

Role of Age and Sex in the Effects of Repeated Methamphetamine Exposure on Hedonic Tone in Sprague-Dawley Rats

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PRECS Phenotypic Plasticity Research Experience for Community College Students

Introduction

Anhedonia is defined as a reduced or complete loss of pleasure from a previously pleasurable stimulus, and it is comprised of two dimensions:

- Hedonic anhedonia consists of a distinct loss of pleasure in consumption of a normally pleasurable stimulus.
- Motivational anhedonia involves the goal-directed behavior to obtain a reward.

Withdrawal-induced anhedonia following use of methamphetamine (METH) is thought to contribute to relapse behaviors^{1,2}. The anhedonic effects of drug withdrawal largely depend on dose, frequency, and the duration of drug exposure^{4,5,6}.

The role of sex and age of exposure in this context has yet to be elucidated.

Study Objectives

Using a rat model, our goal is to:

- determine if repeated exposure to METH induces withdrawal effects that depend on sex and/or age
- utilize an escalating dose, drug treatment paradigm that better models human drug taking behavior⁷

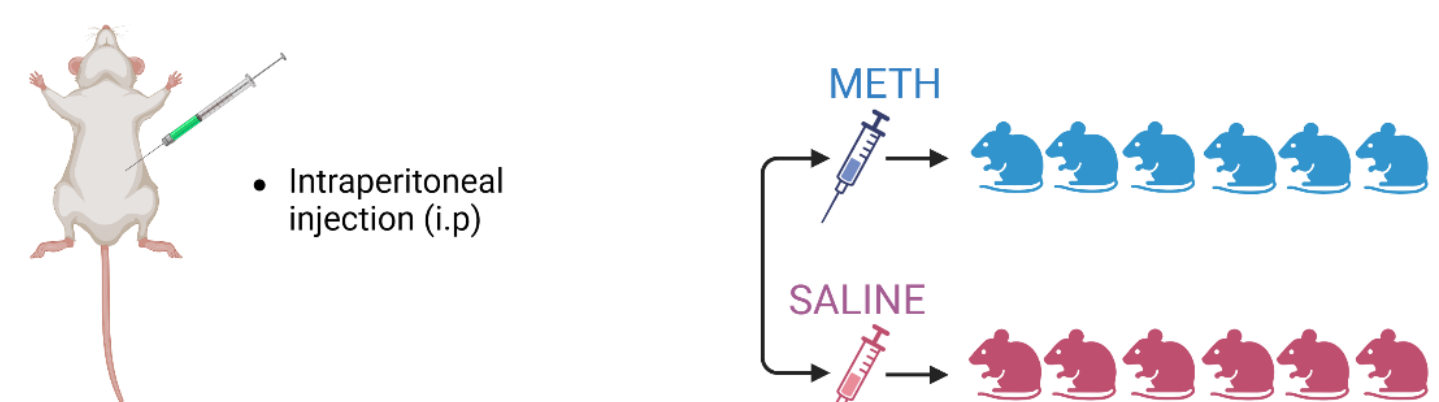
Methods

Subjects

- Male and female Sprague-Dawley rats born in our colony

Drug Exposure

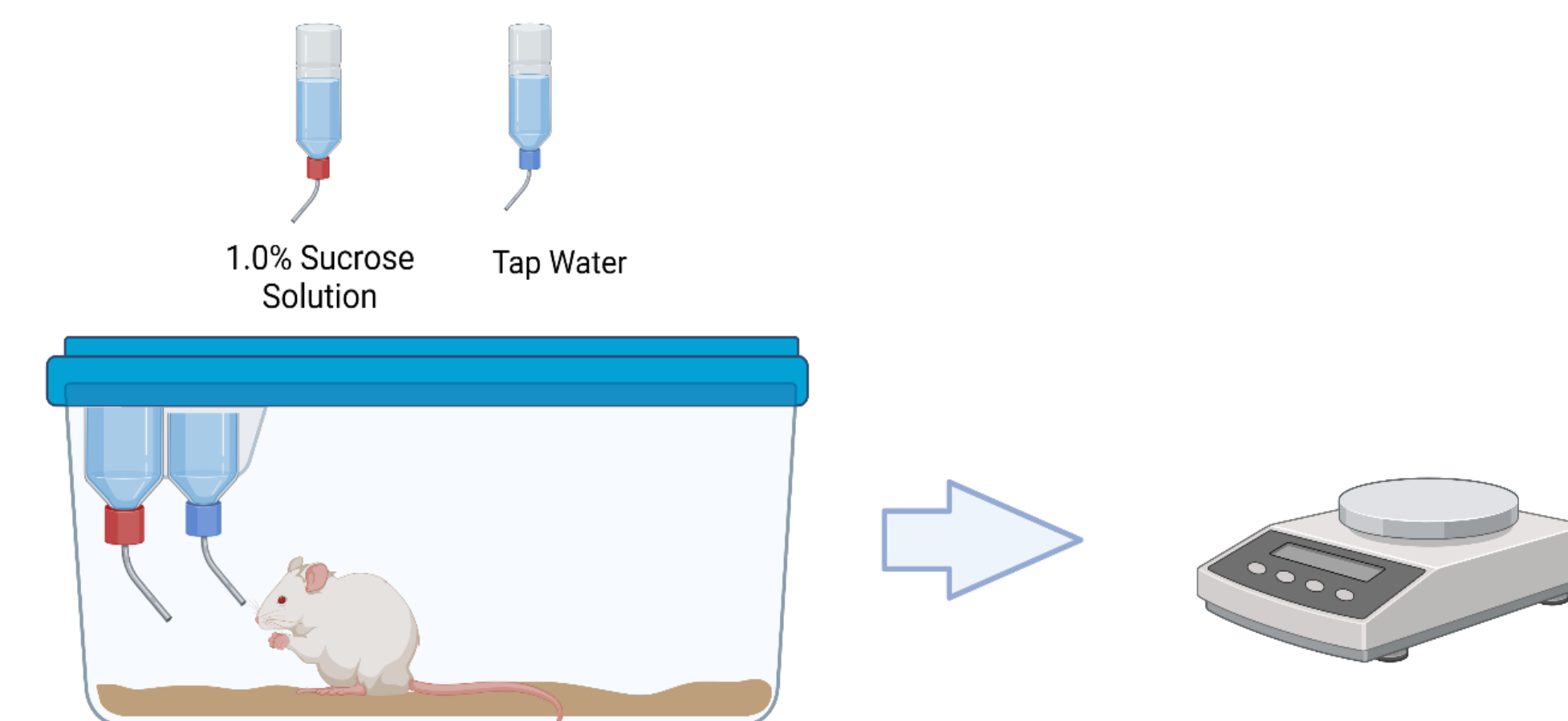
- Adolescent or adult rats were given daily injections of saline or METH from postnatal day (P) 35 to P44 or P75-P84, respectively.
- Treatments were administered twice daily on an escalating dose schedule as follows:



	P35	P36	P37	P38	P39	P40	P41	P42	P43	P44
Morning Treatment (mg/kg)	0.5	1.0	1.5	2.0	2.5	3.0	3.5	4.0	4.5	5.0
Evening Treatment (mg/kg)	0.5	1.0	1.5	2.0	2.5	3.0	3.5	4.0	4.5	5.0

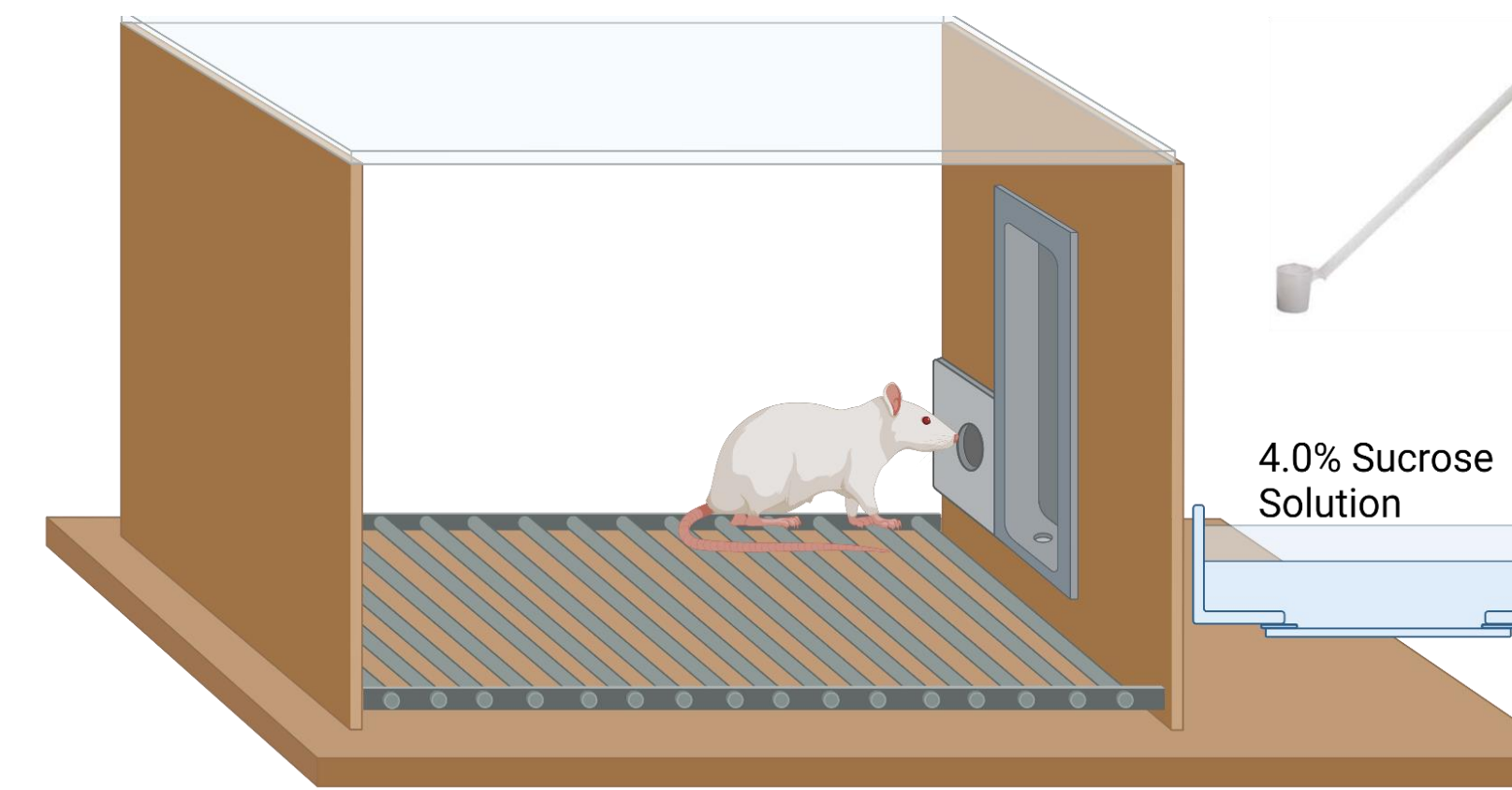
Methods Cont.

Experiment 1: Sucrose Preference Test (SPT)



- Adolescent and adult rats of both sexes (n = 6-12/group) were presented with two bottles containing sucrose and water for 48 h, starting 24h after their last injection.
- Preference for sucrose over water was used to assess withdrawal-induced anhedonia. Preference scores were calculated by the amount of sucrose consumed (g) / total liquid consumption (g) *100.

Experiment 2: Progressive Ratio Test (PR)



- Beginning 17h after last injection (P45-51), male and female adolescent rats (n = 3/group) were tested on a progressive ratio (PR) schedule of reinforcement.
- PR breakpoints were defined as the final PR interval completed.

Exp. 1: SPT

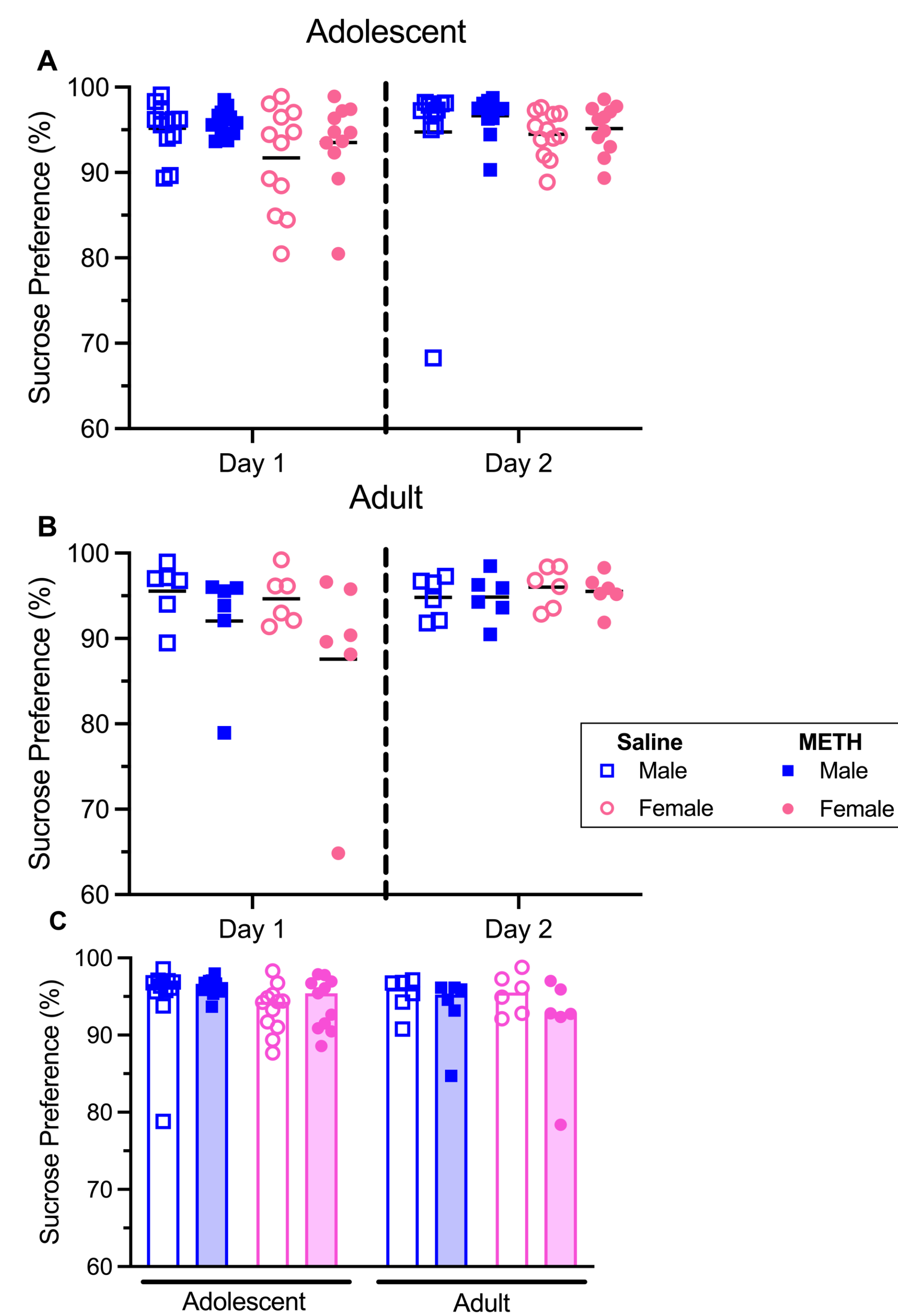


Fig. 1. Effects of METH exposure on sucrose preference (%) (n = 6-12/group). (A) and (B) show daily preference scores for adolescent- and adult-exposed rats during the 48-h SPT. (C) shows mean sucrose preference across the 48-h test. Data collection is ongoing with a target of n = 9 rats/group.

Exp. 2: PR schedule of reinforcement

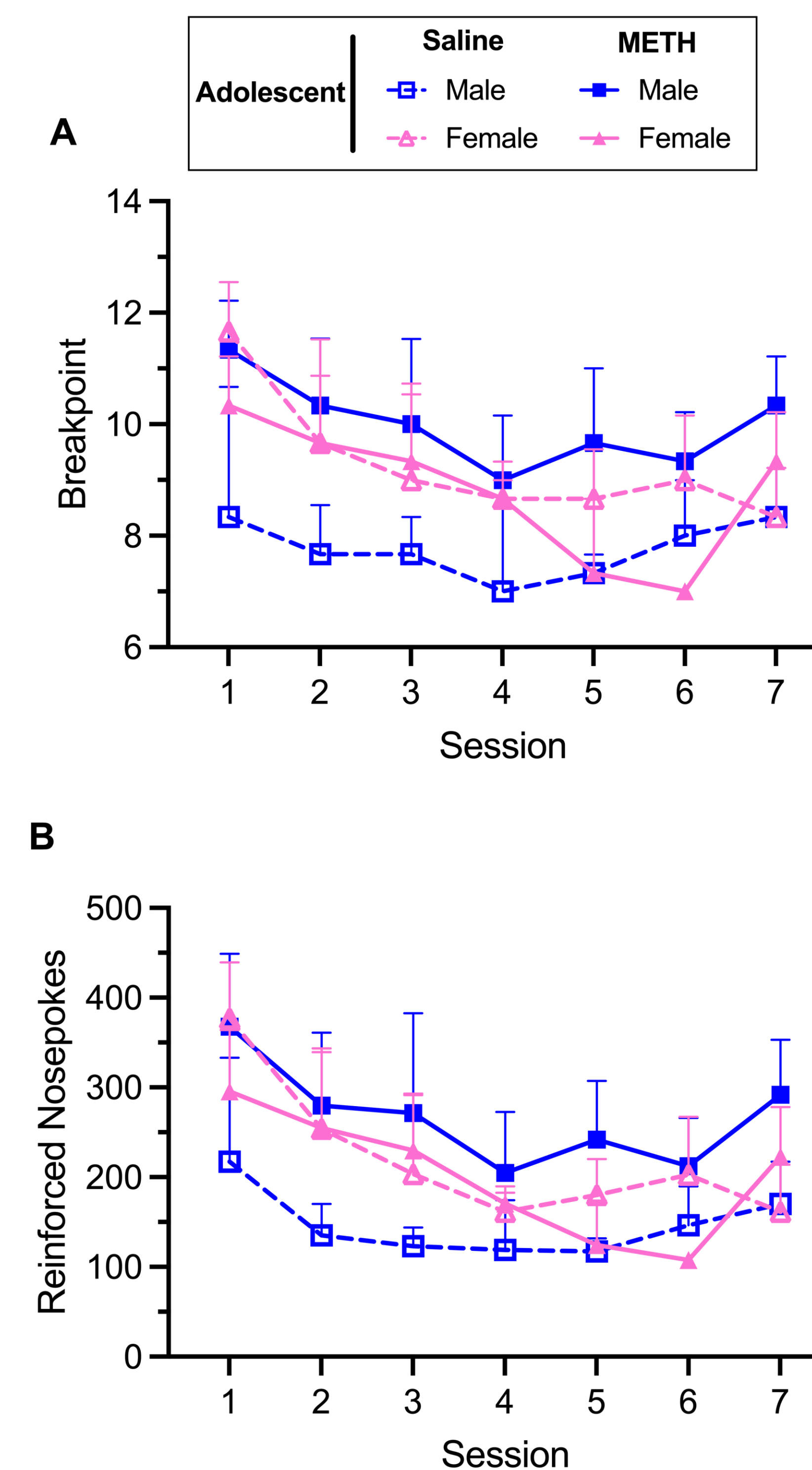


Fig. 2. Effects of METH exposure on PR responding for 4% sucrose in adolescent male and female rats (n = 3/group). (A) The mean post-treatment breakpoints and (B) the total number of reinforced nosepokes. Session 1 was conducted 17 h after the last saline or METH injection. Data collection is ongoing, with a target of n = 13 rats/group.

Conclusions

Preliminary data from Experiment 1 suggest treatment with an escalating dose of METH failed to induce hedonic anhedonia in any of the groups. Data collection is ongoing, but this finding suggests that, following repeated exposure to METH, preference for pleasurable stimulus is left unchanged.

Preliminary data from Experiment 2 suggest that rather than METH-induced motivational anhedonia, we observed enhanced motivation in males. Moreover, both adolescent female groups (METH or saline) had enhanced motivation as compared to saline-treated adolescent males. Although data collection is ongoing, these results suggest that repeated exposure to METH may contribute to temporary increases in goal-directed behavior.

Future Work

Future studies may include a "binge" treatment utilizing a substantial dose administered in close proximity to one another (e.g. 10 mg/kg every 3 hours). In this, we can better characterize a dosing schedule that models human drug taking behavior and its hypothesized state of anhedonia.

We are also collecting brain tissue from all subjects to investigate the potential role of brain derived neurotrophic factor (BDNF) and its receptor tropomyosin kinase receptor B (TrkB) in the effects of repeated exposure to METH.

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Acknowledgments

Financial support was provided by the National Science Foundation under grant #NSF REU 1950819/1950786, as part of the Phenotypic Plasticity Research Experience for Community College Students, through the University of Illinois at Urbana-Champaign Institute for Genomic Biology and Parkland College. <http://precs.igb.illinois.edu/>

Thanks to Gulley Lab members, Joseph Caruana, Lauren Carrica, Linyuan Shi, Nina Hoffman, and Olivia Howell for their support. Special thanks to Holly Fairfield for all of her efforts in animal care and beyond.