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Efficacy of a selective 5-HT₆R antagonist in an innovative 2-hit mouse model of schizophrenia

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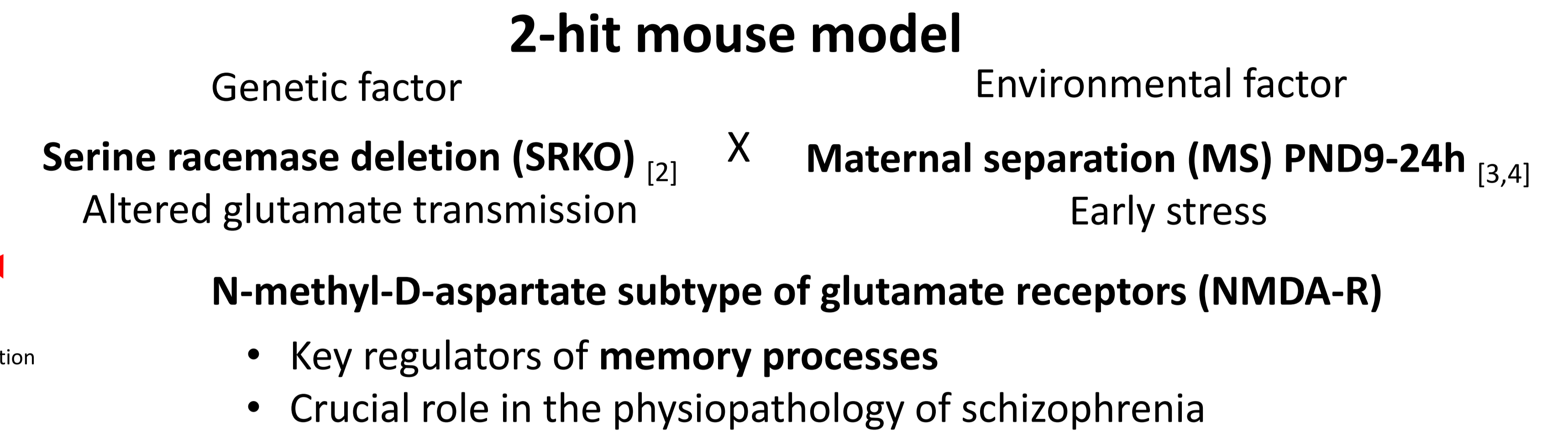
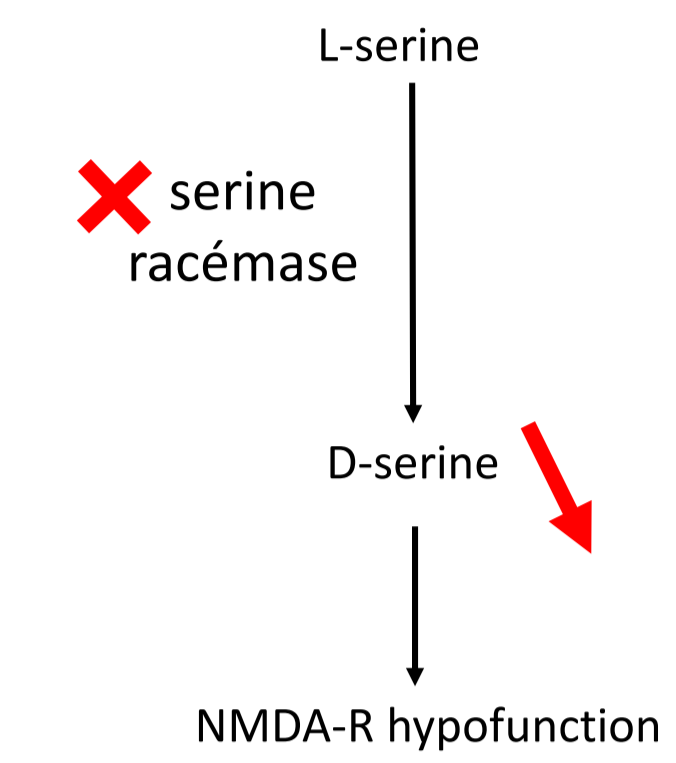
Schizophrenia

- Etiology: still unknown but possibly genetic x environmental factors
- Antipsychotic drugs improve positive symptoms (delirium, hallucination) but not **negative symptoms** (avolition, anhedonia, social withdrawal...) and **cognitive deficits** (memory impairment...)
- ▶ New therapeutic targets need to be tested in animals to improve negative and cognitive symptoms

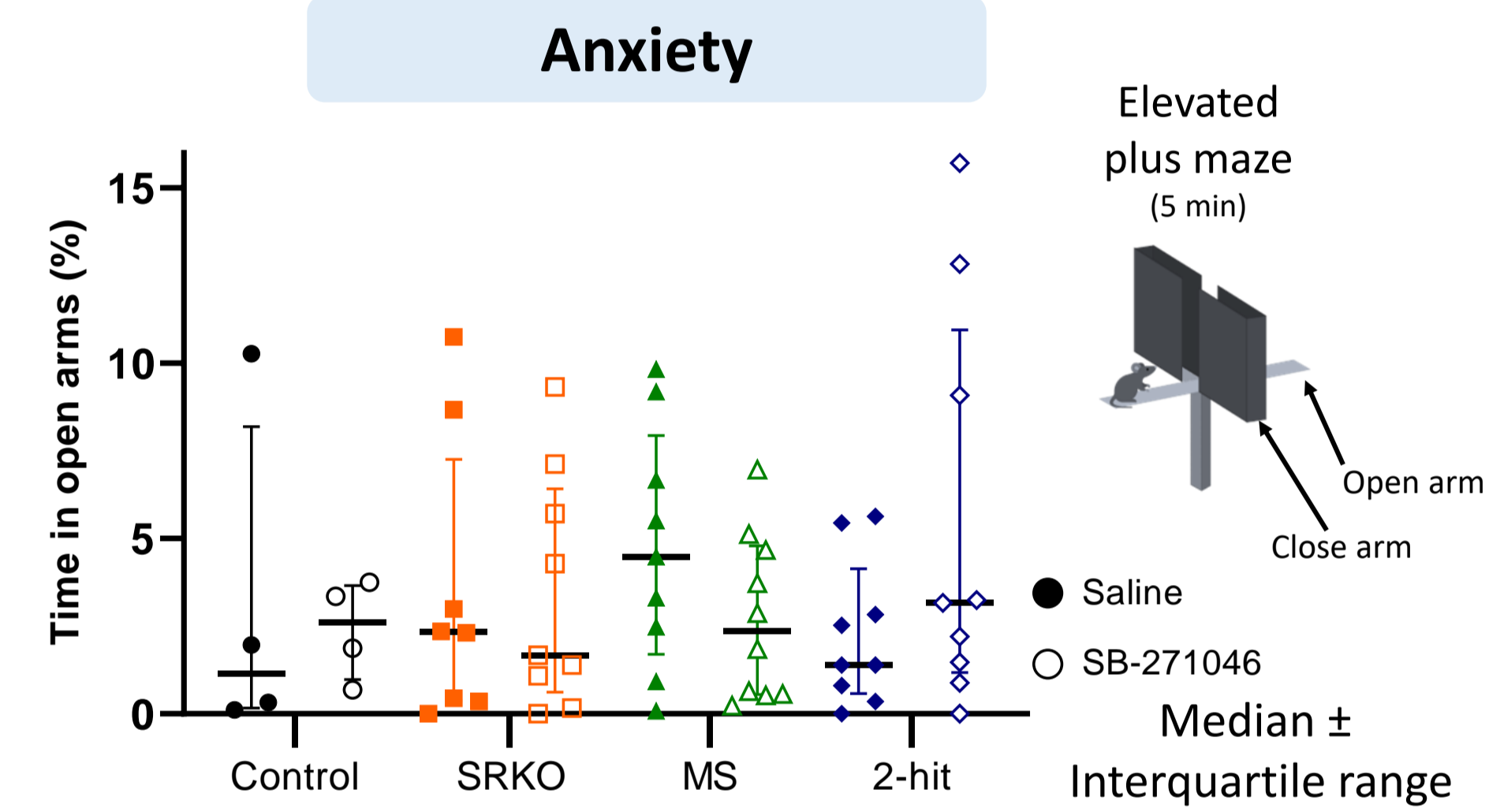
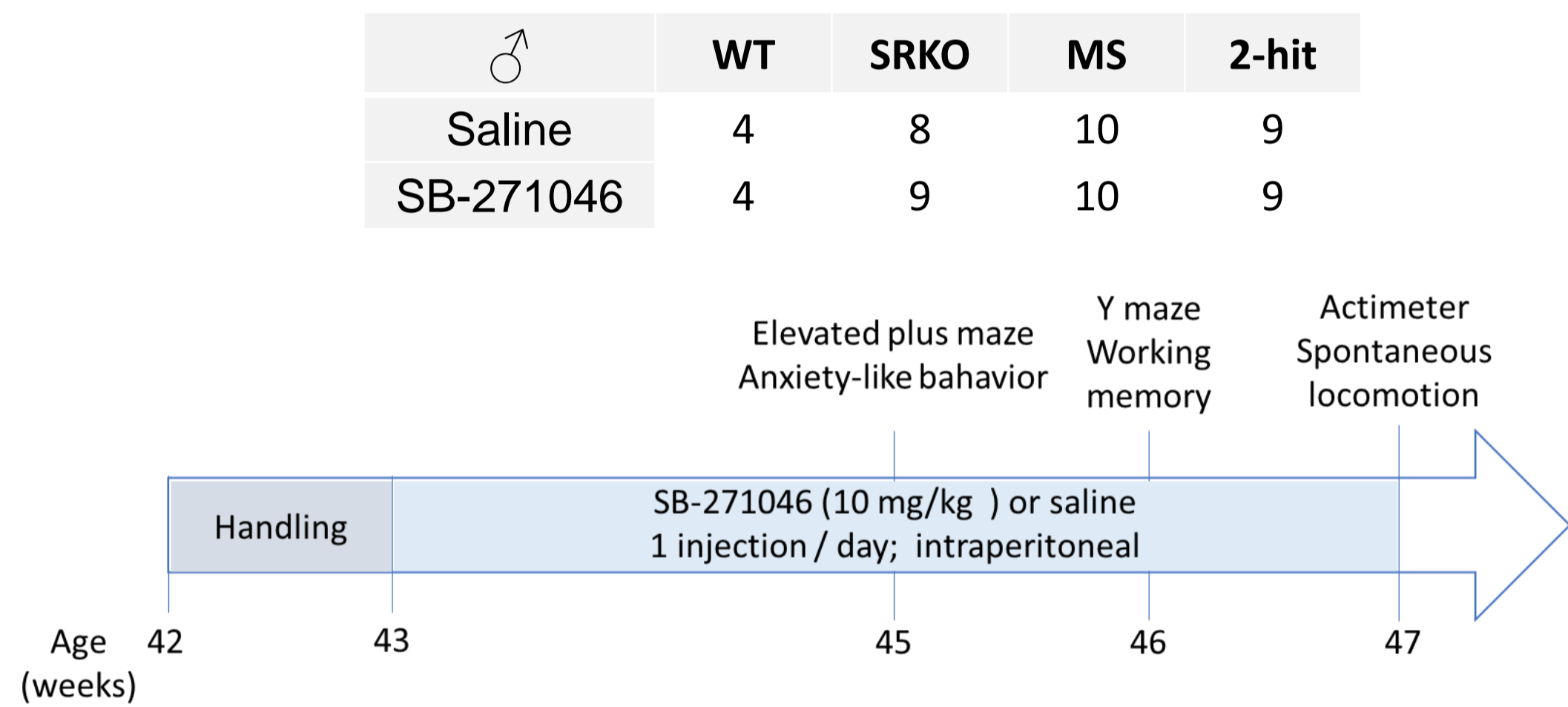
Target: Serotonergic subtype 6 receptors (5-HT6R)

- 5-HT6R expressed in the brain regions involved in schizophrenia such as hippocampus
- Blockade of 5-HT6R reverses memory deficit in aged mice [1]
- **SB-271046** is the most selective 5-HT6R antagonist
- ▶ Blockade of 5-HT6 receptors a promising strategy to improve memory deficits

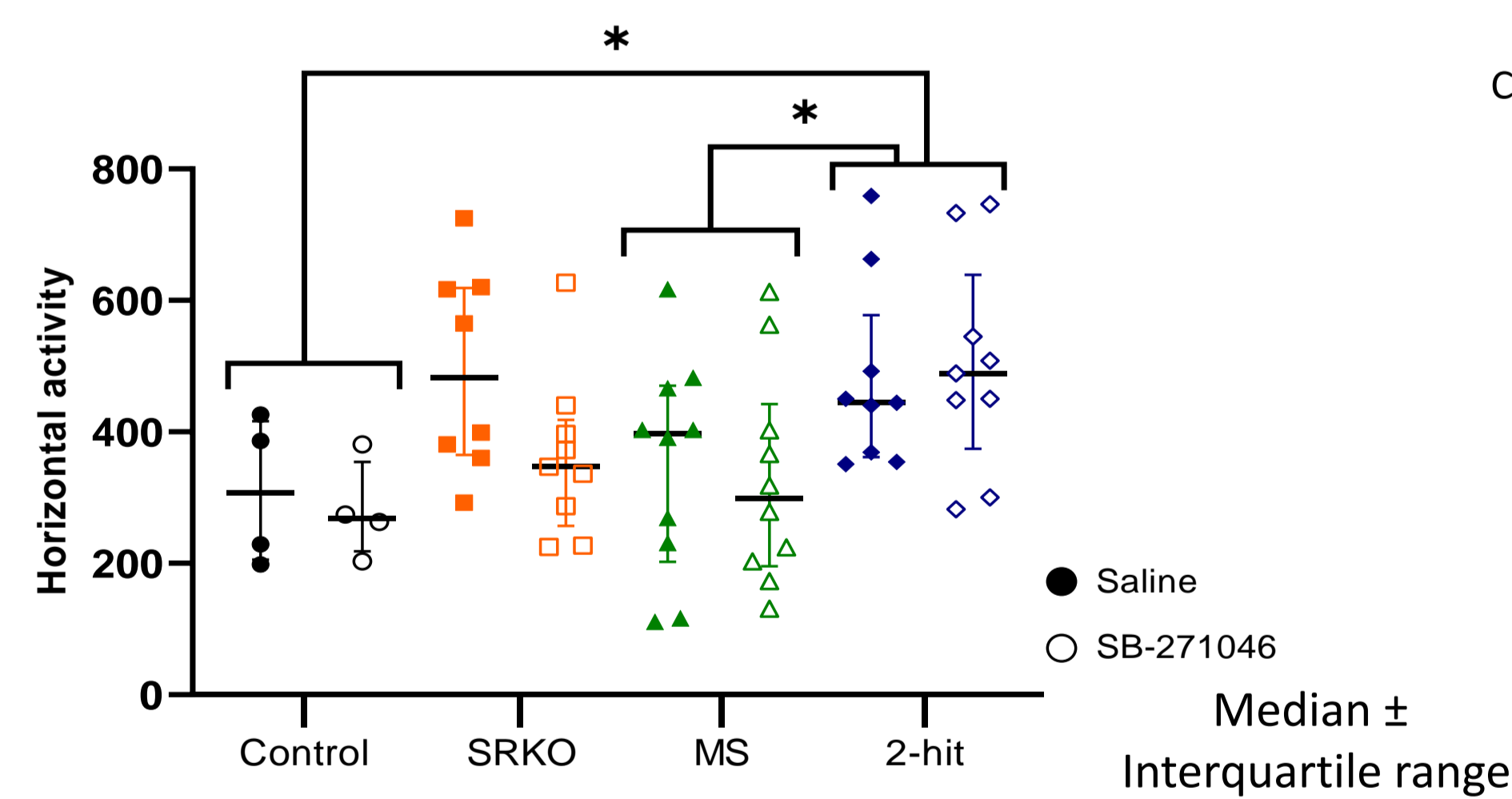
Aim: to characterize the efficacy of pharmacological modulation of 5-HT6R in a new mouse model of schizophrenia



Behavioral study in male mice

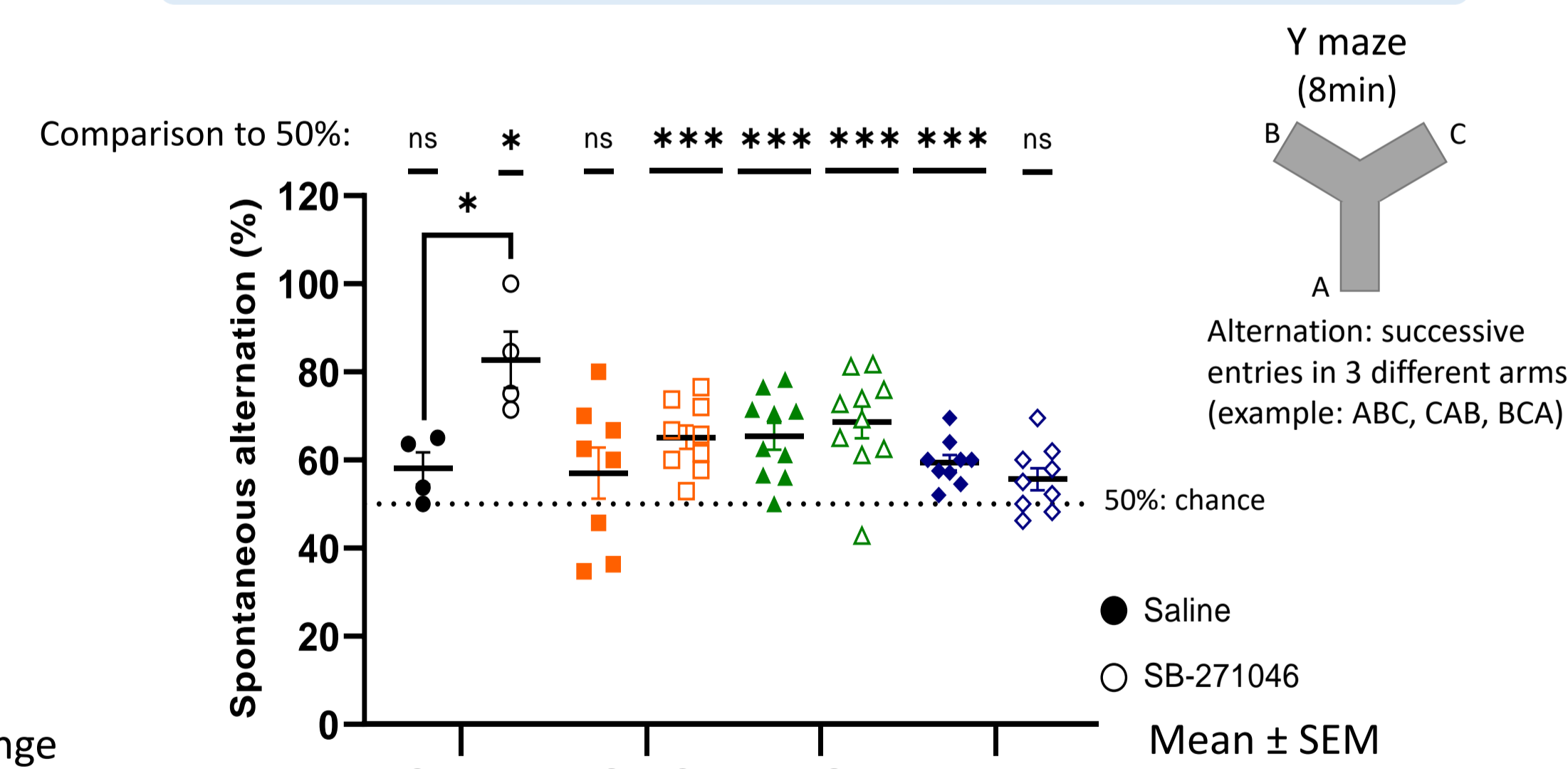


Spontaneous locomotion in actimeter (30min)



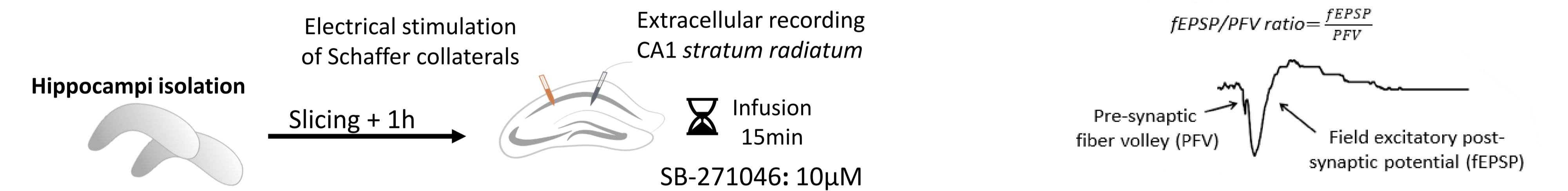
Anova with permutation: genotype effect (F=<2e-16)
Pairwise comparison: * < 0.05

Spontaneous alternation - Working memory



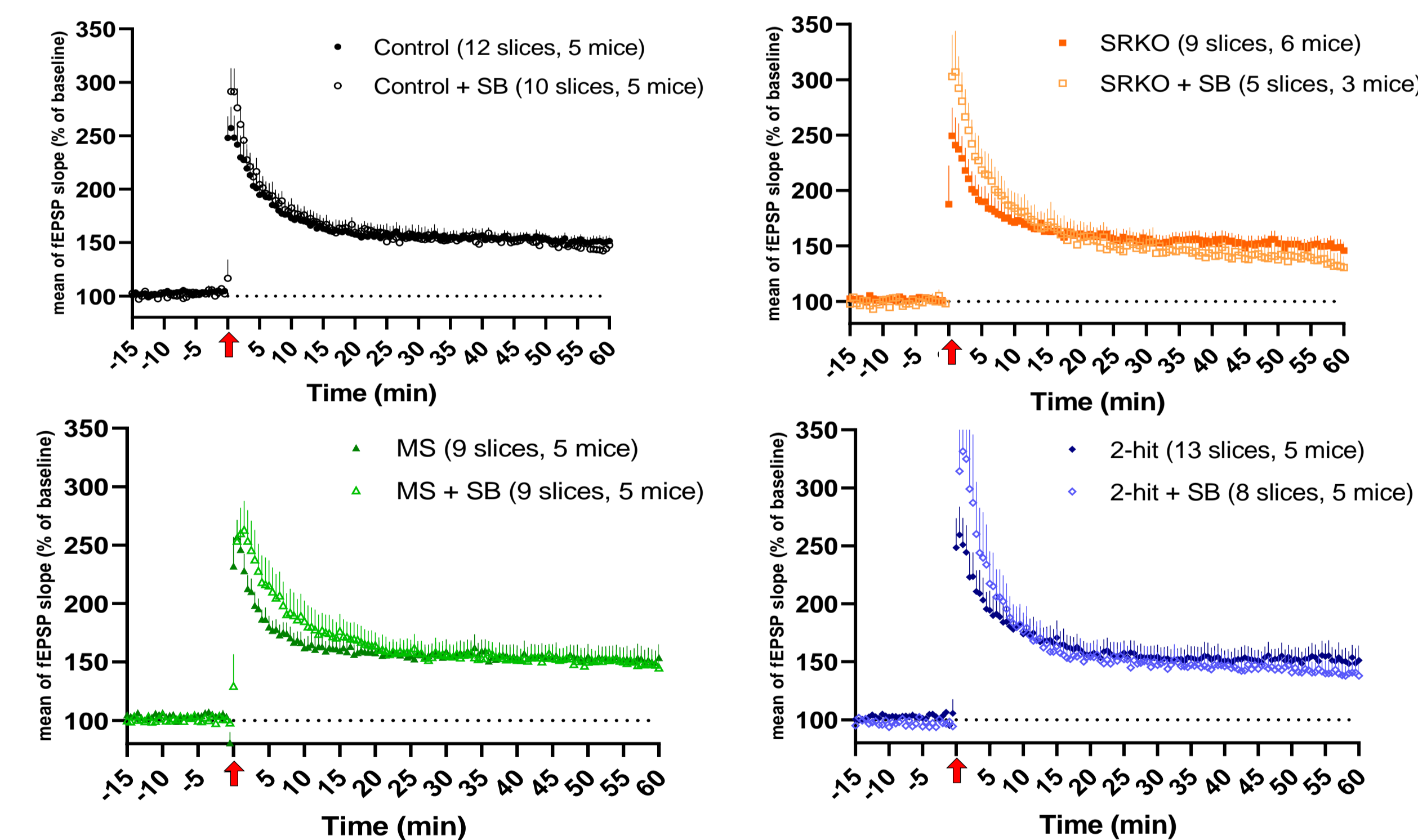
Anova: genotype (F=0.00083) and treatment effect (F=0.04374)
TukeyHSD comparison: * < 0.05
Univariate t.test > 50%: * < 0.05; ***<0.001

Electrophysiological study in 26 – 34 weeks female mice



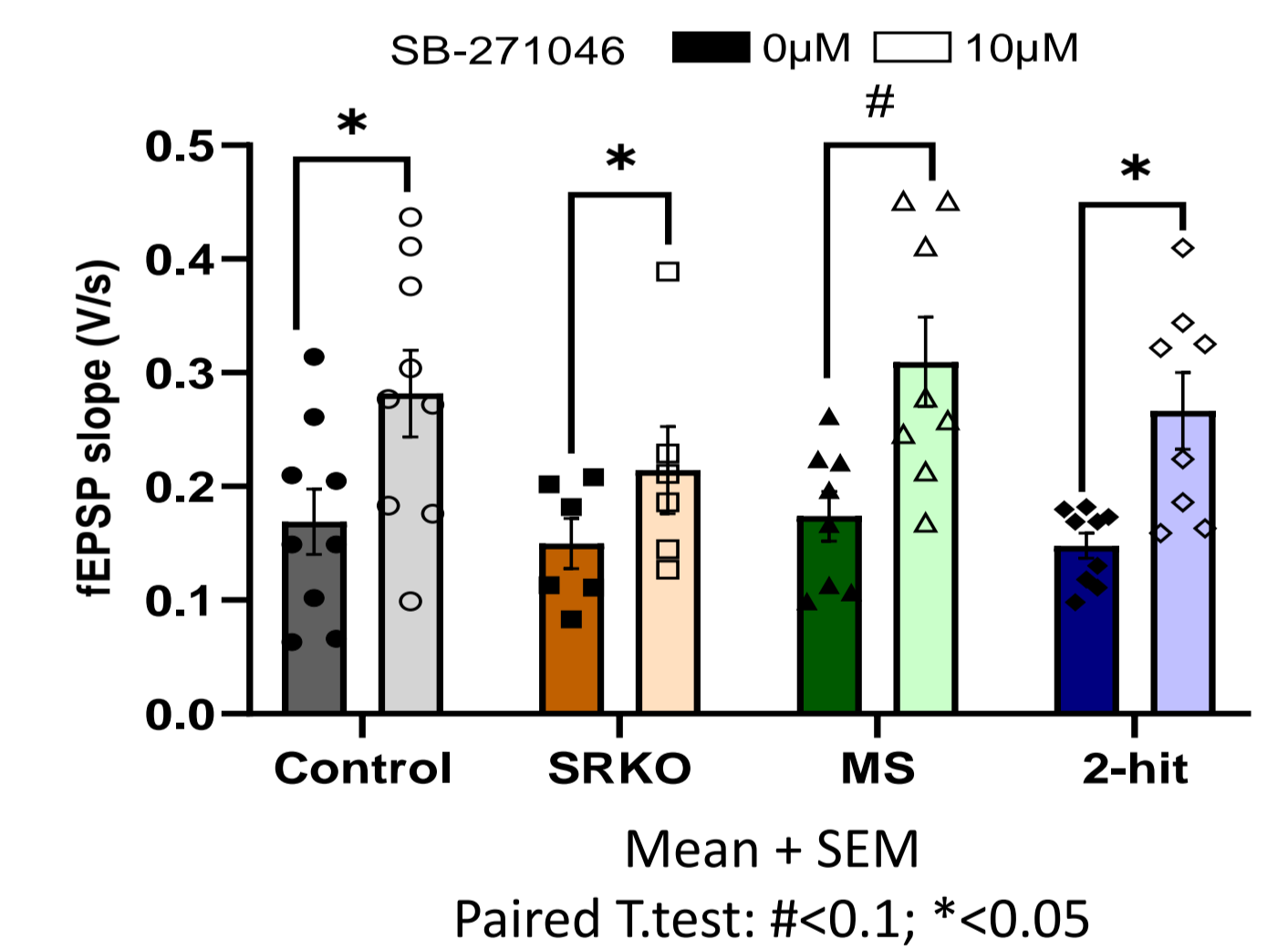
Long-term potentiation (LTP)

High frequency stimulation (HFS, 100Hz 1sec)



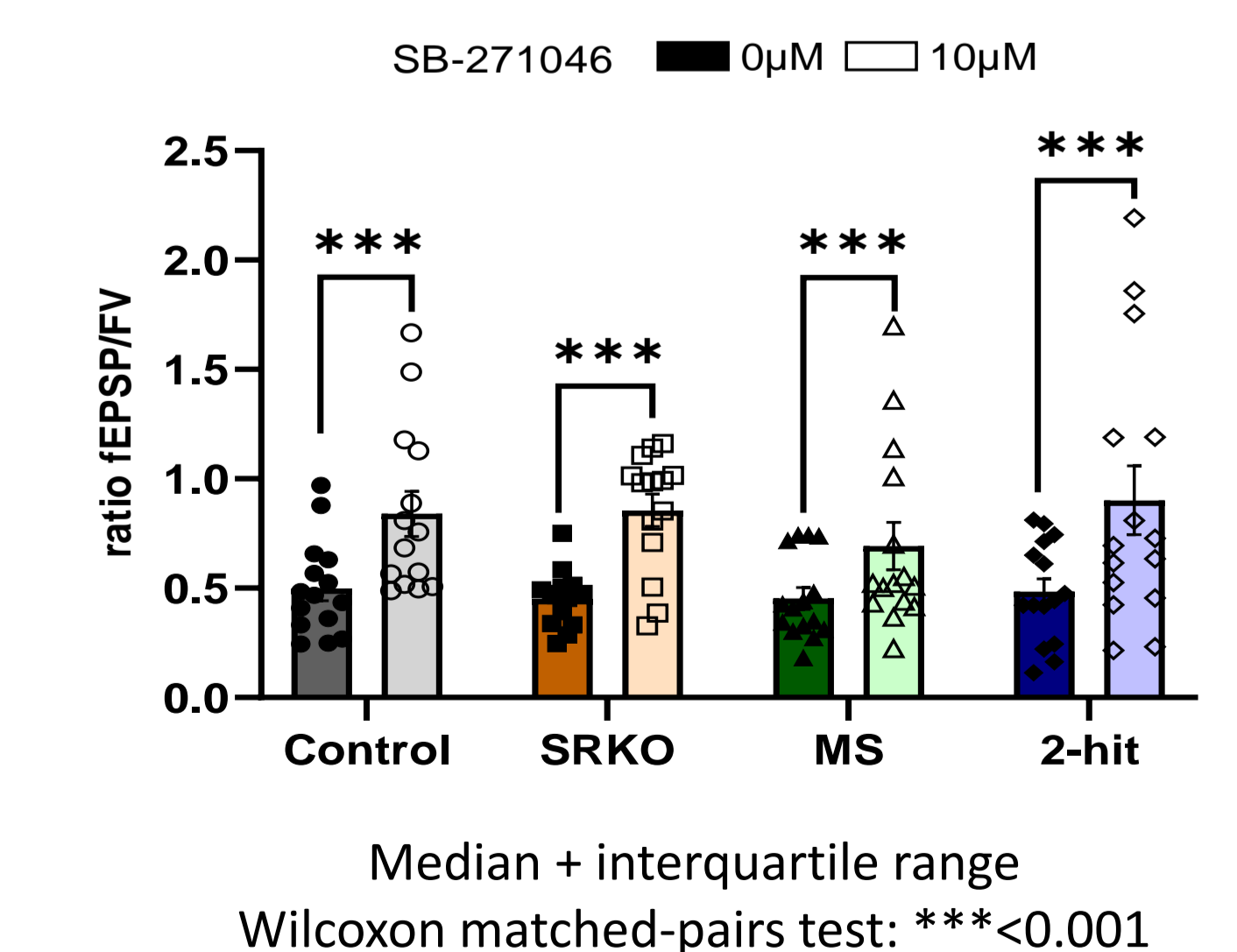
Basal AMPA transmission

(Stimulation: 5V)



Basal NMDA-R activation

(Stimulation: 500µA)



Take home message

Summary: SB-271046 effects

	Anxiety	Working Memory	Spontaneous activity	AMPA transmission	NMDA-R activation	LTP
Control	-	↗	-	↗	↗	-
SRKO	-	-	-	↗	↗	-
MS	-	-	-	~	↗	-
2-hit	-	-	-	↗	↗	-

The combination between genetic x environmental factor does not induce behavioral deficits in 2-hit male mice nor impairments in LTP, basal AMPA transmission and NMDA-R activation in 2-hit female mice. SB-271046 improves working memory in male mice and enhances glutamatergic transmission without impact on HFS-induced synaptic plasticity. We are now investigating effects of SB-271046 on other cognitive processes (sociability and sensory gating) as well as on another kind of synaptic plasticity, induced by theta burst stimulation (TBS), which also involves GABAergic system.

[1] Da Silva Costa-Aze V et al. Behav Brain Res. 2011. DOI: 10.1016/j.bbr.2011.03.046.
[2] Coyle JT, Balu DT. Adv Pharmacol. 2018. DOI: 10.1016/bs.apha.2017.10.002
[3] Ellenbroek BA et al. Schizophr Res. 1998. DOI/ 10.1016/s0920-9964(97)00149-7
[4] Bouet V et al. Neurosci Lett. 2011. https://doi.org/10.1016/j.neulet.2010.11.033.