# Development of Opioid Withdrawal as a Discriminative Stimulus in Rats

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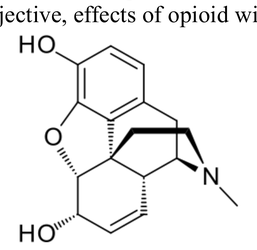
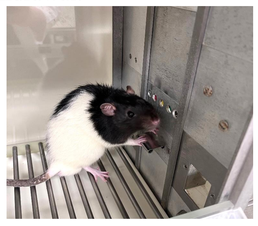
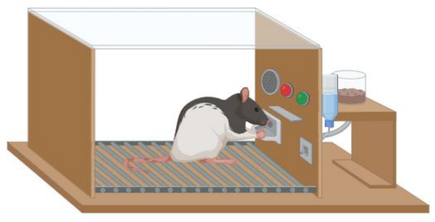
## Introduction

According to NIDA, there were over 105,000 drug-related overdose deaths in the United States during 2023 (2024). These tragic data show the need for reducing opioid abuse and dependence and for understanding the effects of withdrawal from opioids on the body. Whether it is precipitated or spontaneously initiated, withdrawal is accompanied by a range of adverse effects (e.g., diarrhea, gastrointestinal upset, muscle cramping, and chills) produced by a disruption in the body's neurochemical balance (Kosten, 2002). Symptoms of withdrawal are the primary reason opioid-dependent individuals continue administering opioids. Understanding a subject's ability to discriminate between a withdrawal and non-withdrawal state could, therefore, provide new insights into both the overt physical, and covert subjective, effects of opioid withdrawal.



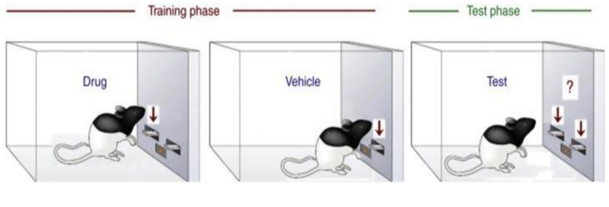
## Methods



A cohort of ten rats (7 male and 3 female) were first trained to lever press under a fixed-ratio 20 (FR 20) schedule for food reinforcers.

Physical dependence on the opioid morphine was then established by administering each rat, 10, 20, 30, and 40 mg/kg twice daily over four days and were then maintained on 40 mg/kg of morphine once daily.

The discrimination of withdrawal was initiated during behavioral sessions in which either saline or 1 mg/kg of naltrexone (NTX) was administered interperitoneally (i.p.).The injection determined which of two levers would provide food reinforcement under the FR-20 schedule (e.g., saline injection was the discriminative stimulus (DS) for responding on the right lever; a NTX injection was the DS for responding on the left lever)




Dependence was maintained between NTX administrations by continuing to re-administer 40 mg/kg of morphine daily.

## Results

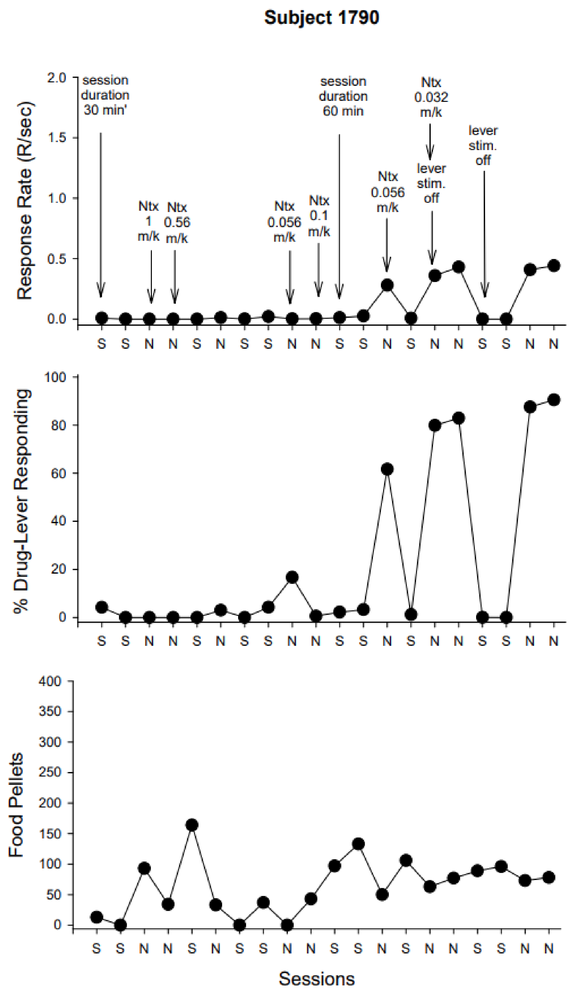



**Figure 1:** Subject 1790 showed some responding when administered 0.056 m/k of NTX, but there was more consistent responding once the dose was changed to 0.032 m/k NTX. There was also a subsequent increase in percentage NTX-lever responding on the days that NTX was administered. This subject has not yet consistently discriminated between the NTX and saline lever on the appropriate days (N= NTX day, S= saline day) as shown by the <95% percent NTX-lever responding following NTX administration.

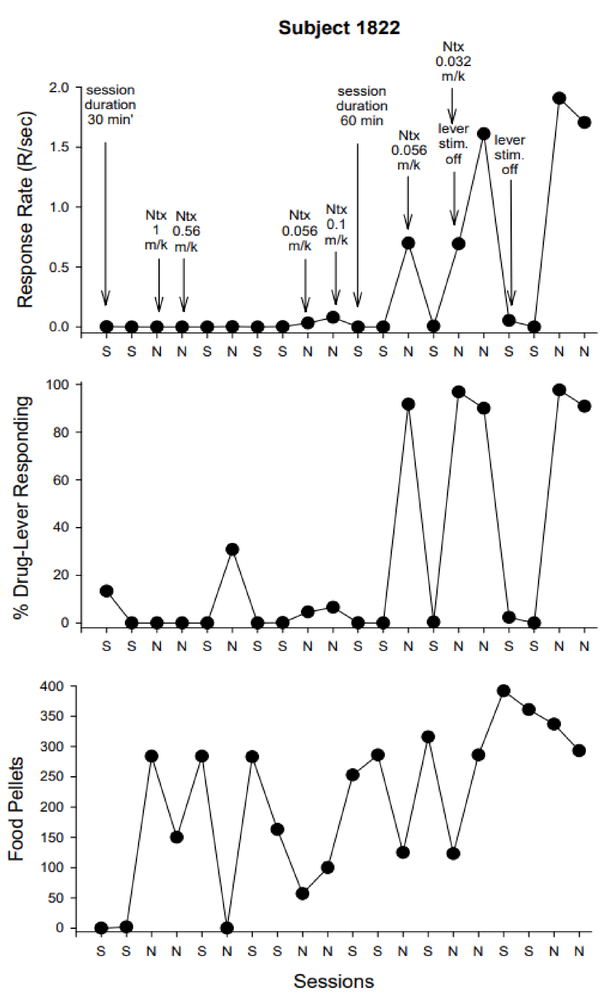



**Figure 2:** The 0.032 m/k dose of NTX has been shown to be effective as subject 1822 showed gradual improvement in responding after the dose was lowered. There was also subsequent increases in the percentage of NTX-lever responding on the days that naltrexone was administered. This subject has not yet consistently discriminated between the NTX and saline lever on the appropriate days (N= NTX day, S= saline day) as shown by the <95% NTX-lever responding following NTX administration.

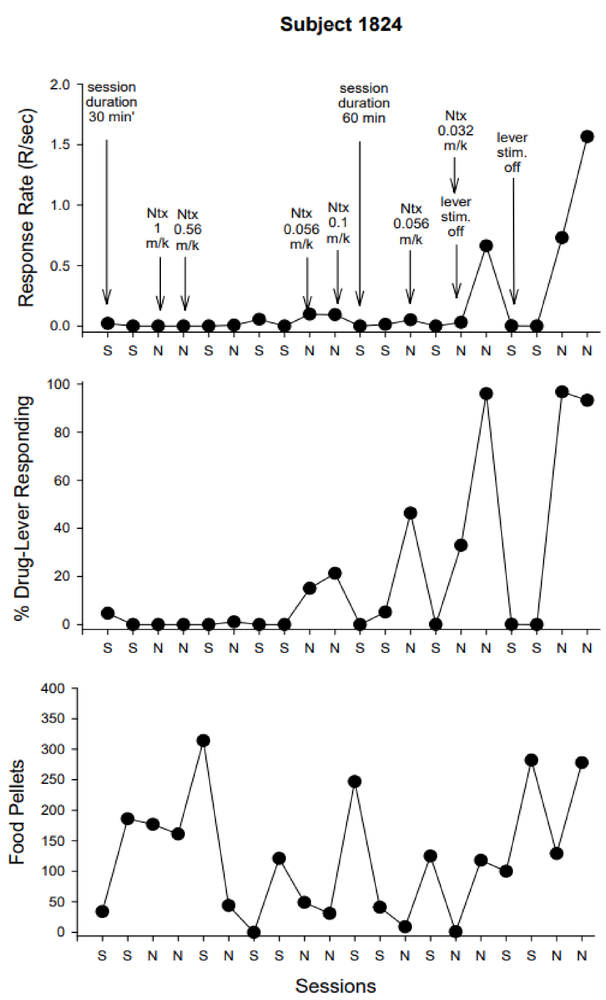



**Figure 3:** The 0.032 m/k dose of NTX has been shown to be effective as subject 1824 showed gradual improvement in their responding after the dose was lowered. There was also a subsequent increase in the percentage of NTX-lever responding on the days that naltrexone was administered. Similar to the other subjects, this subject's discrimination behavior is improving; however, this subject has not met the stability criterion.

## Conclusion and Future Directions

1. We established opioid dependence using chronic injections and confirmed dependence by showing precipitated withdrawal with naltrexone.
2. Training is still in progress; saline and NTX injections will continue until the subjects meet two training criteria for 9 out of 10 consecutive days: (1) less than 20 responses on the incorrect lever prior to the first reinforcement, and (2) at least 95% responding on the correct lever for the entire session.
3. Subjects are reliably responding for food reinforcement during the behavioral sessions irrespective of the injection and subjects are learning to consistently discriminate between a withdrawal state and a non-withdrawal state.
4. The proper dose range to precipitate withdrawal without causing a drastic decrease in response rate has been identified.
5. These findings show that opioid withdrawal produces subjective effects that can serve as discriminative stimuli for behavioral responses. Therefore, this research creates a model for testing new therapies for withdrawal.
6. **Future work will test NAD (nicotinamide adenine dinucleotide) as a treatment for withdrawal. This would ideally lead to better strategies for managing dependence and improving recovery outcomes.**

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## References

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