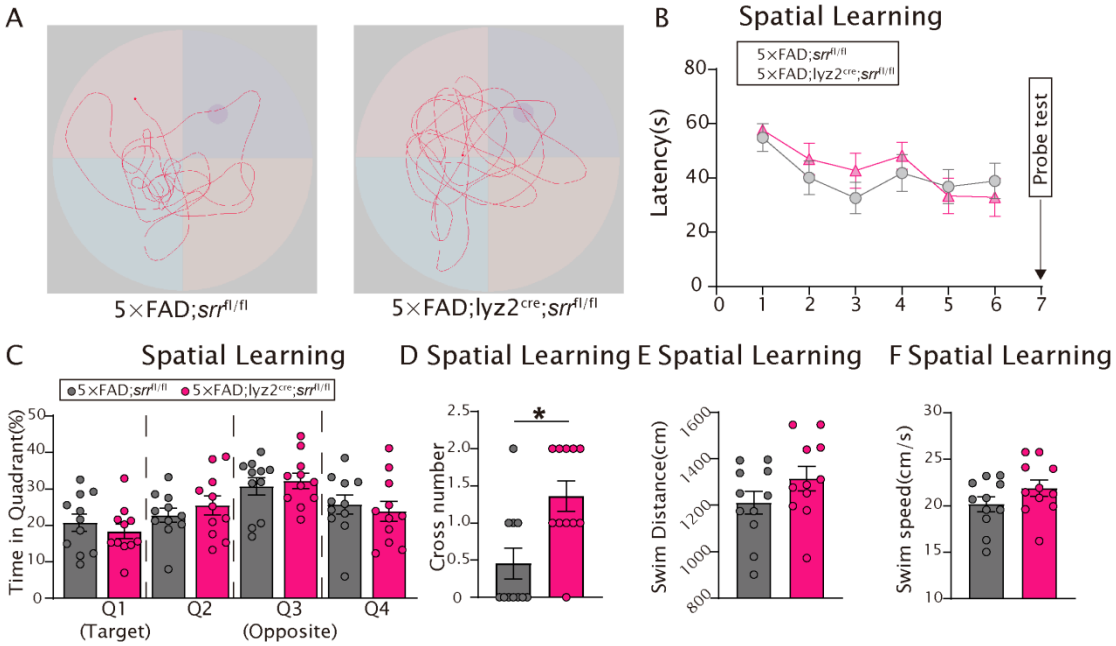

**Supplemental Figure 6. LPS treatment induced steric separation between nuclear SR and p300.**

(**A**) SR (red) and p300 (green) were co-stained for WT microglia under sham or LPS

treatment for 24 h. DAPI was used to indicate nuclei.

(**B**) Quantification of SR co-stained with p300, relative to SR without co-stainings with p300 stainings. Sham treatment (8 dishes, 136 cells), LPS treatment (8 dishes, 146 cells), Mann-Whitney U test was used for comparison, p=0.003.

Error bars denote the variability of the data.




**Supplemental Figure 7. Microglia-specific deletion of *Srr* in male 5×FAD mice improved platform crossings.**

(**A**) Representative swimming trajectories were indicated for the mice.

(**B**) During the training session, male 5×FAD;*Lyz2*$^{cre}$;*Srr*$^{fl/fl}$ mice (n=11) spent equal time to reach the submerged platform compared to male 5×FAD;*Srr*$^{fl/fl}$ mice (n=12) in all time points. Mann-Whitney U test was used to compare escape latency at each time point, p=1.000 at D1, p=0.332 at D2, p=0.300 at D3, p=0.748 at D4, p=0.652 at D5, and p=0.519 at D6.

(**C**) In the probe test, male 5×FAD;*Lyz2*$^{cre}$;*Srr*$^{fl/fl}$ mice spent equal time in the target quadrant compared to male 5 × FAD;*Srr*$^{fl/fl}$ mice at the 7$^{th}$ day (p=0.028). Mann-Whitney U test was used to compare the time spent in each quadrant, Q1(target), p=0.562, Q2, p=0.562, Q3(opposite), p=1.000, and Q4, p=0.401.

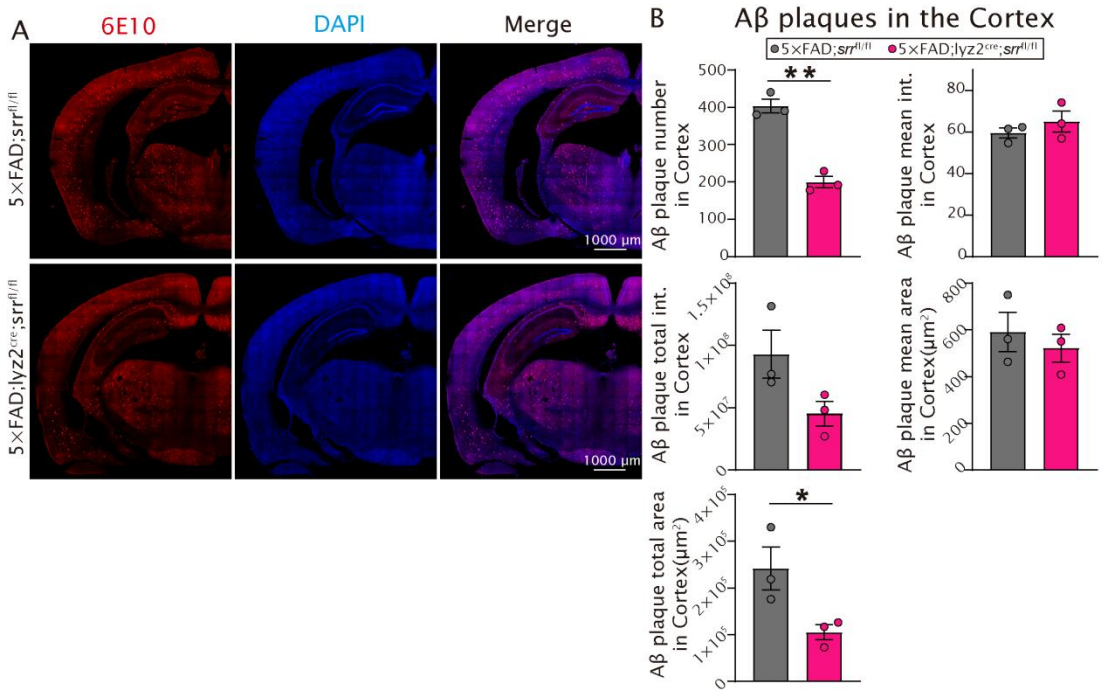
(**D**) In the probe test, the numbers of platform crossings were higher in male 5 × FAD;lyz2$^{cre}$;*Srr*$^{fl/fl}$ mice than the control mice, 5 × FAD;*Srr*$^{fl/fl}$. Mann-Whitney U test was used to compare the frequencies of platform crossing, p=0.010.

(**E**) In the probe test, 5×FAD;*Lyz2*$^{cre}$;*Srr*$^{fl/fl}$ mice exhibited a similar swim distance

than 5×FAD;*Srr*$^{fl/fl}$ mice. A Student's *t* test was used to compare the swim distance, yielding t[20]=1.452, p=0.162.

(**F**) In probe test, 5×FAD;*Lyz2*$^{cre}$;Srr$^{fl/fl}$ mice exhibited similar swimming speed than 5×FAD;*Srr*$^{fl/fl}$ mice. A Student's *t* test was used to compare the swim speed, yielding t[20]=1.452, p=0.162.

Error bars denote the variability of the data.




**Supplemental Figure 8. Conditional knockout of *Srr* in the microglia mitigated Aβ plaques in the cortex of male 5×FAD mice.** The male mouse brains were processed for paraffin-embedded sections, which were subjected to staining with humanized Aβ antibody using 6E10.

(**A**) Representative immunofluorescence images of the cortex were indicated for mice. 6E10 staining (red) was used to visualize Aβ plaques, and DAPI (blue) to mark cell nuclei. Images were captured with ZeissLSM880 confocal laser microscope system (Zeiss) under a 40×objective. Bar: 100 μm for the images.

(**B**) In the cortex, 5×FAD;*Lyz2*$^{cre}$;*Srr*$^{fl/fl}$ mice (n=3) exhibited fewer Aβ plaques compared to 5×FAD;*Srr*$^{fl/fl}$ mice (n=3). Student's *t* test was used to compare the numbers of Aβ plaques in the cortex, t[4]=8.487, p=0.001.

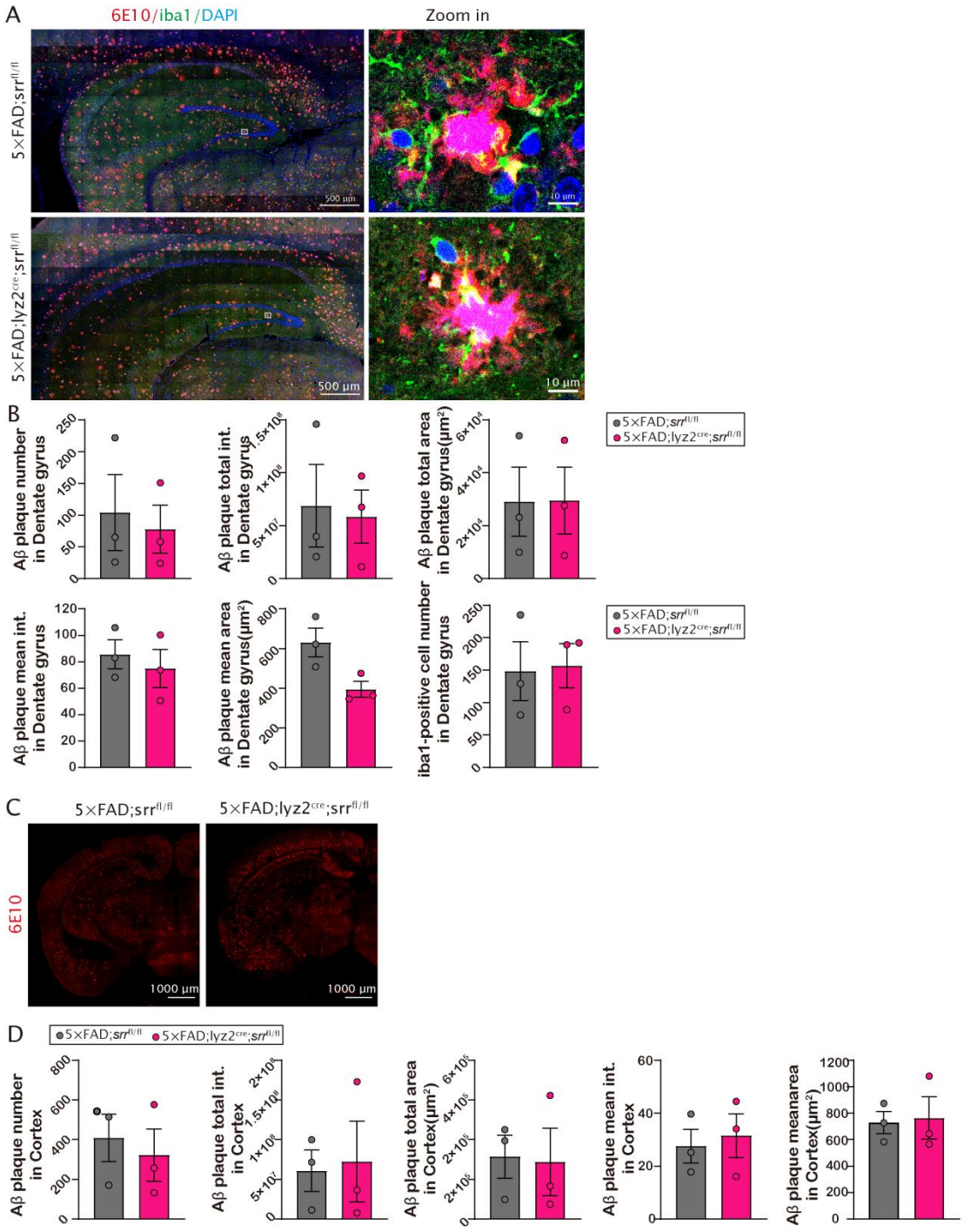
5×FAD;*Lyz2*$^{cre}$;*Srr*$^{fl/fl}$ mice showed a significant reduction in the total fluorescence intensity (int.) of Aβ plaques relative to 5×FAD;*Srr*$^{fl/fl}$ control. Student's t-test was used to compare the total fluorescence intensity(int.) of Aβ

plaques, t[4]=2.206, p=0.092.

The total area of Aβ plaques was less in 5×FAD;*Lyz2*$^{cre}$;*Srr*$^{fl/fl}$ mice than that in 5×FAD;*Srr*$^{fl/fl}$ control. Student's *t* test was used for comparison, t[4]=2.797, p=0.049.

There was no significant differences in the mean fluorescence intensity (int.) or mean area of Aβ plaques between 5×FAD;*Lyz2*$^{cre}$;*Srr*$^{fl/fl}$ mice and 5×FAD;*Srr*$^{fl/fl}$ control (n=3). Student's *t* test was used to compare the mean fluorescence intensity(int.) with t[4]=0.769, p=0.485, and the mean area of Aβ plaques with t[4]=0.668, p=0.541.

Error bars denote the variability of the data.




**Supplemental Figure 9. Conditional knockout of *Srr* in the microglia did not mitigate Aβ plaques in the dentate gyri or cortex of female 5×FAD mice.**

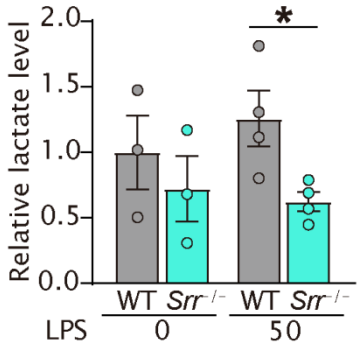
(**A**) Representative immunofluorescence images of the hippocampi were indicated for female mice. 6E10 staining (red) was used to visualize Aβ plaques, iba1(green) to label activated microglia, and DAPI (blue) to mark cell nuclei. Images were captured with ZeissLSM880 confocal laser microscope system (Zeiss) under a 40×objective. (**B**) In the dentate gyri, female 5×FAD;*Lyz2*$^{cre}$;*Srr*$^{fl/fl}$ mice (n=3) exhibited similar Aβ plaques densities compared to female 5×FAD;*Srr*$^{fl/fl}$ mice (n=3). Student's *t* test was

used for comparison; t[4]=0.376, p=0.726. Aβ plaque total intensity in dentate gyri: t[4]=0.220, p=0.836 (Student's *t* test). Total area of Aβ plaque in dentate gyri: t[4]=0.028, p=0.979 (Student's *t* test). Mean intensity of Aβ plaque in dentate gyri: t[4]=0.598, p=0.582 (Student's *t* test). Mean area of Aβ plaque in dentate gyri: t[4]=1.159, p=0.311 (Student's *t* test). Iba1-positive cell number in dentate gyri: p=1.000 (Mann-Whitney U test).

(**C**) Representative immunofluorescence images of the cortex were indicated for female mice.

(**D**) Aβ plaque numbers in the cortex: t[4]=0.489, p=0.651 (Student's *t* test). Total intensity of Aβ plaque in the cortex: t[4]=0.201, p=0.851 (Student's *t* test). Total area of Aβ plaque in the cortex: t[4]=0.134, p=0.900 (Student's *t* test). Mean intensity of Aβ plaque in the cortex: t[4]=0.379, p=0.724 (Student's *t* test). Mean area of Aβ plaque in the cortex: t[4]=0.195, p=0.855 (Student's *t* test).

Error bars denote the variability of the data.




**Supplemental Figure 10. Lower cytosolic lactate levels in *Srr*$^{-/-}$ microglia following LPS stimulation.**

*Srr*$^{-/-}$ and WT microglia were treated with an LPS (50 ng/ml) for 24 h. The cells were lysed to determine intracellular lactate. Student's t-test was employed to compare the differences of relative lactate levels between the two groups (t[6] = 2.830, p =0.030).

Error bars denote the variability of the data.