# Role of mGlu5 Receptor in Cocaine-Mediated Neuroplastic and Behavioral Changes

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## 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 (d3, d10).
- mGluR5 regains its function after day 60 of abstinence in LgA.

### Research Goals

- To illicit 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 350-430g 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 presses are noticed.
  - Criteria: 5%-10% food restricted.
    - Received sugar pellets.
    - Animals then are implanted with catheters and go through self-administration of either cocaine or saline at either: ShA Duration(2hrs)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[5].
- Habituation: 4 hours in testing room for 4 days before test.
- Rats are tested for 15 minutes.

### Locomotor + Novel Object Recognition

- Tests with the Versamax Animal Activity Monitor (pictured 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 1 hour.

| 15 Mins | 10 Mins | 15 Mins | 10 Mins | 15 Mins |
|---|---|---|---|---|
| Empty Box | Rest | Box with Similar Objects | Rest | Box with Novel & Familiar Objects |

### 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.

| 15 Mins | 10 Mins | 15 Mins | 10 Mins | 15 Mins |
|---|---|---|---|---|
| Empty Arena | Rest | Arena with Empty Cages | Rest | Arena with novel/familiar animal |

## Cocaine Self-Administration Data

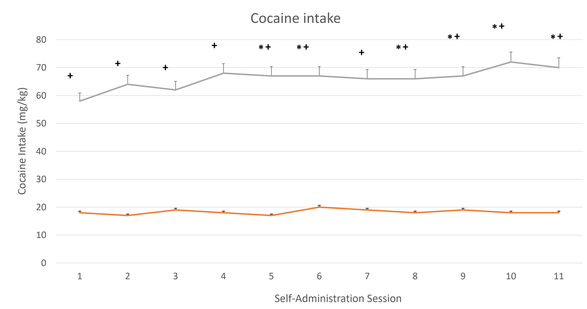


**Fig. 1:** Cocaine intake in LgA and ShA animals over multiple days *p<0.01 significant difference compared to day 1 intake +p<0.05 significant difference of intake between days between groups using Fisher LSD with Bonferroni correction

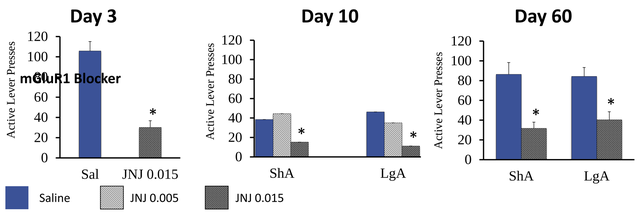


**Fig. 2:** Active lever presses after systemic injection of mGluR1 blocker **A.** Active Lever Presses after 3 Days of abstinence **B.** Active Lever Presses after 10 Days of abstinence **C.** Active Lever Presses after 60 Days of abstinence. *p<0.05 compared to saline.

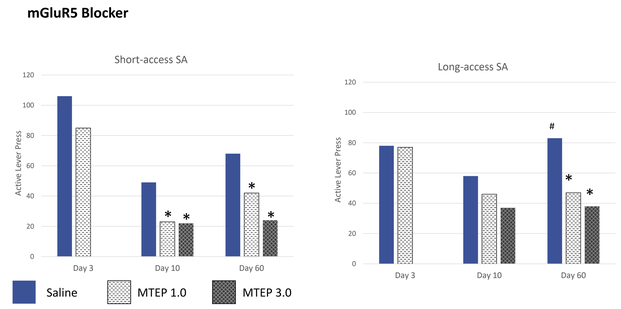


**Fig. 3: A.** Active lever presses in animals in the ShA SA group at abstinence days 3, 10, and 60 when given an injection of either saline, MTEP1.0mg/kg i.p. or MTEP3.0mg/kg i.p. *p<0.05 **B.** Active lever presses in animals in the LgA SA group at abstinence days 3, 10, and 60 when given an injection of either saline, MTEP1.0mg/kg i.p. or MTEP3.0mg/kg i.p *p<0.05 compared to saline #p<0.05 comparing D10 to D60

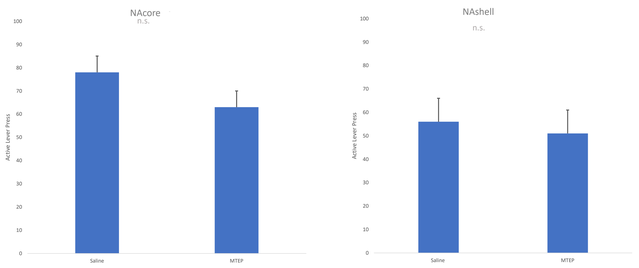


**Fig. 4:** After 10 days of abstinence, direct injections into the NAcore or NAshell of MTEP to block mGluR5, there was no reduction of cocaine seeking. **A.** Active lever presses of cocaine after injections of saline ($n$ = 5) or MTEP ($n$ = 9) into NAcore. **B.** Active lever presses of cocaine after injections of saline ($n$ = 5) or MTEP ($n$ = 8) into NAshell.

## Basal Behavioral Performance

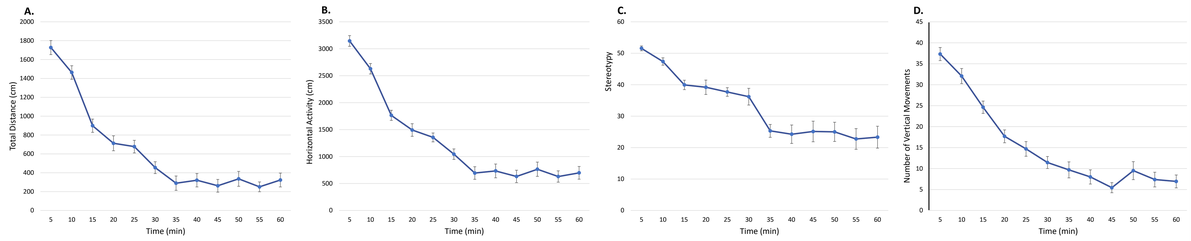


**Fig. 5:** Locomotor behavior in a novel environment **A. T**otal distance (cm) **B.** Horizontal Activity **C.** Stereotypy number over time **D.** Vertical activity over time

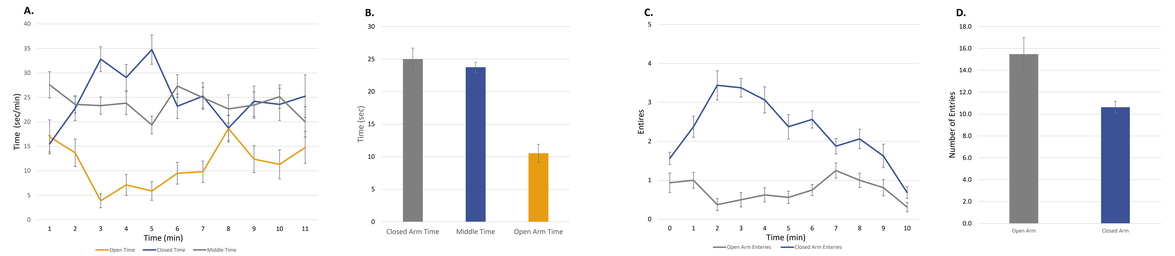


**Fig. 6:** Anxiety behavior in elevated plus maze. **A. T**ime spent in each arm for duration of test **B.** Amount of time spent during arm entry **C.** Number of entries in each arm for duration of test **D.** Number of entries.

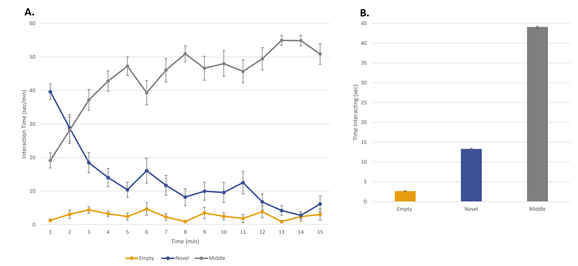


**Fig. 7:** Spatial Sociality. **A.** Time spent interacting with novel animal v.s. empty cage **B.** Interaction time across test.

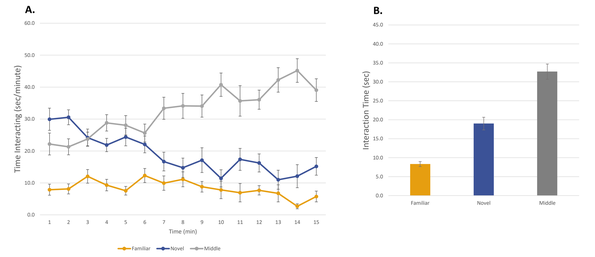


**Fig. 8:** Social Novelty interaction. **A.** Time spent interacting with animal for duration of test **B.** Interaction time across test.

## 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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