

Supplemental Material

Research Articles | Neurobiology of Disease

Amelioration of symptomatic Alzheimer's Disease after selective impairment of p75NTR function in adult forebrain excitatory neurons

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Supplementary figure legends

Figure S1. Generation of conditional knock-in p75^{NTR} alleles Δ DD and C259A

(A) Schematic of the *Ngfr* locus (not at scale) with strategy for generation of the conditional Δ DD mutant allele.

(B) Schematic of the *Ngfr* locus (not at scale) with strategy for generation of the conditional C259A mutant allele.

Figure S2. p75^{NTR} expression is not affected by Δ DD and C259A flox alleles

(A) Western blot analysis of p75^{NTR} expression in lysates of hippocampus from 2-month-old wild type (WT), Δ DD^{Camk2a} and C259A^{Camk2a}. The lower panel shows GAPDH as a control for equal loading amount.

(B) Quantification of p75^{NTR} expression in the hippocampus normalized to GAPDH. Mean $\pm$ SD; N=4, one-way ANOVA.

(C) Western blot analysis of p75^{NTR} expression in lysates of hippocampus from 6-month-old wild 5xFAD, Δ DD^{CreERT2}/5xFAD and C259A^{CreERT2}/5xFAD mice. The lower panel shows GAPDH as a control for equal loading amount.

(D) Quantification of p75^{NTR} expression in the hippocampus normalized to GAPDH. Mean $\pm$ SD; N=3, one-way ANOVA.

Figure S3. Verification of Cre-mediated recombination specificity in Camk2a-cre mouse strain

(A, B) Quantification results of recombination efficiency in the hippocampus (A) and cortex (B) of Camk2a-cre; Ai14 mice of different ages. Mean $\pm$ SD, N=3 mice per age.

(C-E) Immunostaining for NeuN (C), GFAP (D), Iba1 (E) in the brain of 6 month Camk2a-Cre; Ai14 mice. Scale bar, 50 μ m.

(F) Electrophoretic results of Cre recombination PCR assay of forebrain genomic DNA from 2 month old ΔDD^{Camk2a} genotyped mice, with bands at 560 bp corresponding to the recombined flox allele; and bands at 2,000 bp corresponding to the unrecombined flox allele.

(G) Electrophoretic results of Cre recombination PCR assay of forebrain genomic DNA from 2 month old $C259A^{Camk2a}$ genotyped mice, with bands at 760 bp corresponding to the recombined flox allele; and bands at 2,000 bp corresponding to the unrecombined flox allele.

Figure S4. Death domain of p75^{NTR} is specifically deleted in the forebrain of $\Delta DD^{Camk2a}/5xFAD$ mice

(A) Western blot analysis of p75^{NTR} death domain in the lysates of hippocampus of 6-month-old mice detected by anti-p75^{NTR} DD antibody. N=3. Mean±SD. T-test.

(B) Western blot analysis of p75^{NTR} extracellular domain in the lysates of hippocampus of 6-month-old mice detected by anti-p75^{NTR} ECD antibody. N=3. Mean±SD. T-test.

(C) Immunostaining for p75^{NTR} ECD and DD in basal forebrain, cortex and hippocampus of 12-month-old mice. Scale bar, 50 μm .

Figure S5. Reduced A β burden in the hippocampus of female 5xFAD mice carrying inactive p75^{NTR} variants

(A) Immunofluorescence staining images of A β plaques in the hippocampus of female mice of different genotypes at 6 months of age.

(B, C) Histograms of the area occupied by A β plaques in the hippocampus (B) and cortex (C) of mice (mean±SD). N=6 (Control/5xFAD), 3 ($\Delta DD^{Camk2a}/5xFAD$), 3 ($C259A^{Camk2a}/5xFAD$). One-way ANOVA followed by Tukey's multiple comparisons test. *p<0.05, **p<0.01 versus Control/5xFAD mice.

Figure S6. Cre recombination is specific in neurons and can be controlled by tamoxifen in Camk2a-CreERT2 mice

(A-C) Immunostaining for NeuN (A), GFAP (B), Iba1 (C) in the brain of Camk2a-CreERT2; Ai14

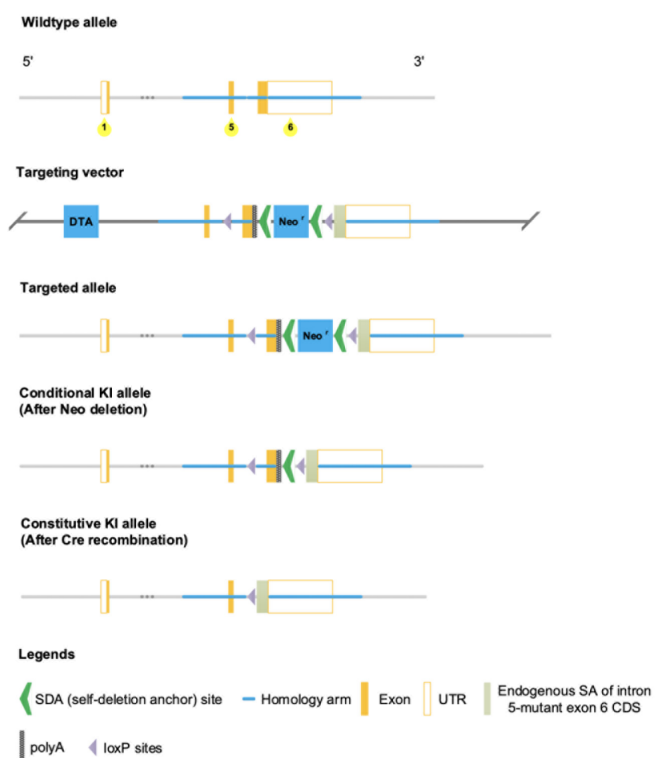
53 mice with tamoxifen injection at 2-month-old. Scale bar, 50 μ m.

54 (D, E) Quantification results of recombination efficiency in the hippocampus (D) and cortex (E) of
55 Camk2a-CreERT2; Ai14 mice with tamoxifen injection at different ages. Mean $\pm$ SD, N=3-5 mice
56 per age.

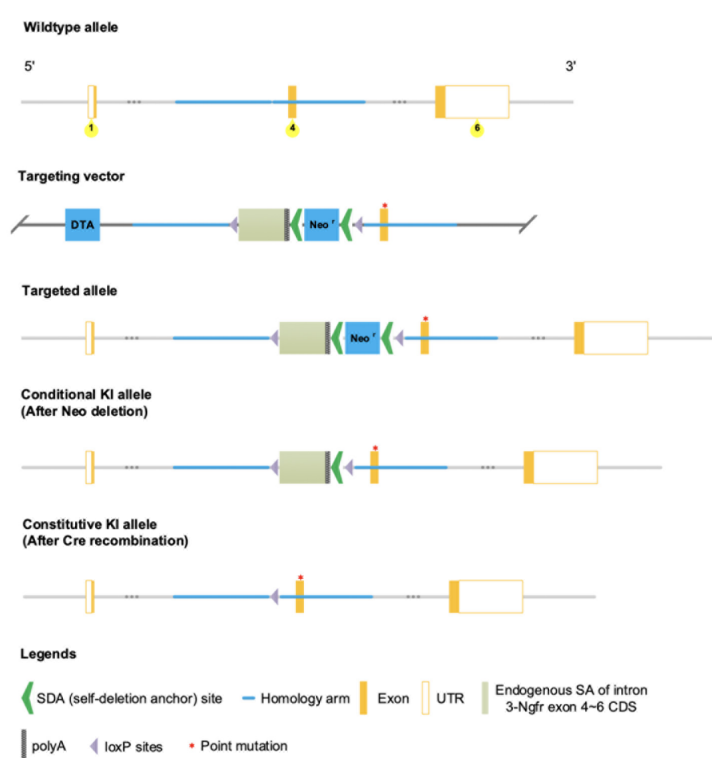
57 (F) Immunostaining for NeuN in the brain of Camk2a-CreERT2; Ai14 mice with corn oil (vehicle)
58 injection at 2-month-old. Scale bar, 50 μ m.

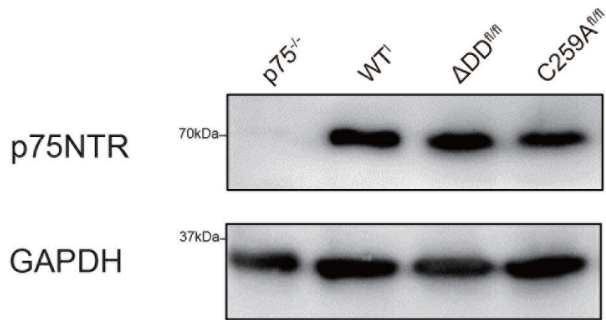
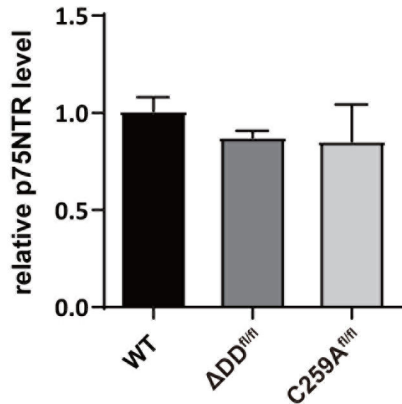
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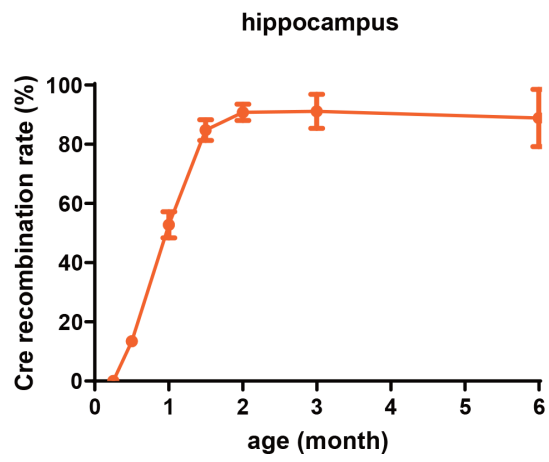
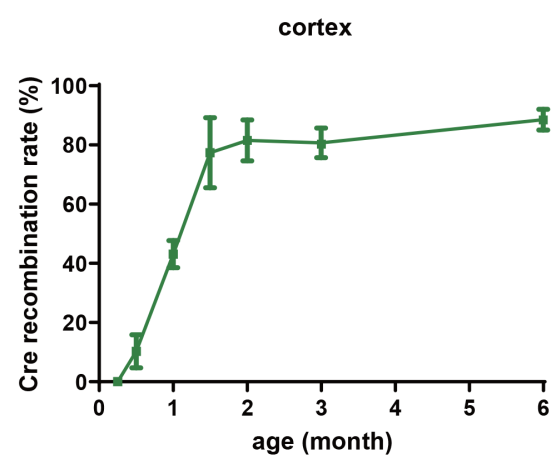
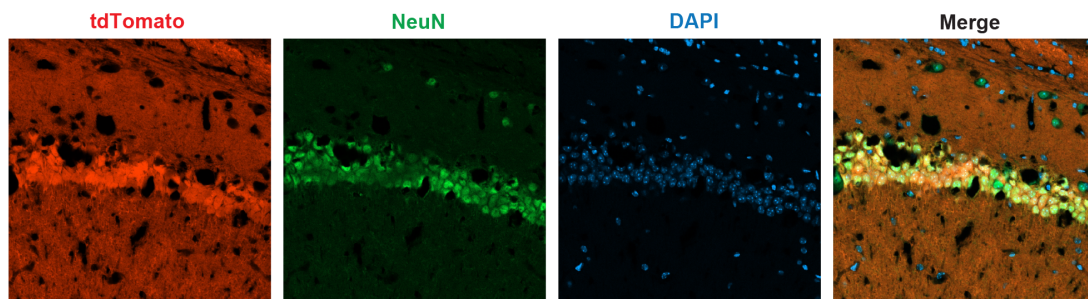
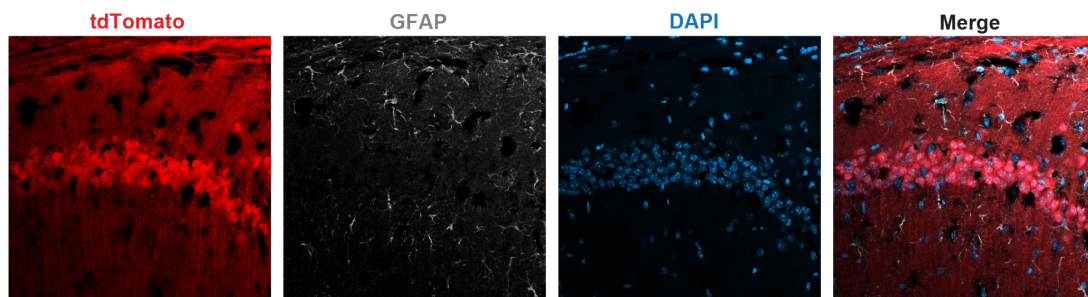
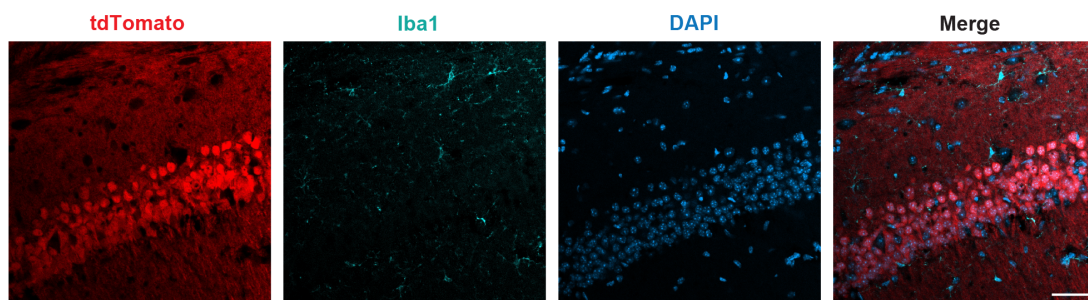
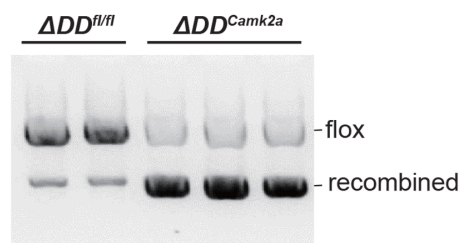
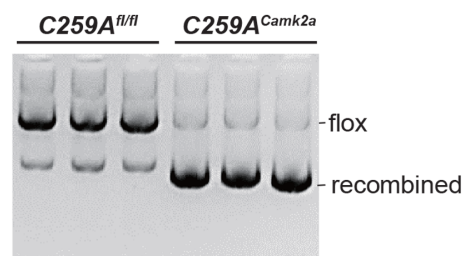
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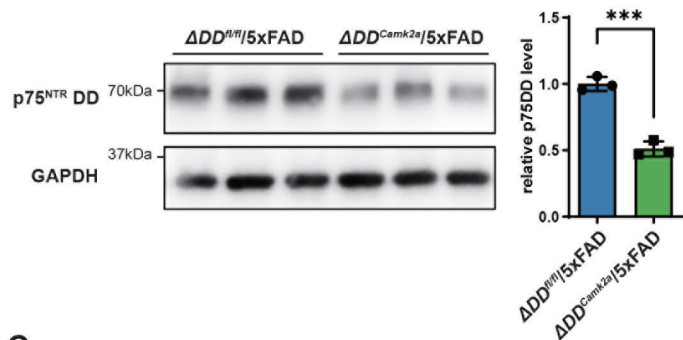
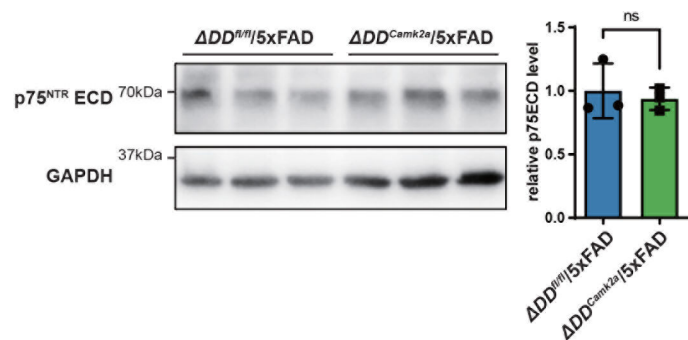
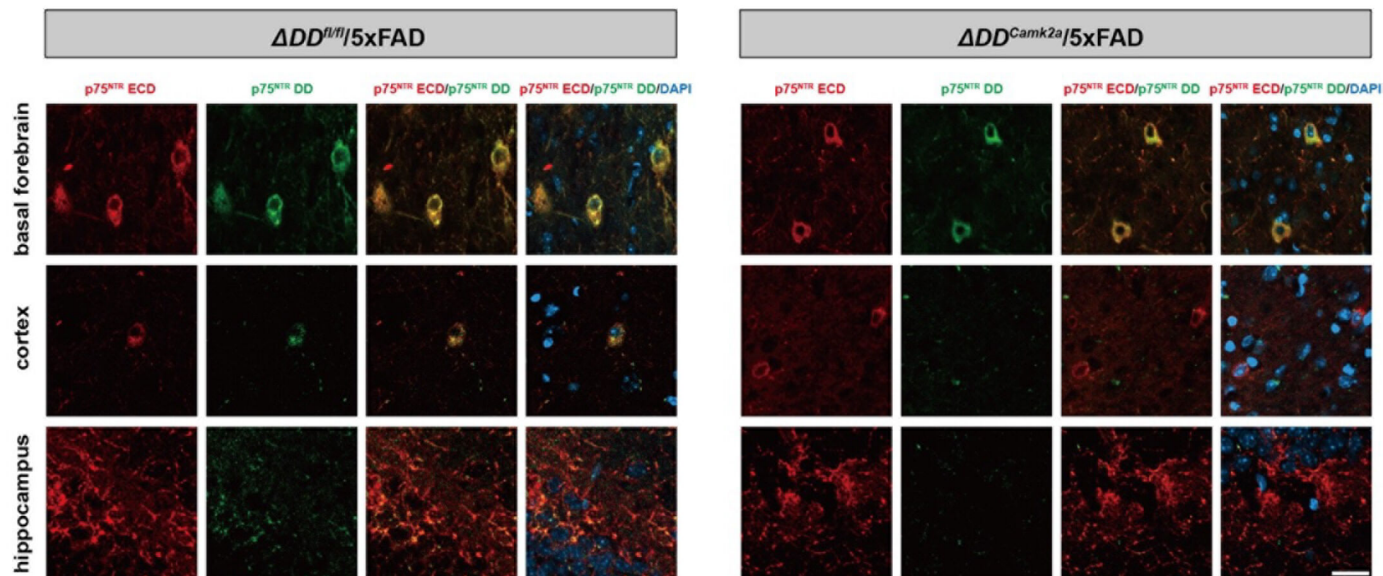


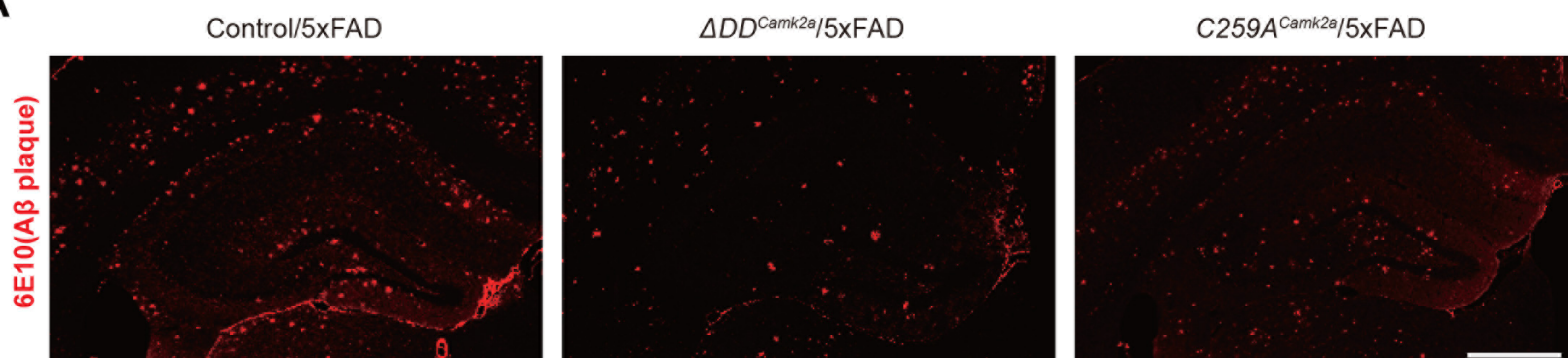
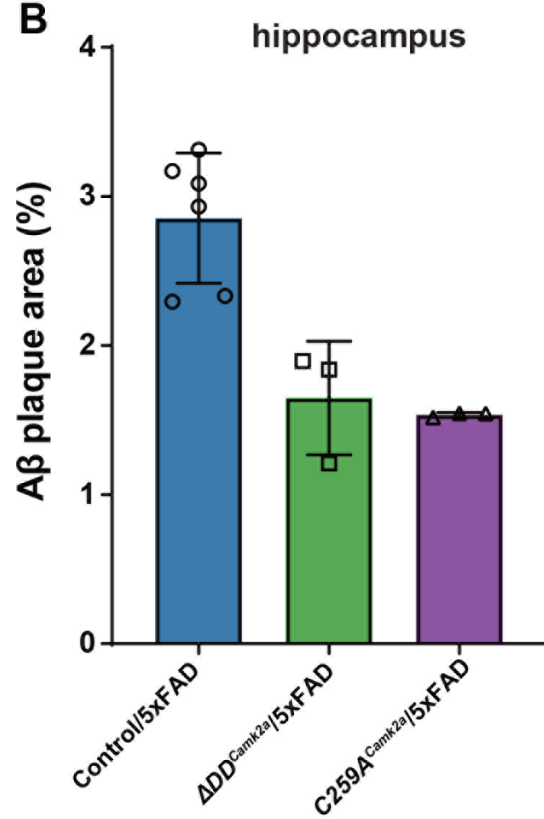
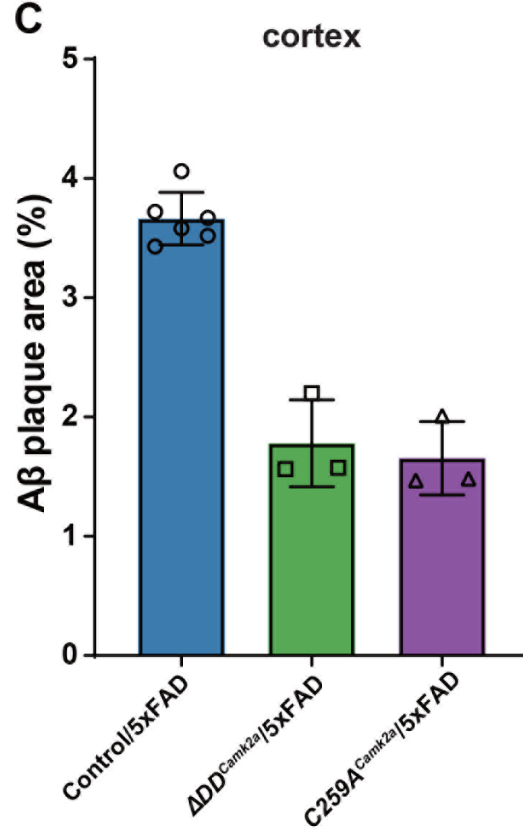
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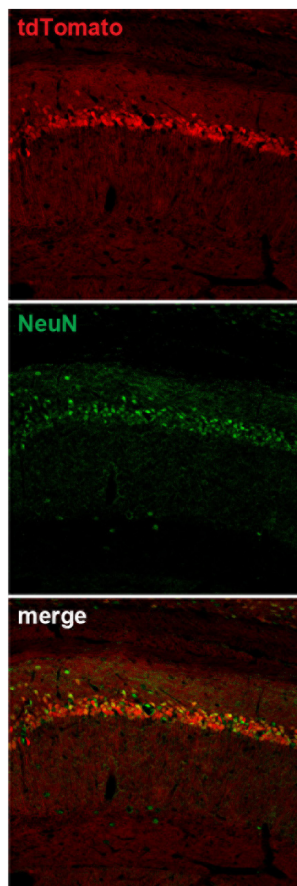
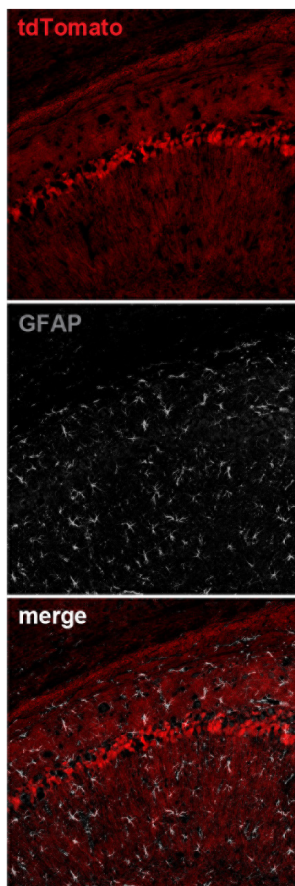
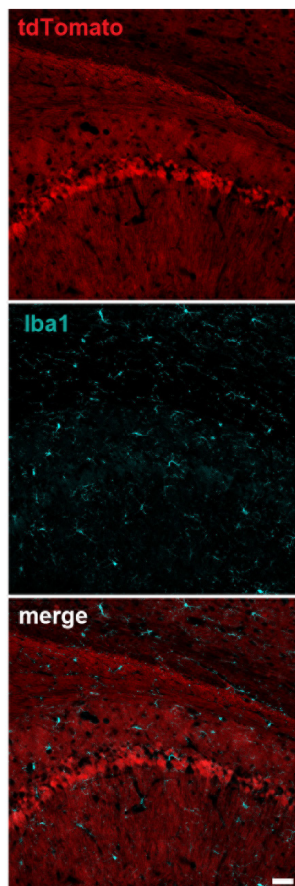
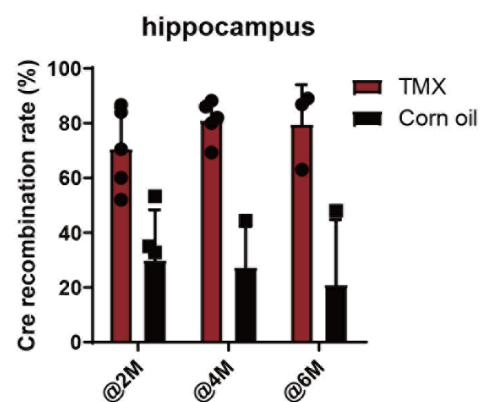
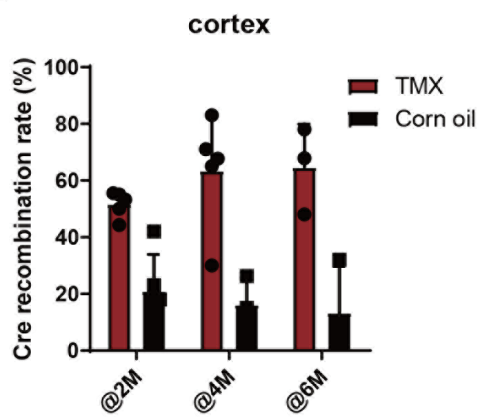


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