New mouse model of schizophrenia: ”3 hits” model, genetic and environmental factors

Solenn Percelay, Valentine Bouët, Thomas Freret, Michel Boulouard

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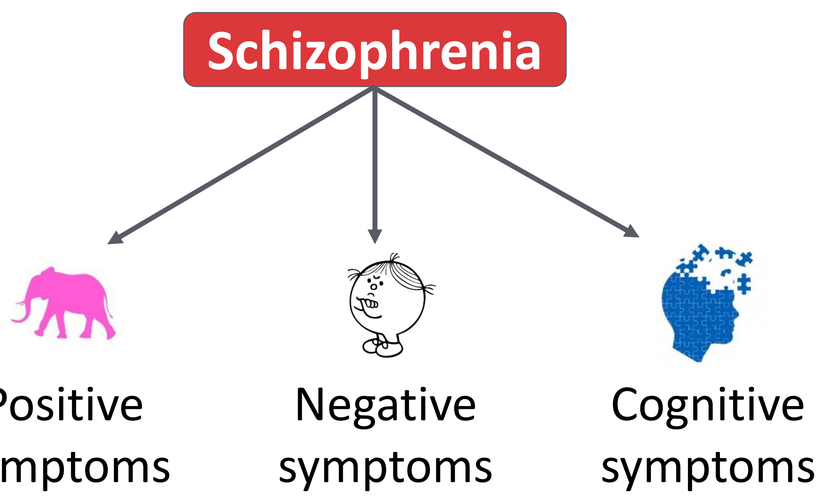
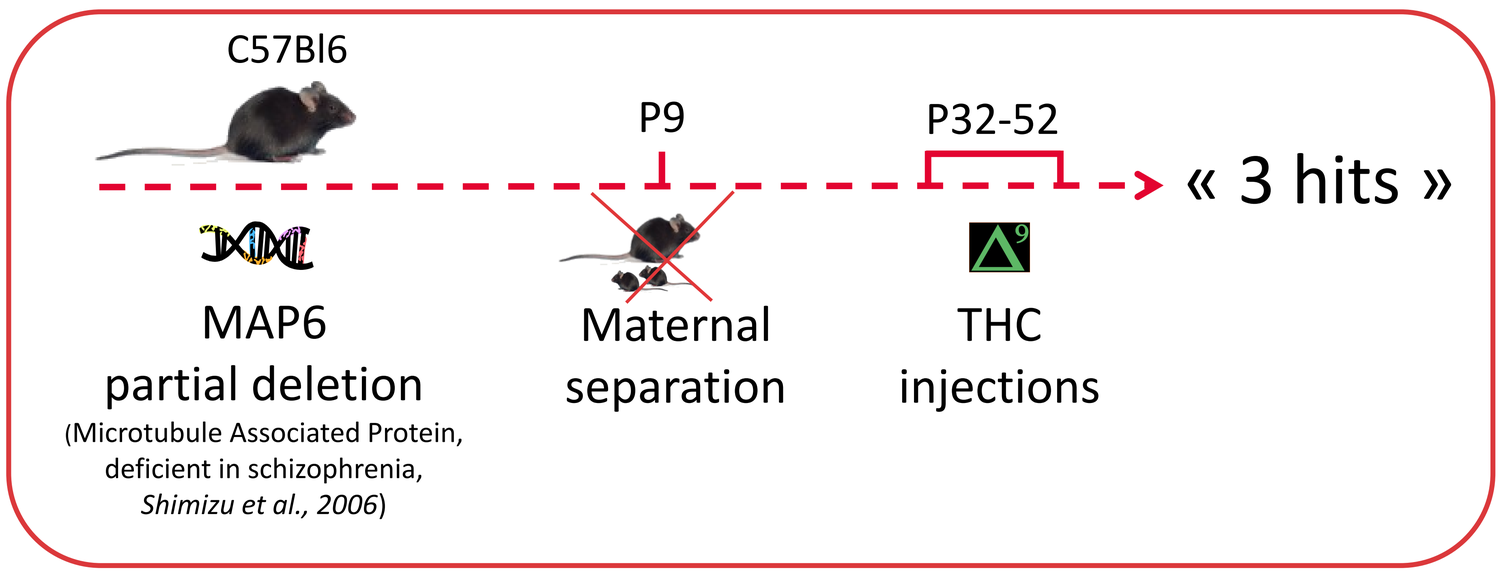
Introduction

Schizophrenia is a frequent psychiatric disease (1% of population), with an unknown multifactorial etiology. Even if pharmacological treatments exist, they don’t cover all symptoms and 30% of patients are resistant *(Millan et al., 2016)*. Numerous animal models have been developed, but unfortunately, they are often based on a sole factor. To design a model taking into account the multifactorial nature of this pathology, we chose to use 3 factors, “3 hits” *(Ellenbroek et al., 2003)*, one genetic and two environmental. Preliminary data revealed that 3 hits combination induced behavior alterations that mimic cognitive and sociability deficits observed in patients. Further behavioral characterization is ongoing with a particular focus on mood (anxiety), memory (spontaneous alternation), and sensory-motor gating deficits (pre-pulse inhibition).

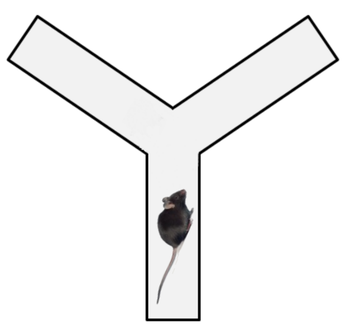


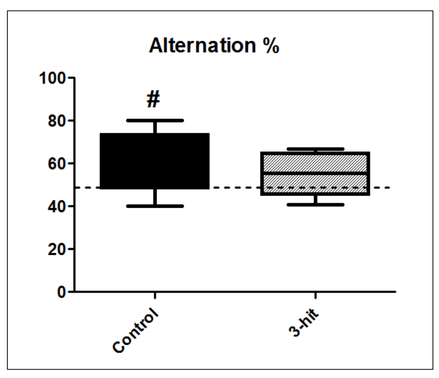


Preliminary results

Working memory

Spontaneous **alternation**

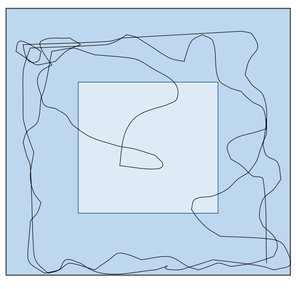




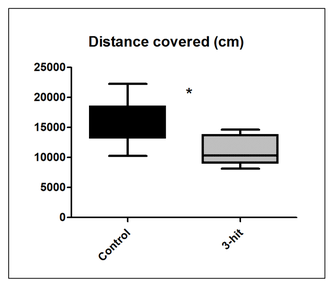
↘ working memory performances

Activity and anxiety

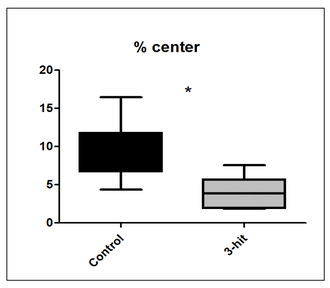
Open Field



↘ Activity

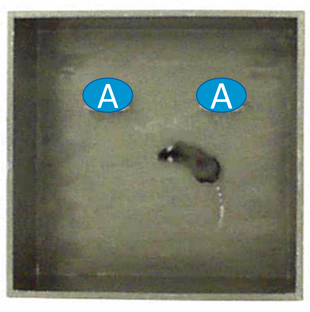


↗ Anxiety-like behavior

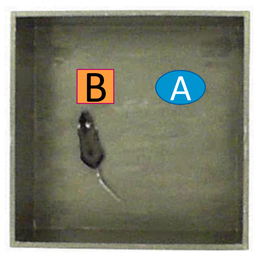


Future investigations

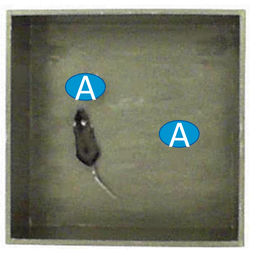
1. Acquisition



2. Retention



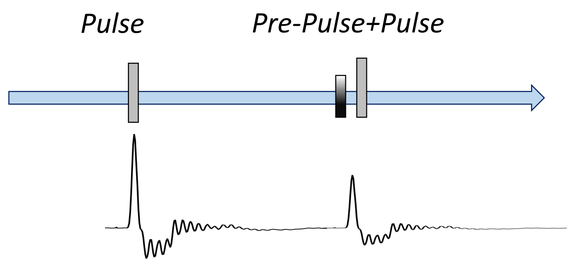
Object recognition

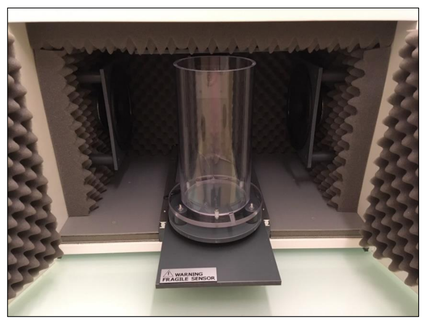


Place recognition

Exploration time (s)

Startle reflex, sensory-motor gating





Discussion and conclusion

- Preliminary data revealed behavioral deficits: decreased working memory performance, increased anxiety-like behavior, decreased spontaneous activity, altered sociability *(not shown)*.
- Now, we are going further in the characterization of cognitive alterations by studying : spatial and non-spatial recognition memory, sensory-motor gating (both altered in schizophrenia) through the assessment of place and object recognition prepulse inhibition of acoustic startle reflex (Imetronic, Pessac, France).
- Next, we will assess the effects of pharmacological treatments to obtain a pharmacological validation of the model. We will study the effects of lurasidone (atypical neuroleptic, recently marketed in USA), galantamine (acetylcholinesterase inhibitor and agonist of nicotinic central receptors, currently used for early forms of Alzheimer’s disease).

Millan et al. (2016). Altering the course of schizophrenia: progress and perspectives. Nature reviews Drug discovery, 15(7), 485.
Shimizu et al. (2006). Genetic and expression analyses of the STOP (MAP6) gene in schizophrenia. Schizophrenia research, 84(2), 244-252.
Ellenbroek et al. (2003). Animal models in the genomic era: possibilities and limitations with special emphasis on schizophrenia. Behavioural pharmacology, 14(5-6), 409-417.