Effects of NMDA Inhibition on Rodent Decision-Making and Reward-Seeking Behavior

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THE BAKER LAB
Neurocircuitry of Decison-Making

Abstract

- This research aims to examine NMDA receptor agonists and antagonists and how they influence neural processes and pathways involved in memory, time comprehension, and more.
- We attempt to enhance our understanding of the relationship between NMDA receptor antagonists and optimal decision-making through a series of trials with co-housed male and female Sprague Dawley rats.
- This research, inspired by Schuweiler et al. (2021), will be testing reward-seeking behavior and decision-making through the use of operant-conditioning chambers that allow the rats to choose between a Fixed-Delay (FD) lever that dispenses a sugar pellet at a ten-second delay and a Progressive-Delay (PD) lever that dispenses a sugar pellet at progressively increasing time intervals, starting with zero seconds and increasing by one second after each consecutive choice.
- After a week of training on the optimal decision-making task, rats were injected with MK-801 in a randomized sequence of dosage over several days.
- The dosages used were 0.06 ml/kg, 0.1 ml/kg, 0.2ml/kg based upon the rats current weight with saline used for control.
- With the addition of the NMDA receptor-inhibitory drug condition, we are currently working to find significant results that point toward the relationship between these receptors and optimal decision-making, time comprehension, and memory.

Methodology

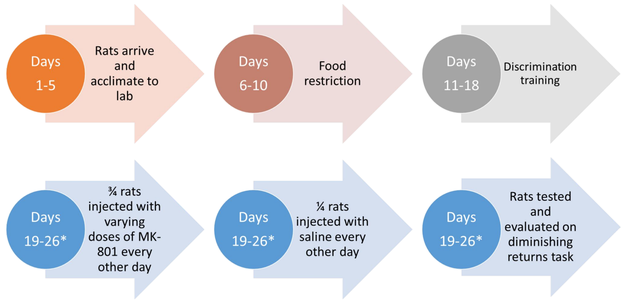
Subjects

- 12 male and 12 female Sprague Dawley rats were co-housed and maintained on a reverse 12-hour light-dark cycle.
- After 5 days of acclimation, they were food restricted to 85% of their free-feeding weight with unrestricted access to water.

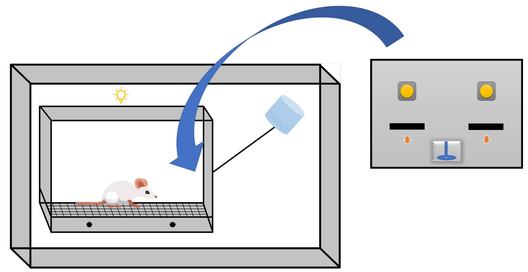
Measures

- 3-5 days of training in 30 minute increments in the operant conditioning chamber until behavior stabilizes.
- Rats went through training 1-2 times a day in operant conditioning boxes.
- After completion of training, rats started discrimination training for either fixed delay or progressive delay task.
- Fixed Delay (FD) lever dispenses a sugar pellet every 10 seconds at a fixed rate.
- Progressive Delay (PD) lever dispenses a sugar pellet starting at 0 seconds and increasing by one second with each lever press.
- Diminishing Returns Task:
  - Reset vs no reset and reverse vs. no reverse.
  - The reset task allows for the time to reset on the increasing PD lever every time the FD lever is pressed.
  - The no-reset task does not reset the progressive delay lever timer.
  - Reverse and no reverse conditions established to eliminate lever biases.
- Treatments of MK-801 included doses of 0.06, 0.1, 0.2 ml/kg based on weight of rat and saline for control.
  - MK-801 is an NMDA receptor antagonist, similar to ketamine and PCP:
    - MK-801 inhibits neural activity but does not change cognitive processing
    - Used because it binds more effectively than ketamine
    - NMDA receptor antagonist are widely used and have mixed reviews
      - Important to understand how these drugs alter neural activity
  - Rats injected every other day to allow for drug clearance.
  - One female and one male rat per dosage for each injection.

Experimental Timeline

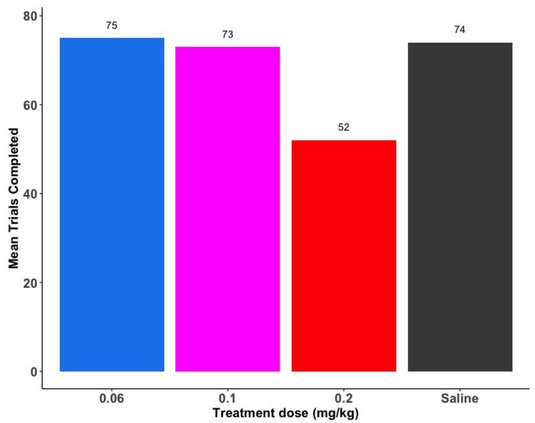


Operant Decision Task



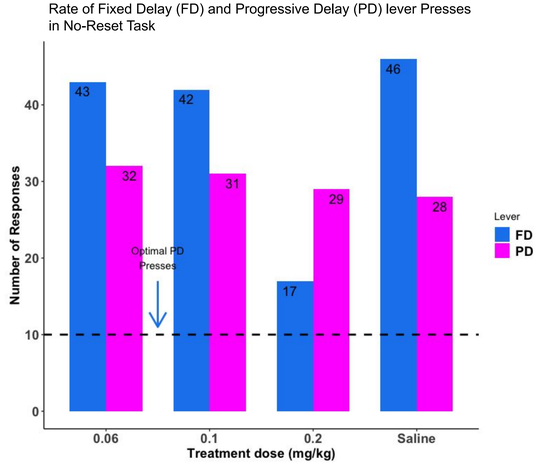
- *Figure 1* shows the operant conditioning chamber that the rats are put in during experimental trials.
- Two levers are placed on opposing sides of the same wall, with a dispenser for the sugar pellet between them.
- The house light at the top of the box indicates when it is appropriate to make a decision on which lever to press.
- Two lights are connected to each lever that signify a lever being pressed.
- Sugar pellets are released at variable time intervals, which are dependent on the individual choices of PD/FD lever.
- Once a choice is made, the levers are inactivated as the sugar pellet is dispensed.
- The levers are reactivated once the appropriate time interval is completed based upon the choice made.

Mean Number of Trails Completed of MK-801 in No-Reset Task



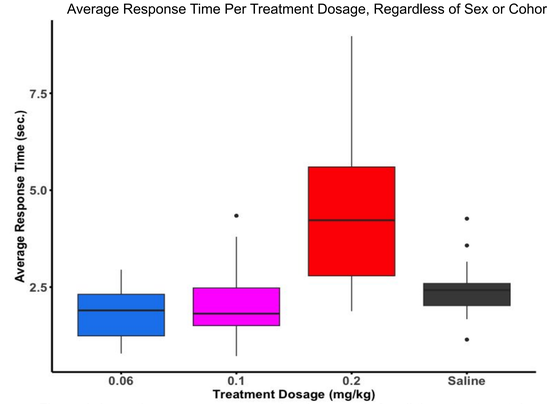
- *Figure 2* shows the mean trials completed per treatment dose (mg/kg).
- Mean trials completed refer to number of sugar pellets received.
- 0.2 mg/kg dosage shows a decreased mean in trials completed.
- 0.06 mg/kg and 0.1 mg/kg mean trials were similar to the control (saline).

Rate of Fixed Delay (FD) and Progressive Delay (PD) lever Presses in No-Reset Task



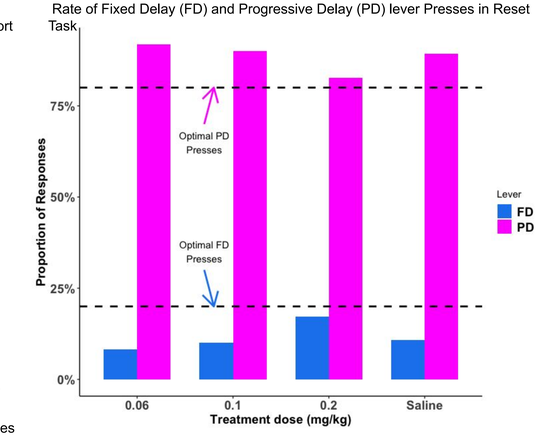
- *Figure 3* shows the average choice of progressive delay (PD) and fixed delay (FD) lever presses for each treatment dosage.
- The dashed line represents optimal lever presses for PD.
- The 0.2 mg/kg dosage was closest to optimal decision making for the FD lever.

Average Response Time Per Treatment Dosage, Regardless of Sex or Cohort



- *Figure 4* shows the average response time in seconds for all three treatment doses in comparison to control. The 0.2 mg/kg dose had the most delayed response compared to all other doses. Saline had an increased delay in response time compared to 0.06 mg/kg and 0.1 mg/kg.
- 0.06 mg/kg and 0.1 mg/kg had close mean response times with 0.1 mg/kg having increased variation.
- Data suggest that the high dose had the most significant effect on response time with 0.06 mg/kg and 0.1 mg/kg having little effect.

Rate of Fixed Delay (FD) and Progressive Delay (PD) lever Presses in Reset Task



- *Figure 5* shows the proportion of responses with each treatment dosage for both fixed delay and progressive delay.
- Data concludes that 0.06 mg/kg and 0.1 mg/kg doses were close to our control.
- Highest dose 0.2 mg/kg was closest to optimal under the two different lever conditions.

Results

- Mean Trials for No-Reset: *Figure 2*
  - MK-801 doses of 0.06 mg/kg and 0.1 mg/kg resulted in very similar outcomes in rodent decision making when compared to each other and the control (saline).
  - 0.06 mg/kg compared to 0.2 mg/kg was statistically significant with 0.2 mg/kg completing 23 less trials on average.
  - Rodents dosed with 0.2 mg/kg completed 21 less trials on average compared to 0.1 mg/kg.
  - 0.2 mg/kg compared to the control (saline) completed 22 less trials on average.
  - Decrease in rodent activity for the 0.2 mg/kg dose.
- Lever presses for both FD and PD in No-Reset: *Figure 3*
  - 0.2 mg/kg was the closest to optimal lever presses for both FD and PD.
  - 0.06 mg/kg and 0.1 mg/kg had similar results which suggests no statistical significant between doses.
- *Average Response Time: Figure 4*
  - This suggests how 0.2 mg/kg dosage was statistically different from saline (p = 0.0006***), 0.06 mg/kg (p = 0.00006***), and 0.1 mg/kg (p = 0.00003***) when comparing time to make a decision.
  - 0.2 mg/kg of MK-801 had a significantly increased delay time when compared to MK-801 doses 0.06 mg/kg and 0.1 mg/kg.
  - Greatest variation within 0.2 for response time.
  - 0.06 mg/kg and 0.1 mg/kg had a similar median response time with slight variation.
  - 0.06 mg/kg and 0.1 mg/kg resulted in a faster response time than expected and when compared to the control.
  - Saline group had an increased response time compared to 0.06 mg/kg and 0.1 mg/kg.
- Fixed and Progressive Delay Ratio: *Figure 5*
  - Shows how 0.02 mg/kg had closest to optimal decision making with PD/FD ratio.

Discussion & Future Research

- When beginning trials, 0.03 mg/kg was used as a treatment dose. This dose did not elicit the desired reaction, so it was replaced with a new high dosage of 0.2 mg/kg.
- In the no-reset task, the 0.2 mg/kg dosage slowed in their decision making (*Figure 2*).
- Different number of observations for each dose:
  - 16 observations for saline
  - 16 observations for 0.06 mg/kg dose
  - 16 observations for 0.1 mg/kg dose
  - 8 observations for 0.2 mg/kg dose
- Data was inconclusive in proving our hypothesis since the 0.2 mg/kg was the closest to optimal in regards to the PD/FD lever-pressing ratio (*Figure 3 and 5*).
- There was a statistically significant change in response time for all three doses when compared to 0.2 (*Figure 4*):
  - Saline to 0.2: 2.07 seconds slower
  - 0.1 to 0.2: 2.48 seconds slower
  - 0.06 and 0.2: 2.68 seconds slower
- Findings suggest that at the 0.2 mg/kg dosage of MK-801, rats were less optimal in decision-making time by a significant margin.
- Although higher doses caused optimal lever presses, time between presses was delayed.
- The 0.2 mg/kg dose was closest to optimal for lever presses, but response time was the most delayed.
  - This suggests that the rats under 0.2 mg/kg doses were not under optimal conditions since an optimal response time would be as small as possible.
  - MK-801 doses 0.06 and 0.1 mg/kg resulted in more optimal decision making than the control in regard to time taken.
- Attempts to investigate optimal decision making and NMDA receptor antagonists were successful in understanding dose response in relation to three different MK-801 dosages.
- Further experiments are currently being conducted as a means of increasing our validity through our sample size.
- Future research should hope to build upon this by exploring dosage at greater intervals and examining the relationship between response time and dosage.

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All authors contributed to this poster equally