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## **A robust link between d-serine and amyloid pathology in a mouse model**

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N-methyl-D-aspartate receptor (NMDAr) plays a crucial role in neuronal plasticity and higher brain functions such as memory and learning. Its activation requires, additionally to glutamate, binding of a **coagonist, such as D-serine**. NMDAr are affected by the **β-amyloid (Aβ) pathology** and growing number of evidences suggest an involvement of D-serine in plasticity and cognitive-related impairments. Therefore, transgenic 5xFAD mice (bearing 5 familial Alzheimer disease-linked mutations) which shows accentuated amyloidogenesis, was crossed with mice having a deletion of the gene coding for Serine-Racemase (SR), converting L- into D-serine, to generate a bigenic line of mice: 5xFAD/SR<sup>-/-</sup>.

To assess the role of D-serine within Aβ-induced alterations, transgenic lines of mice (10-12 months old) were compared through a combined approach (gathering biochemical analyses, hippocampal-dependent behavioral tests and extracellular electrophysiological recordings at CA3/CA1 hippocampal synapses).

### Transgenic mouse line comparison

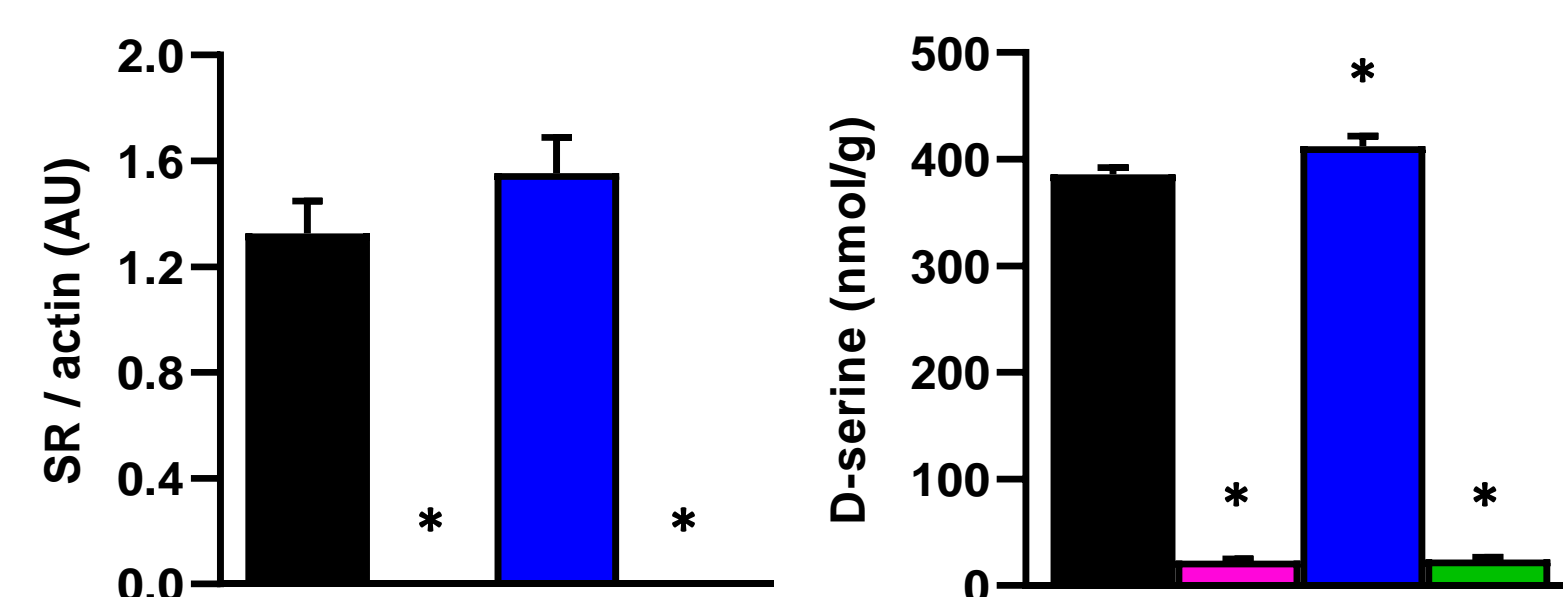
■ WT      ■ 5xFAD  
■ SR<sup>-/-</sup>      ■ 5xFAD/SR<sup>-/-</sup>

- Data are expressed in 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

### Biochemical analyses

- Hippocampal expression of Serine-Racemase and D-serine level

(N=4-7 per group)

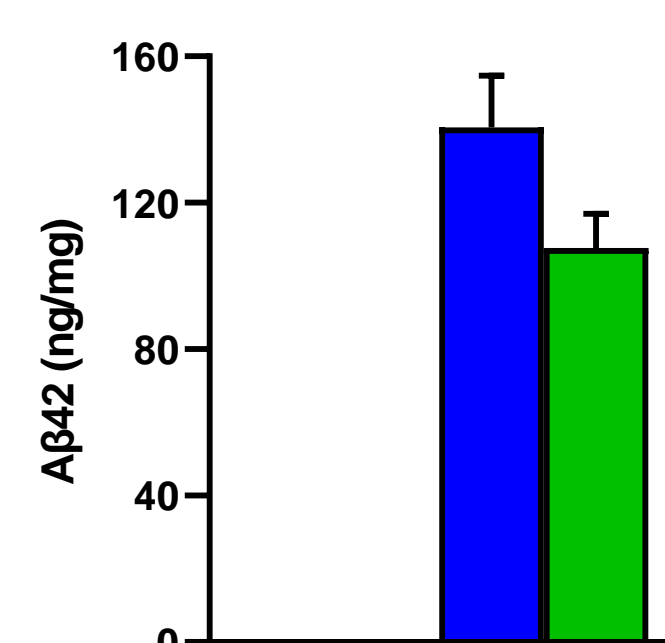


No expression of Serine Racemase in SR<sup>-/-</sup> and bigenic mice, agreeing with the very low level of D-serine in these lines.

Of note, higher levels of D-serine were noticeable in 5xFAD mice (compared to WT).

- Hippocampal Aβ<sub>42</sub> level

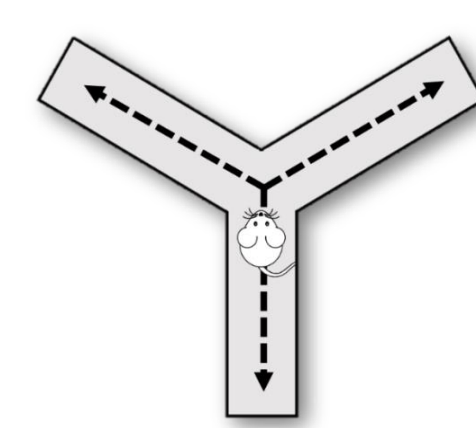
(N=4-6 per group)



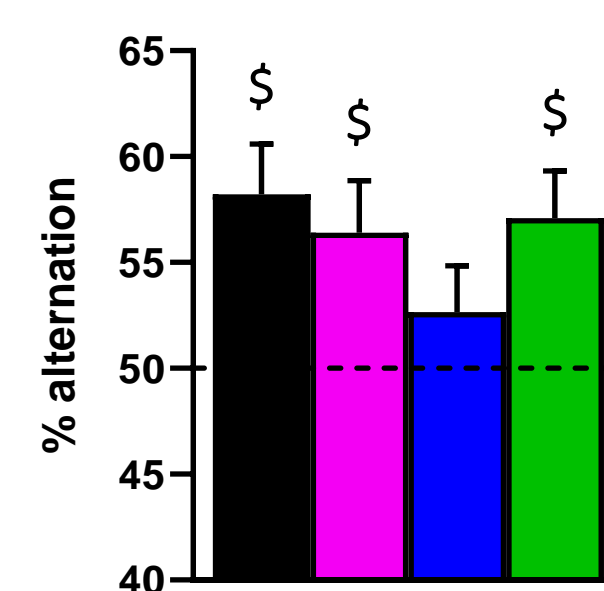
Slight – but non significant – decrease of Aβ<sub>42</sub> in bigenic mice (compared to 5xFAD)

### Behavior

- Spontaneous alternation test

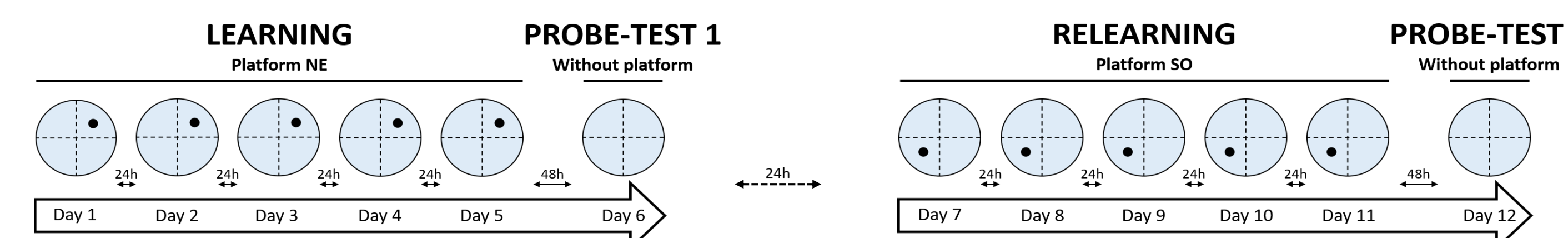


- N=15-21 per group
- Free exploration in the Y-maze for 8-min
- Successive entries in the 3 arms of the maze were considered as an alternation
- The percentage of alternation was calculated as follows: NB of alternations / (total NB of arms visited - 2) x 100. This percentage was compared to the chance value (50%)



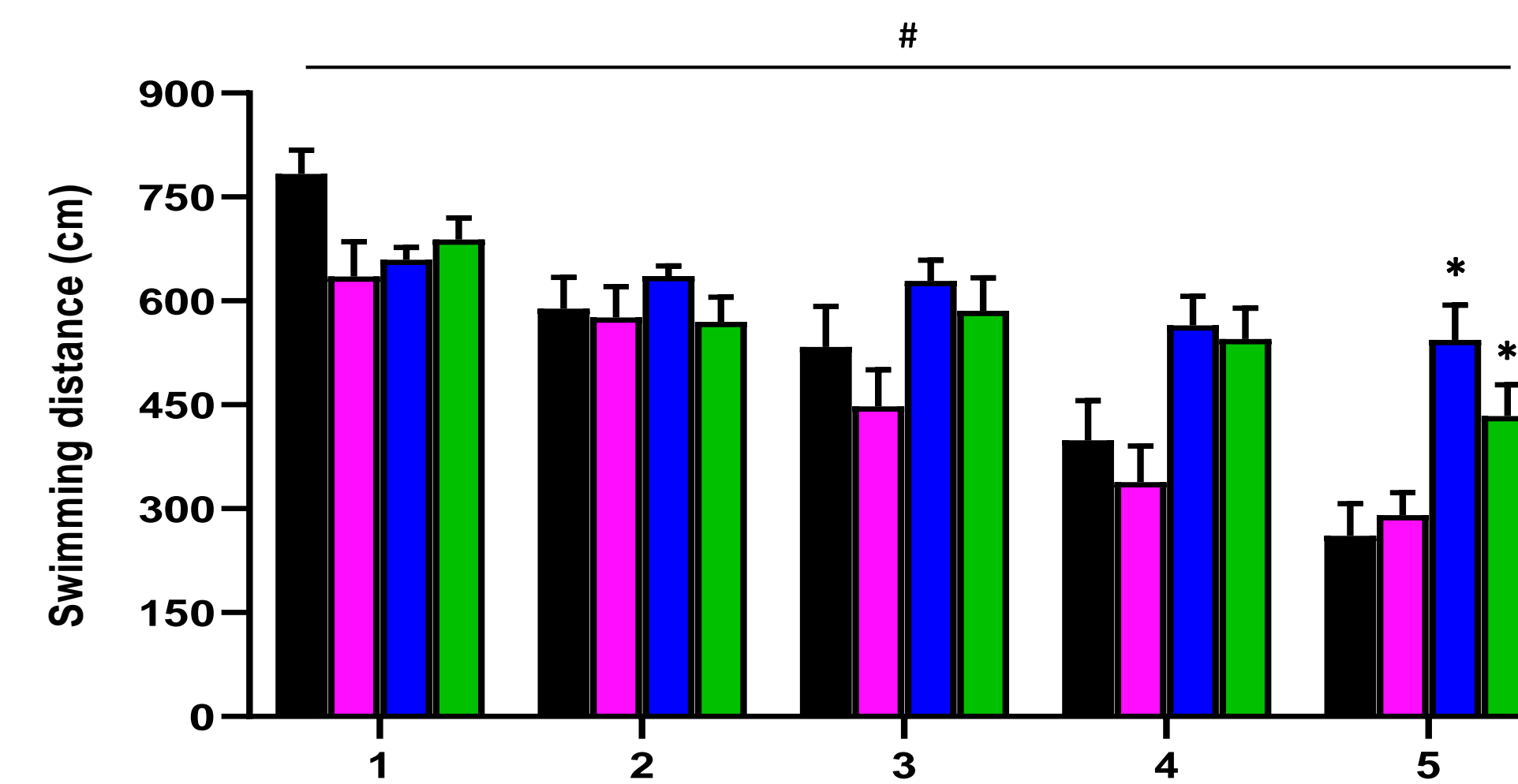
SR deletion in the bigenic reverses working memory deficits displayed by 5xFAD mice

- Morris Water Maze

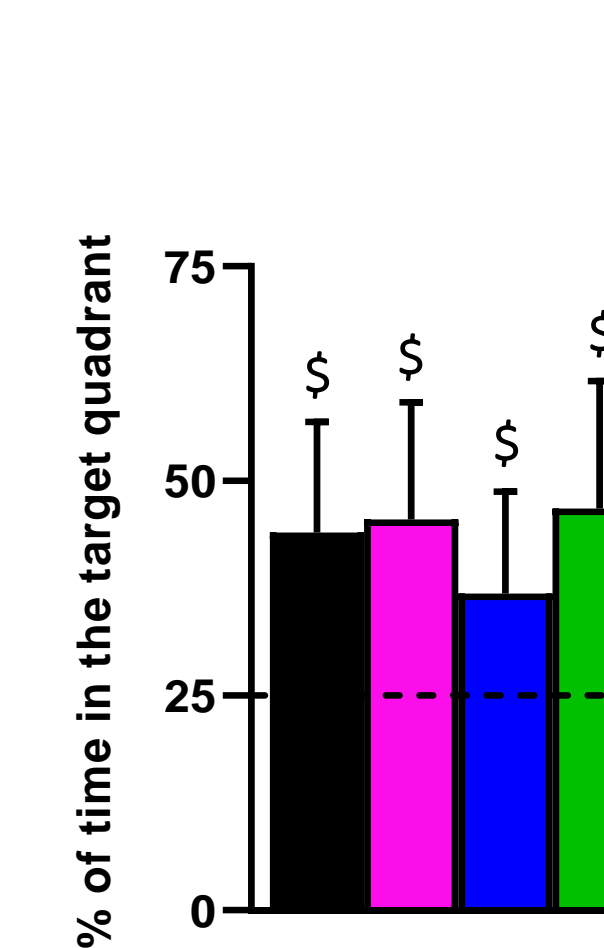


- Mice (N=16-22 per group) were trained to learn the location of the hidden platform (through distinct visual cues)
- Learning and relearning session: 4 trials of 60 sec / day during 5 days (60 sec inter-trial interval)
- Probe tests: performed 48h after last trial of respectively, learning and relearning session. Platform was removed and mice were free to explore the maze during 60 sec

#### Learning

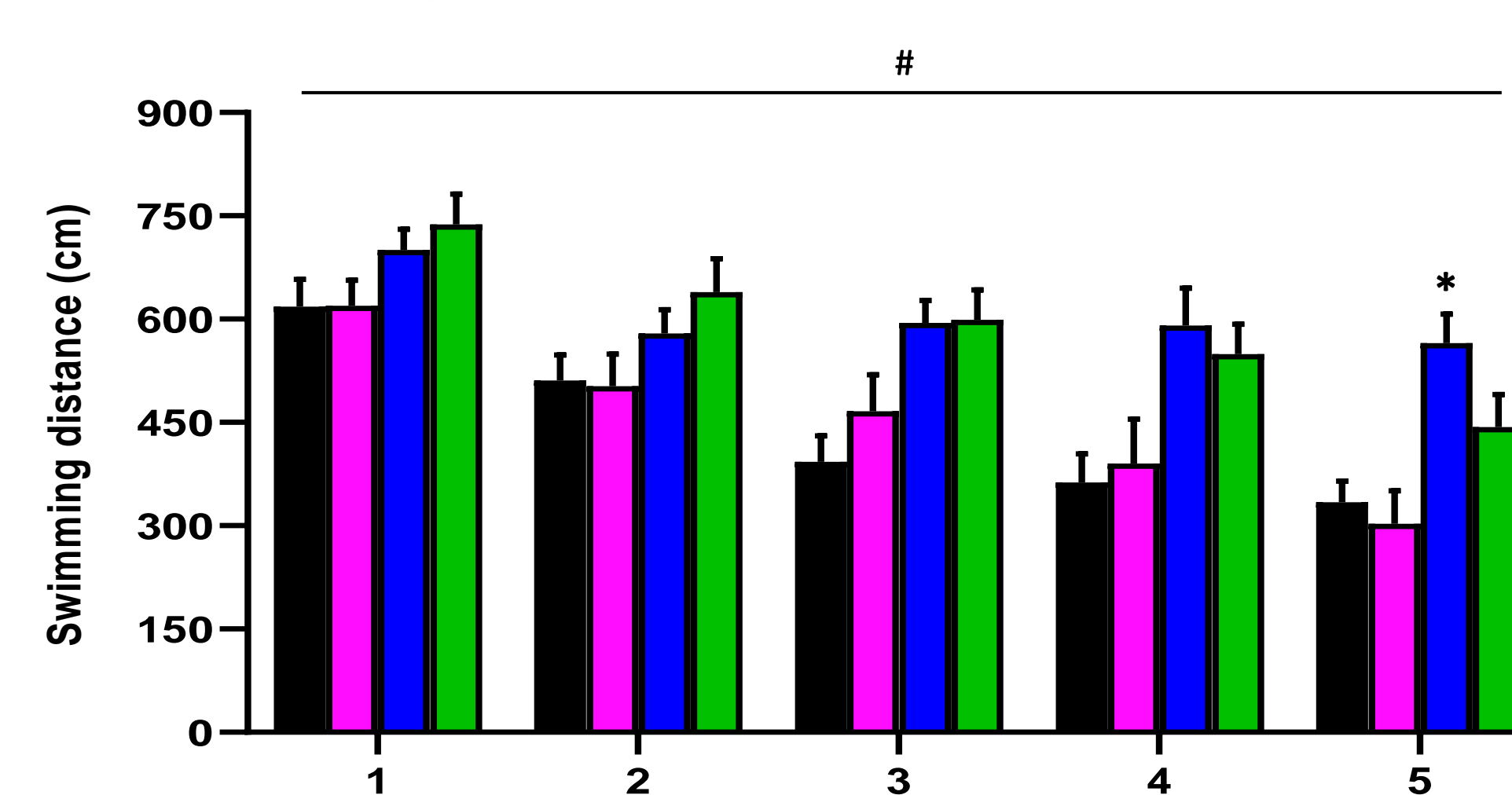


#### Probe-test 1

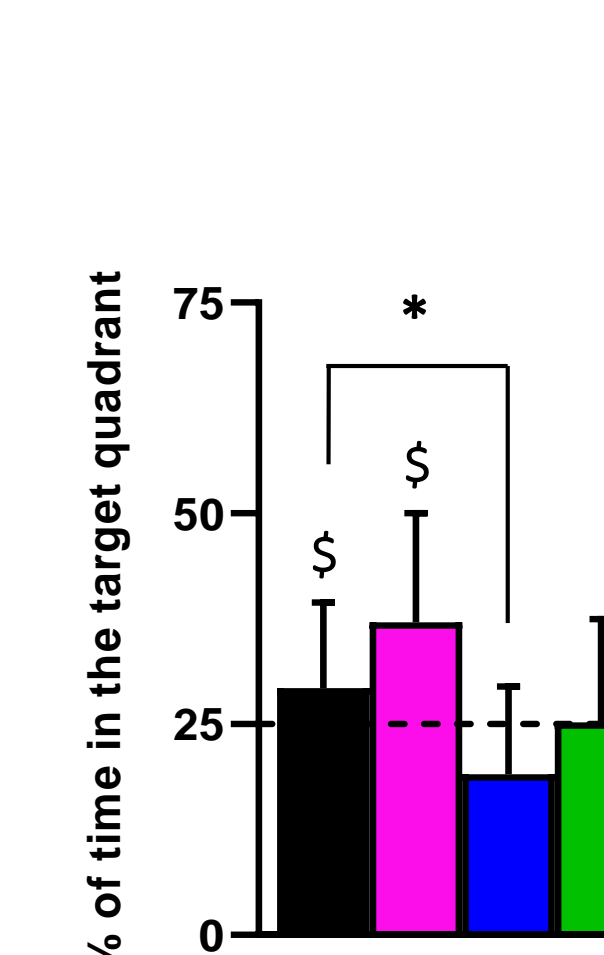


Compared to WT mice, 5xFAD and bigenic mice display reduced spatial learning performances, but unaltered reference memory

#### Relearning



#### Probe-test 2



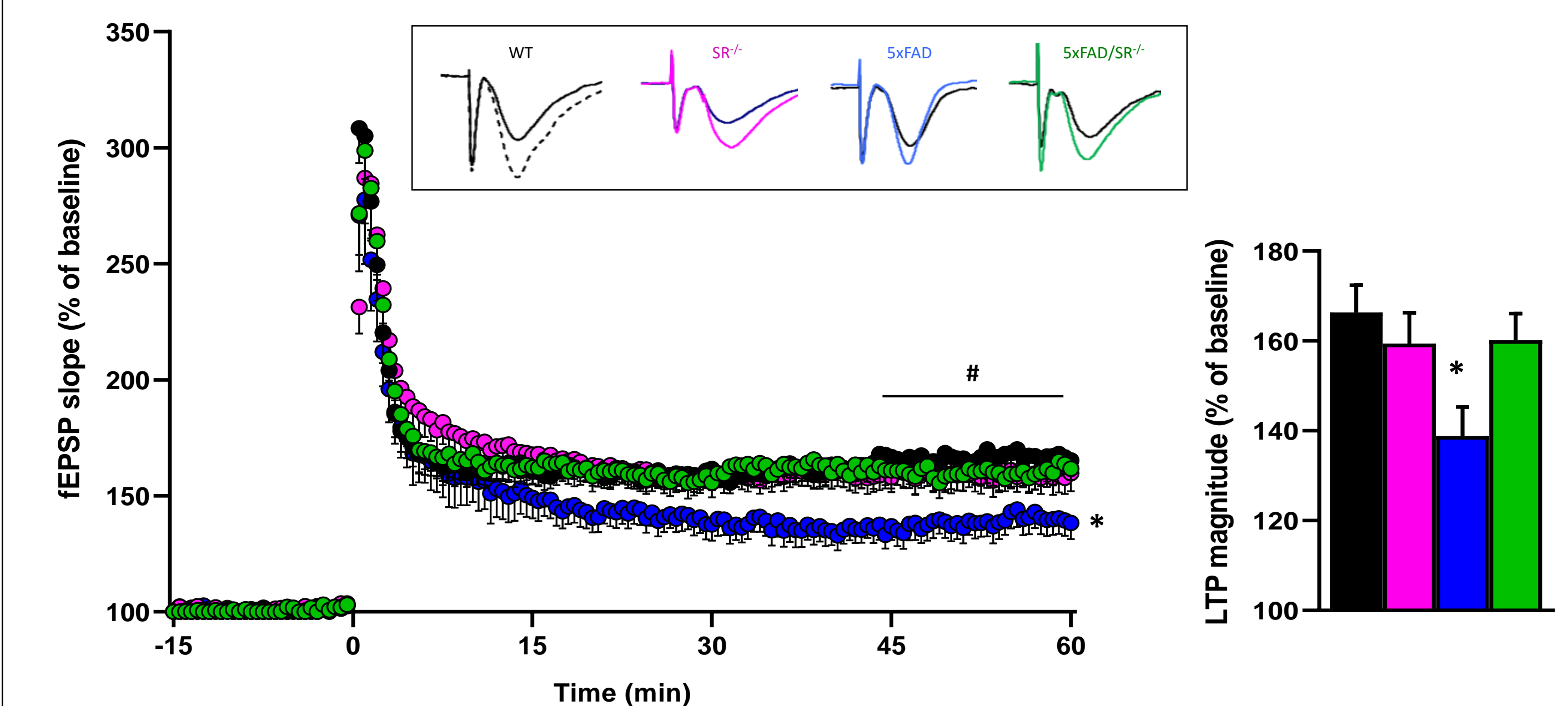
Compared to WT mice, 5xFAD mice display a flexibility deficit, noticeable during relearning and thus in the probe test. Adding SR deletion alleviates this deficit during relearning hence partially reverses reference memory deficits.

### Ex vivo electrophysiological recording

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

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

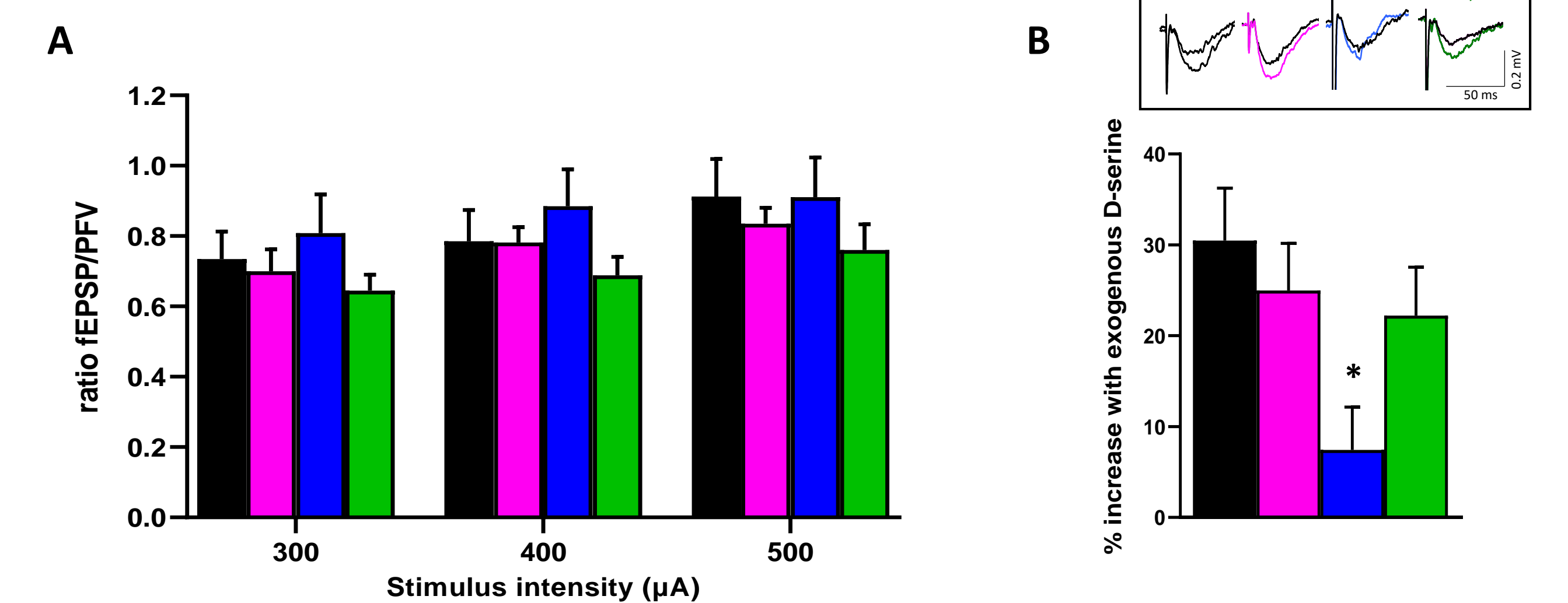
- N=10-16 mice per group
- Testing stimulation (average of 3 stimulations at 0,1 Hz) for 15min baseline and then resumed for 60 min after conditioning stimulation
- Conditioning : 1 electrical train at 100 Hz for 1 sec



- Isolated NMDAr-mediated fEPSPs (field Excitatory PostSynaptic Potentials)

- N=11-13 mice per group
- Presynaptic Fiber Volley (PFV) and fEPSPs were recorded in low magnesium supplemented medium with the non-NMDAr antagonist NBQX (10μM)

(A): Input/Output graph of fEPSP/PFV ratio  
(B): Percentage of increase of fEPSP/PFV ratio (at 400μA) 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 NMDA receptor density, which is reversed when the SR is deleted concomitantly.

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