A novel modular labyrinth for assessing cognitive flexibility in mice

*I. LUNA[1,2], C. LIU[1], E. HOU[1,3], E. HO[1], A. ENOS[1], M. NESBIT[1], V. S. SOHAL[1];

[1]University of California, San Francisco, San Francisco, CA; [2]Biology, San Francisco State University, San Francisco, CA; [3]University of California, Berkeley, Berkeley, CA
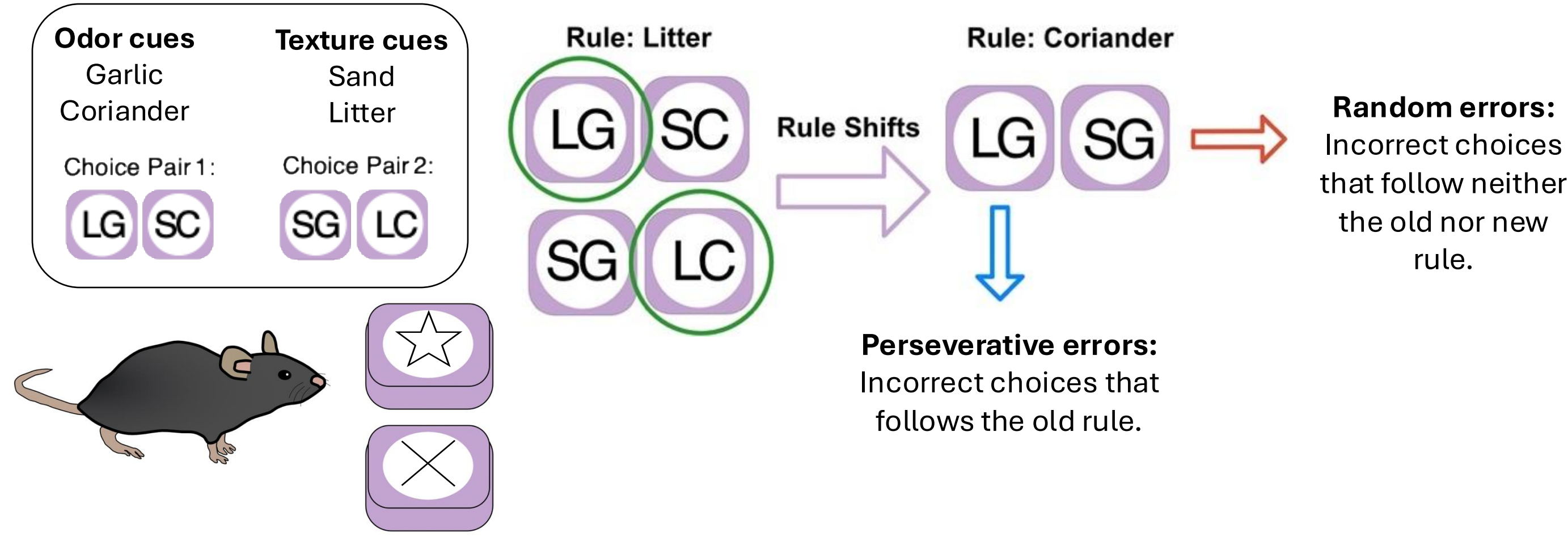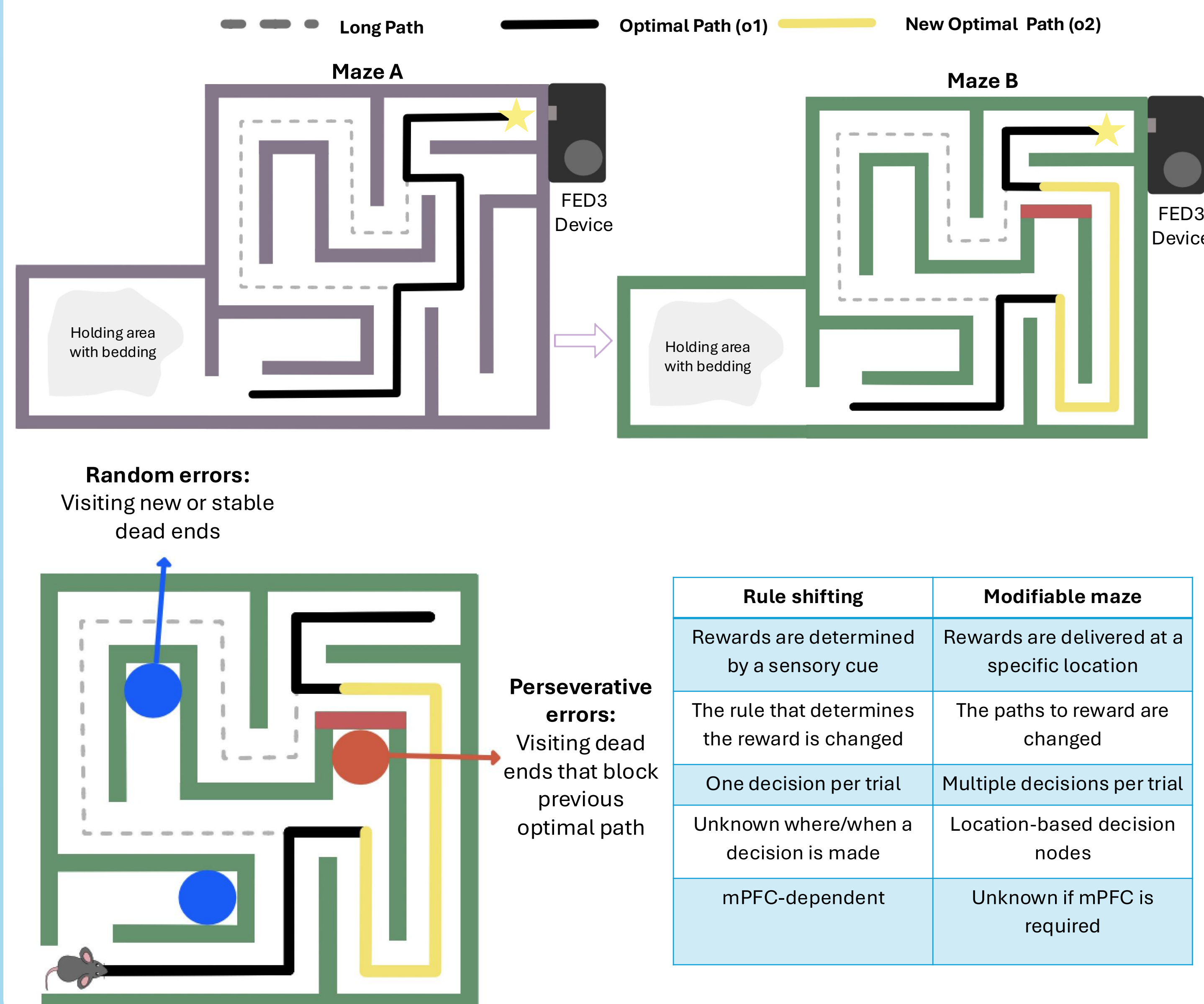
Overview

- Cognitive flexibility, the ability to adapt to changing environments, is mediated by the medial prefrontal cortex (mPFC)

- Tasks such as extradimensional rule shifting are robust for detecting impairments in cognitive flexibility but lack temporal and spatial resolution during the decision-making process

- We sought to establish a novel navigation-based assay for cognitive flexibility using an automated feeding device (FED) and a LEGO-based maze with paths that can be changed across sessions

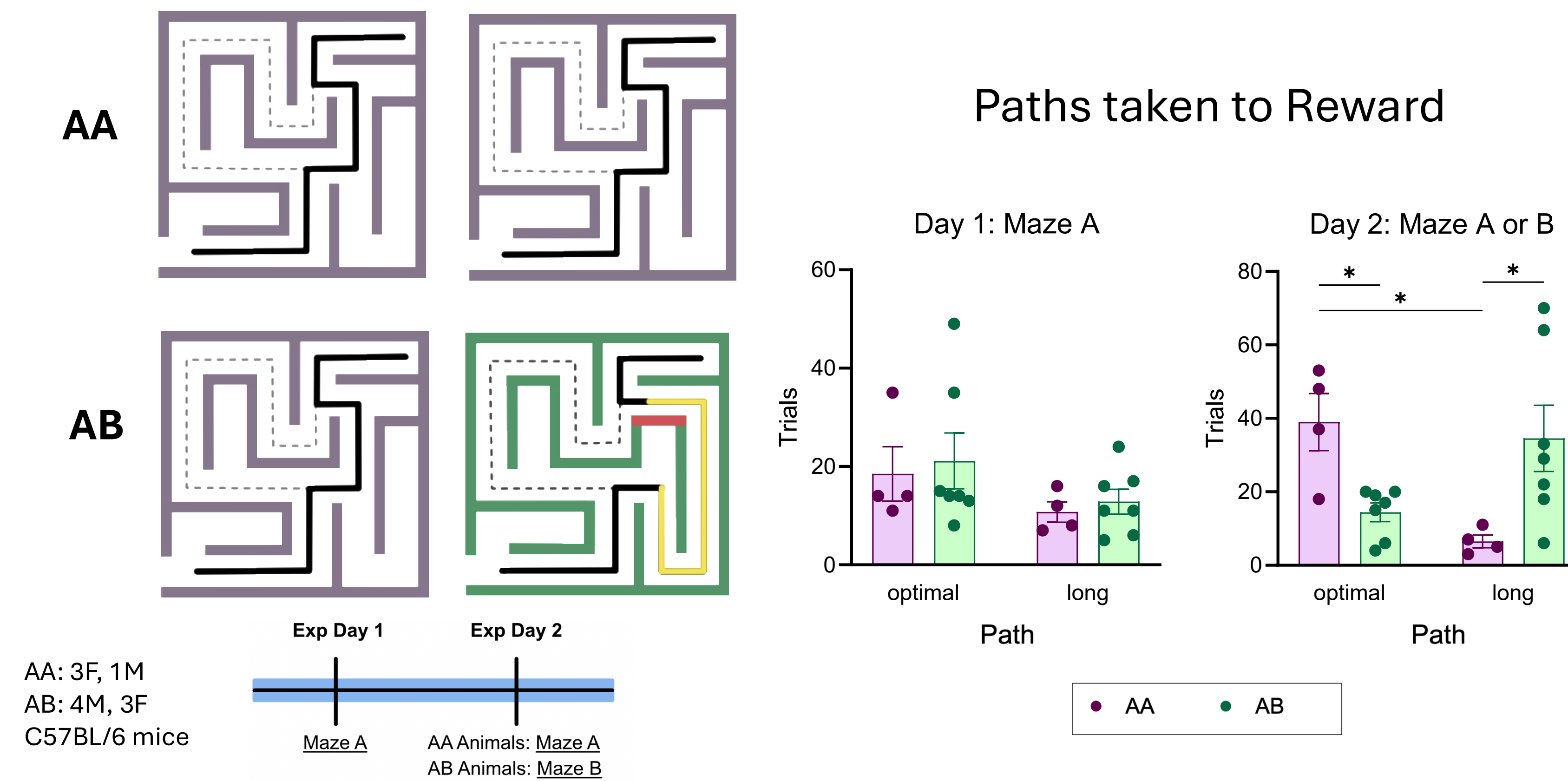## Developing a Modular Maze to Assess Cognitive Flexibility
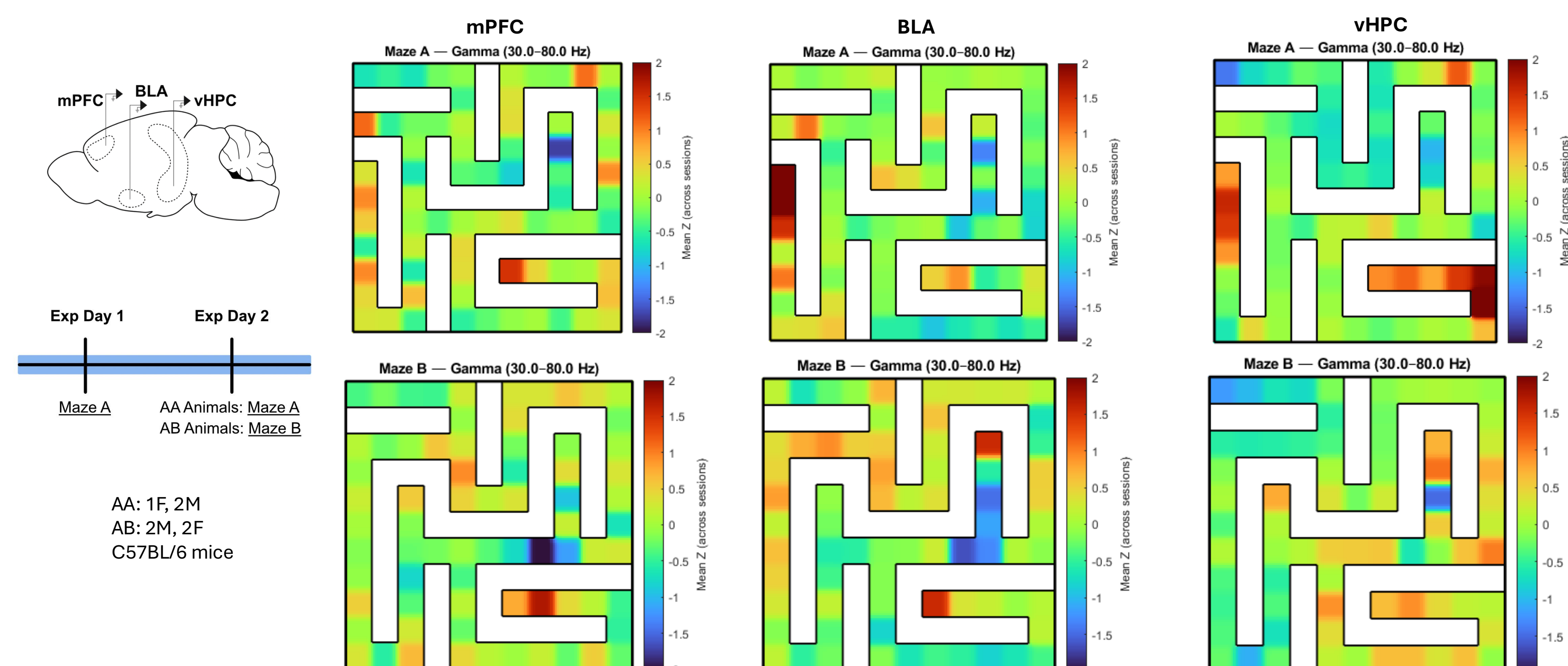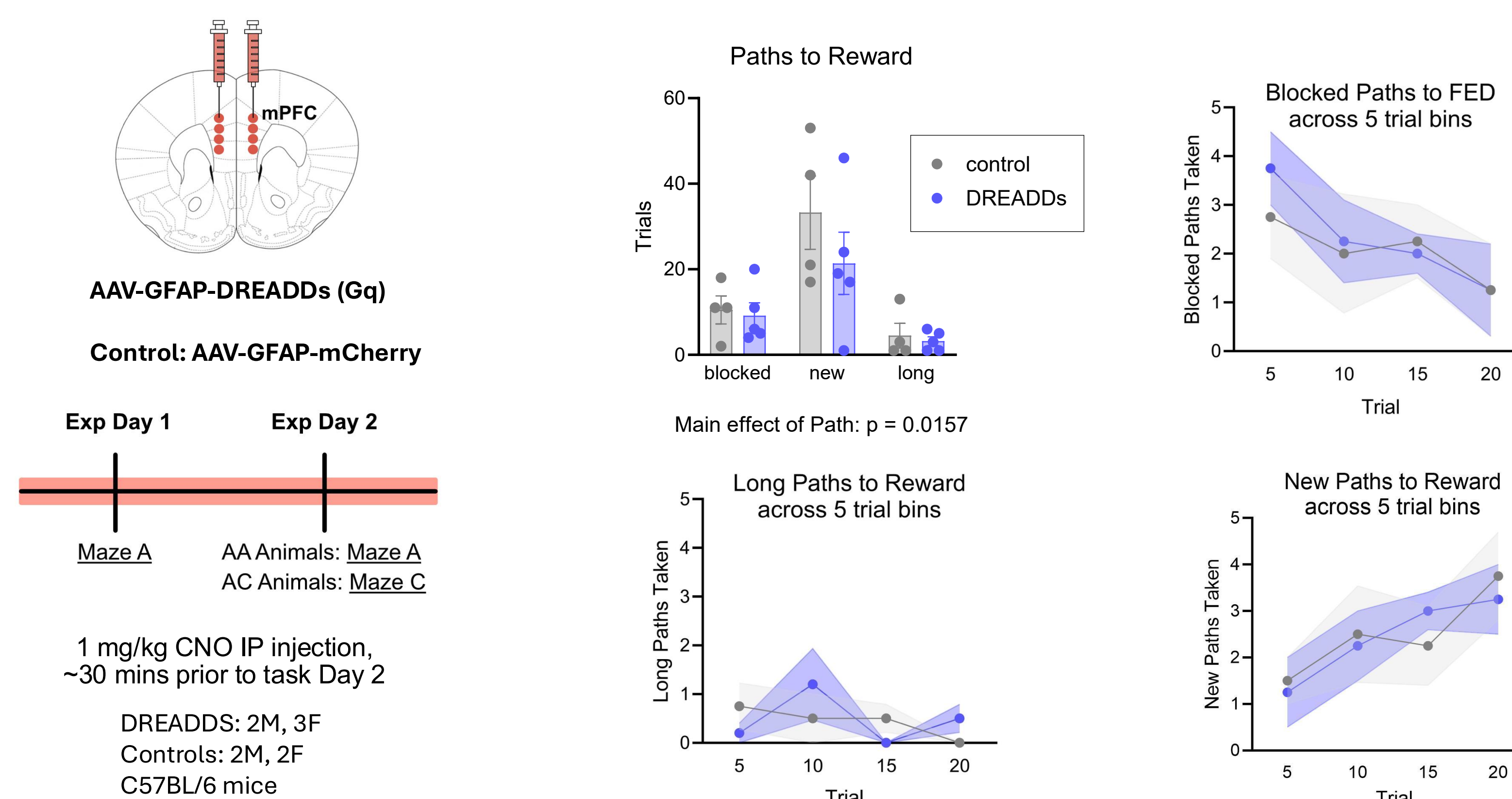
Extradimensional Rule Shift Task

Odor cues
Garlic
Coriander

Texture cues
Sand
Litter

Choice Pair 1: LG SC
Choice Pair 2: SG LC

Rule: Litter → Rule Shifts → Rule: Coriander

Random errors: Incorrect choices that follow neither the old nor new rule.

Perseverative errors: Incorrect choices that follows the old rule.

LEGO Modular Labyrinth

- - - Long Path
——— Optimal Path (o1)
——— New Optimal Path (o2)

Maze A — FED3 Device — Holding area with bedding
Maze B — FED3 Device — Holding area with bedding

Random errors: Visiting new or stable dead ends

Perseverative errors: Visiting dead ends that block previous optimal path

	Rule shifting	Modifiable maze
	Rewards are determined by a sensory cue	Rewards are delivered at a specific location
	The rule that determines the reward is changed	The paths to reward are changed
	One decision per trial	Multiple decisions per trial
	Unknown where/when a decision is made	Location-based decision nodes
	mPFC-dependent	Unknown if mPFC is required

Mice Navigate Less Optimally When the Environment has Changed

AA
AB

Exp Day 1   Exp Day 2
Maze A
AA Animals: Maze A
AB Animals: Maze B

AA: 3F, 1M
AB: 4M, 3F
C57BL/6 mice

Paths taken to Reward

Day 1: Maze A
Day 2: Maze A or B

Trials / Path

* * *

AA   AB

Extracting Neural Dynamics from LFP Recordings

mPFC → BLA → vHPC

Exp Day 1   Exp Day 2
Maze A
AA Animals: Maze A
AB Animals: Maze B

AA: 1F, 2M
AB: 2M, 2F
C57BL/6 mice

mPFC — Maze A — Gamma (30.0–80.0 Hz)
BLA — Maze A — Gamma (30.0–80.0 Hz)
vHPC — Maze A — Gamma (30.0–80.0 Hz)
Maze B — Gamma (30.0–80.0 Hz)
Maze B — Gamma (30.0–80.0 Hz)
Maze B — Gamma (30.0–80.0 Hz)

Exploring Chemogenetic Inhibition During Task Adaptation

AAV-GFAP-DREADDs (Gq)
Control: AAV-GFAP-mCherry
mPFC

Exp Day 1   Exp Day 2
Maze A
AA Animals: Maze A
AC Animals: Maze C

1 mg/kg CNO IP injection, ~30 mins prior to task Day 2

DREADDS: 2M, 3F
Controls: 2M, 2F
C57BL/6 mice

Paths to Reward
control
DREADDs
Trials: blocked, new, long

Main effect of Path: p = 0.0157

Blocked Paths to FED across 5 trial bins
Long Paths to Reward across 5 trial bins
New Paths to Reward across 5 trial bins

Summary

- Established the modular LEGO maze as a potential behavioral assay to assess cognitive flexibility

- Designed the task to capture rule-shifting relevant metrics, including perseverative errors and random (exploratory) errors

- Mice rely on familiar but less efficient routes when the maze configuration is modified and a new optimal path is available

- Integrated DREADDs manipulation, LFP recordings, and optogenetic inhibition

Future Directions

- Examine how choices at decision nodes vary based on recent reward history

- Measure latency and time spent at each decision node to capture hesitation or deliberation

- Head-turning behavior and backtracking events quantified to assess exploratory versus goal-directed strategies and levels of uncertainty

- Sex differences in cognitive flexibility and navigation patterns will be explored to determine differences in distinct behavioral strategies or neural pathways

Acknowledgements