



BACKGROUND

40-50% of **people with HIV (PWH)** experience **HIV-associated neurocognitive impairment (NCI)**, but no treatments exist¹

Cannabis use (CU); also known to impact cognition), is 2-3x ↑ in PWH than the general population², but the interactive effects of CU & HIV on cognition are unclear. Clinical studies suggest:

- Effects are **task-dependent**
 - May benefit learning and verbal fluency domains³
 - May worsen memory⁴
- Effects are **modulated by several confounding factors** (e.g. age of onset, chronicity of use etc.)

* Each factor can be held constant in animal models

The **HIV-1 transgenic (TG)** rat expresses most of the HIV-1 genome, and provides a model of chronic low level HIV infection similar to PWH on combined antiretroviral medications⁵



RESEARCH OBJECTIVES

Test the impact of acute and chronic THC on multiple cognitive domains in HIV1-TG rats and identify whether physiological responses to THC differ across genotypes.

METHODS

Exp. 1: Male & female HIV1-TG (n=35) and wildtype (WT; n=37) rats tested in an operant cognitive battery at baseline then retested during **acute** and **chronic steady-state** THC (VEH, 0.3, or 3 mg/kg 1x/day; i.p.; within subjects) exposure.

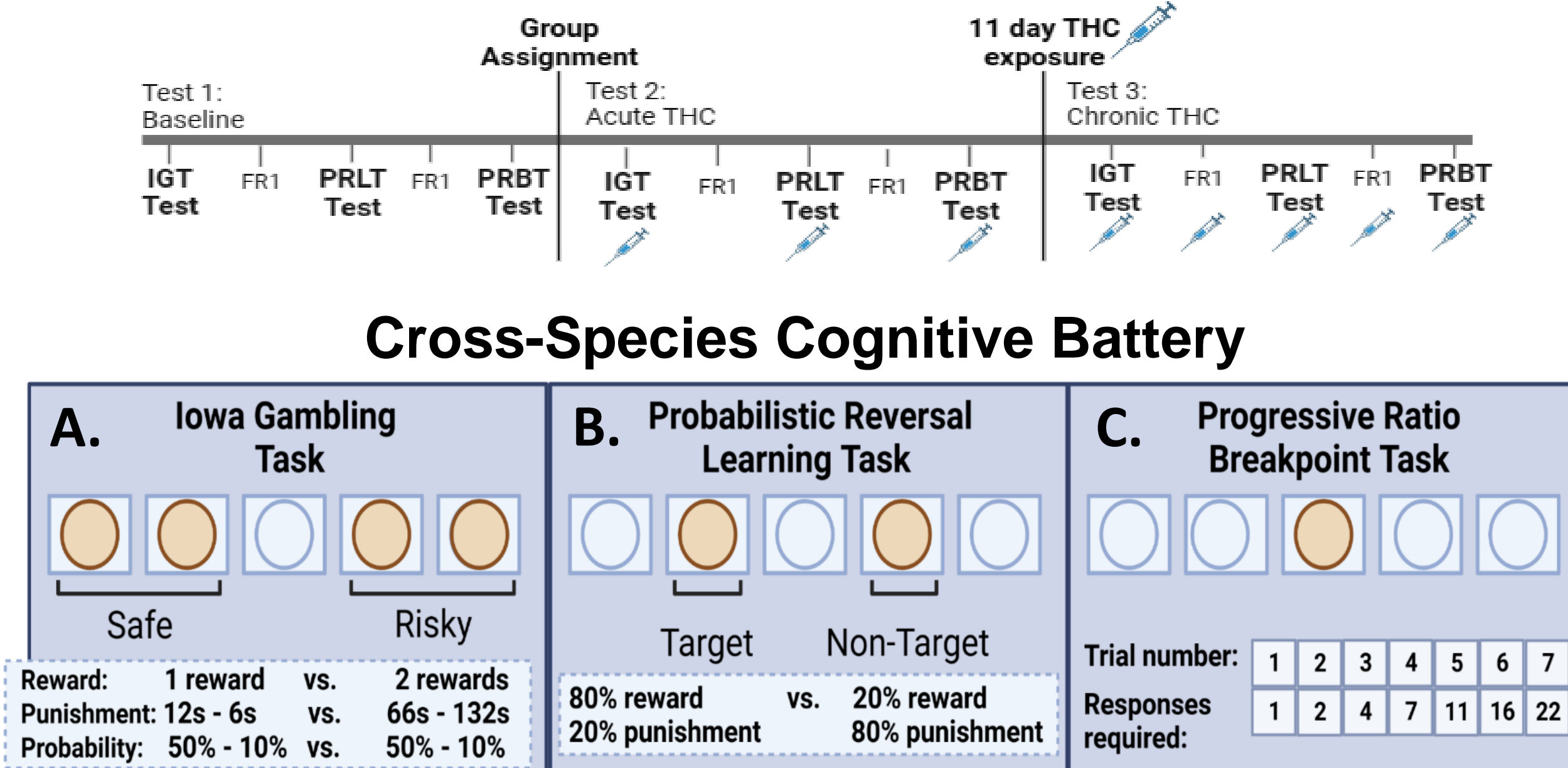
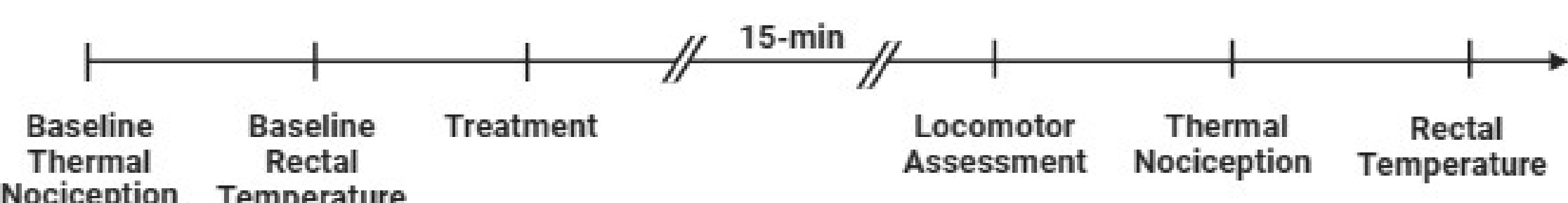


Figure 1. A) Iowa Gambling Task (IGT): risk-based decision-making; pits high-risk high-reward vs. low-risk low-reward options; outcome variable = difference score (safe-risky choices). **B) Probabilistic Reversal Learning Task (PRLT):** learning and cognitive flexibility; preferentially rewards target, which switches locations after 8 consecutive target responses; outcome variable = # of trials to the first reversal (initial learning) and # reversals achieved (reversal learning). **C) Progressive Ratio Breakpoint Task (PRBT):** motivation; requires an exceedingly greater number of responses across trials to earn a single reward; outcome variable = breakpoint (i.e. trial in which the animal stops responding).

Exp. 2: TG (n=41) and # WT (n=35) rats tested in the cannabinoid tetrad following exposure to acute THC (VEH, 0.3, or 3 mg/kg; ip; between subjects). Catalepsy not measured.

- **Locomotor and exploratory activity:** 20 min monitoring in the behavioral pattern monitor
- **Nociception:** thermal tail flick
- **Temperature:** rectal thermometer readings



TG Rats Exhibited Lower Baseline Motivation

- Sex, not genotype, influenced baseline IGT and PRLT performance
- Males and TG rats exhibited lower motivation in PRBT

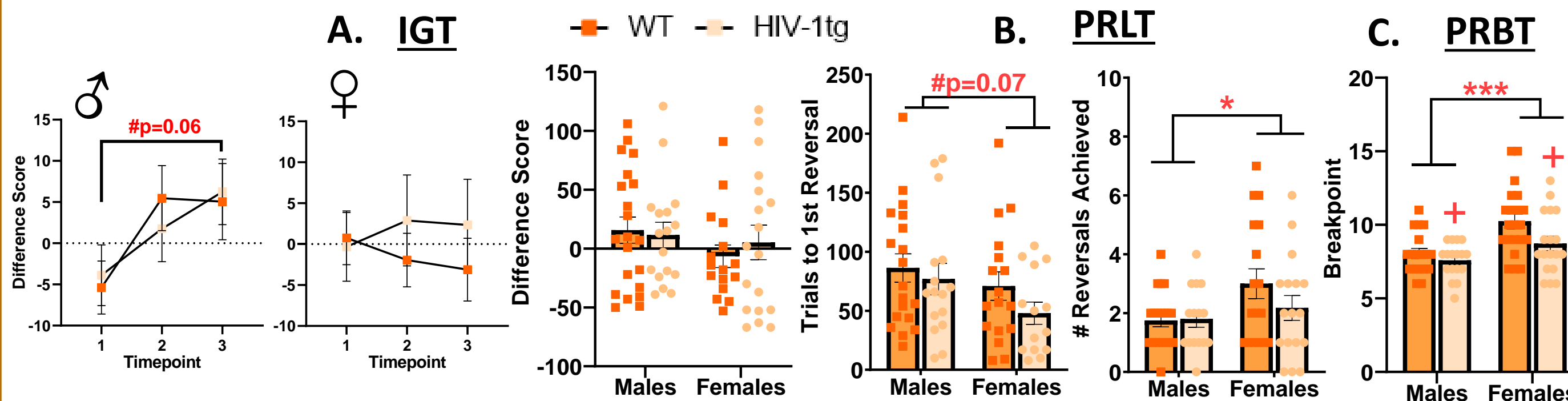


Fig. 2. Baseline cognitive behavior. IGT: A) males learned to choose safer options across trials; did not differ by genotype. PRLT: B) no genotype effect on initial or reversal learning, but females performed better than males across measures. PRBT: C) Females and WTs achieved higher breakpoints #= $p<0.1$, *= $p<0.05$, ***= $p<0.001$; += $p<0.05$ diff vs. WT controls.

Physiological Responses to Acute THC Were Consistent Across Genotype

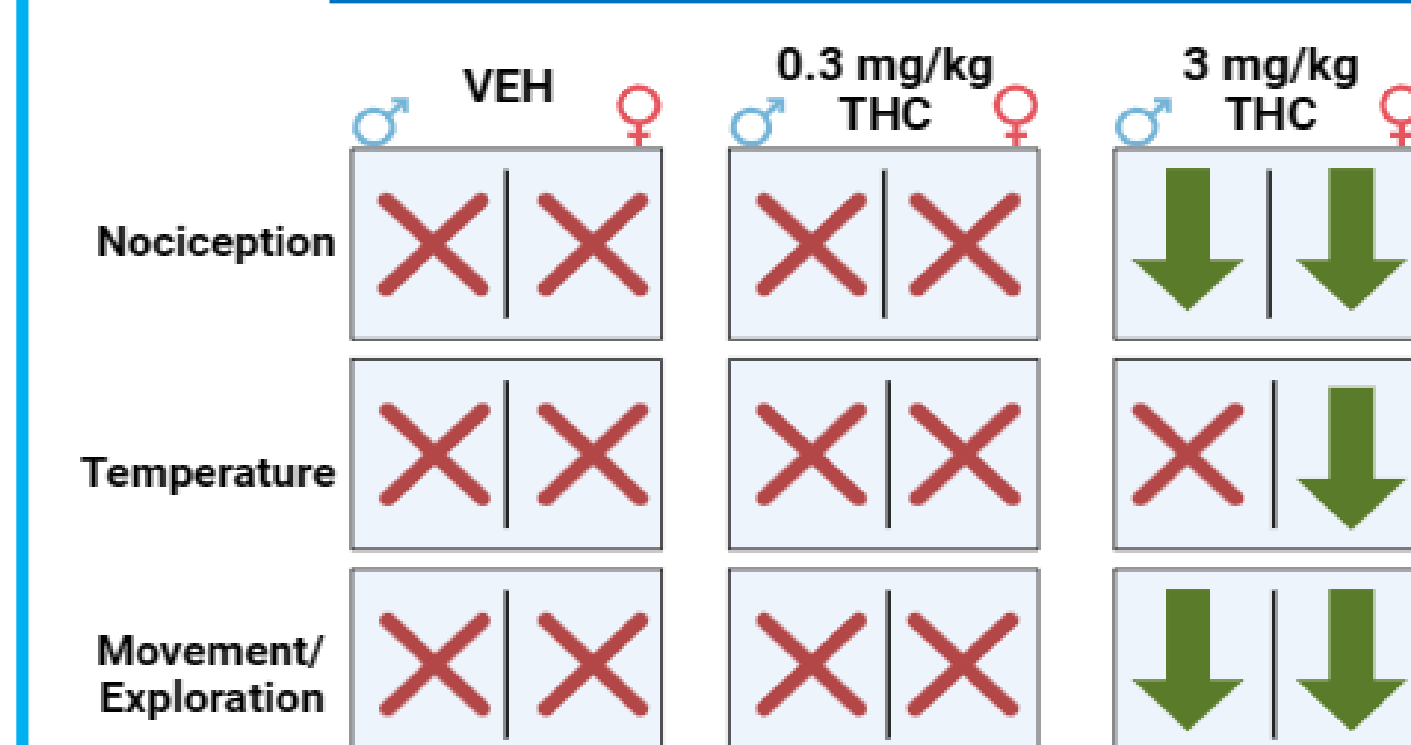


Fig. 6. Behavioral effects across genotypes and sex following acute THC treatment in the cannabinoid tetrad (catalepsy not measured). All effects $p<0.05$ unless otherwise indicated

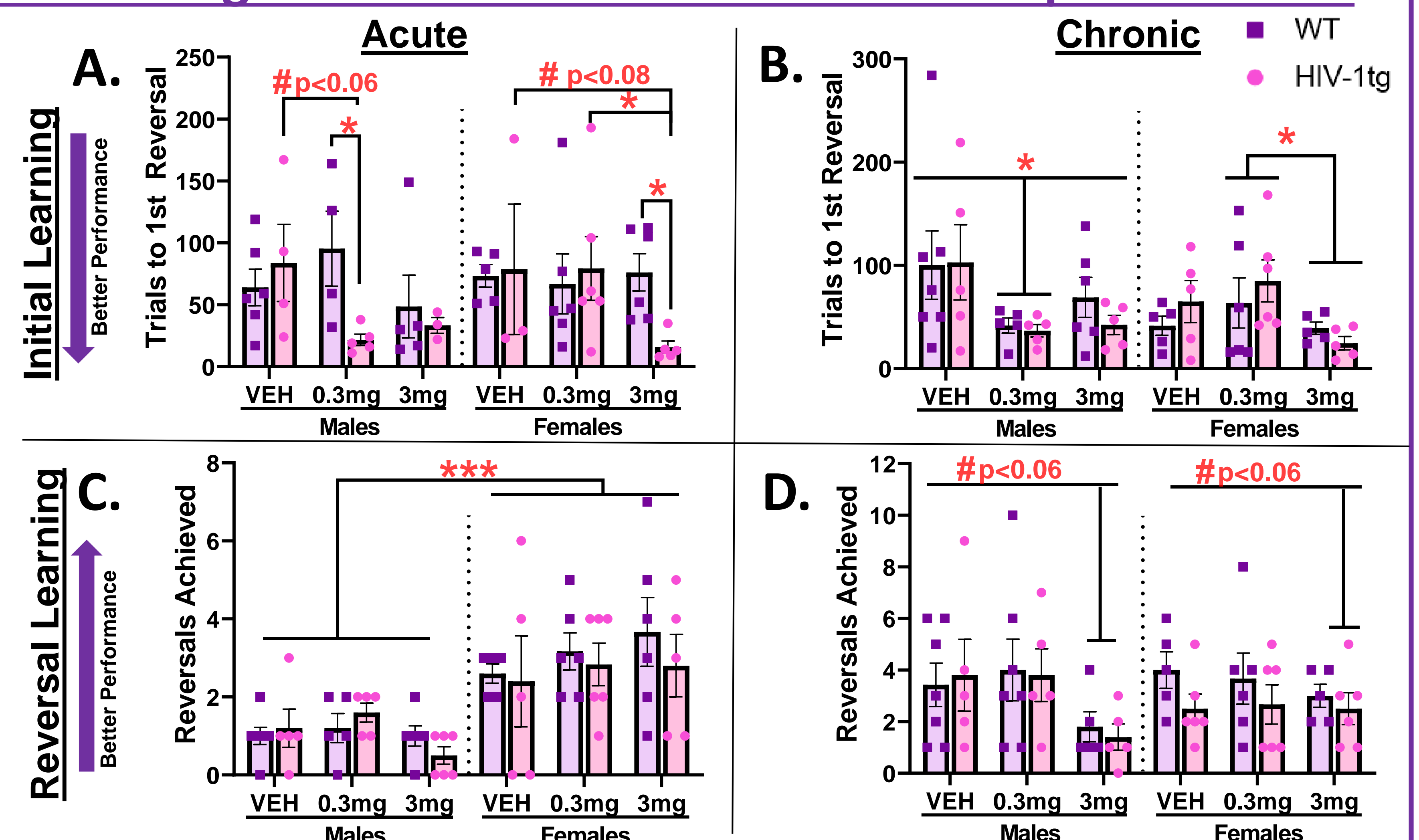
- High-dose THC decreased nociception, temperature (females only), and tended ($p=0.1$) to decrease movement and exploration across genotypes
- No effects of low-dose

PRLT: Acute THC Improves Initial Learning in HIV-1TG Rats - Chronic THC Improves Initial Learning Across Genotypes

- Acute THC improved initial learning selectively in TG rats, with higher doses needed in females (Fig. 3A)
- Chronic low-dose THC improved initial learning across all males (Fig. 3B)

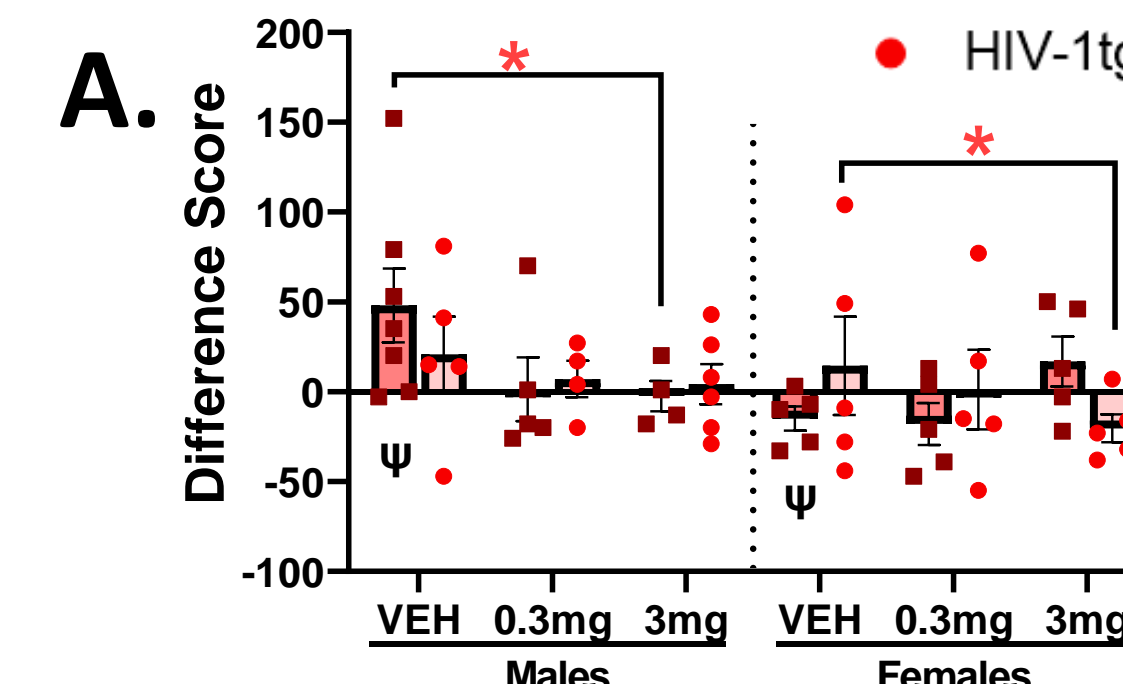
Fig. 3. Reinforcement learning in the PRLT. A) Sex*Genotype*Dose interaction ($p=0.090$) on Trials to First Reversal at acute test. B) Sex effect ($p=0.052$) and Dose*Sex interaction ($p=0.070$) on Trials to First Reversal at chronic test. C) Sex effect ($p<0.001$) on Reversals Achieved at acute test. D) Dose effect ($p=0.061$) on Reversals Achieved at chronic test. #= $p<0.1$, *= $p<0.05$, ***= $p<0.001$

- Females > reversal learning than males, consistent with baseline (Fig. 3B)
- Chronic high-dose THC tended to interfere with reversal learning (Fig. 3B)



IGT: Acute and Chronic THC Alters Risk-Taking in a Genotype & Sex Dependent Manner

- Acute (Fig. 4A):**
- VEH treated WT males < risky than WT females
 - High-dose THC increased risk taking in WT males and TG females



- Chronic (Fig. 4B):**
- Female TGs > risky than male TGs
 - VEH treated TG males < risky and TG females > risky vs. WTs
 - Chronic THC increased risk taking in male WTs and in female TGs

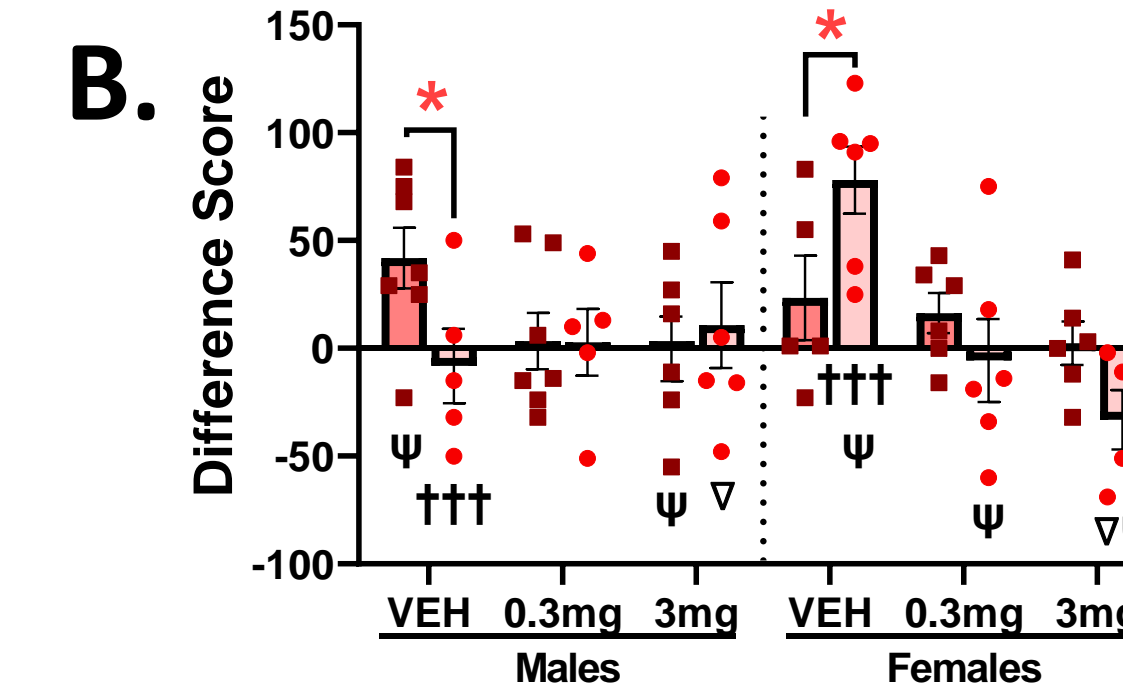


Fig. 4. Risk-taking in the IGT following THC. *= $p<0.05$; Ψ =sex diff. $p<0.05$; $\Psi\Psi\Psi$ =sex diff. $p<0.001$; †=within-sex dose diff. from VEH $p<0.05$, Δ=between-sex dose diff. $p<0.05$

PRBT: Acute THC Altered Motivation

- Females and WTs > motivation at acute testing (Fig. 5A)
- Acute high-dose THC decreased motivation while low-dose THC increased motivation across sexes and genotypes (Fig. 5A)
- No drug, genotype, or sex effects during chronic testing (Fig. 5B)

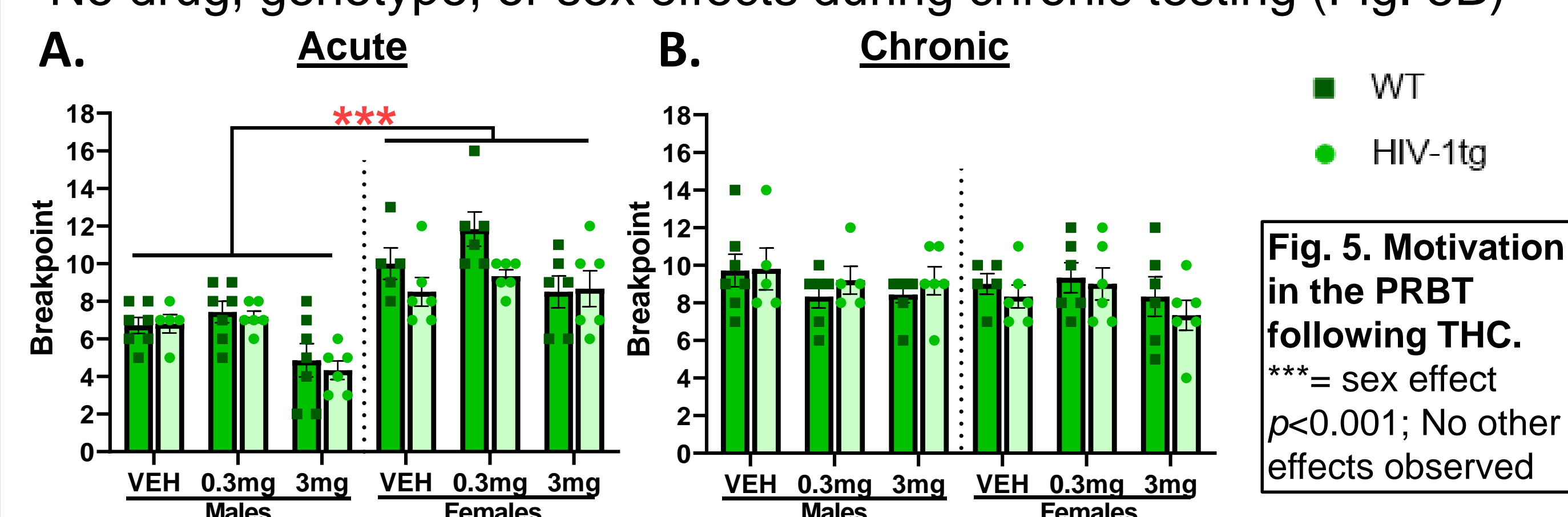


Fig. 5. Motivation in the PRBT following THC. ***=sex effect $p<0.001$; No other effects observed

DISCUSSION

- Acute THC *improved* reinforcement learning of HIV-1 TG rats (Fig. 3A) and chronic THC *improved* reinforcement learning of HIV-1 TG and control rats (Fig. 3B), ** Consistent with CU effects in PWH being task-dependent, with benefits seen in learning domains⁵
- THC-induced improved learning was seen irrespective of acute THC dose-dependently altering motivation (Fig. 5A) while chronic THC did not affect motivation (Fig. 5B).
- Acute & chronic THC increased risk-taking in WT males and TG females. (Fig. 4).
- Despite genotype- and sex- effects of THC on cognition, HIV1-TG rats did not respond physiologically different to THC (Fig. 6), i.e., effects are specific to cognition
- Limitations: sample size, multiple test exposures

CONCLUSIONS

- THC may have procognitive effects in HIV-1tg rats specifically in the domain of reinforcement learning
- Highlights the importance of task, dose, and chronicity when testing THC effects on cognition in relation to HIV

ACKNOWLEDGEMENTS

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All authors declare no conflicts of interest.

REFERENCES

[1] Wang et al. (2020). *Neurology*, 95(19), e2610-e2621. [2] Shiao et al. (2017). *Addictive behaviors*, 68, 39-44. [3] Watson et al. (2020). *Journal of acquired immune deficiency syndromes (1999)*, 83(1), 56-64. [4] Cristiani et al. (2004). *The Journal of Neuropsychiatry and Clinical Neuroscience*, 16(3), 330-335. [5] Vigorito et al. (2015). *Brain, behavior, and immunity*, 48, 336-349.