**Introduction**

**State of Cocaine Worldwide + US**
- Consolidation in the manufacturing and shipping of cocaine in South America has led to an increase in cocaine purity and a decrease in price.
- Global cocaine use is at an all-time recorded high.
- The number of active cocaine users in the United States has increased by over one million in the past 20 years.

**What is Cocaine?**
- Cocaine is a central nervous system (CNS) stimulant.
- Cocaine primarily blocks the reuptake of dopamine in the synaptic cleft, leading to a feeling of euphoria.
- Enhances glutamate transmission after intake.

**Animal Models of Addiction**

- In research, Short Access (ShA) and Long Access (LgA) are paradigms for the self-administration of cocaine. Each represents different types of cocaine use:
  - Self-administration is the most common paradigm for addiction work.
  - They normally consist as:
    - ShA (1-2 hrs/day) = meant to represent recreational cocaine use.
    - LgA (6 hrs/day) = meant to represent high intake, chronic cocaine use.

**Role of mGluR1 and mGluR5 in Drug Seeking**

- mGluR1 is functional during all stages of cocaine abstinence (both ShA and LgA).
- mGluR5 is functional during all stages of cocaine abstinence in ShA SA model.
- mGluR5 demonstrates reduced level of functional activity during the early stages of cocaine abstinence in LgA (e.g., d10).
- mGluR5 regains its function after day 60 of abstinence in LgA.

**Research Goals**

- To elucidate the role mGluR5 plays in cocaine addiction.
- To determine how the transient neuroplastic properties of mGluR5 in cocaine addiction effect cognition.
- To determine if mGluR5 positive allosteric modulators can reduce drug seeking and drug intake after prolonged abstinence.

**Methods**

Naive Sprague-Dawley rats weighing between 350-450g were used. Animals are on a 12-hour light/dark cycle, lights come on at 6 A.M. All animals were habituated to housing rooms for 4 hours/4 days before each test.

**Self-Administration**

- Animals first go through food training to teach them how to use the self-administration boxes.
- Duration = until consistent pressures are noticed.
- Criteria: 5%-10% food restricted.
- Animals are trained to obtain food pellets via foodport.
- Animals then are implanted with catheters and go through self-administration of either cocaine or saline at either: ShA Duration 6hrs (or LgA Duration 6hrs).
- After self-administration:
  - Abstinence Phase = Colony Room
  - Experimental Groups Post Abstinence (drug seeking tests).

**Elevated Plus Maze (EPM)**

- The EPM measures an animal anxiety and stress levels.
- All animals were habituated to housing rooms for 4 hours/4 days before each test.
- Animals are on a 12-hour light/dark cycle, lights come on at 6 A.M.

**Locomotor + Novel Object Recognition**

- Tests with the Versamaze Animal Activity Monitor (picture left) measure animal movement over time.
- Novel object test measures affinity towards novel object over a familiar object.
- Habituation: 1 hour in empty cage for 4 days before test.
- Rats are tested for 15 minutes.

**Social Novelty + Sociability**

- Both of these tests are meant to test an animal’s willingness to engage in social activity.
- Social novelty rats are expected to interact with a novel rat over a familiar rat.
- Sociability: rats are expected to interact more with another rat as opposed to an empty chamber.
- Habituation: 15 minutes in arena for 4 days before test.

**Cocaine Self-Administration Data**

- Fig. 1: Cocaine intake in LgA and ShA animals over multiple days. *p<0.05 significant difference compared to day 1 intake.*
- Fig. 2: Active lever presses after systemic injection of mGluR1 blocker. A. Active Lever Presses after 3 days of abstinence. B. Active Lever Presses after 10 Days of abstinence. C. Active Lever Presses after 60 Days of abstinence. *p<0.05 compared to saline.

**Basal Behavioral Performance**

- Fig. 3: A. Activity lever presses in animals in the ShA SA group at abstinence days 3, 10, and 60 when given an injection of either saline, MTEP(5mg/kg) or MTEP(10mg/kg) p<0.01, B. Active lever presses in animals in the LgA SA group at abstinence days 3, 10, and 60 when given an injection of either saline, MTEP(5mg/kg) or MTEP(10mg/kg). *p<0.05 compared to saline. *p<0.05 compared to saline.

**Conclusions**

- In naïve animals, the test animal interacts more with the novel animal compared to the familiar animal.
- Having this data will be helpful in comparing to the animals who have been treated with any modulator used as well as those undergoing cocaine exposure.
- The test animal is more likely to enter and spend more time in a closed arm compared to an open arm.
- Locomotor response to a novel environment showed that the test animal explores a novel environment more when first exposed to an environment and over time interacts less.

**Future Directions**

To correlate mGluR5 malfunction and drug seeking with cognitive and behavioral tasks.

mGluR5 PAM/agonist in 60 day abstinence
- Behavioral changes via EPM, Locomotor, NOR, Social Novelty, Sociability, and Lever Press
- Neurobiological changes via electrophysiology

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**Image Sources**

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- Fig. 4: Social novelty interaction. A. Time spent interacting with novel animal. B. Interaction time across test.
- Fig. 5: Locomotor behavior in a novel environment. A. Total distance (cm). B. Horizontal Activity. C. Stereotypy number over time. D. Vertical activity over time.
- Fig. 6: Anxiety behavior in elevated plus maze. A. Time spent in each arm for duration of test. B. Amount of time spent during arm entry. C. Number of entries in each arm for duration of test. D. Number of entries.
- Fig. 7: Spatial sociality. A. Time spent interacting with novel animal. B. Empty cage. Interaction time across test.
- Fig. 8: Social novelty interaction. A. Time spent interacting with animal for duration of test. B. Interaction time across test.