

# The Effect of Glucocorticoid Receptor Knockdown in a Corticostriatal Pathway on Cue-Motivated Behaviors

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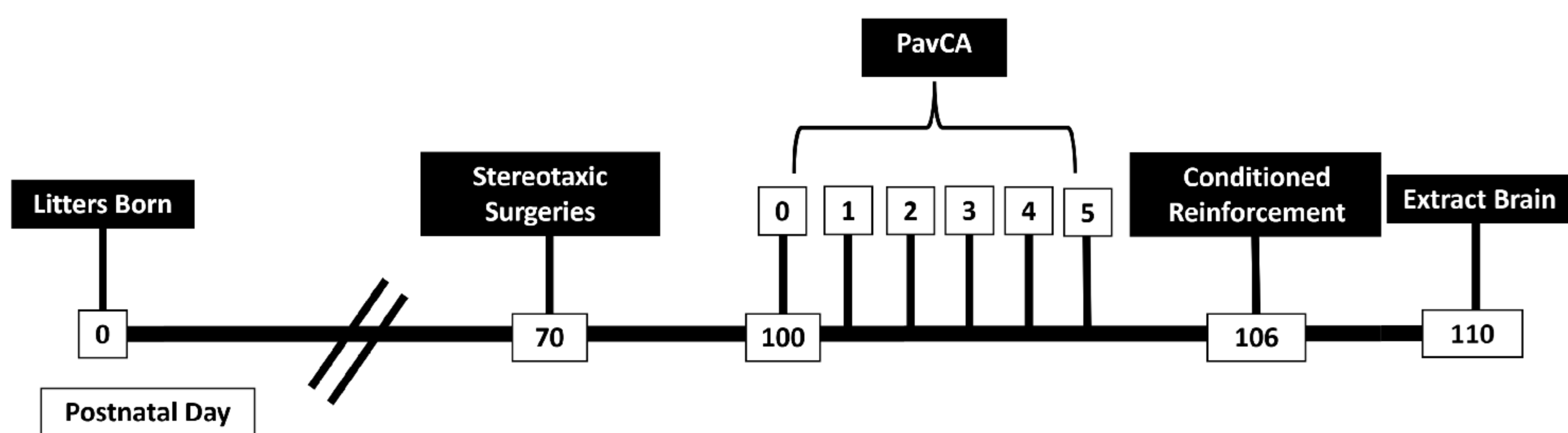


## Introduction

- The sign-tracker/goal-tracker animal model uses a Pavlovian conditioned approach (PavCA) procedure to capture individual variation in the propensity to attribute incentive salience to reward cues<sup>1</sup>.
- In sign-trackers, dopamine in the nucleus accumbens core (NAcC) is critical for the attribution of incentive value to reward cues<sup>2</sup>.
- Dopamine signaling in the NAcC is regulated in part by neuronal input from the prelimbic cortex (PrL)<sup>3</sup>.
- Glucocorticoids enhance dopamine activity in the NAcC and in turn regulate individual differences in reward-seeking behaviors<sup>4</sup>.
- Here, we investigate whether glucocorticoid receptors (GRs) in a top-down corticostriatal (PrL-NAcC) circuit mediate dopamine-dependent incentive learning.

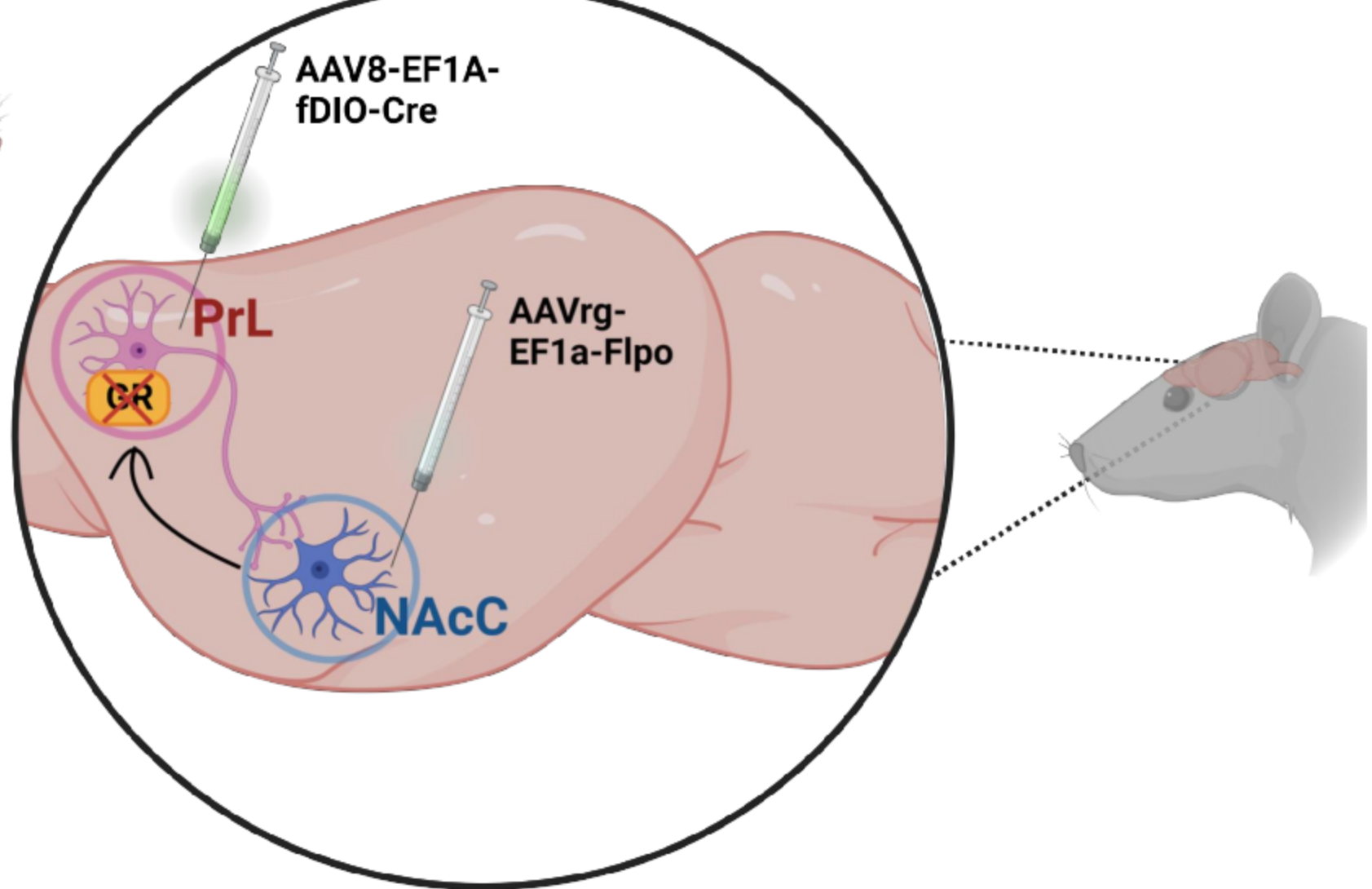
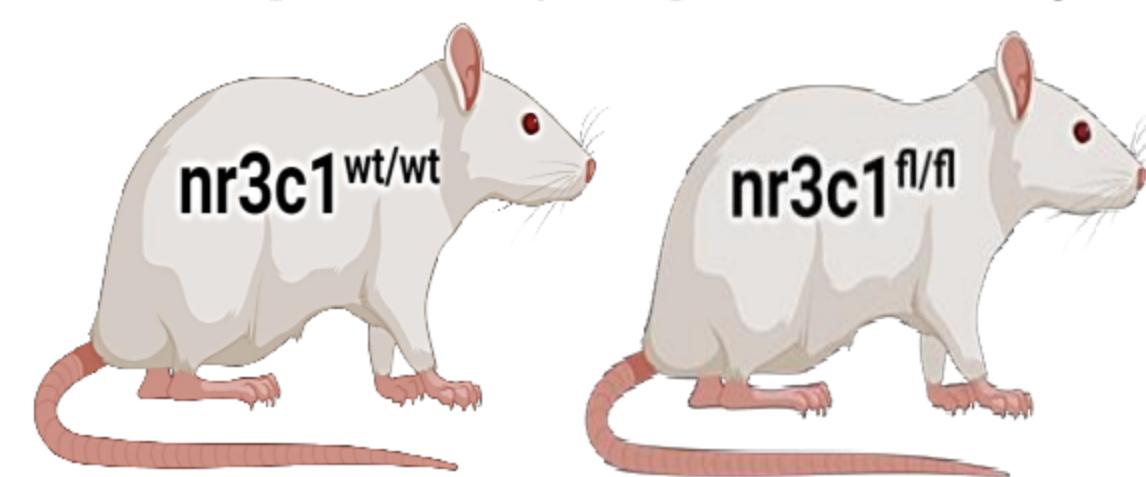
## Methods

### Experimental timeline



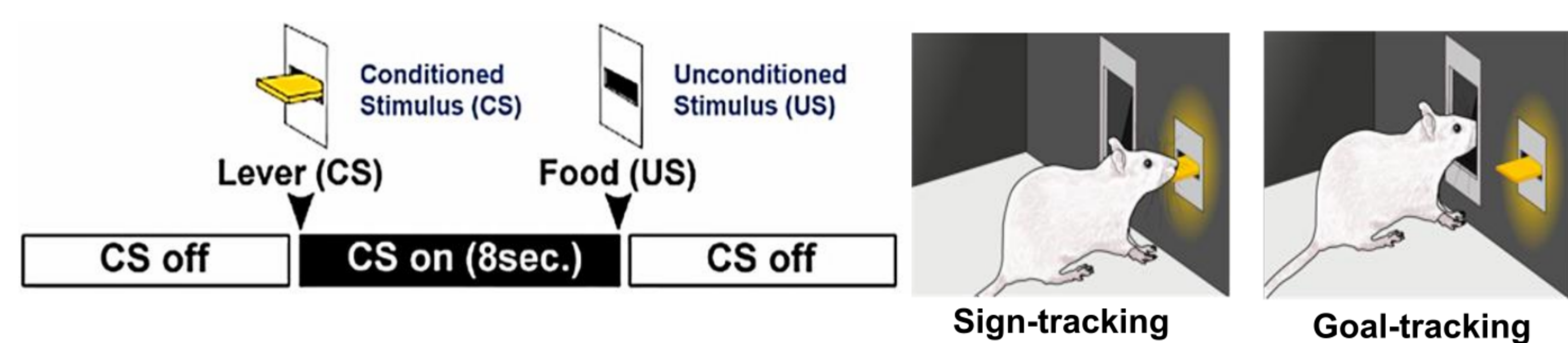
### Stereotaxic Surgery

#### Transgenic Sprague-Dawley rats

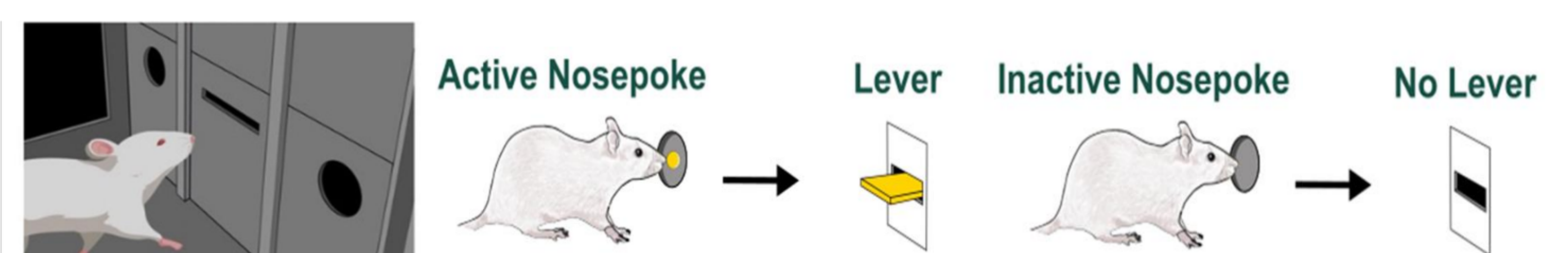


**GR knockdown in PrL-NAcC.** Retrograde transport of FLPase from the NAcC to the PrL activates Flpo-dependent Cre in PrL-NAcC projection neurons for circuit-specific knockdown in nr3c1<sup>fl/fl</sup> rats.

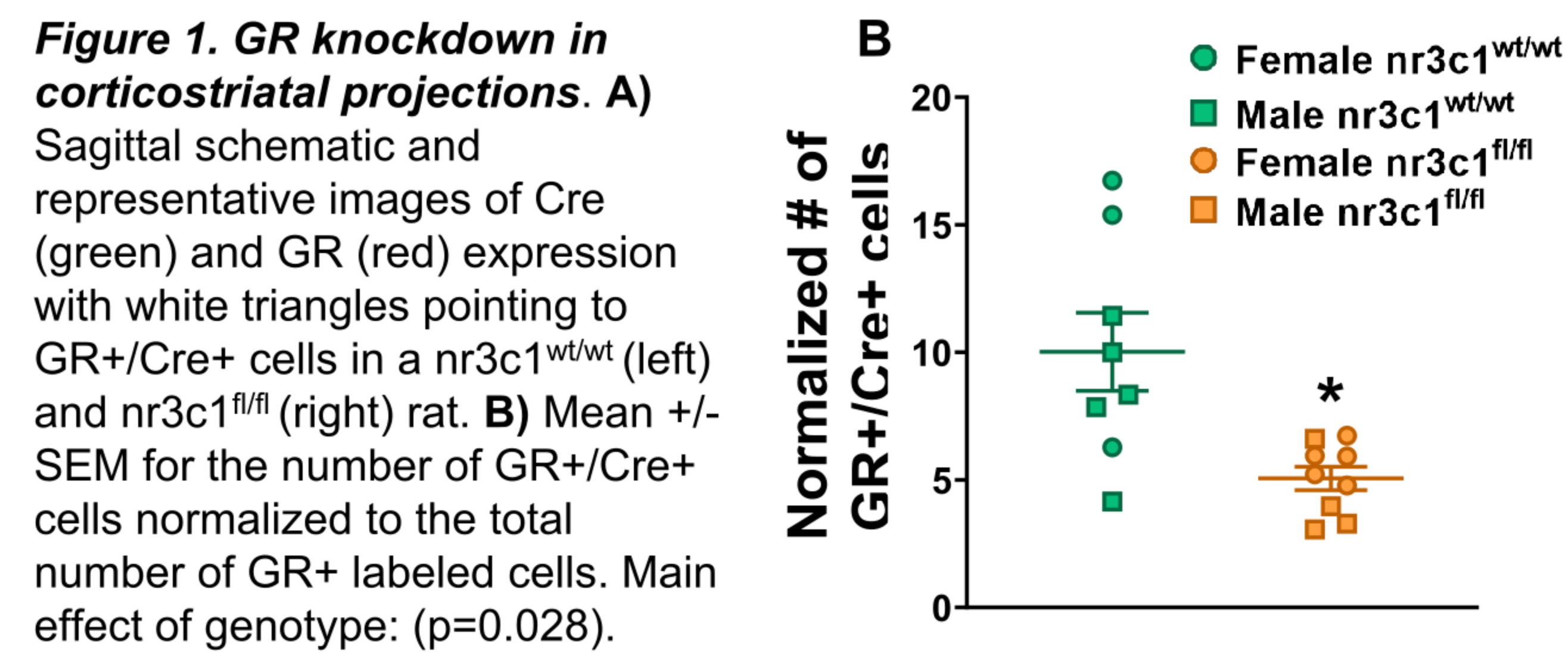
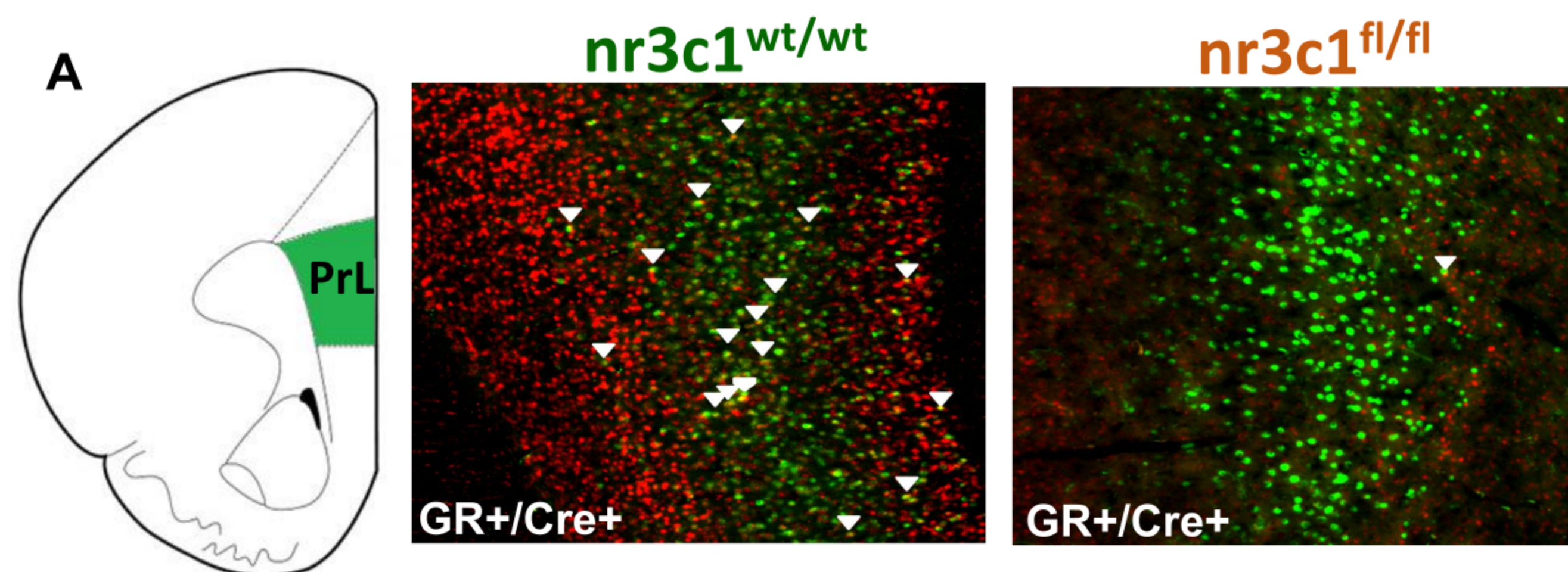
### Pavlovian Conditioned Approach (PavCA)



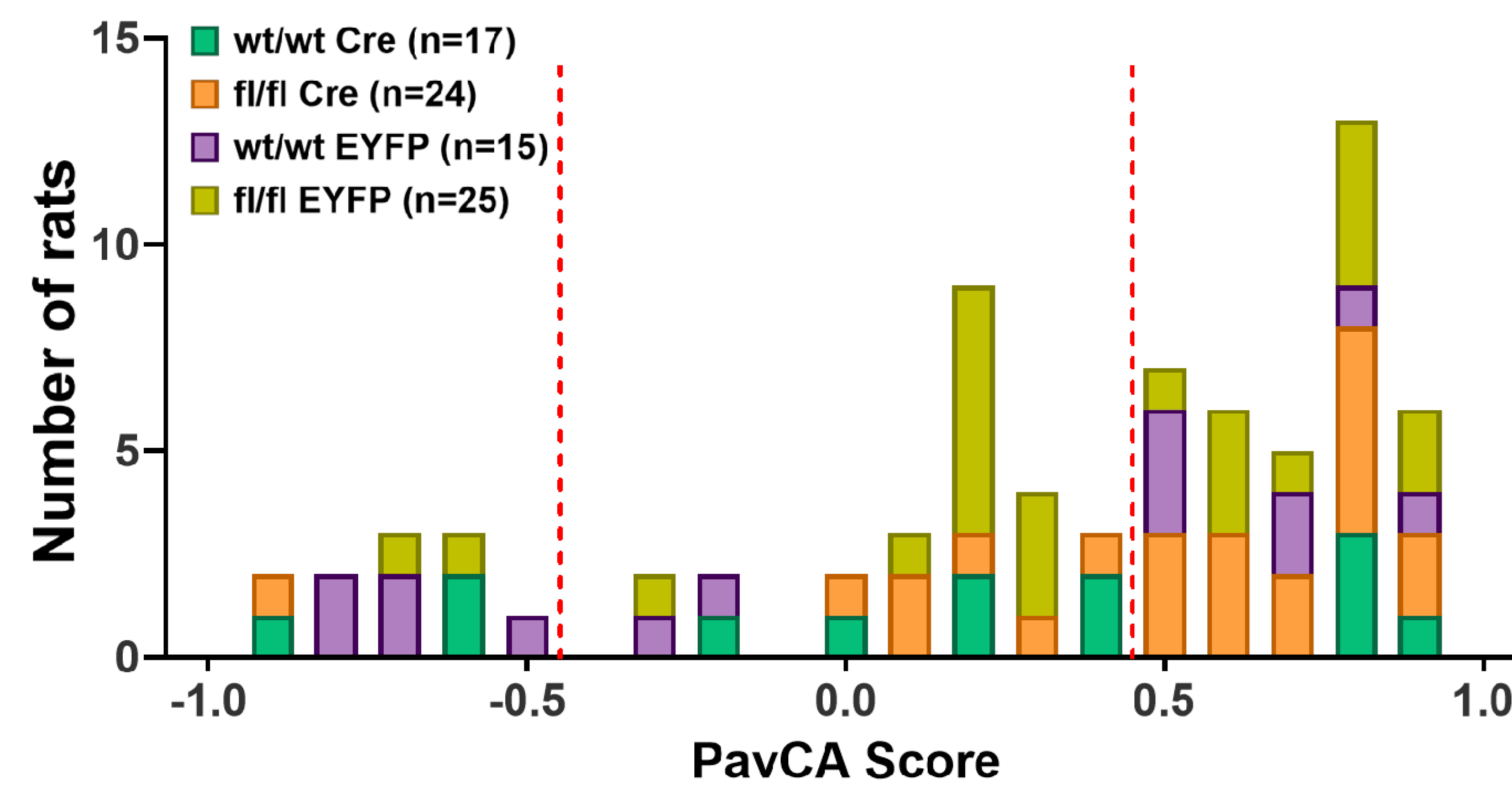
### Conditioned Reinforcement



## GR knockdown occurs selectively in the PrL-NAcC pathway



## GR knockdown in the PrL-NAcC pathway enhances the tendency to sign-track



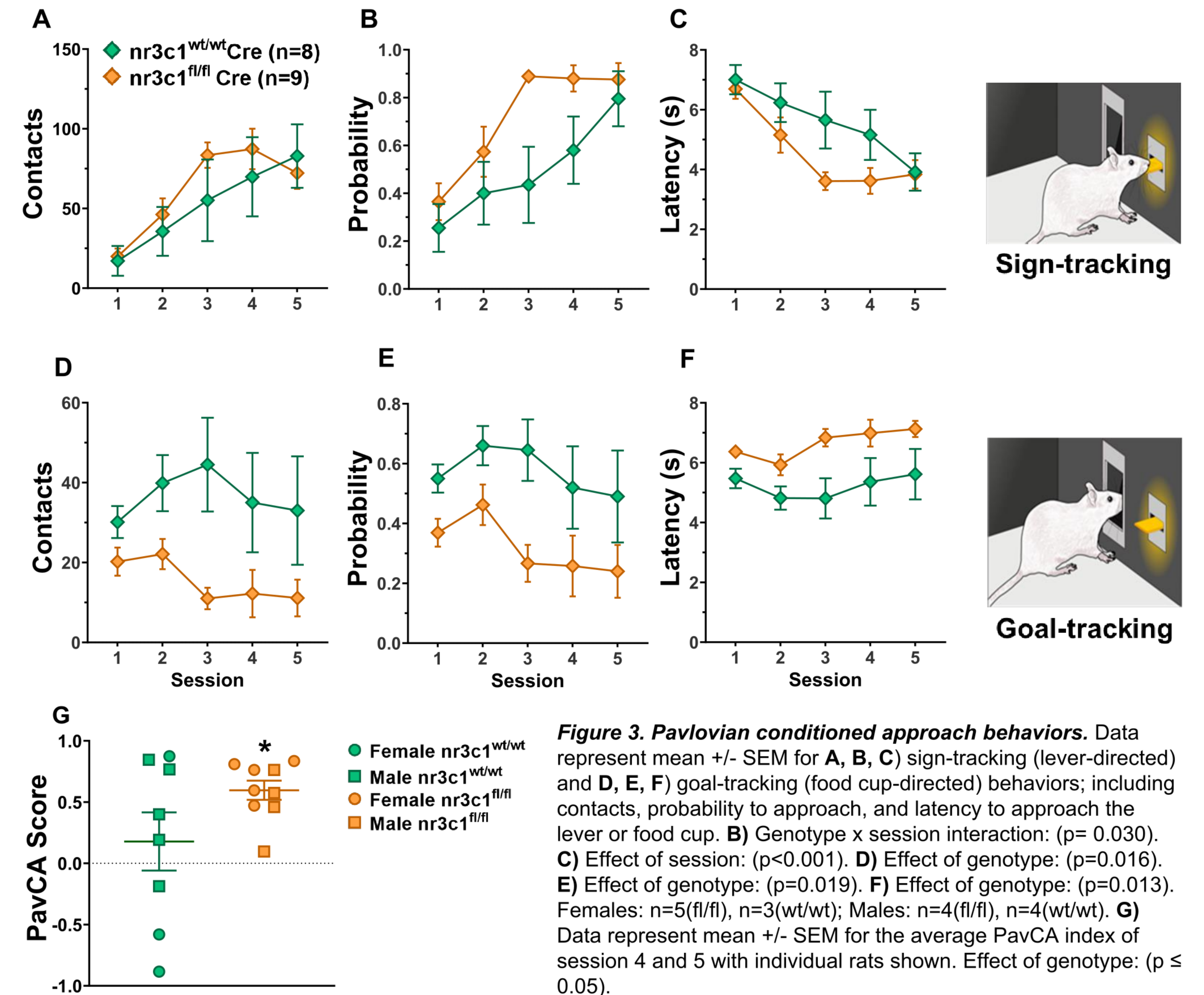
**Figure 2. Behavioral distribution across genotypes.** PavCA score represents a composite index that reflects the contacts, probability, and latency to approach the lever vs. the food cup, averaged across sessions 4 and 5. Histogram portrays the spread of the propensity to sign-track (+0.5 → 1.0) or goal-track (-0.5 → -1.0) across genotypes (wt/wt and fl/fl) and/or virus (Cre or EYFP) injected into the PrL. Fl/fl rats with GR knockdown (orange) tend to sign-track more than wildtype or EYFP controls.

## Conclusions and Future Directions

- Using a dual viral vector approach in nr3c1<sup>fl/fl</sup> rats, we successfully knocked down GR in PrL neurons that project to the NAcC.
- GR knockdown in nr3c1<sup>fl/fl</sup> rats appears to increase the propensity to sign-track.
- GR knockdown does not affect the conditioned reinforcing properties of a reward cue.
- Future studies will assess the effects of PrL-NAcC GR knockdown on cue-elicited dopamine activity in the NAcC.

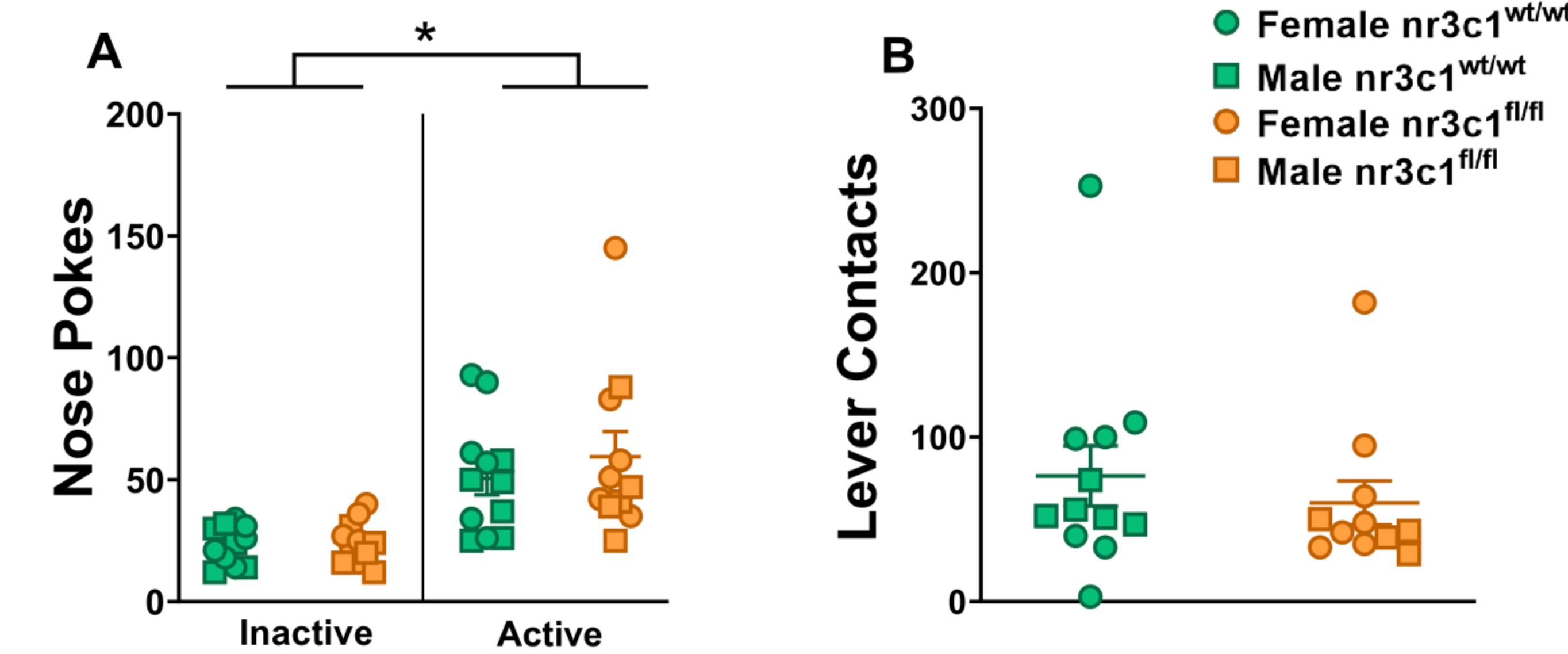
## Results

### GR knockdown in the PrL-NAcC pathway enhances the tendency to sign-track



**Figure 3. Pavlovian conditioned approach behaviors.** Data represent mean +/- SEM for **A, B, C** sign-tracking (lever-directed) and **D, E, F** goal-tracking (food cup-directed) behaviors; including contacts, probability to approach, and latency to approach the lever or food cup. **B**) Genotype x session interaction: (p= 0.030). **C**) Effect of session: (p<0.001). **D**) Effect of genotype: (p=0.016). **E**) Effect of genotype: (p=0.019). **F**) Effect of genotype: (p=0.013). Females: n=5(fl/fl), n=3(wt/wt); Males: n=4(fl/fl), n=4(wt/wt). **G**) Data represent mean +/- SEM for the average PavCA index of session 4 and 5 with individual rats shown. Effect of genotype: (p ≤ 0.05).

### GR knockdown in the PrL-NAcC pathway does not affect the conditioned reinforcing properties of a reward cue



**Figure 4. Responses during conditioned reinforcement.** Data represent mean +/- SEM for the number of **A**) nose pokes into the "inactive" and "active" ports, and **B**) lever contacts. Both nr3c1<sup>wt/wt</sup> and nr3c1<sup>fl/fl</sup> rats poked their nose in the active (lever presenting) port significantly more times than in the inactive (non-presenting) port (Port: p<0.001). There were no significant differences between genotypes in the number of nose pokes or lever contacts.

## References

- [1] Robinson & Flagel (2009) *Biol Psych* 65(10), 869-873
- [2] Flagel et al. (2011) *Nature* 469(7328), 53-57
- [3] Stefanik et al. (2013) *Addict Biol* 18, 50-53
- [4] Piazza & Le Moal (1996) *Ann Rev Pharm Tox* 36, 359-378

## Acknowledgements

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