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# Altering glutamate transmission in combination with an early post-natal stress to mimic schizophrenia in male and female mice

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## Schizophrenia

1% population, onset 15-25 years  
Multifactorial: genetic x environmental factors  
Symptoms: positive, negative, cognitive  
Debilitating disease → heavy costs

Treatments: not efficient on negative and cognitive symptoms, multiple side-effects

### Crucial need to refine treatments

- Improving validity of animal models of schizophrenia
- Combining genetic x environmental factors

Total Serine racemase deletion  
Coyle et al., 2018



X

Maternal separation  
PND9-24h

Ellenbroek et al., 1998; Bouet et al., 2011



C57Bl6 male and female mice

Altered glutamate transmission:

➢ Serine racemase KO mice **SRKO**

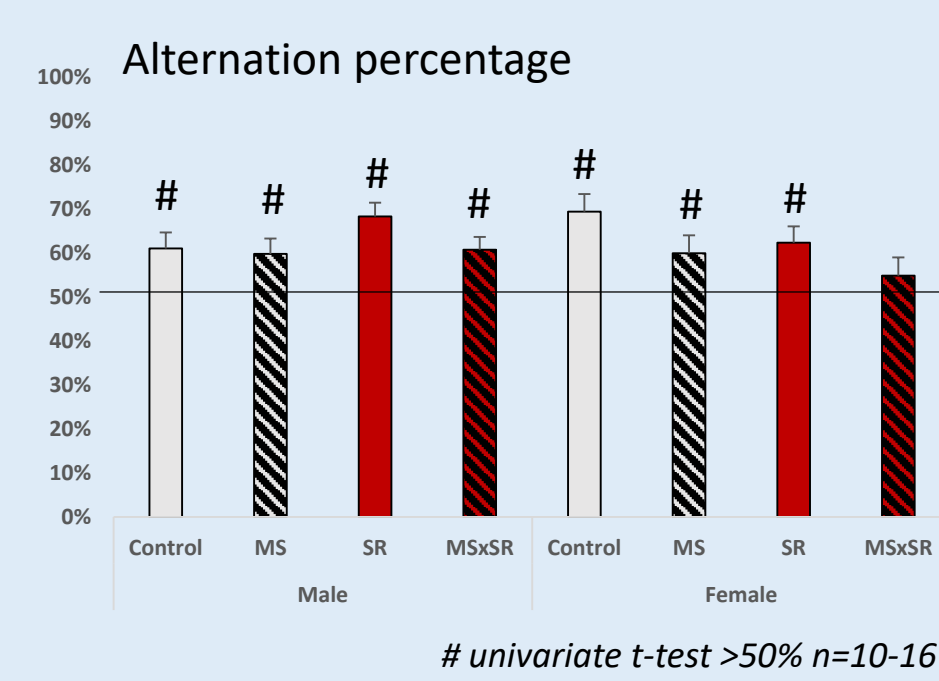
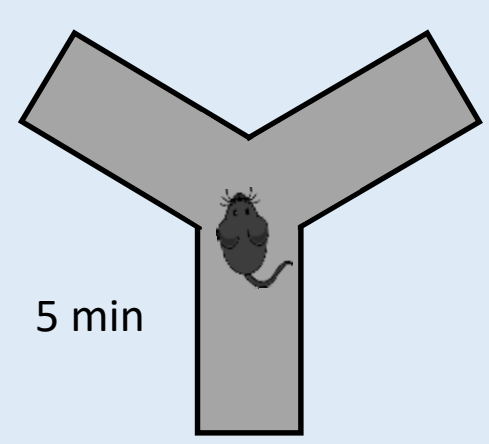
Early stress:

➢ Maternal separation **MS**

Behavioural testing

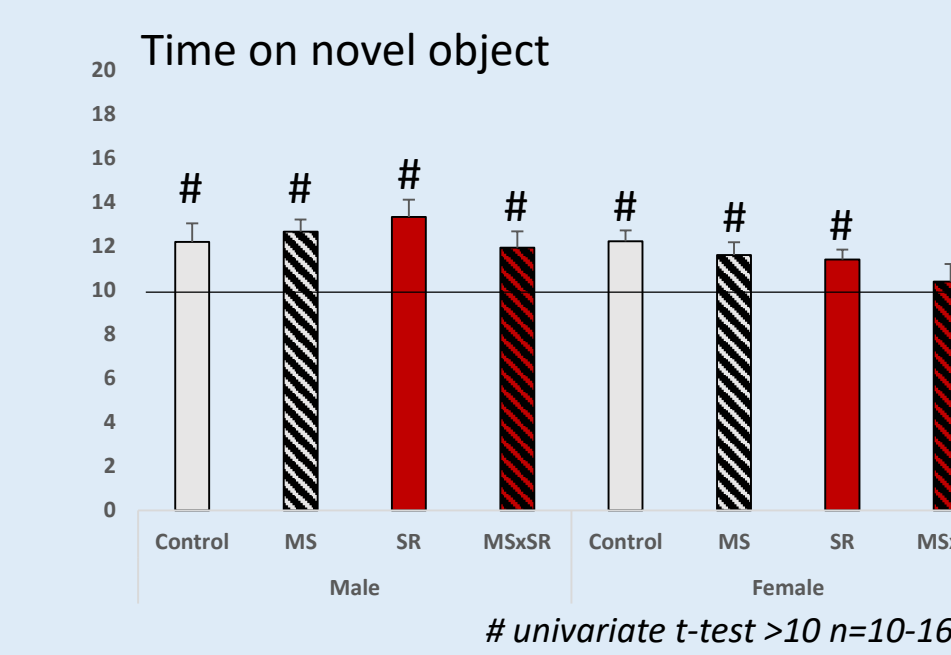
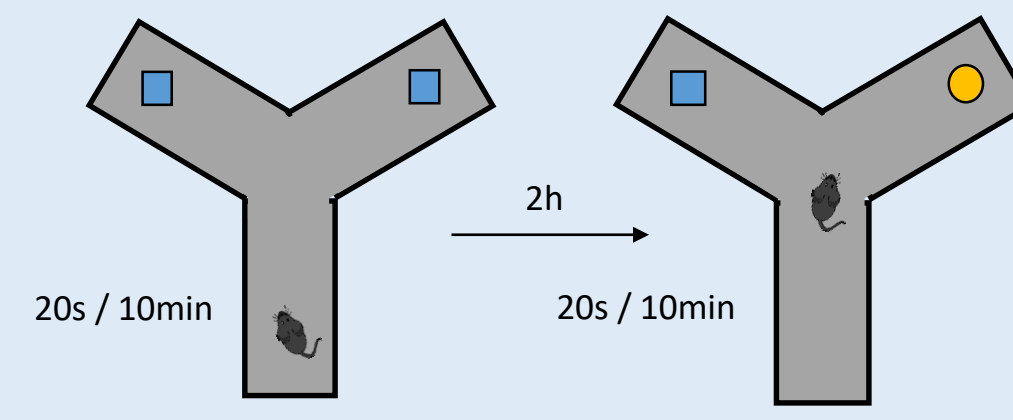
- Anxiety-like behavior
- Short and long-term memory
- Social behavior
- Sensory-motor gating

### Short-term memory Spontaneous alternation



MSxSR combination induced working memory deficit in female but not in male mice

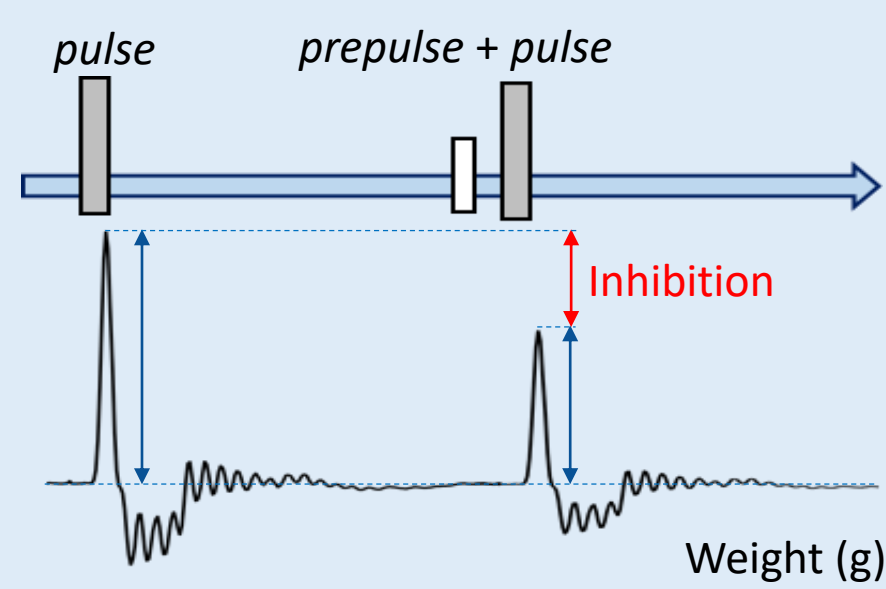
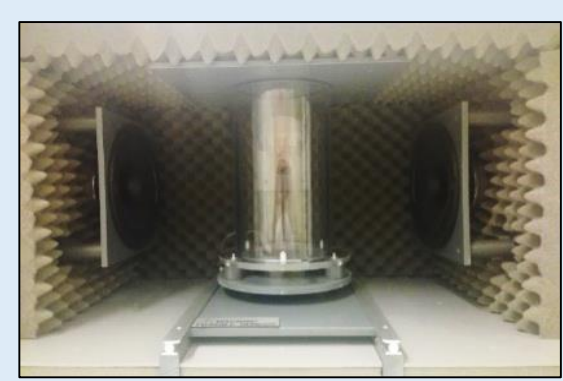
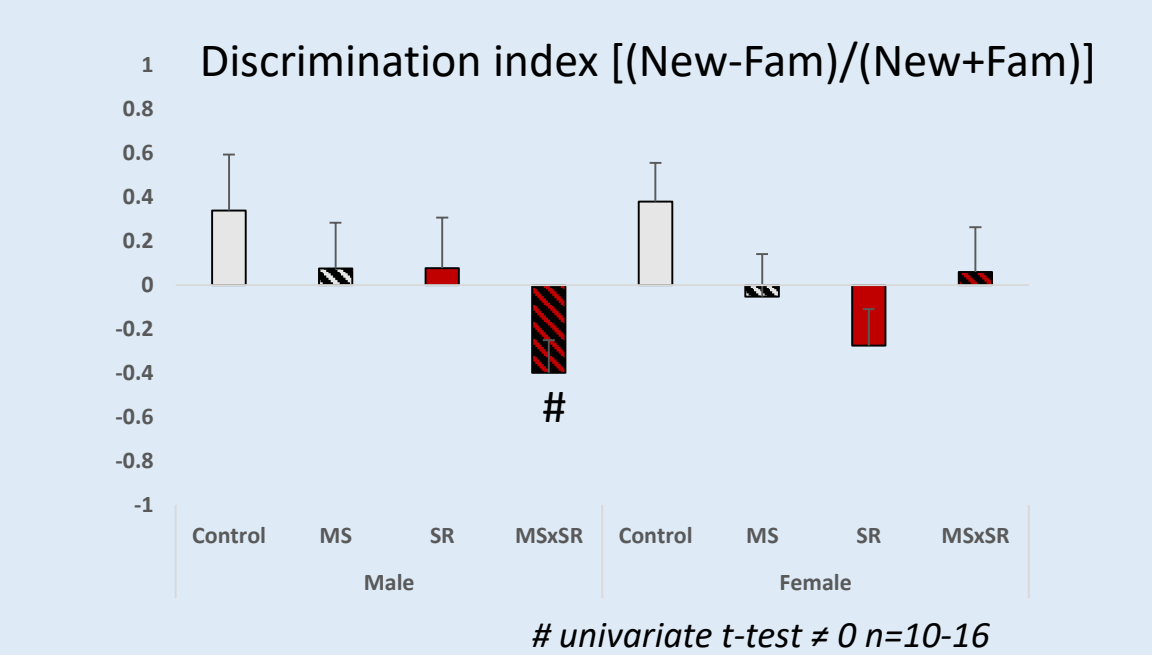
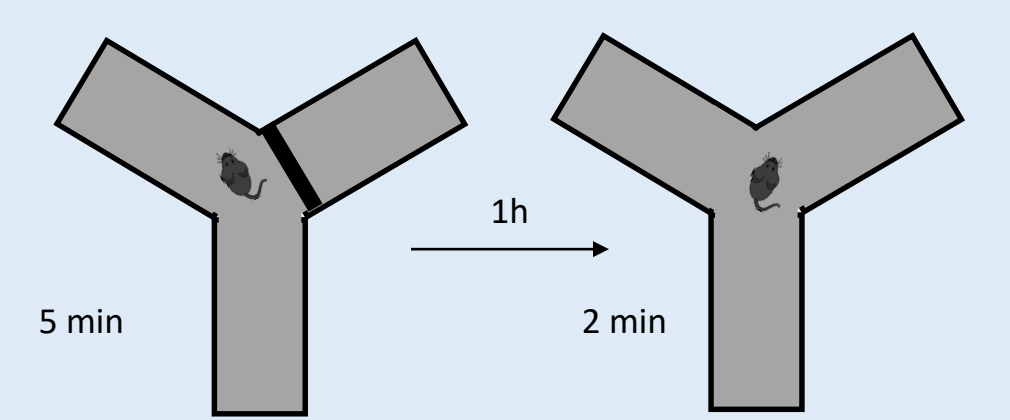
### Object recognition memory



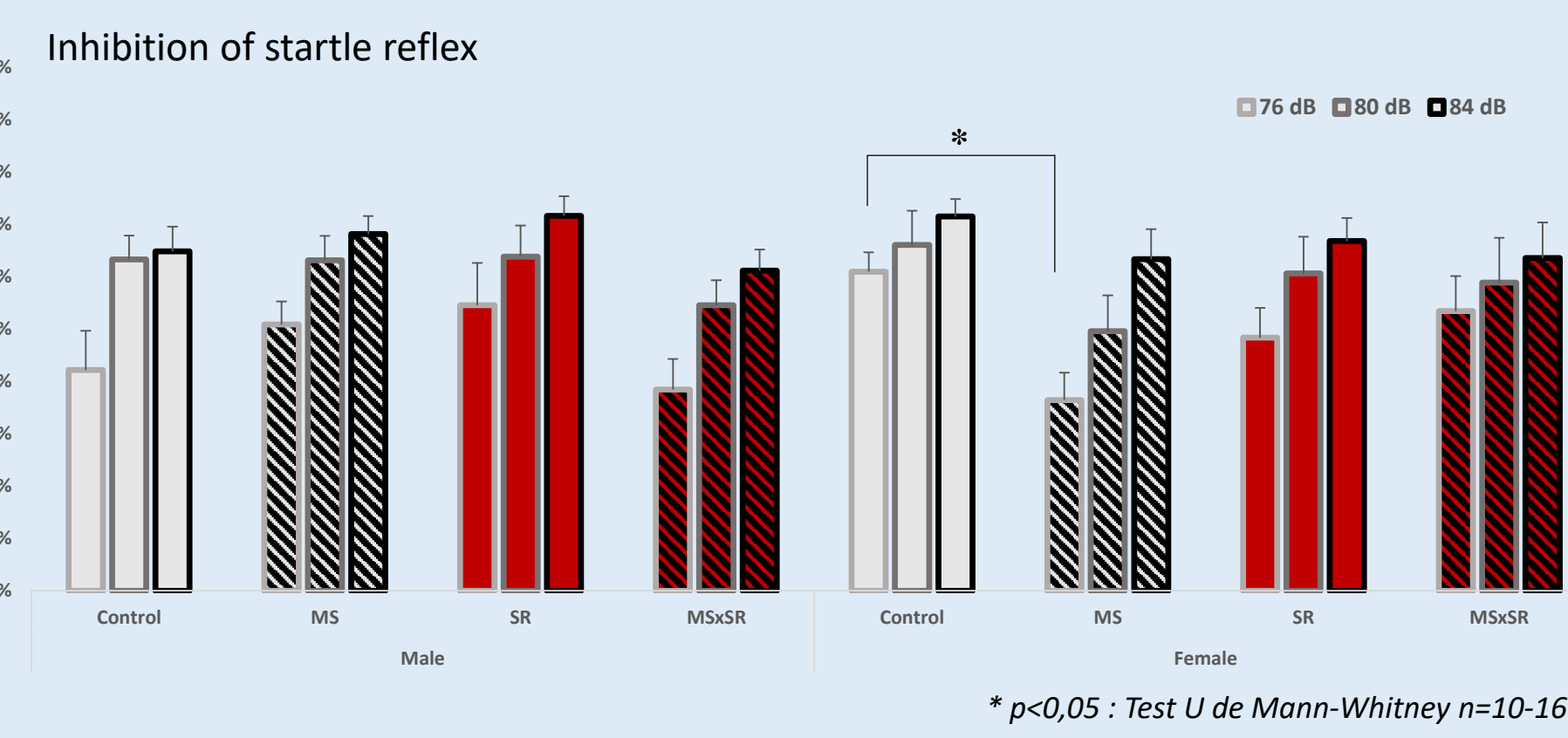
← Object recognition: MSxSR combination altered performances in female mice

→ Place recognition: MSxSR combination altered performances in male mice

### Place recognition memory

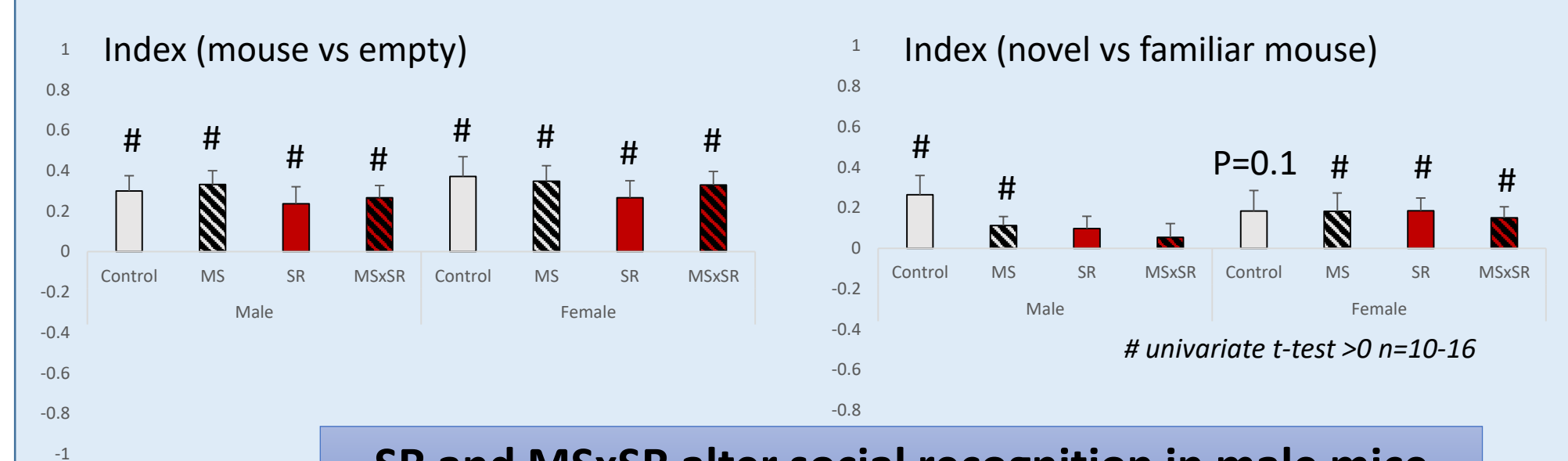
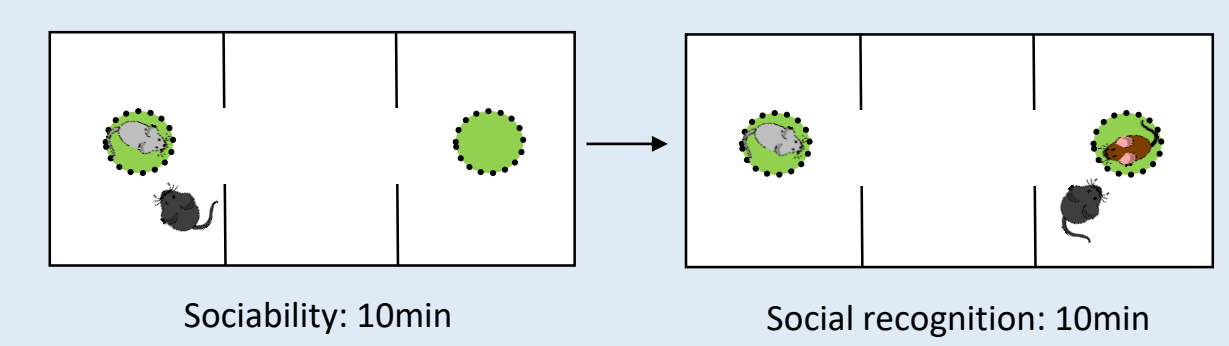


### Sensorimotor gating



MS decreased PPI in female mice

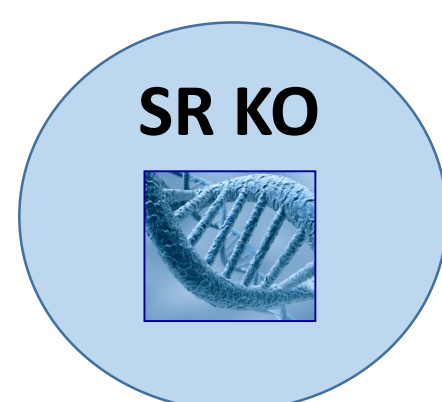
### Social behavior



SR and MSxSR alter social recognition in male mice

## Summary of the results

1-hit  
SR



- Locomotor activity in all experiments
- Place recognition
- Social recognition

1-hit  
MS



- Place recognition
- Prepulse Inhibition

SR KO



2-hit

X

Maternal separation



- Activity
- Social recognition in male mice
- Working memory in female mice
- PPI in female mice
- Anxiety-related behavior
- Place recognition performances
- Object recognition performances in female mice
- Neophobia in males

**2-hit animal models** gathers several deficits considered as hallmarks of schizophrenia.

**Serine racemase deletion** induces an **increase in activity**, promotes **social memory troubles**, and contributes to a **higher sensitivity** to maternal separation.

**Maternal separation** mostly contributes to **sensorimotor gating deficits**.

**2-hit model** differentially affect males and females.

Because some deficits (working memory, object recognition, social recognition) appears only in 2-hit mice, combining factors may help in improving validity of animal models of schizophrenia.

Moreover, combining factors reveals differences between males and females, probably accounting for gender vulnerability/resilience differences.