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IMPACT OF D-SERINE DEPLETION IN THE β -AMYLOID CASCADE RELATED TO ALZHEIMER'S DISEASE

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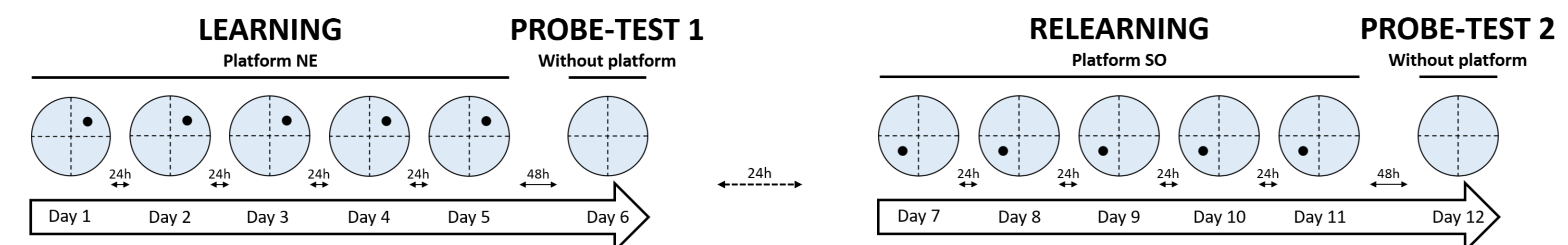
D-serine, as a co-agonist of N-methyl-D-aspartate subtype of glutamate receptors (NMDAR), is a key regulator of their activation. Hence, D-serine is involved in functional brain plasticity and memory processes. In the course of Alzheimer's disease (AD), homeostasis of NMDA receptors is precociously affected by beta-amyloid peptides ($A\beta$). However, while early functional dysregulations of NMDAR are well known, contribution of D-serine in early phases of the pathology remains so far to be determined. To this end, we compared behavioral performances and hippocampal synaptic functioning (extracellular electrophysiological recordings) in the well-known 5xFAD transgenic mice model of amyloidogenesis (bearing 5 familial Alzheimer disease-linked mutations), having or not a depletion for serine-racemase gene (allowing D-serine synthesis). Adequate control groups (WT and serine-racemase KO mice) were also performed.

- WT ■ SR^{-/-} ■ 5xFAD ■ 5xFADSR^{-/-}
- All data expressed as mean + sem
- Univariate t-test:
 - \$ p<0.05 vs 50%
 - § p<0.05 vs 25%
- ANOVA one-way: * p<0.05 vs WT
- ANOVA repeated measures: # p<0.05 vs WT

Behavior

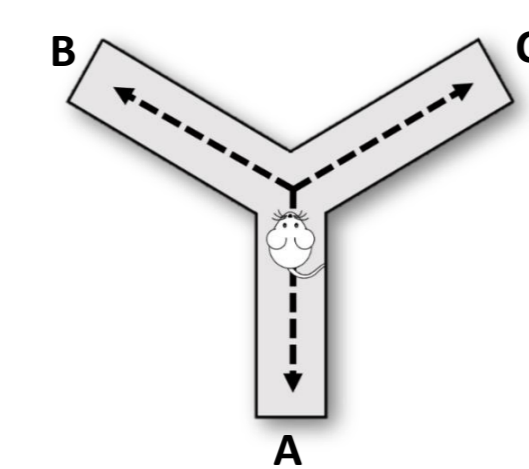
➤ 10-12 months old
➤ n = 15-22 per group

Morris-water-maze

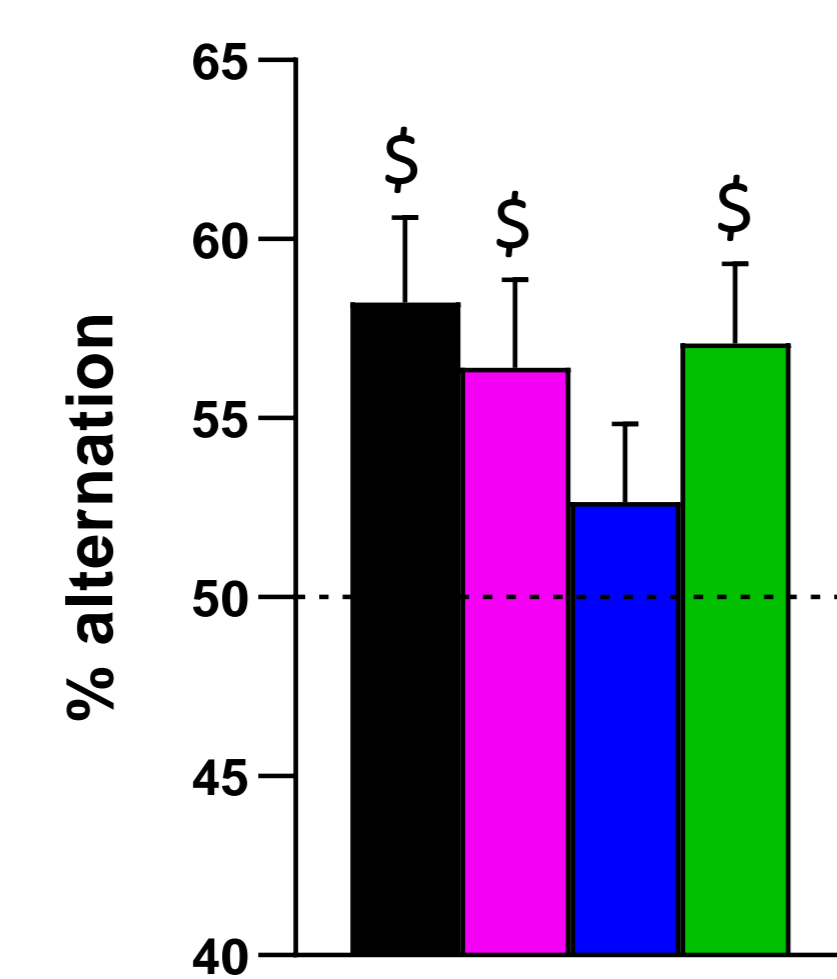


- Mice were trained to learn the location of the hidden platform (through distinct visual cues)
- Learning and relearning session: 4 trials of 60 sec / day during 5 days (60 sec inter-trial interval)
- Probe tests: 48h after last trial of learning and relearning session and mice were free to explore the maze without platform during 60 sec

Spontaneous alternation

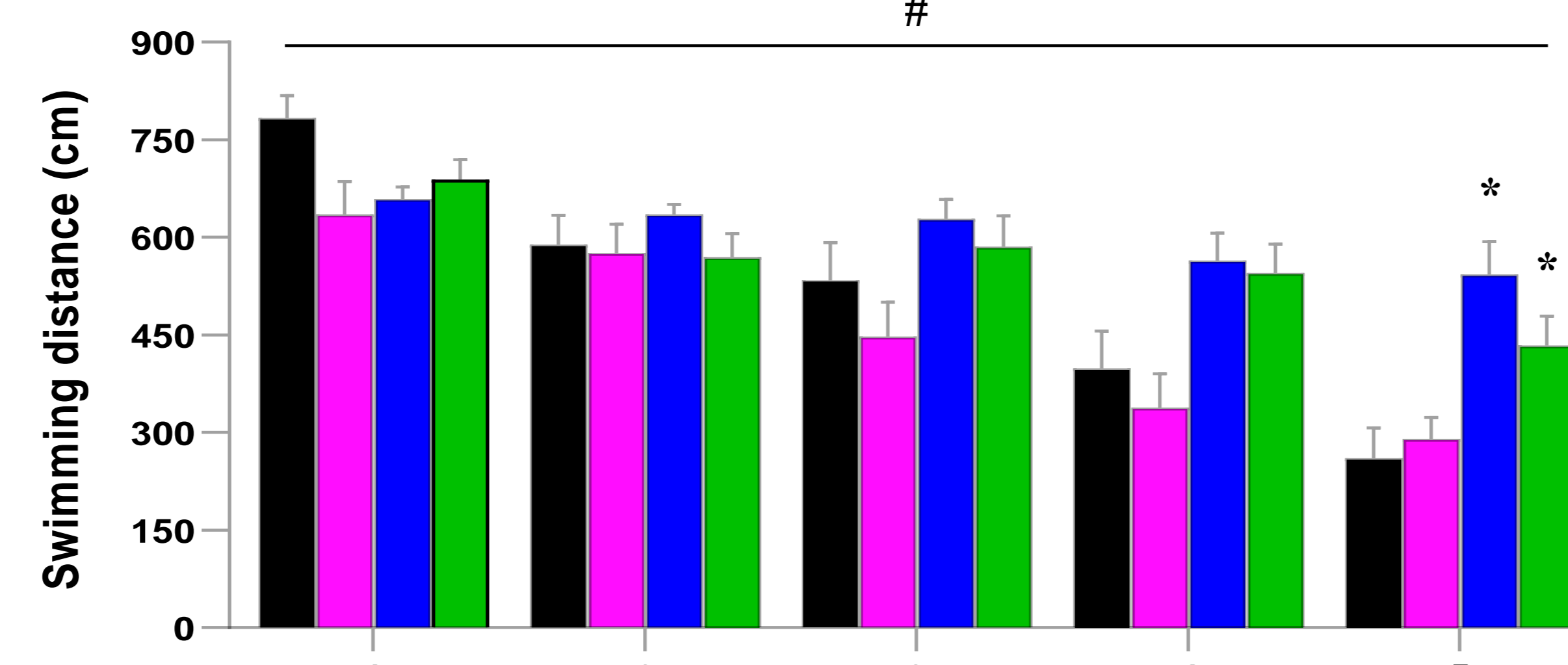


- Exploration in the Y-maze for 8-min
- Alternation = successive entries in the 3 arms
- Percentage of alternation (compared to the chance value 50%)
NB of alternations / (total NB of arms visited - 2) x 100

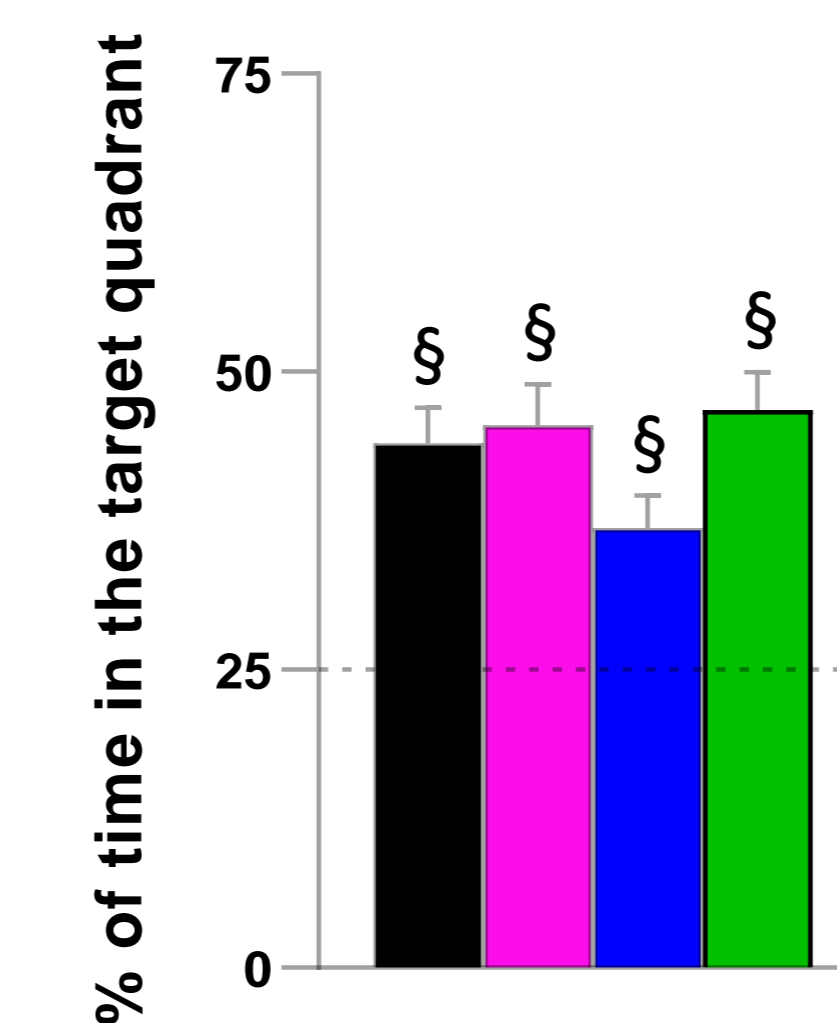


SR deletion in the bigenic mice reverses working memory deficits displayed by 5xFAD mice

Learning

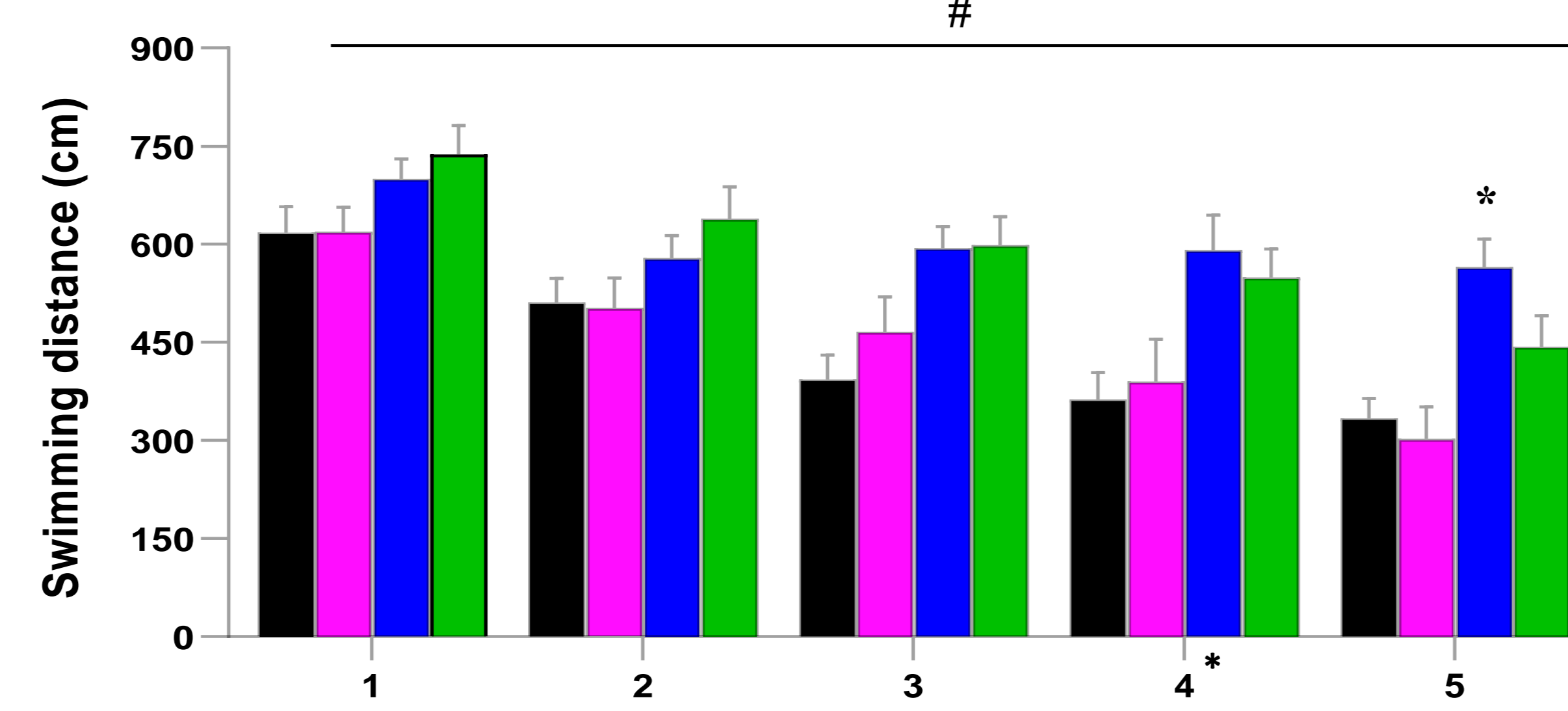


Probe-test 1

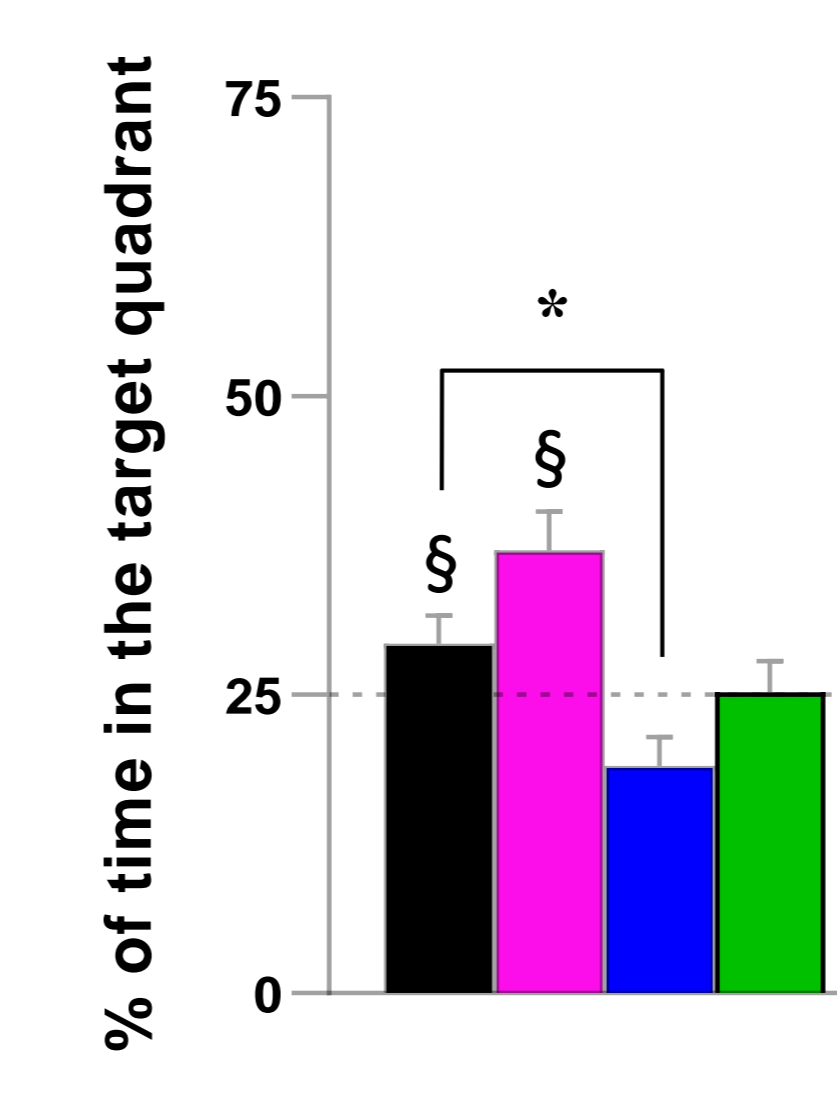


Compared to WT mice, 5xFAD and bigenic mice display reduced spatial learning performances, but unaltered reference memory

Relearning



Probe-test 2



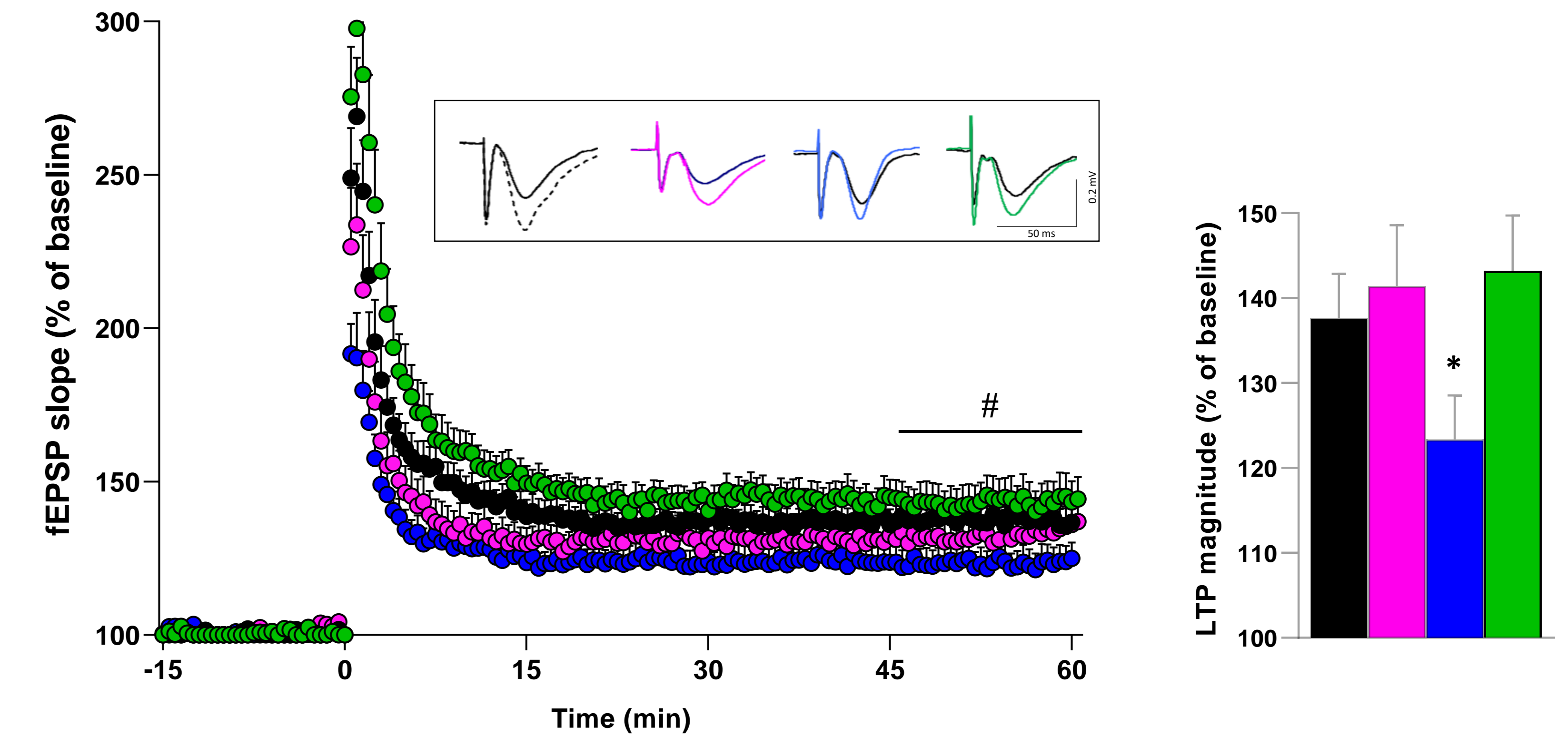
Compared to WT mice, 5xFAD mice display a flexibility deficit, noticeable during relearning and thus in the probe test. Adding SR deletion alleviates this deficit during relearning hence partially reverses reference memory deficits.

Ex vivo electrophysiological recording

➤ 3-4 months old
➤ n = 8-16 per group

Extracellular recording in CA1 stratum radiatum of hippocampal slices (after electrical stimulation of Schaffer collaterals)

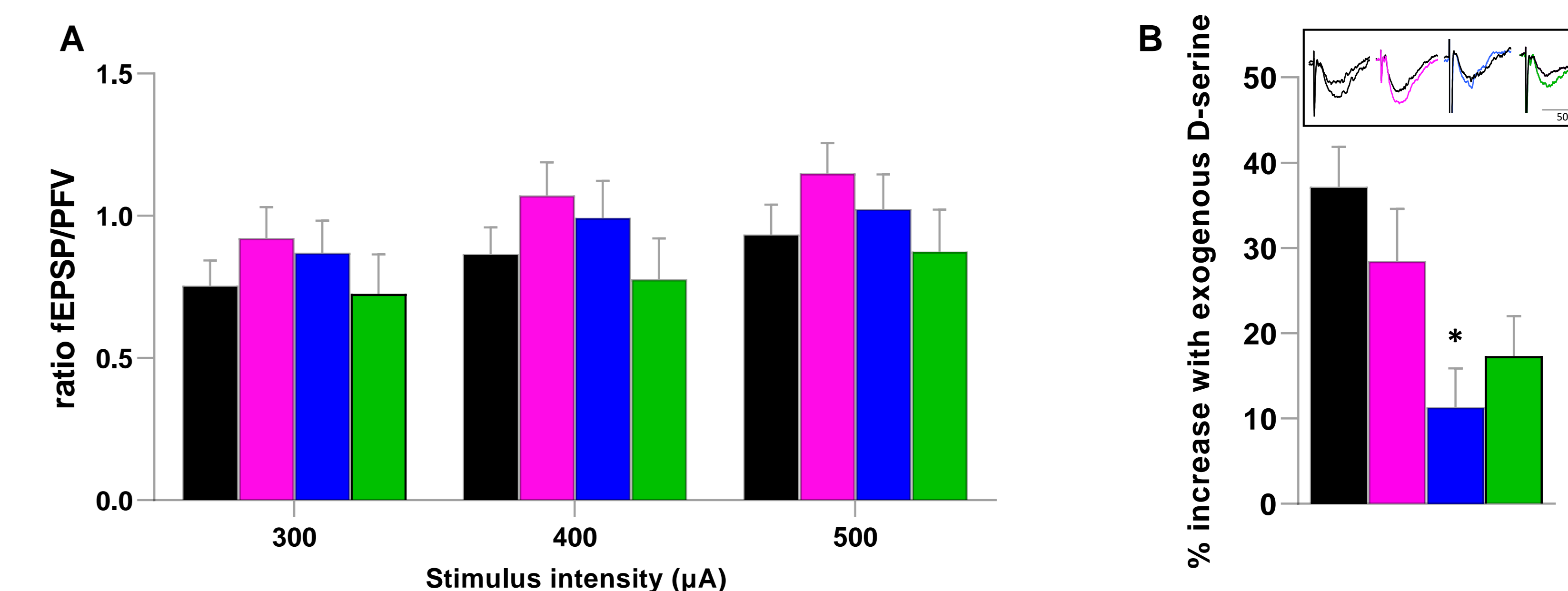
High frequency stimulation (HFS)-induced long-term potentiation (LTP) (1x100Hz)



SR deletion reverses LTP deficits displayed by 5xFAD mice

Isolated NMDAR-mediated fEPSPs (field Excitatory Post-Synaptic Potentials)

Presynaptic Fiber Volley (PFV) and fEPSPs were recorded in low magnesium supplemented medium with the non-NMDAR antagonist NBQX (10 μ M)
(A): Input/Output graph of fEPSP/PFV ratio (B): Percentage of increase of fEPSP/PFV ratio (at 300 μ A) either before and 15 min after addition of D-serine

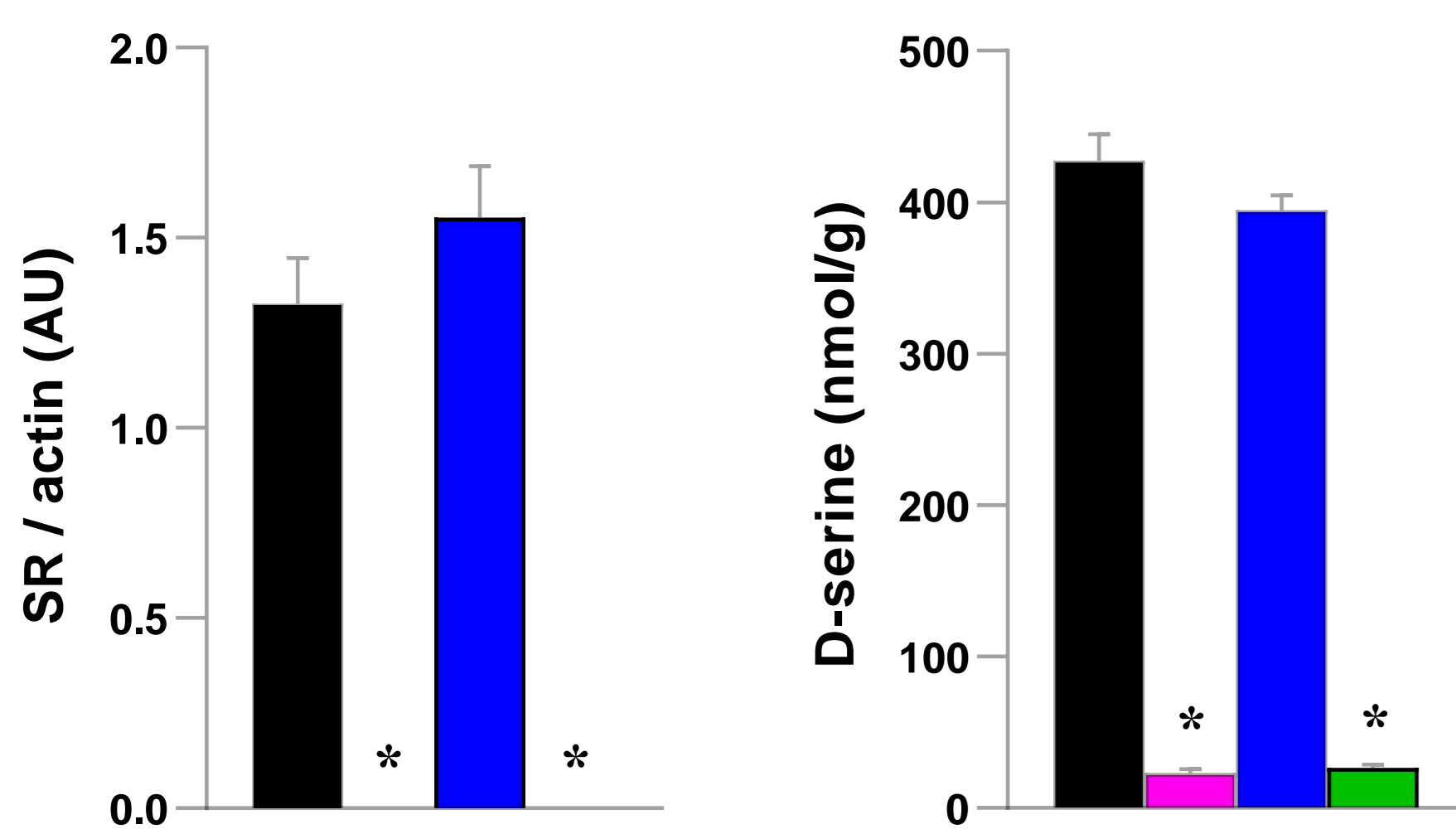


(A) No genotype difference of NMDAR activation is observed in basal conditions
(B) The increase in NMDAR activation induced by exogenous-D-serine is significantly lower in 5xFAD mice, suggesting a decrease in NMDAR density, which is reversed when the SR is deleted concomitantly.

BIOCHEMICAL ANALYSES

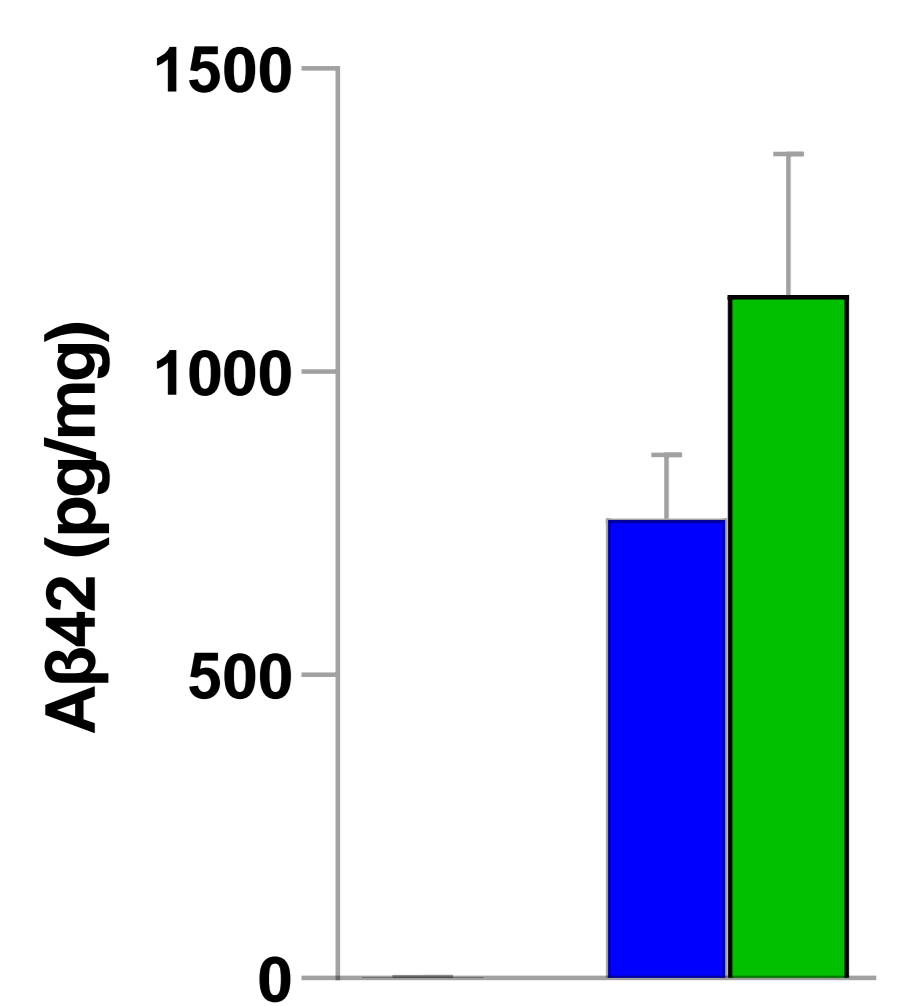
➤ 3-4 months old
➤ n = 3-7 per group

Hippocampal expression of Serine-racemase and D-serine level



No significant difference levels of D-serine were noticeable in 5xFAD mice (compared to WT).

Hippocampal $A\beta_{42}$ level



5xFAD and 5xFAD/SR^{-/-} display similar hippocampal level of $A\beta_{42}$ (only traces were observed in WT and SR^{-/-} mice)

Altogether, these results highlight critical involvement of D-serine in $A\beta$ -induced hippocampal network dysfunctions and related cognitive disabilities.

