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New 3-hit model of schizophrenia: behavioral and electrophysiological investigations

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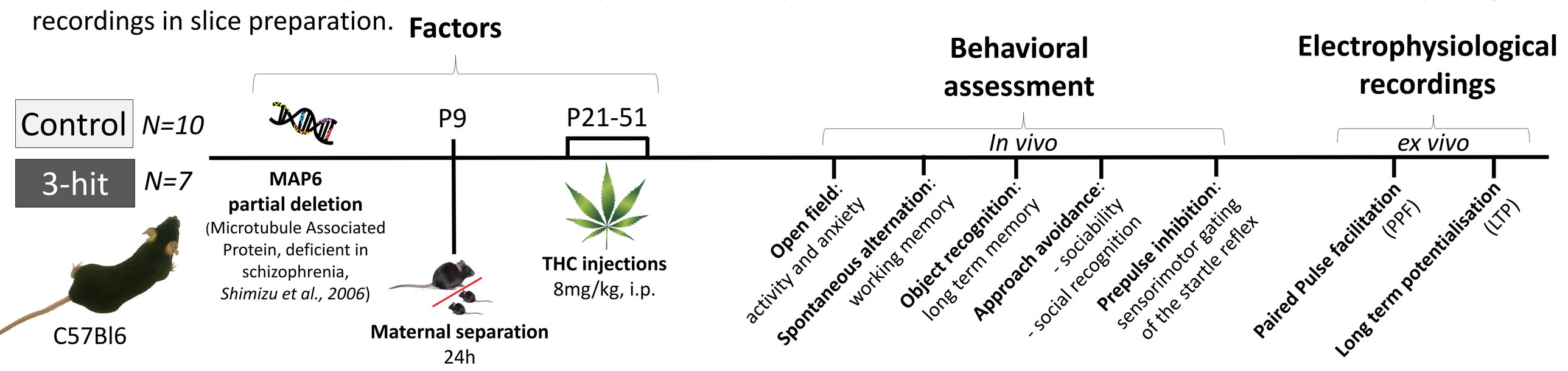
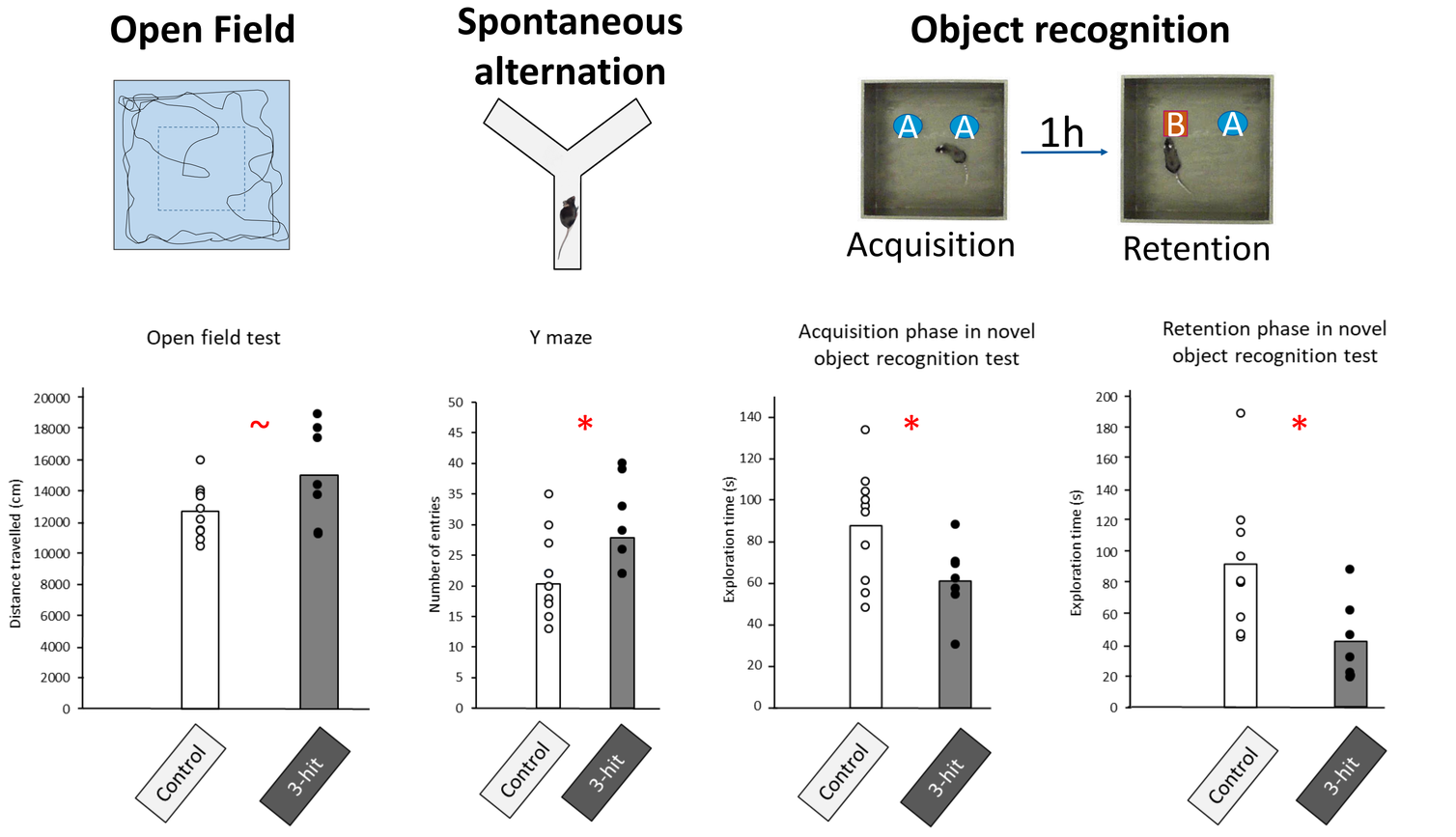
INTRODUCTION

Schizophrenia is a disabling psychiatric disease found in approximately 1% of the population. Current antipsychotic drugs are only symptomatics and not satisfying for a part of symptoms and patients. In this context, for a better translation from treatment design to clinical efficiency, there is a need to refine preclinical models. We developped a new mouse model associating three factors (3-hit), which takes into account the multifactorial nature of the pathology *(Ellenbroek et al., 2003)*. Positive, negative and cognitive-like symptoms of schizophrenia have been assessed respectively through a set of behavioral tests, and functional properties and plasticity of hippocampal networks were assessed *ex vivo via* electrophysiological recordings in slice preparation.

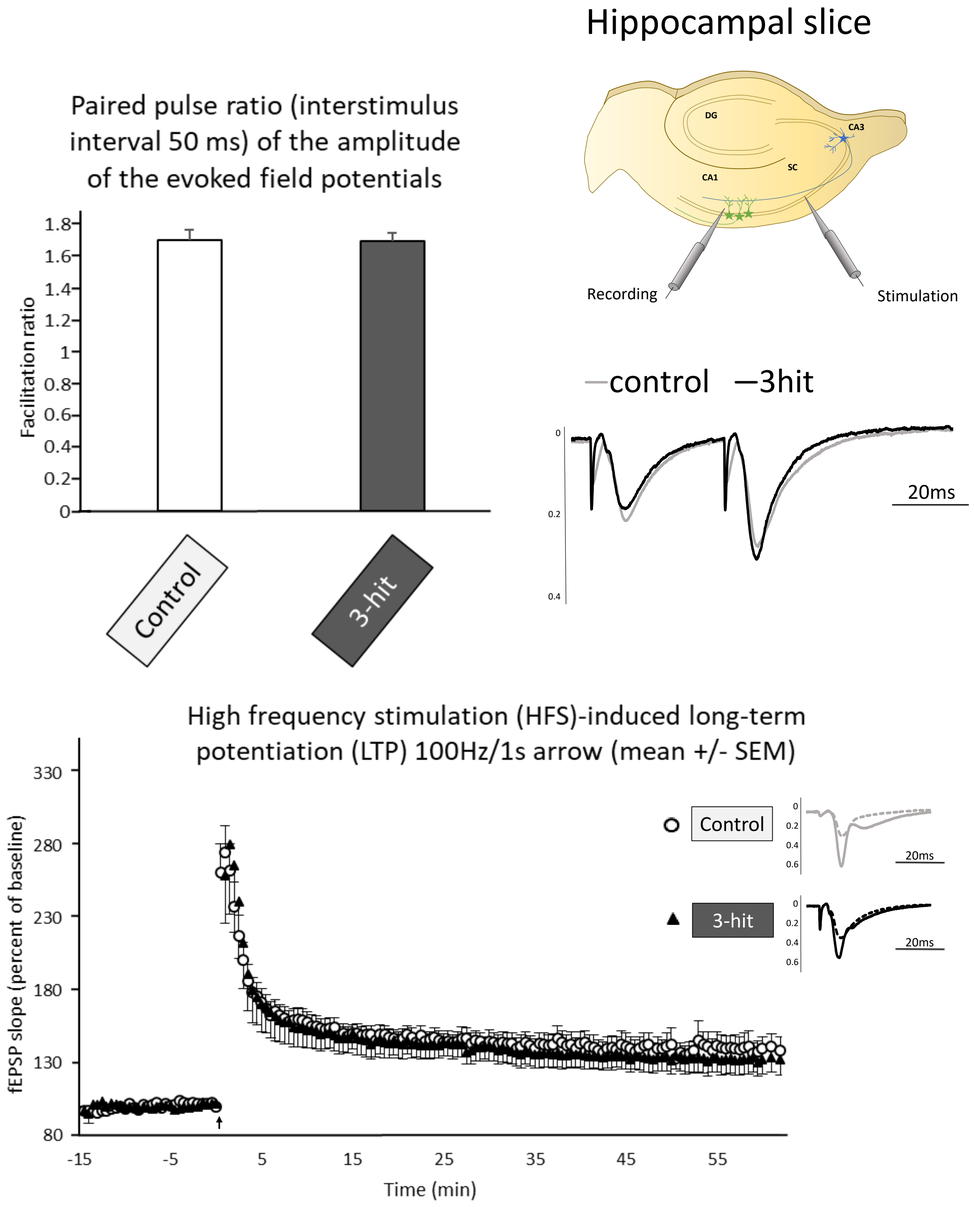


RESULTS

Behavioral assessment



Electrophysiological recordings



For approach avoidance test and prepulse inhibition, we did not observe any significant differences. Concerning alternation percentage and recognition index, all groups were significantly higher than reference value.

Anova test were used for comparison between groups (: p<0.05; ~= 0.06). T test were used for comparison to reference value. Results are represented with means and individuals data.*

DISCUSSION / CONCLUSION

Our results show that 3-hit mice displayed an increased locomotor activity, a decrease in object exploration time, and no modifications of mechanisms regulating basal hippocampal neurotransmission, paired pulse facilitation, or functional plasticity (LTP).

Our new 3-hit model displays a high construct validity, since it implies both genomic and exposomic factors. Face validity is sustained by apparition of positive-like symptoms with hyperlocomotion, negative-like symptoms with decrease in exploration (Mitra *et al*., 2016), but behavioural assessment and electrophysiological recordings do not permit to reveal cognitive-like symptoms and some of their mechanisms. With the large inter-individual variability observed, characterization of correlates in each individual would help distinguishing possible individual profiles.

Ellenbroek et al. (2003). Behavioural pharmacology. Lewis, D. A. et al. (2012). Mitra, S., Mahintamani, T., Kavoor, A. R., & Nizamie, S. H. (2016). Negative symptoms in schizophrenia. *Industrial psychiatry journal*, *25*(2), 135–144. doi:10.4103/ipj.ipj_30_15