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

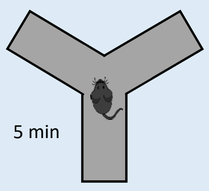
Maternal separation PND9-24h
Ellenbroek et al., 1998; Bouet et al., 2011

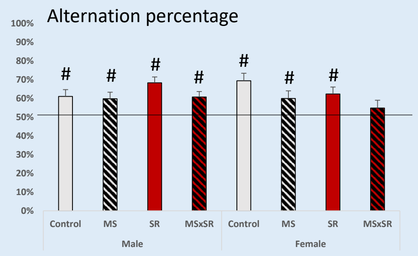
C57Bl6 male and female mice
Altered glutamate transmission:
- ➢ *Serine racemase KO mice* ***SRKO***

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

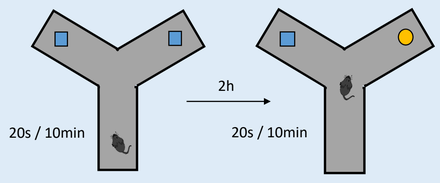


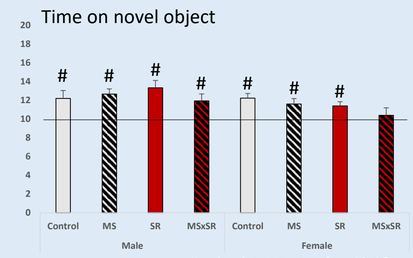


 # univariate t-test >50% n=10-16

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

Object recognition memory



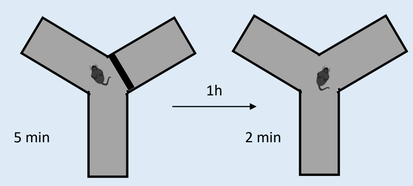


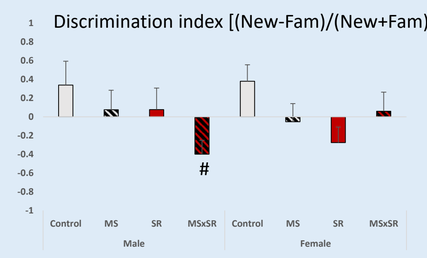
 # univariate t-test >10 n=10-16

➔ Object recognition: MSxSR combination altered performances in female mice

➔ Place recognition: MSxSR combination altered performances in male mice

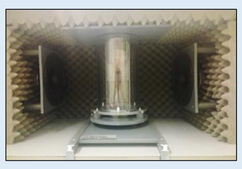
Place recognition memory

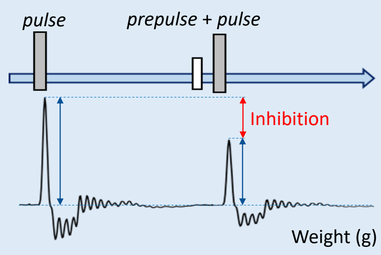


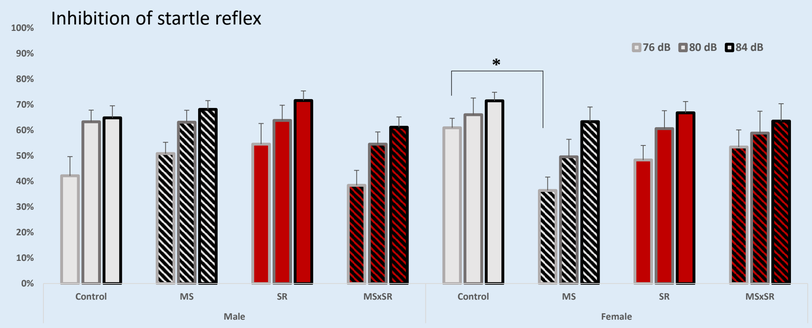


 # univariate t-test ≠ 0 n=10-16

Sensorimotor gating



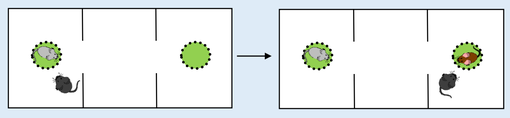


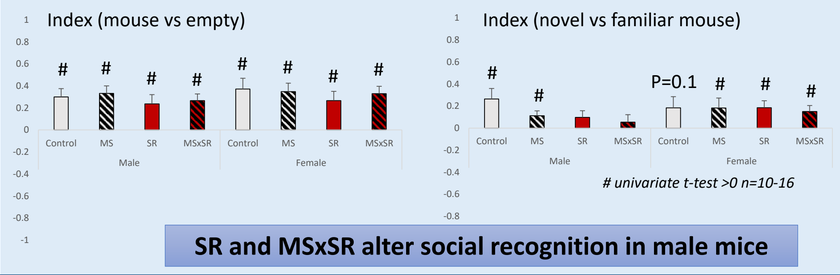


** p<0,05 : Test U de Mann-Whitney n=10-16*

MS decreased PPI in female mice

Social behavior





 # univariate t-test >0 n=10-16

SR and MSxSR alter social recognition in male mice

Summary of the results

1-hit SR

SR KO

➚ Locomotor activity in all experiments
➘ Place recognition
➘ Social recognition

1-hit MS

Maternal separation

➘ Place recognition
➘ Prepulse Inhibition

2-hit

SR KO

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.