



**HAL**  
open science

## Impact of d-serine depletion in the $\beta$ -amyloid cascade related to Alzheimer's disease

T. Freret, E Ploux, L. Gorisse, I Radzishovsky, H Wolosker, Jean-Marie Billard

► **To cite this version:**

T. Freret, E Ploux, L. Gorisse, I Radzishovsky, H Wolosker, et al.. Impact of d-serine depletion in the  $\beta$ -amyloid cascade related to Alzheimer's disease. Annual Meeting of the Society for Neuroscience (SFN), Oct 2019, Chicago, United States. hal-02330837

**HAL Id: hal-02330837**

**<https://normandie-univ.hal.science/hal-02330837>**

Submitted on 24 Oct 2019

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

# IMPACT OF D-SERINE DEPLETION IN THE $\beta$ -AMYLOID CASCADE RELATED TO ALZHEIMER'S DISEASE

T. FRERET<sup>1</sup>, E. PLOUX<sup>1</sup>, L. GORISSE<sup>2</sup>, I. RADZISHEVSKY<sup>3</sup>, H. WOLOSKER<sup>4</sup>, J.-M. BILLARD<sup>1</sup>

<sup>1</sup>Normandie Univ, UNICAEN, INSERM, COMETE GIP CYCERON, 14000 Caen, France  
<sup>2</sup>INSERM, Paris, France  
<sup>3</sup>Department of biochemistry, Technion, Israel Institute of Technology, Haifa, Israel

**Contact information:**  
[thomas.freret@unicaen.fr](mailto:thomas.freret@unicaen.fr)

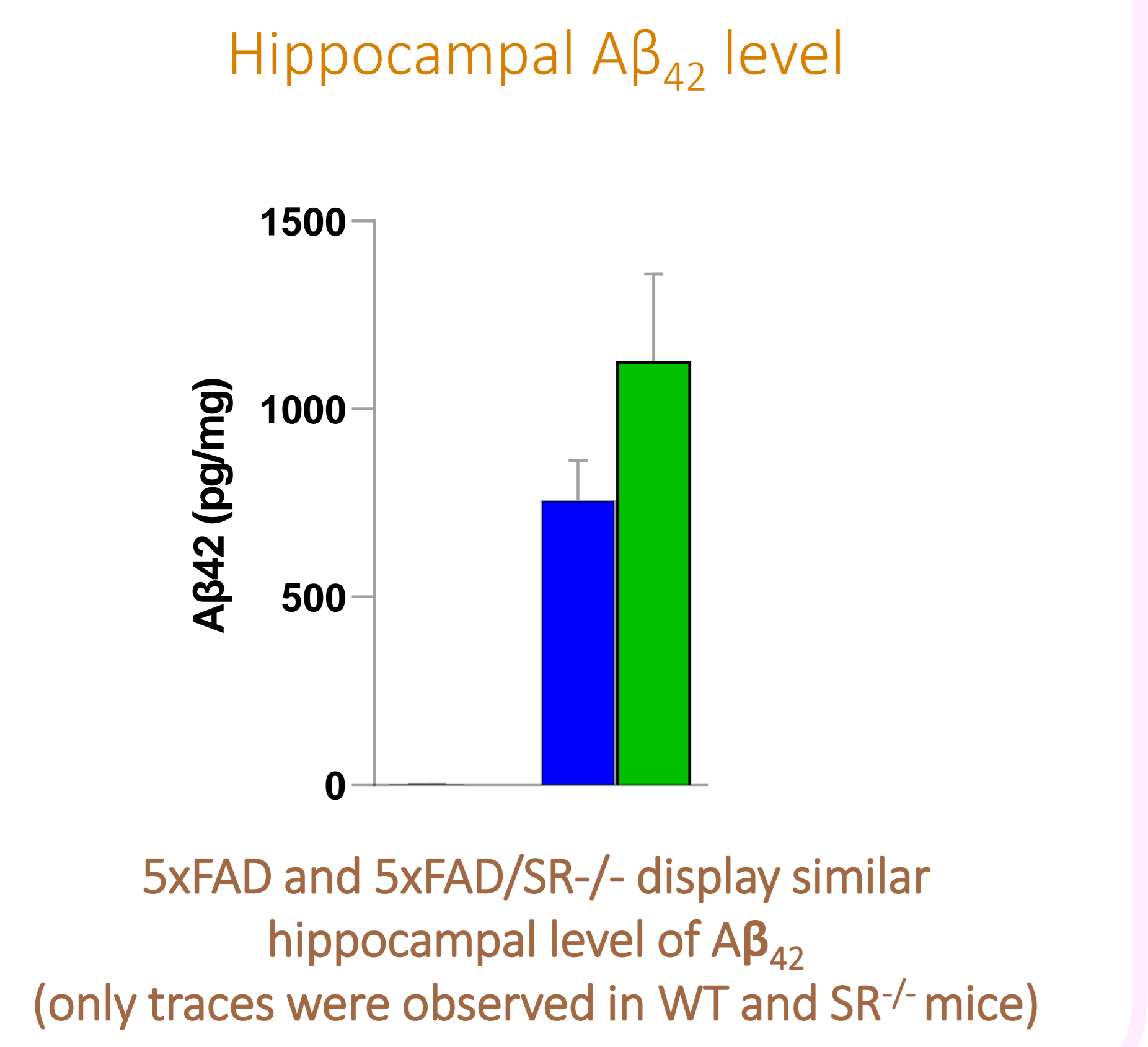
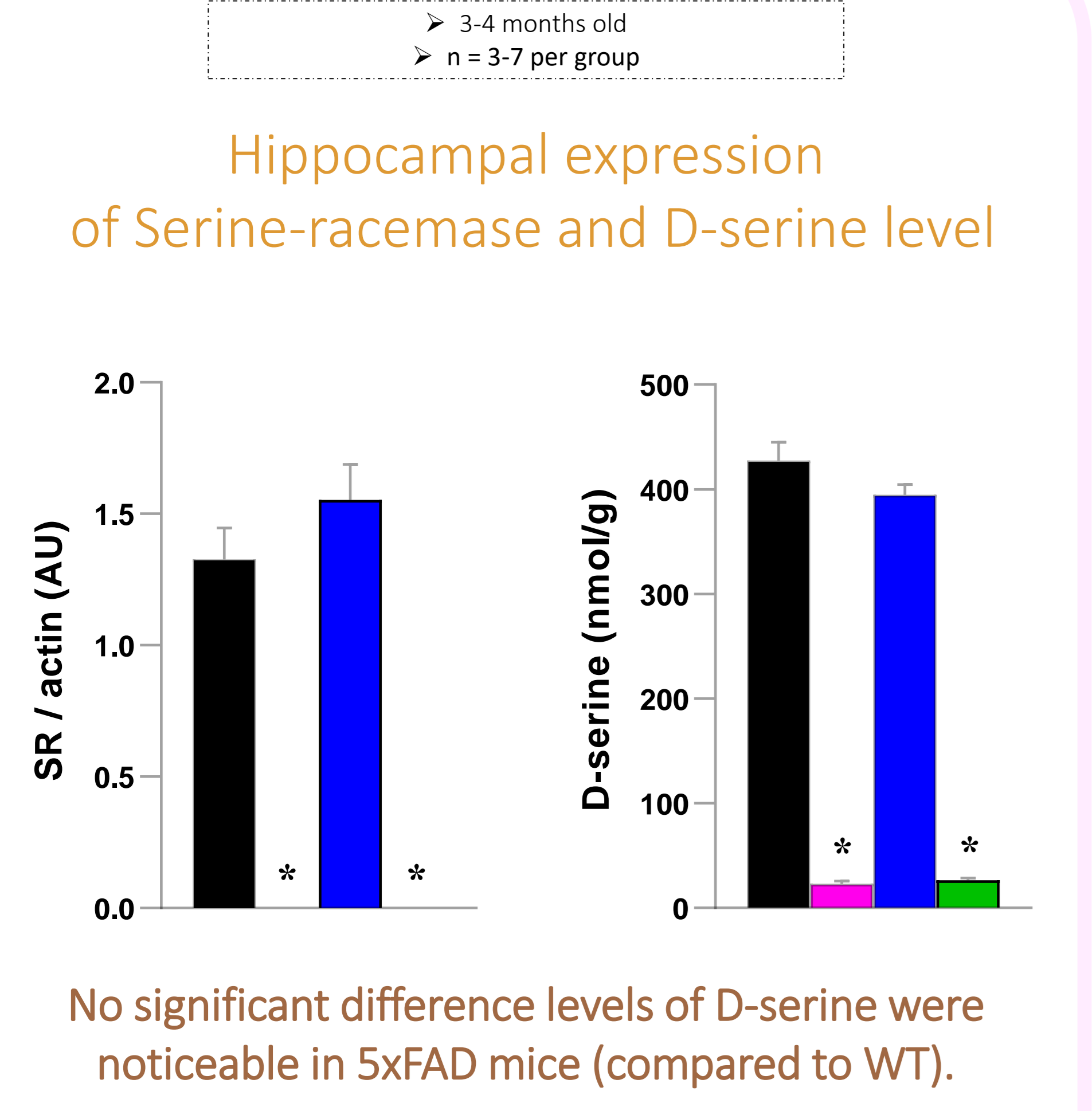
D-serine, as a co-agonist of N-methyl-D-aspartate subtype of glutamate receptors (NMDAR), is a key regulator of their activation. Hence, D-serine is involved in functional brain plasticity and memory processes. In the course of Alzheimer's disease (AD), homeostasis of NMDA receptors is precociously affected 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.

**Legend:** ■ WT ■ SR<sup>-/-</sup> ■ 5xFAD ■ 5xFADSR<sup>-/-</sup>

**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

## BIOCHEMICAL ANALYSES



**Behavior**  
 > 10-12 months old  
 > n = 15-22 per group

**Morris-water-maze**

**Behavioral protocol:** LEARNING (Platform NE) Days 1-5, PROBE-TEST 1 (Without platform) Day 6, RELEARNING (Platform SO) Days 7-11, PROBE-TEST 2 (Without platform) Day 12.

**Learning:** Swimming distance (cm) significantly reduced in 5xFAD and SR<sup>-/-</sup> mice compared to WT (#). 5xFADSR<sup>-/-</sup> mice show improved performance compared to 5xFAD mice (\*).

**Probe-test 1:** % of time in the target quadrant significantly reduced in 5xFAD and SR<sup>-/-</sup> mice compared to WT (§). 5xFADSR<sup>-/-</sup> mice show improved performance compared to 5xFAD mice (§).

**Relearning:** Swimming distance (cm) significantly reduced in 5xFAD and SR<sup>-/-</sup> mice compared to WT (#). 5xFADSR<sup>-/-</sup> mice show improved performance compared to 5xFAD mice (\*).

**Probe-test 2:** % of time in the target quadrant significantly reduced in 5xFAD and SR<sup>-/-</sup> mice compared to WT (§). 5xFADSR<sup>-/-</sup> mice show improved performance compared to 5xFAD mice (§).

**Spontaneous alternation:** % alternation significantly reduced in 5xFAD and SR<sup>-/-</sup> mice compared to WT (§). 5xFADSR<sup>-/-</sup> mice show improved performance compared to 5xFAD mice (§).

**Y-maze diagram:** A, B, C arms.

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

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

**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 $\mu$ M)

**(A):** Input/Output graph of fEPSP/PFV ratio vs Stimulus intensity ( $\mu$ A). No genotype difference is observed in basal conditions.

**(B):** Percentage of increase of fEPSP/PFV ratio (at 300 $\mu$ A) either before and 15 min after addition of D-serine. 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.

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

SCAN ME