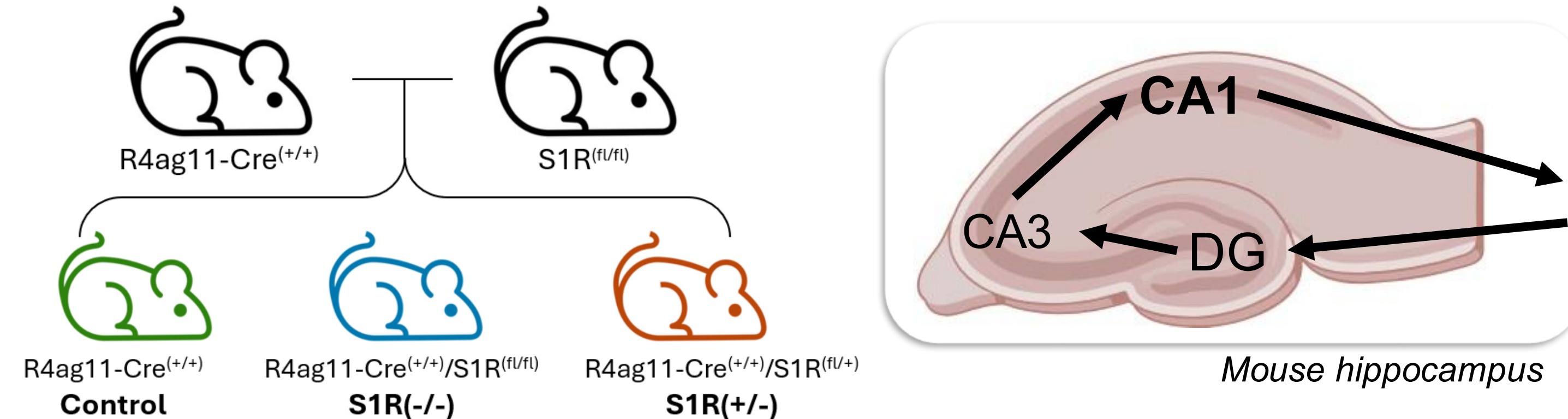


## Background

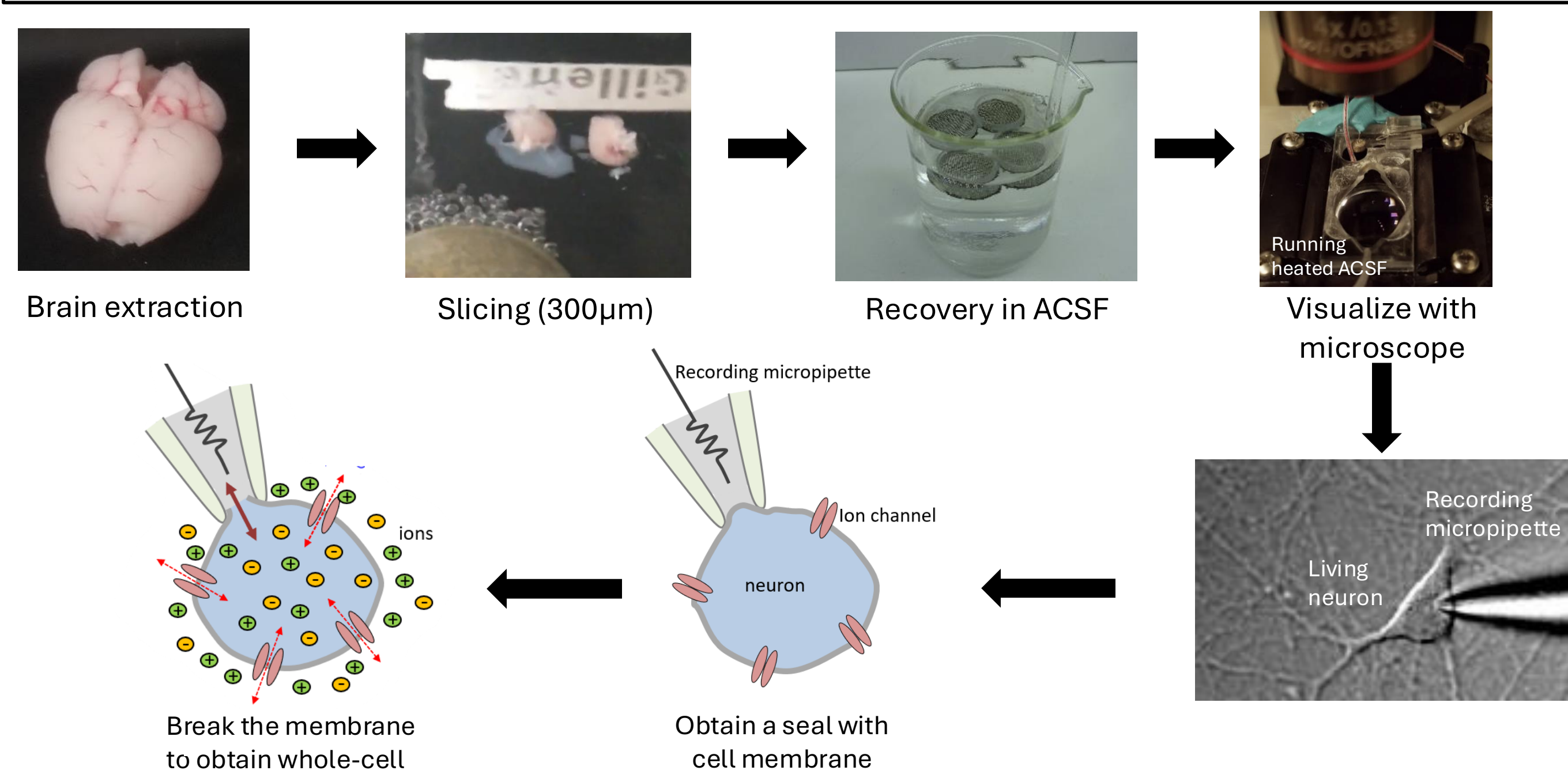
Sigma-1 Receptor (S1R) is a ligand-operated transmembrane chaperone protein. S1R has been shown to act as an auxiliary subunit modulating location and properties of multiple voltage-gated ion channels (Na<sup>+</sup>, K<sup>+</sup>, Ca<sup>2+</sup>). S1R full knockout has been observed to increase anxiety-like and depression-like behavior, and to alter spatial memory, in a sex-specific manner.

## Method

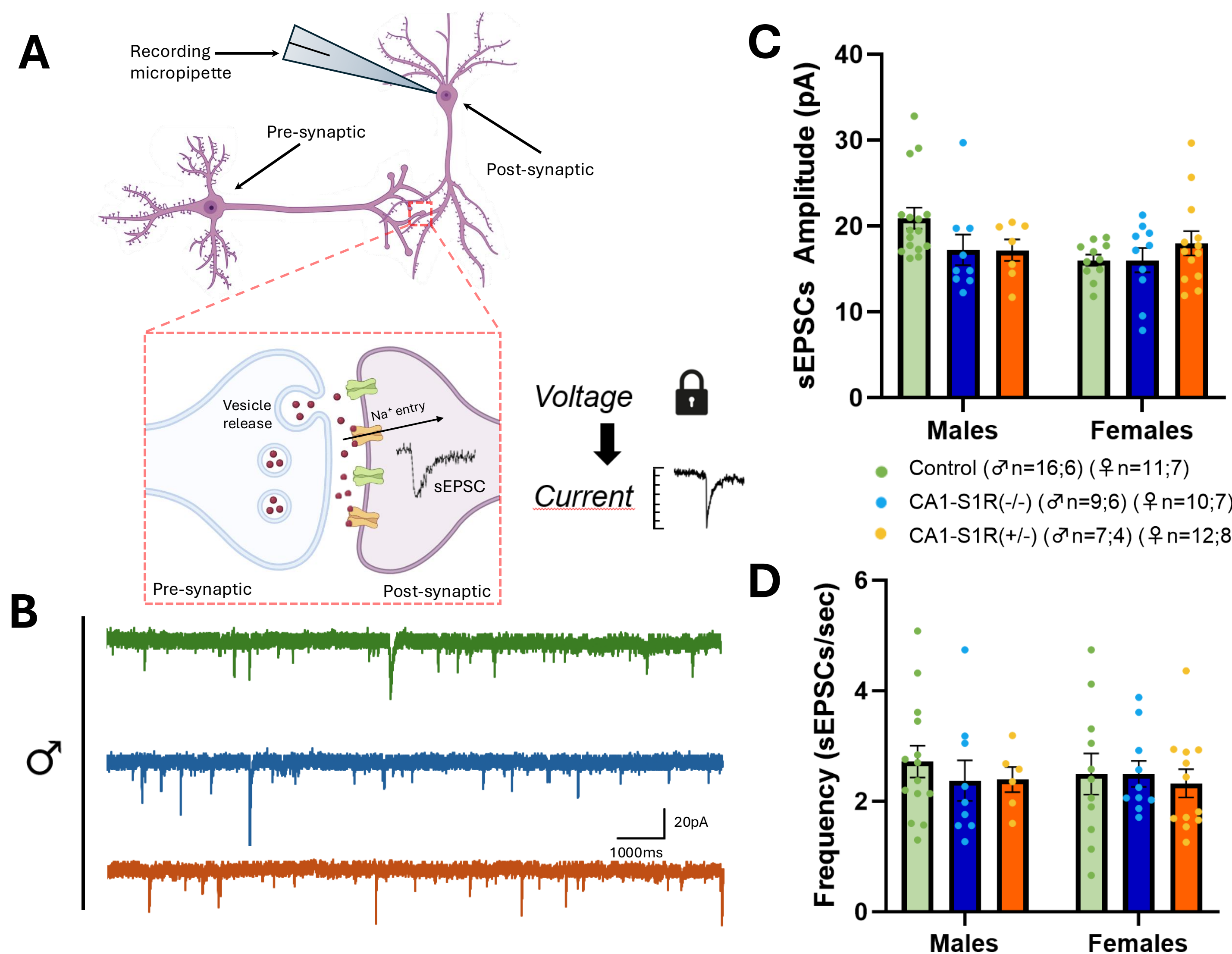
R4ag11(CAMKIIα)-Cre mice express Cre recombinase in CA1 and DG (partially) regions of the hippocampus and were crossed with mice with floxed *SIGMAR1* alleles (S1R<sup>fl/fl</sup>) enable a region-specific knockout of S1R. Whole-cell patch clamp was used to record electrophysiological activity of pyramidal neurons in CA1.



## Method : Electrophysiology

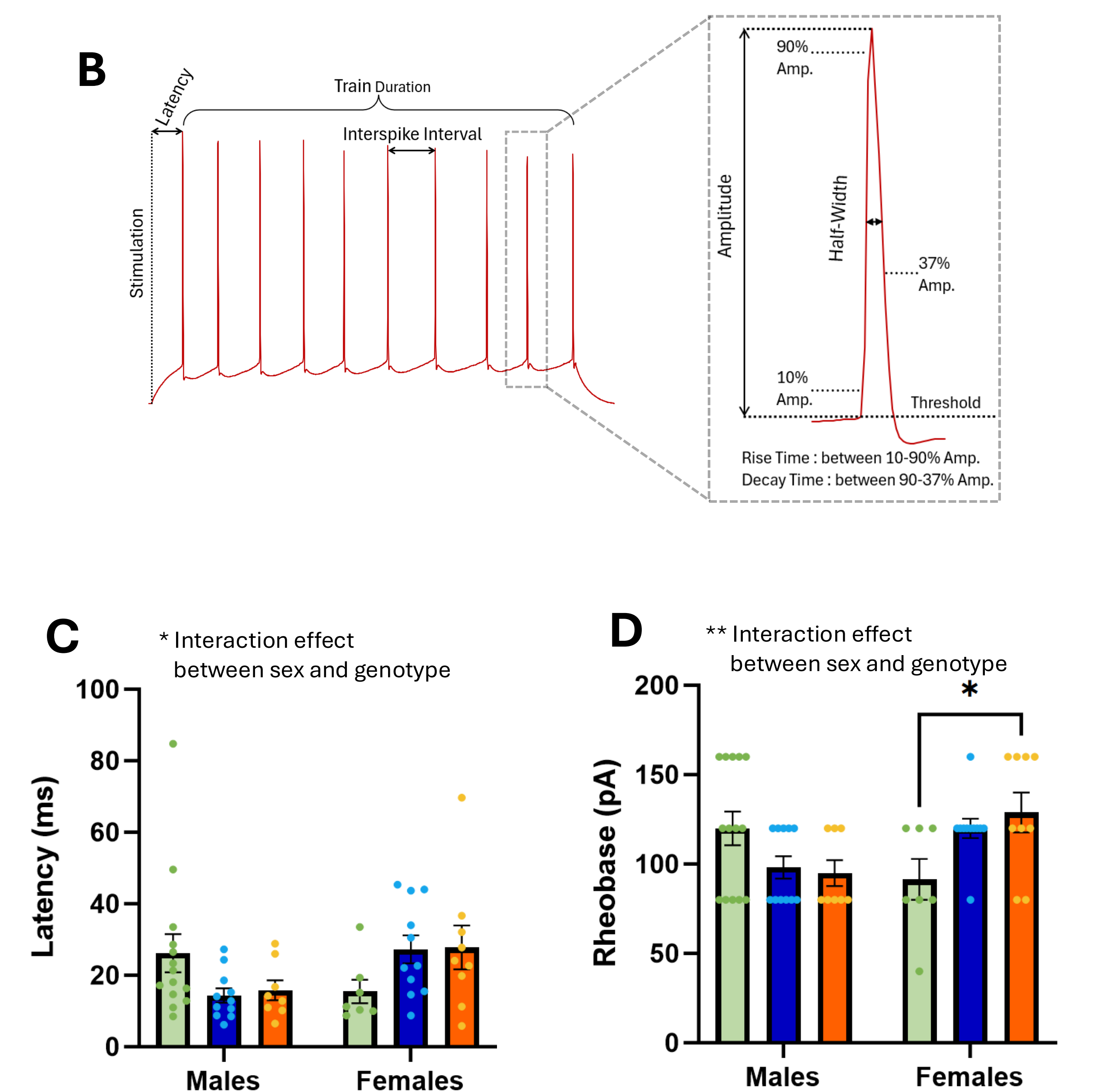
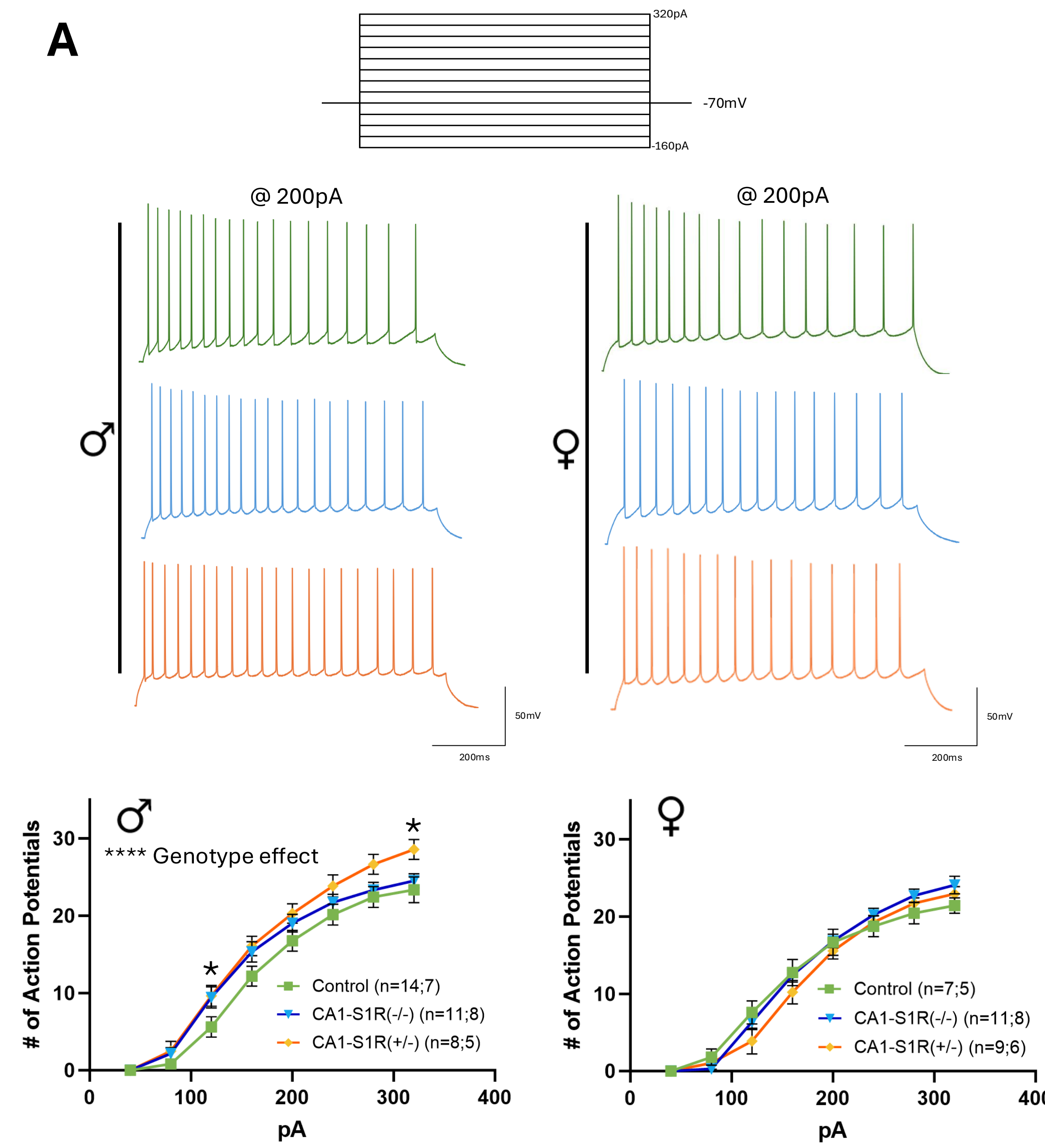


## EPhys : Synaptic Excitability



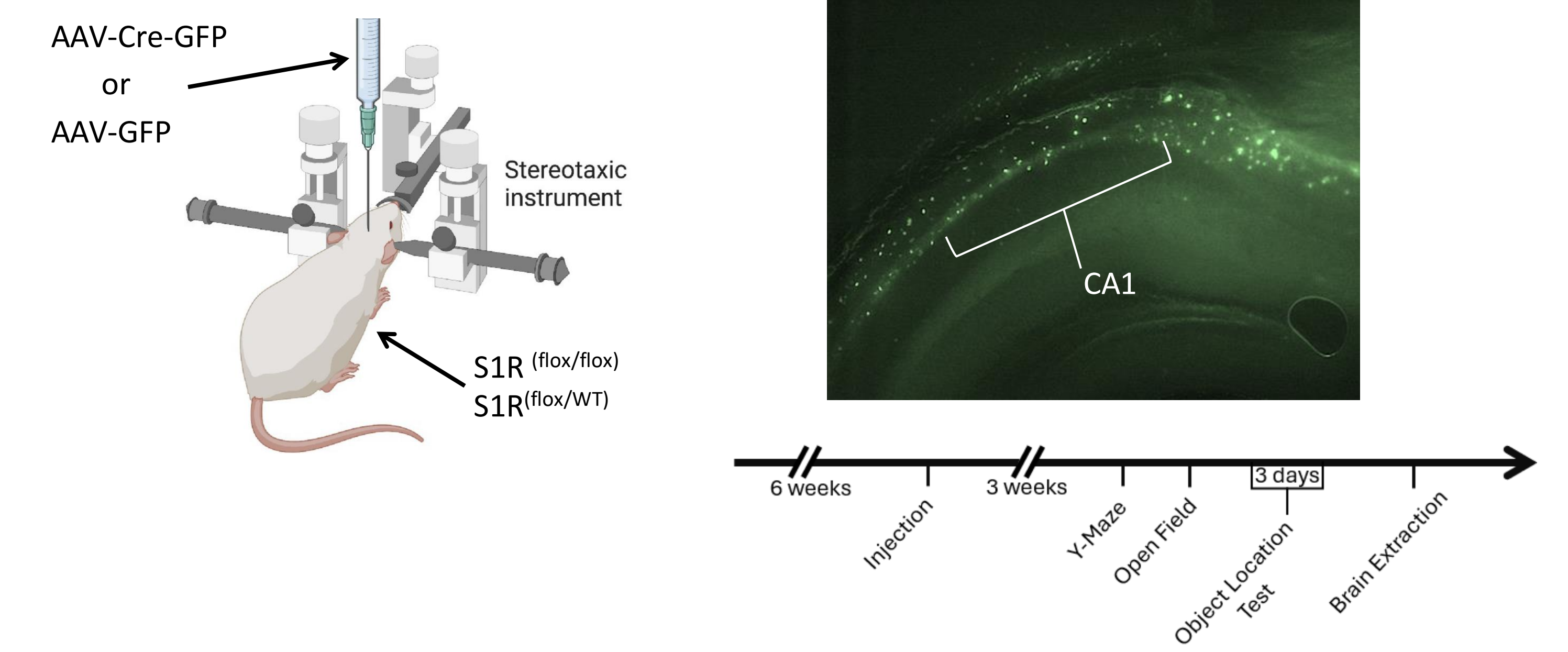
**Figure 1 : Synaptic excitability of CA1 pyramidal neurons in CA1-S1R(-/-) and CA1-S1R(+/-) mice.** (A) Graphic depiction of a synapse generating sEPSC. (B) Representative trace of sEPSCs recorded. (C) Amplitude, and (D) frequency of 300±50 sEPSCs events recorded with voltage clamped at -70mV. Statistical significance was assessed using a two-way ANOVA. Error bars ± SEM.

## EPhys : Intrinsic Excitability

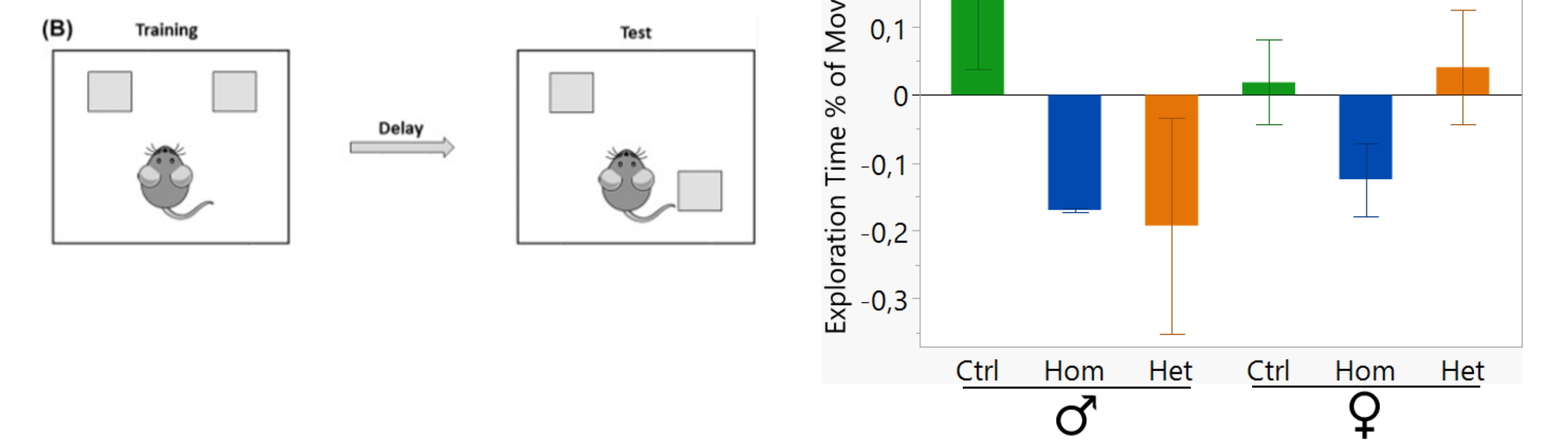


**Figure 2 : Intrinsic excitability of CA1 pyramidal neurons in CA1-S1R(-/-) and CA1-S1R(+/-) mice.** (A) Above : Representative trace of action potentials (AP) response to a 200pA step current. Below : Summary plot of the number of action potentials (AP) in response to a 200pA step current. (B) Graphic depiction of the different parameters analyzed in intrinsic excitability. (C) Latency to first spike (D) Rheobase (first current step provoking AP). Statistical significance was assessed using a two-way ANOVA followed by a Tukey's multiple comparisons test. Error bars ± SEM. \*p<0.05, \*\*p<0.01, \*\*\*p<0.0001.

## Behavior



## Object Location Test (spatial memory)



**Figure 3 : Spatial memory in S1R CA1-specific knockout mice.** (A) Graphic depiction of the stereotaxic procedure. (B) Epifluorescence microscopy image of Cre-GFP expressed in CA1. (C) Timeline of injection and behavioral testing. (D) Left : Graphic Depiction of the Object Location Test. Right : Exploration time (in percent) of the moved object on test day after 5 minutes compared to the unmoved object (Male : Control n=4, S1R(-/-) n=2, S1R(+/-) n=2. Female : Control n=7, S1R(-/-) n=2, S1R(+/-) n=3.)

## Conclusions & Perspectives

- Synaptic excitability is unchanged by the knockout of S1R in CA1.
- Intrinsic excitability is increased in males, but not females.
- No significant effect on hippocampus-dependent behavior is observed yet.

To further study the role of S1R in CA1, R4ag11-Cre mice will be submitted to behavioral test targeting the hippocampus.

Expression levels of ion channels involved in latency of first spike and rheobase will be assessed to investigate the change in intrinsic excitability.



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 • R4ag11(CAMKIIα)-Cre were provided by Timothy E Kennedy, McGill.