



**HAL**  
open science

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

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

► **To cite this version:**

E Ploux, L. Gorisse, I Radzishovsky, H Wolosker, Thomas Freret, et al.. A robust link between d-serine and amyloid pathology in a mouse model. 4th International Conference of D-Amino Acid Research, Sep 2019, Tokyo, Japan. hal-02331029

**HAL Id: hal-02331029**

**<https://normandie-univ.hal.science/hal-02331029>**

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.

Contact:

[eva.ploux@unicaen.fr](mailto:eva.ploux@unicaen.fr)



Eva PLOUX<sup>1</sup>, Lucile GORISSE<sup>1</sup>, Inna RADZISHEVSKY<sup>2</sup>, Herman WOLOSKER<sup>2</sup>, Thomas FRERET<sup>1</sup>, Jean-Marie BILLARD<sup>1</sup>

<sup>1</sup>Normandie Univ, UNICAEN, INSERM, COMETE, GIP CYCERON, 14000 Caen, France

<sup>2</sup>Department of biochemistry, Technion, Israel Institute of Technology, Haifa, Israel

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

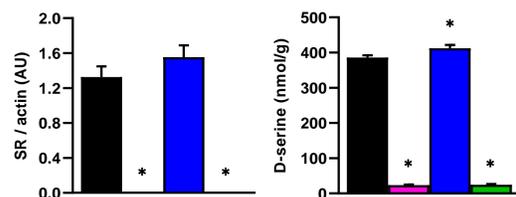
■ WT      ■ 5xFAD  
■ SR<sup>-/-</sup>      ■ 5xFAD/SR<sup>-/-</sup>

- 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)

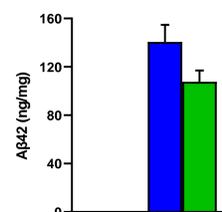


No expression of Serine Racemase in SR<sup>-/-</sup> and bigenic mice, agreeing with the very low level of D-serine in these lines.

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)



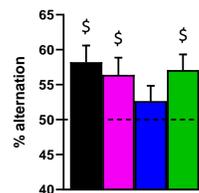
Slight – but non significant – decrease of Aβ<sub>42</sub> in bigenic mice (compared to 5xFAD)

### Behavior

#### Spontaneous alternation test

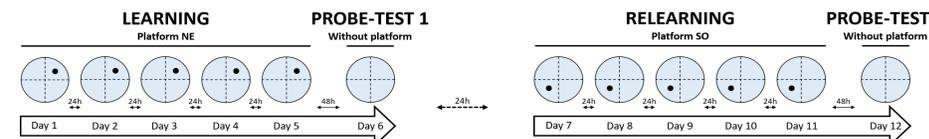


- N=15-21 per group
- Free exploration in the Y-maze for 8-min
- Successive entries in the 3 arms of the maze were considered as an alternation
- The percentage of alternation was calculated as follows: NB of alternations / (total NB of arms visited - 2) x 100. This percentage was compared to the chance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

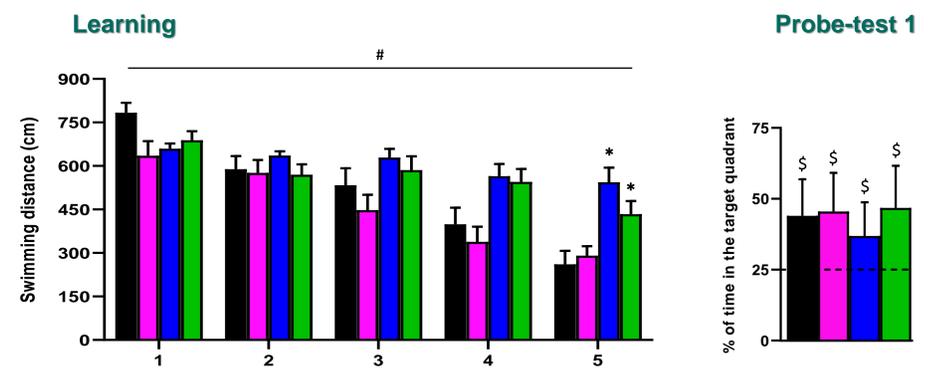


SR deletion in the bigenic reverses working memory deficits displayed by 5xFAD mice

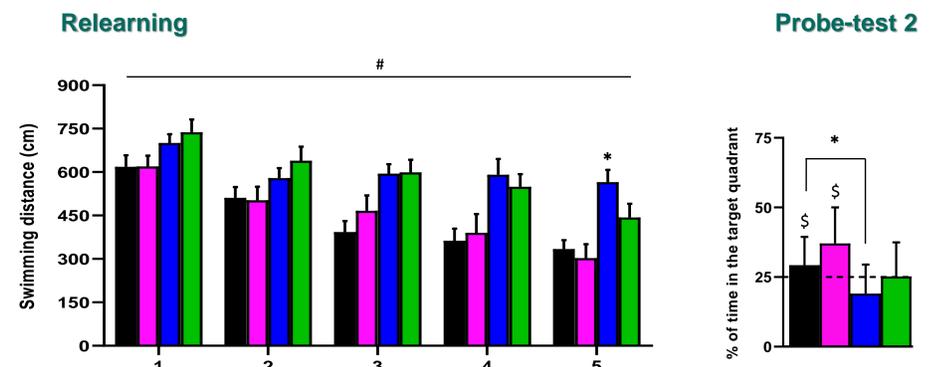
#### Morris Water Maze



- 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



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

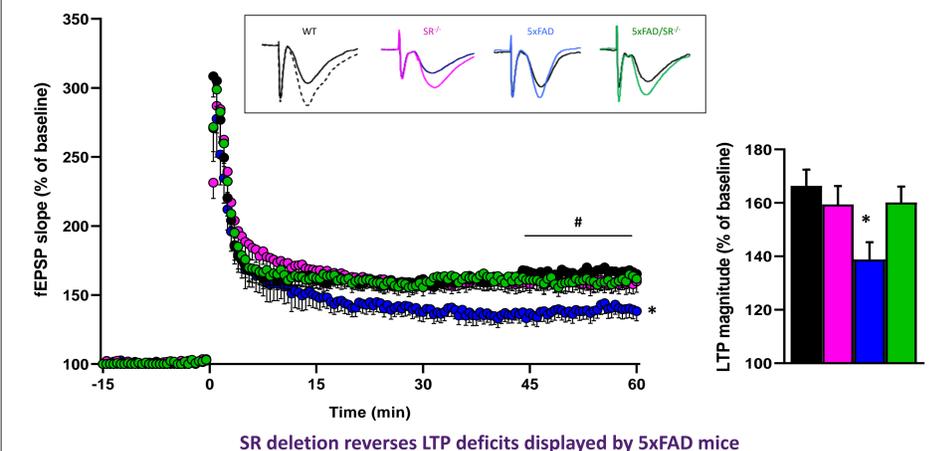


Compared to WT mice, 5xFAD mice display a flexibility deficit, noticeable during relearning and thus in the probe test. Adding SR deletion alleviates this deficit during relearning hence partially reverses reference memory deficits.

### Ex vivo electrophysiological recording

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

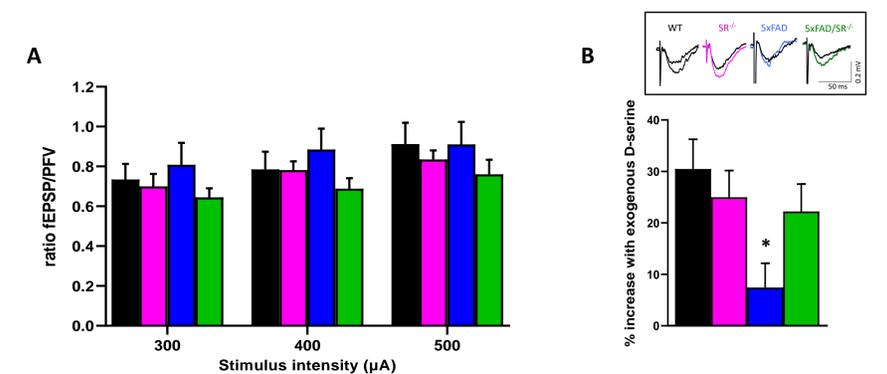
- High frequency stimulation (HFS)-induced long-term potentiation (LTP)
- N=10-16 mice per group
- Testing stimulation (average of 3 stimulations at 0,1 Hz) for 15min baseline and then resumed for 60 min after conditioning stimulation
- Conditioning : 1 electrical train at 100 Hz for 1 sec



SR deletion reverses LTP deficits displayed by 5xFAD mice

#### 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.**