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NMDA Receptor Inhibition on Rodent Optimal Decision-Making in the Diminishing Returns Task

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NMDA Receptor Inhibition on Rodent Optimal Decision-Making in the Diminishing Returns Task

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Table of Contents

List of Tables

List of Figures

Abstract

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Words: 350

There has been growing interest in using N-methyl-D-aspartate (NMDA) receptor antagonists as treatments for mood disorders, but there is still much to learn about their cognitive effects. Research shows NMDA receptors can affect decision-making, and the antagonist MK-801 has had varying effects in rodents. Specifically, some have reported impairments in working memory while foraging behaviors remained intact, while others have demonstrated changes in choice behavior related to delay or risk in behavior tasks. We investigated the role of NMDA receptors in the specific paradigm of optimal decision-making to further confirm MK-801's effects and to explore whether inhibiting NMDA receptors alters optimal decision-making processes. To accomplish this, we used the Diminishing Returns task, in which rats were placed in a chamber containing two levers that returned rewards after delays. One lever had a fixed delay (FD) returning a reward after 10 s. The other lever had a progressive delay (PD) that increased by 1 s after each press. The task included two conditions allowing rats to change the delay schedule: no-reset and reset. In both conditions, there was an optimal response rate that returned the most rewards at the least amount of delay. A total of 24 male and female Sprague-Dawley rats were injected with doses of MK-801 (0.06 mg/kg, 0.1 mg/kg, 0.2 mg/kg) and saline as the control before testing in the task. We hypothesized MK-801 would diminish the ability to make optimal decisions. In the no-reset condition, rats on the 0.2 mg/kg dose made significantly more choices for the PD lever compared to the other treatments (56.9% ± 4.8%). In the reset condition, females made significantly more PD lever presses than males after receiving saline (females: 93.8% ± 1.1%, males: 88.7% ± 1.8%). Also, males and females on the 0.2 mg/kg dose made

more optimal sequences of choices (females: 3.38 ± 0.87, males: 6.48 ± 1.67). These results reveal complex effects of sex and NMDA receptors on optimal foraging behaviors and overall task responsiveness. Therefore, the findings suggest inhibiting NMDA receptors may not detrimentally affect the cognitive mechanisms involved in optimal decision-making as it is measured in this task.

Keywords: NMDA receptor, MK-801, diminishing returns, decision-making, foraging, rat

Chapter I: Introduction

In recent years, there has been a substantial increase in research on the clinical and therapeutic uses of N-methyl-D-aspartate (NMDA) receptor antagonists for neurological disorders (Kalia et al., 2008; Moore et al., 2022). These drugs, which include ketamine, memantine, and dextromethorphan, have been researched heavily as potential treatments for psychiatric conditions such as Parkinson's disease, Alzheimer's disease, schizophrenia, and bipolar disorder (Henter et al., 2021; Kalia et al., 2008). Ketamine specifically has become a focus of investigation into the antidepressant capabilities of NMDA receptor antagonists, though several factors like short-term effectiveness and safety concerns have prevented its widespread clinical use (Henter et al., 2021; Moore et al., 2022). Meanwhile, the enantiomer esketamine did receive Food and Drug Administration (FDA) approval in 2019 as an intranasal spray for treatment-resistant depression (Moore et al., 2022).

Having an exhaustive understanding of the physiological and cognitive effects of NMDA receptor antagonists before they become accessible to the public is vitally important to mitigate any potential harm and to prevent misuse or abuse. The NMDA receptor antagonist phencyclidine (PCP), first used as an anesthetic, is now discontinued because of its adverse effects and heavy abuse as a street drug (Moore et al., 2022). Another NMDA receptor antagonist that received FDA approval was felbamate, and it was not until after it was marketed to the public that a black box warning was warranted because of rare complications of aplastic anemia and hepatotoxicity (Kalia et al., 2008). The more research that continues to be done on NMDA receptor antagonists, the more supportive documentation there will be on the full range of effects that NMDA receptor antagonists have on the body and mind, reducing potential risk to the public.

NMDA Receptors and Antagonists

NMDA receptors are ionotropic receptors that bind glutamate and glycine to allow ions like calcium to flow into a neuron for functions related to learning and memory, among others (Réus et al., 2016; Xu et al., 2022). NMDA receptor antagonists can competitively or noncompetitively bind to or block the receptor to inhibit its function (Réus et al., 2016). In humans and animals, this can cause impairments in learning, working memory, psychomotor functioning, decision-making, attention, and impulse control (Newcomer et al., 2000; Floresco et al., 2008).

MK-801

Dizocilpine (MK-801) is a noncompetitive NMDA receptor antagonist that has been found to have protectant effects in cases of stroke, Parkinson's disease, and seizures, as well as a role for modeling schizophrenia-like symptoms (Kovacic & Somanathan, 2010; Xu et al., 2022). There is also evidence that doses greater than 1 mg/kg can result in neuronal necrosis called Olney's lesions, which has prevented its clinical use (Fix et al., 1993; Kovacic & Somanathan, 2010; Olney et al., 1989). However, MK-801 is more potent than both ketamine and PCP, making it a useful model for understanding the effects of inhibiting NMDA receptors (Kovacic & Somanathan, 2010; Lodge & Mercier, 2015).

In general, MK-801 dose-dependently results in hyperlocomotion, ataxia, difficulties in visual-spatial reasoning, and impaired memory (Kovacic & Somanathan, 2010). There have been several inconsistencies around its many effects, and it is evident that more research is warranted to better understand it and the involvement of NMDA receptors in cognitive processes. Specifically, research has shown MK-801 treatment acutely and chronically impaired the working memory of non-human primates through its effects on dopamine transmission in the

prefrontal cortex (Tsukada et al., 2005). Whereas earlier research with rats concluded that MK-801 does not interrupt working memory performance but instead impairs the learning process and the access of recently acquired memories (Shapiro & Caramanos, 1990). Another study found that MK-801 slows temporal processing ability so that rats overestimate time delays, which conflicted with research that stated it sped up temporal processing (Miller et al., 2006).

There are also complex sex-dependent effects of MK-801. In rats, MK-801 has a stronger effect on females than males possibly due to hormonal differences between sexes (Kovacic & Somanathan, 2010). Although, D'Souza et al. (2002) had determined that female rats express a greater behavioral effect after receiving MK-801 as compared to males, independently of the effect of sex hormones. With MK-801 having sex-dependent effects through a mechanism that is still not known, it is important to continue investigating how these effects manifest in cognitive and behavioral tasks.

MK-801 has been shown to also affect decision-making, with rats demonstrating reduced foraging decision-making in the social presence of another rat after receiving 0.1 and 0.2 mg/kg doses, while non-competitive foraging remained unaffected (Li et al., 2016). In the study by Miller et al. (2006), when rats were presented with lever presses that resulted in a reward after a delay had passed, rats that received 0.2 mg/kg doses of MK-801 demonstrated the previously mentioned overestimation of delay while also showing increased response rates and increased variability in responses (Miller et al., 2006). Other studies found that doses of MK-801 resulted in increased response times, impulsive choices, and impulsive actions (Higgins et al., 2003; Higgins et al., 2016; Leite-Almeida et al., 2013).

When measuring impulsive decision-making, research studies using the delay discounting task have produced somewhat conflicting results in terms of the effects of MK-801. In the delay

discounting task, a rat in an operant chamber presses one of two levers to receive a reward during blocks of trials to measure decision-making and impulsivity (Yates et al., 2014). Responses tend to result in one having an immediate small reward and another providing a delayed larger reward (da Matta et al., 2012). The delays can vary or change by increments, and the choices for them can become discounted where the subject does not value the reward as much anymore due to the delay attributed to it, so they make more impulsive decisions (da Matta et al., 2012). Lower delay discounting then implies more self-control and tolerance for delayed larger rewards (da Matta et al., 2012). Floresco et al. (2008) found that ketamine administration increased delay discounting so that rats were more impulsive, having made more choices for immediate small rewards. When rats received MK-801 in the delay discounting task, they actually exhibited lower levels of discounting, indicating less impulsive decision-making (Yates et al., 2014; Yates et al., 2019; Higgins et al., 2016; Higgins et al., 2018). However, rats were more impulsive in their decision-making when the delay intervals were presented in descending order (Higgins et al., 2018).

In summary, previous research using MK-801 has found some contradictory results when it comes to the effects it has on rodent cognition. It is apparent that the mechanisms through which MK-801 functions are complex. There is still more that can and should be learned about MK-801 and its effects on decision-making through the inhibition of NMDA receptors, especially when it comes to new methods of measuring different variations of rodent decision-making, such as using the Diminishing Returns task to evaluate optimal decision-making.

Optimal Decision-Making

One specific paradigm of decision-making is optimal decision-making. While foraging, an animal may make the decision to invest more time into consuming food from a patch of resources before moving to another (Charnov, 1976). In this scenario, invested time is considered

effort, and if the expended effort surpasses an equilibrium point, or a balance between time spent in the patch and the rate of resources harvested, the return of benefits will begin to diminish (Charnov, 1976; Kubanek, 2017).

According to Charnov's Marginal Value Theorem, an optimal decision is made when an animal foraging a patch of resources moves to another without overly depleting the available resources or the animal's energy so that the rate of return is still higher than if they stayed (Charnov, 1976; Kamil & Roitblat, 1985). The choices being made are focused on maximizing return and minimizing cost with the goal being to reap the most return at the most optimal utilization of cost (Kamil & Roitblat, 1985; Kubanek, 2017). Therefore, if a task were to present rats with choices that can result in obtaining the most rewards over the course of a set amount of time, optimal decision-making could be measured. This is exactly what Schuweiler et al. (2021) have successfully made possible using rodent models in the Diminishing Returns task.

The Diminishing Returns Task

The Diminishing Returns task uses an operant chamber with two levers that return sugar pellet rewards after a delay. There are two conditions of the task: no-reset and reset. In the no-reset condition, one lever returns a reward after a fixed delay (FD) of 10 s when it is chosen. The other lever returns a reward after a progressive delay (PD) that begins at a 0 s delay and progressively increases by 1 s each time it is chosen (Schuweiler et al., 2021). The reset condition uses the same principles, but each time the FD lever is chosen, the PD resets to 0 s.

Schuweiler et al. (2021) explain how the Marginal Value Theorem defines optimal decision-making in the Diminishing Returns task relating it to foraging behavior. Rats can make choices to wait through delays that may not be as rewarding as others but can result in obtaining more rewards by the end of each session completed in the task (Schuweiler et al., 2021). The

challenge is to track changing delays associated with lever presses so as to receive the most rewards at the lowest amount of delay. The ratio of lever decisions and the associated delays during the task simulate the time and energy a rat is investing into foraging a patch before moving to another (Schuweiler et al., 2021).

For the no-reset condition, the optimal performance would be to choose the PD lever until the delay is equal to that of the FD lever (10 s or 11 PD lever presses), at which point the rat should choose the FD lever for the rest of the session because more choices on the PD lever will have a longer delay with less return of reward (Schuweiler et al., 2021). In the reset condition, optimal performance is based on the proportion of rewards per seconds of delay accumulated by pressing the PD lever before resetting the delay with the FD lever (Schuweiler et al., 2021). As Schuweiler et al. (2021) described mathematically, the most optimal return of rewards occurs after pressing the PD lever four times (or until a delay of 3 s) and then choosing the FD lever to reset the delay. In this situation, rats are making the choice to wait through a 10 s delay, rather than shorter delays from more PD lever presses, to maintain the equilibrium point that provides more rewards by the end of the session.

Schuweiler et al. (2021) found that rats significantly chose the FD lever over the PD lever in no-reset conditions, the PD lever over the FD lever in reset conditions, and the optimal number of consecutive PD lever presses in the majority of reset sessions. The performance of rats in the no-reset condition was largely suboptimal (Schuweiler et al., 2021). These results come from the schedule of 10 s FD and 1 s PD delays described earlier. The authors also performed two other schedules of different delay amounts per lever that were not replicated in the current study.

The task is similar to delay discounting tasks, but as explained by Schuweiler et al. (2021), the Diminishing Returns task provides a different level of decision-making because of the choices rats can make that are not immediately beneficial but result in higher reward over the entire course of the task. The delays are also dynamic based on the choices rats are making between levers throughout the task to maintain that high rate of reward by the end of a session (Schuweiler et al., 2021).

Present Study

The results from the Schuweiler et al. (2021) study provide a baseline performance of rats in the Diminishing Returns task with specific threshold values attributed to the decisions rats make during the sessions. This allows for an altered experimental design introducing the NMDA receptor antagonist MK-801 as an independent variable to measure its effect on optimal decision-making. To our knowledge, this is a novel research study exploring the effect of MK-801 on this specific decision-making process. Based on the findings of previous literature, we hypothesized that MK-801 would dose-dependently diminish the ability to make optimal decisions, thereby providing insight into the involvement of NMDA receptors in optimal decision-making. We also sought to further confirm other effects of MK-801 such as its sex-dependent effects in a foraging-related task as well as its effects on impulsivity. We hypothesized that we would observe a stronger effect of the drug on female rats and an increase in impulsive behaviors.

Through investigating optimal decision-making, our goal was to build upon existing literature's understanding of NMDA receptor antagonists in light of their developing potential in clinical use. Secondly, it was to learn more about how animals and humans choose to sacrifice effort for rewards or benefits because this is an important decision-making process for humans as well. According to Milkman et al. (2009), making an optimal decision is to make a choice that is

not influenced by bias, not prone to error, more logical, and objectively right, which leads to more benefits in life.

Chapter II: Methods

Subjects

We obtained 24 Sprague-Dawley rats (n = 12 males/females) in three cohorts of eight from Envigo Laboratories (Indianapolis, IN, USA). Rats ranged from two to four months old and weighed from 207-335 g at the time of arrival. The rats were pair-housed in clear polycarbonate 19" x 10.5" x 8" cages with a metal grated top. Each cage contained corncob bedding (7097) from Envigo Laboratories and a Bio-Serv nylon half bone chew toy (K3581). *Ad libitum* access to water and grain rat chow (2018) from Envigo Laboratories was provided for five days as rats acclimated to their environment. They were then food-restricted and maintained at 85% of their free-feeding body weight for the duration of the study. The animal facility was humidity and temperature-controlled on a reverse 12 hr light-dark cycle. Rats were tested during the dark phase and were fed immediately after each day's testing concluded. At the end of the experiment, the rats were sacrificed using an anesthetic overdose of isoflurane. The use of animals in this research study was approved by Seattle Pacific University's Institutional Animal Care and Use Committee (Protocol 2022-23-01-R).

Drug

We obtained (+)-MK-801 maleate (0924) from Tocris Bioscience (Bristol, UK) and aliquots were prepared using pharmaceutical grade isotonic saline (0.9% NaCl) for doses of 0.06 mg/kg, 0.1 mg/kg, and 0.2 mg/kg of MK-801 (Higgins et al., 2018; Li et al., 2016; Miller et al., 2006; Yates et al., 2014; Yates et al., 2019).

Apparatus

Training and testing utilized operant chambers from Lafayette Instruments (Lafayette, IN, USA) consisting of two fixed levers on the right wall, cue lights above each lever, and a trough pellet receptacle equidistant between the levers and 2 cm above the floor of the chamber. The operant chambers were housed within sound-attenuating cubicles (Med Associates ENV-022MD) with a ventilation fan, a house light fixed to the ceiling of the cubicle, and a pellet dispenser containing Bio-Serv 45 mg sucrose pellets (F0023). The operant chambers were connected to a computer using Abet II software (version 22.03.22.0) for programming the boxes and recording data.

Procedure

Lever Training

Upon reaching target weights, rats began discrimination training in the operant chambers to learn to associate lever presses with sugar pellet rewards. This training consisted of the house light illuminating along with one of the two cue lights. The rats had to correctly depress the associated lever within 10 s to receive a sugar pellet reward followed by a 15 s intertrial interval. Each session lasted 30 min with a maximum of 20 trials. We considered rats proficient when they made 20 correct lever presses within 10 min. Training was conducted up to twice per day and tended to take three to nine sessions for rats to move onto training in the Diminishing Returns task.

The Diminishing Returns Task

The procedure for the Diminishing Returns task followed the PD-1/FD-10 schedule described in the article by Schuweiler et al. (2021), with some deviations. The following is how the task was implemented in the present study. The two conditions of the Diminishing Returns

task were presented to the cohorts of rats on a counterbalanced schedule so that they either would start in the no-reset condition or the reset condition. The order of the PD/FD levers were reversed between even and odd-numbered operant chambers.

The rats were placed in the operant chamber and the house light illuminated to indicate the beginning of a trial. Rats had 30 s to make a decision by depressing either the PD or FD lever. If they did not choose a lever in that time, the trial was counted as an omission and the intertrial interval began without any pellet being rewarded. When a lever was selected during the trial, the cue light above it lit up and remained lit until a sugar pellet was dispensed, even if the rat pressed the opposite lever or made repeated presses. This was in lieu of retractable levers so the rats would associate the cue light with their choice and the sugar pellet. When the pellet was dispensed, the cue light and the house light turned off and a 30 s intertrial interval began, during which any lever presses would not result in a cue light turning on but would still count as premature responses. The house light then turned on again to start the next trial. The rats continued to make decisions in each trial until the time limit of 60 min was reached.

During the no-reset condition, the optimal performance is to choose the PD lever until a delay equal to that of the FD lever (11 PD presses or 10 s) is reached, and the rats should choose the FD lever for the rest of the session (Schuweiler et al., 2021). This is because more choices on the PD lever will result in rats waiting longer than necessary to receive a reward than if they chose the FD lever, which is suboptimal behavior.

During the reset condition, rats are tasked with tracking the accumulated delay from PD lever presses and choosing the FD lever at the optimal point to obtain the most rewards, which is mathematically determined as reaching a delay of 3 s or making four consecutive PD lever presses before pressing the FD lever (Schuweiler et al., 2021). Optimal behavior is 80% response

probability on the PD lever. Too few or too many PD lever presses before pressing the FD lever is considered suboptimal. However, the 80% PD value could be obtained by rats making suboptimal sequences of choices that result in an overall 80% PD response probability. The median consecutive PD lever presses were also used to assess the optimal performance of the rats, with four consecutive PD lever presses before pressing the FD lever being optimal in this condition (Schuweiler et al., 2021).

We trained the rats in either of these conditions up to twice per day until their choices were statistically consistent by a repeated-measures ANOVA model evaluating for an effect of the most recent three sessions on the performance of the rats as the percent of PD lever presses. We decided to train rats until their responses were consistent across three sessions, not until they were performing optimally, to prevent overtraining or becoming too familiar with a memorized pattern of responses to receive the most rewards. When there was no significant difference between sessions, the rats had completed the training for that condition. Rats achieved consistent responses after approximately 8-17 sessions. The rats then moved onto the injection phase of the experiment.

Drug Injections

The injections consisted of four treatment levels: three doses of MK-801, which were 0.06 mg/kg, 0.1 mg/kg, and 0.2 mg/kg, and an injection of saline as the control treatment. The injections were administered intraperitoneally on an increasing Latin square counterbalanced schedule with male doses mirroring female. Doses were injected at 1 ml/kg with a pretreatment time of 10 min before beginning the task (Higgins et al., 2018). All rats were scheduled to receive each level of treatment once across four days of injections, which occurred every other

day to prevent carryover effects. Rats still completed a session of the Diminishing Returns task as normal on days between injections.

When rats completed the injection schedule, they moved onto training in the next condition of the Diminishing Returns task. The training in the second condition was repeated as previously described, but the levers between boxes were reversed again to prevent side bias (Schuweiler et al., 2021). Upon reaching consistent behavior in the second condition, the injection phase was repeated with a flipped counterbalanced injection schedule. Once the second phase of injections concluded, the data was collected for analysis.

There are three important caveats we would like to report. First, the pilot cohort of rats did not receive the 0.2 mg/kg dose as it was added to the injection schedule when there was not a strong observable behavioral difference between the 0.06 mg/kg dose and the 0.1 mg/kg dose. There were eight fewer subjects in the reset and no-reset conditions that received it compared to the other doses. Second, one cohort did not receive one treatment level each during the no-reset condition as the wrong condition was mistakenly ran. Our research schedule did not allow for this to be made up, so this data was eliminated for the affected cohort. Third, there was one day where rats were injected on a consecutive day in error, approximately 24 hr after the previous injection. With the half-life of MK-801 in rats being approximately 2 hr for a 2 mg/kg dose, this was unlikely to have an impact on the data collected from that day (Vezzani et al., 1989).

Data Analysis

The Diminishing Returns task allows for the comparison of lever choices made during the task to be compared to optimal values. The decisions rats made during the task were evaluated for whether rats accounted for the delays associated with lever presses to obtain the most rewards by the end of a session. As previously stated, the reset condition defines optimal

performance as making 80% of the choices on the PD lever or by making four consecutive PD lever presses before resetting the delay with an FD lever press (Schuweiler et al., 2021). These were calculated from the data as the percent of PD lever presses out of the total trials completed or as the median consecutive PD lever presses, respectively (Schuweiler et al., 2021).

The no-reset condition defines optimal performance as 11 PD lever presses divided by the total trials each rat completed (Schuweiler et al., 2021). This value was different for each session as rats completed a different number of trials depending on the decisions they made. To determine the optimal value for comparison, 11 was divided by the number of trials completed by each rat, then the median value was found for each treatment level by sex, and those median values were compared to the average performances across treatments and sex.

We used the four treatment levels (saline, 0.06 mg/kg, 0.1 mg/kg, and 0.2 mg/kg of MK-801) and the sex of the rats as the independent variables in our data analyses. The dependent variables included the number of omissions to determine whether a treatment level had a greater sex-dependent effect resulting in rats not making a choice during a trial (Yates et al., 2019). The proportion of PD to FD lever response probability implied overall lever preference and optimal decision-making as a percentage of PD lever presses (Schuweiler et al., 2021). Median consecutive PD lever presses were used to determine optimal sequences of lever responses in the reset condition (Schuweiler et al., 2021). The number of rewards suggested whether differences in lever choices rats made were more successful. We used average response time, or latency to make a lever response, and total lever presses, which included premature responses made during intertrial intervals, to indicate whether rats demonstrated more impulsive behaviors (Higgins et al., 2016; Leite-Almeida et al., 2013; Renda et al., 2018).

Data analyses were conducted using generalized linear mixed models (GLMMs) and Wald tests (Renda et al., 2018; Schuweiler et al., 2021). These statistical methods are useful for modeling non-normally distributed data, random effects, and unbalanced designs (Bolker, 2015). Models were constructed to evaluate the dependent variables as the outcomes with the independent variable predictors being a fixed effect of treatment level, a fixed effect of sex, and an interaction between them, with a random intercept for subject to assess for variance across subjects due to repeated measures. These models used Laplace approximations for parameter estimations. Saline and male rats were used as the reference levels for treatment and sex, respectively. Model comparisons were conducted using the corrected Akaike's Information Criterion (AICc) to account for the small sample size (Bolker et al., 2009).

GLMMs evaluating proportion data between PD and FD lever choices used a binomial distribution family with a logit link function (Bolker et al., 2009). In cases of overdispersion using a binomial distribution, a random observation-level effect was added to the model (Bolker, 2015). The models analyzing for effects of the independent variables on number of omissions, obtained rewards, and lever presses used a Poisson distribution family with a log link function, except in cases of overdispersion when a negative binomial distribution was used (Bolker, 2015).

When evaluating median consecutive PD lever presses and average response time, the data was log-transformed and a linear mixed model was used for analysis. Normal distribution was confirmed with the Shapiro-Wilk's test. These models used restricted maximum likelihood for parameter estimations.

Pairwise comparisons of estimated marginal means from the models were performed with a Bonferroni adjustment to compare the percent PD lever presses and median consecutive PD

lever presses to optimal values (Figner et al., 2020). These were also done to further explore significant results between sexes. A *p*-value of .05 was used to determine significance.

Only data collected on injection days were analyzed in R version 4.3.0 (R Core Team, 2023). The additional R packages used were bbmle (version 1.0.25; Bolker & R Development Core Team, 2022), car (Fox & Weisberg, 2019), DHARMa (version 0.4.6; Hartig, 2022), dplyr (version 1.1.2; Wickham et al., 2023), effects (Fox & Weisberg, 2019), emmeans (version 1.8.5; Lenth, 2023), ggplot2 (Wickham, 2016), ggpubr (version 0.6.0; Kassambara, 2023), glmmTMB (Brooks et al., 2017), jtools (Long, 2022), lme4 (Bates et al., 2015), lmerTest (Kuznetsova et al., 2017), performance (Lüdecke et al., 2021), rstatix (version 0.7.2; Kassambara, 2023), sjPlot (version 2.8.14; Lüdecke, 2023), tfse (version 0.4.1; Kearney, 2018), and tidyverse (Wickham et al., 2019).

Chapter III: Results

Reset

Omissions

First, we investigated whether MK-801 significantly affected males versus females in terms of omissions made during the reset condition. The overall effect of the doses and the effect of sex on omissions were not significant as shown in **Table 1**. It was found that there was a significant interaction of the 0.2 mg/kg dose with females having a significantly higher occurrence of omissions than males ($\beta = 3.55$, $SE = 1.02$, $z = 3.48$, $p < .001$, 95% CI [1.55, 5.55]; $n = 8$).

Table 1

Omissions by Treatment and Sex in Reset

	Omissions				
Random Effects	Variance	*SD*			
Subject	2.88	1.70			
Fixed Effects	β	*SE*	*z*	*p*	95% CI
Intercept	-1.06	0.80	-1.33	> .05	[-2.62, 0.50]
0.06 mg/kg	-0.91	0.74	-1.23	> .05	[-2.36, 0.54]
0.1 mg/kg	-0.84	0.75	-1.11	> .05	[-2.31, 0.63]
0.2 mg/kg	-0.57	0.81	-0.71	> .05	[-2.17, 1.02]
Female	0.40	1.01	0.39	> .05	[-1.58, 2.37]
0.06 mg/kg:Female	-0.60	1.10	-0.54	> .05	[-2.76, 1.57]
0.1 mg/kg:Female	1.08	0.98	1.11	> .05	[-0.83, 2.99]
0.2 mg/kg:Female	3.55	1.02	3.48	< .001	[1.55, 5.55]

Note. The model used a negative binomial distribution and a Laplace approximation. Reference levels were saline for treatment and male rats for sex. *SD* = standard deviation, β = estimated coefficient, *SE* = standard error, CI = confidence interval. The effects written as Dose:Female indicate interactions.

Proportion of PD to FD Responses

Across all treatment levels, rats responded on the PD lever more often with a mean response probability ranging from 82.1% ± 3.6% to 94.5% ± 1.1% (**Figure 1**). Response probability was analyzed for an effect of the doses of MK-801 on this proportion. Compared to saline, the effect of the drug doses on response probability was not significant (**Table 2**). Overall, female rats performed significantly differently than male rats by responding with a higher percent on the PD lever ($\beta = 0.66$, $SE = 0.27$, $z = 2.50$, $p < .05$, 95% CI [0.14, 1.18]; $n = 12$). A pairwise comparison of the estimated marginal means demonstrated a significant difference between males and females after receiving saline with males having a lower average PD response probability of 88.7% ± 1.8%, while for females it was 93.8% ± 1.1% (z-ratio = -2.50, $p < .05$, 95% CI [-1.18, -0.14]; $n = 24$).

There was also a significant interaction effect of the 0.2 mg/kg dose on the female rats, which decreased their probability of choosing PD levers on that dose ($\beta = -1.05$, $SE = 0.40$, $z = -2.60$, $p < .01$, 95% CI [-1.84, -0.26]; $n = 8$).

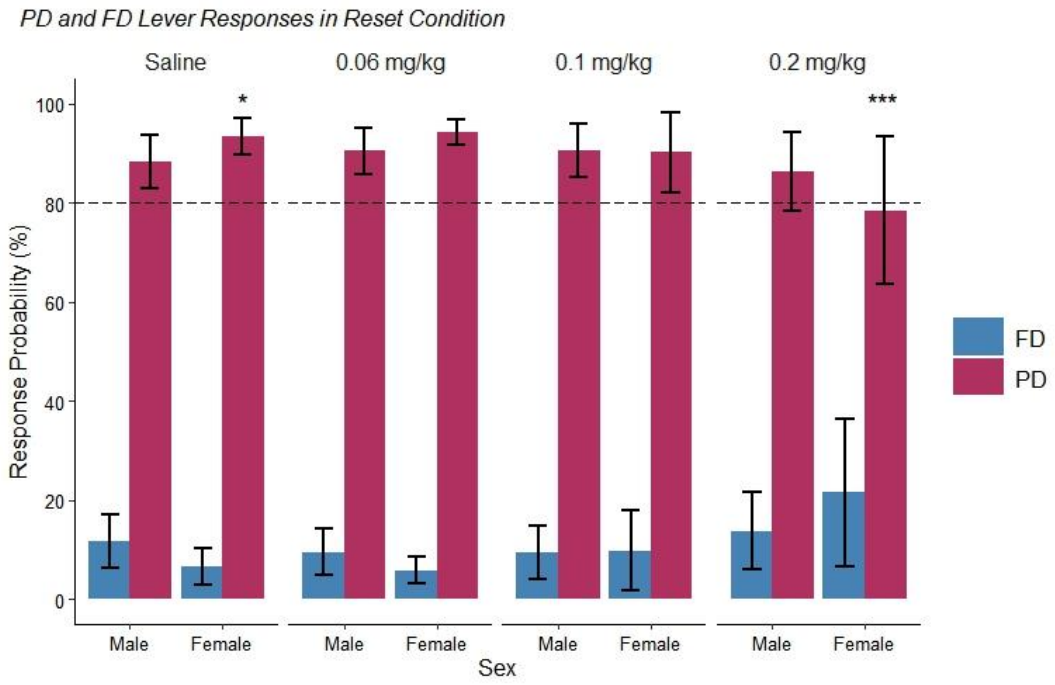
Table 2

Proportion of PD to FD Lever Presses in Reset

	PD to FD Response Probability				
Random Effects	Variance	*SD*			
Subject	0.04	0.19			
Observation-level	0.22	0.47			
Fixed Effects	*β*	*SE*	*z*	*p*	95% CI
Intercept	2.06	0.18	11.58	< . 001	[1.71, 2.41]
0.06 mg/kg	0.25	0.24	1.04	> .05	[-0.22, 0.73]
0.1 mg/kg	0.29	0.24	1.17	> .05	[-0.19, 0.77]
0.2 mg/kg	-0.15	0.27	-0.57	> .05	[-0.68, 0.37]
Female	0.66	0.27	2.50	< .05	[0.14, 1.18]
0.06 mg/kg:Female	-0.13	0.37	-0.35	> .05	[-0.84, 0.59]
0.1 mg/kg:Female	-0.66	0.36	-1.84	> .05	[-1.36, 0.04]
0.2 mg/kg:Female	-1.05	0.40	-2.60	< .01	[-1.84, -0.26]

Note. The model used a binomial distribution with a Laplace approximation and an observation-level random effect to account for overdispersion.

Figure 1



Note. Proportion of PD and FD lever presses in the reset condition across treatment level and sex. Dashed line represents optimal 80% response. *; $p < .05$, female PD lever presses on saline compared to male PD lever presses on saline. ***; $p < .001$, female PD lever presses on 0.2 mg/kg compared to female PD lever presses on saline.

Rewards

These results were further explored by analyzing the number of rewards obtained across sessions to find out if differences in the proportions of PD to FD lever choices led to significantly more or less rewards. Under the effect of the 0.2 mg/kg dose, female rats obtained significantly fewer rewards than male rats (β = -0.48, SE = 0.14, z = -3.55, $p < .001$, 95% CI [-0.75, -0.22]; n = 8). The rewards obtained at the other doses were not significantly different (**Table 3**).

Table 3

Rewards Obtained by Rats in Reset

	Rewards				
Random Effects	Variance	*SD*			
Subject	0.0002	0.02			
Fixed Effects	*β*	*SE*	*z*	*p*	95% CI
Intercept	4.44	0.06	76.80	< . 001	[4.33, 4.55]
0.06 mg/kg	-0.008	0.08	-0.10	> .05	[-0.17, 0.15]
0.1 mg/kg	-0.02	0.08	-0.28	> .05	[-0.18, 0.14]
0.2 mg/kg	-0.01	0.09	-0.15	> .05	[-0.19, 0.17]
Female	-0.05	0.08	-0.66	> .05	[-0.22, 0.11]
0.06 mg/kg:Female	-0.006	0.12	-0.05	> .05	[-0.23, 0.22]
0.1 mg/kg:Female	0.02	0.12	0.19	> .05	[-0.21, 0.25]
0.2 mg/kg:Female	-0.48	0.14	-3.55	< .001	[-0.75, -0.22]

Note. The model used a negative binomial distribution with a Laplace approximation.

Optimal PD Responses

Based on the above lever response probabilities, we evaluated whether rats were performing optimally (**Figure 2**). Males and females on the majority of treatments were significantly different than the optimal value of 80%, including saline (**Table 4**). However, females on the 0.2 mg/kg dose did not perform significantly differently than optimal having responded with a PD probability of 82.1% ± 3.6% (z-ratio = 2.43, $p > .05$; $n = 8$). Males on the 0.2 mg/kg dose also performed optimally with a probability of 87.1% ± 2.4% (z-ratio = 0.56, $p > .05$; $n = 8$).

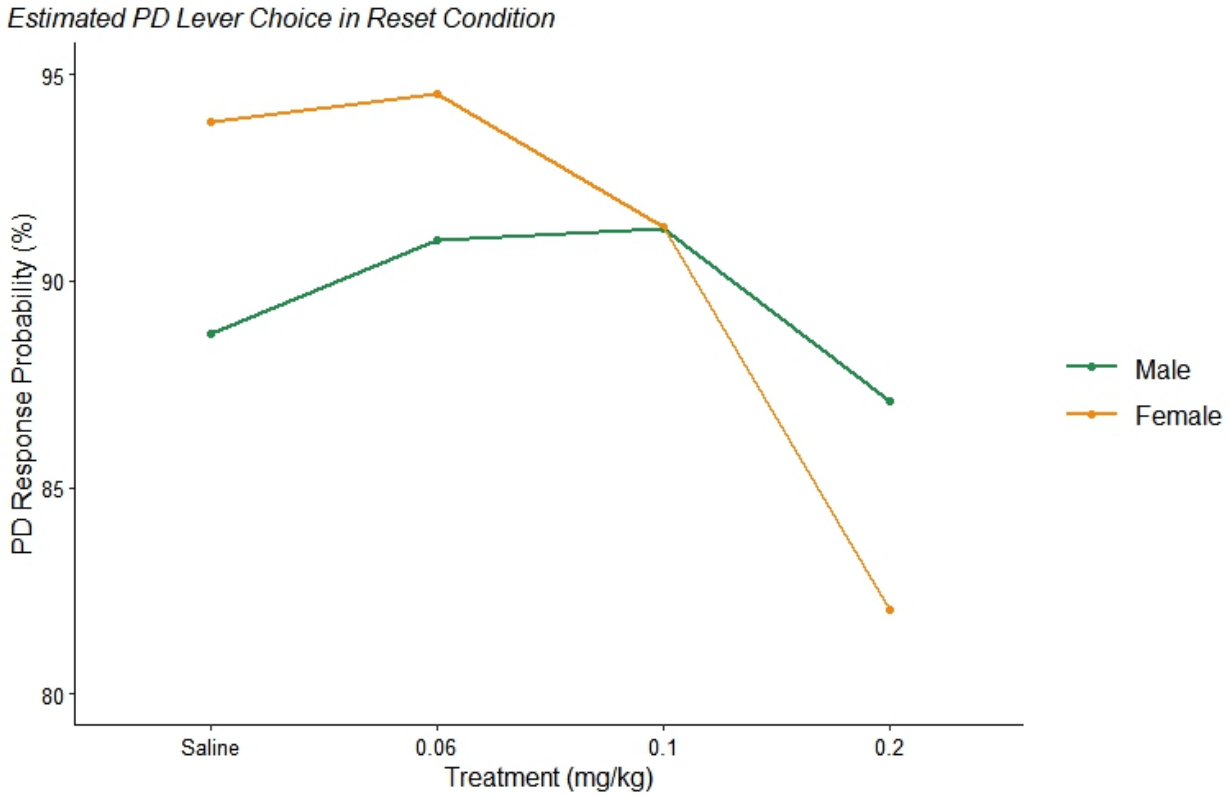
Table 4

Comparisons of Performance to the Optimal Value of 80% PD in Reset

Treatment	Sex	Estimate	*SE*	*z*-ratio	*p*
Saline	Male	0.89	0.02	3.79	< .001
0.06 mg/kg	Male	0.91	0.02	5.04	< .001
0.1 mg/kg	Male	0.91	0.01	5.19	< .001
0.2 mg/kg	Male	0.87	0.02	2.43	> .05
Saline	Female	0.94	0.01	6.77	< .001
0.06 mg/kg	Female	0.95	0.01	7.21	< .001
0.1 mg/kg	Female	0.91	0.01	5.16	< .001
0.2 mg/kg	Female	0.82	0.04	0.56	> .05

Note. Estimated marginal means of PD lever response probability predicted from the GLMM on the logit scale with 0.80 as the comparison value and using a Bonferroni adjustment. The *p*-values less than .05 indicate a significant difference from the optimal value.

Figure 2



Note. Percent PD lever presses made by male and female rats across treatment levels in the reset condition. Optimal responding is 80%.

When using median consecutive PD lever presses to compare to the optimal value, it was found that there was a significant interaction of the 0.2 mg/kg dose with female rats, suggesting a decreased number of consecutive lever presses (β = -1.09, SE = 0.47, t(65.18) = -2.34, $p < .05$; n = 8). There was not a significant effect of sex or of the other treatment levels (**Table 5**).

Table 5

Consecutive Median PD Lever Presses Predicted by Sex and Treatment

	Median Consecutive PD Lever Press					
Random Effects	Variance	*SD*				
Subject	0.003	0.05				
Residual	0.52	0.72				
Fixed Effects	*β*	*SE*	*df*	*t*	p	95% CI
Intercept	2.06	0.21	80.00	9.85	< .001	[1.66, 2.45]
0.06 mg/kg	0.22	0.29	59.12	0.74	> .05	[-0.34, 0.78]
0.1 mg/kg	0.06	0.29	59.12	0.22	> .05	[-0.49, 0.62]
0.2 mg/kg	-0.19	0.33	65.18	-0.57	> .05	[-0.81, 0.44]
Female	0.44	0.30	80.00	1.49	> .05	[-0.12, 1.00]
0.06 mg/kg:Female	-0.15	0.42	59.12	-0.36	> .05	[-0.94, 0.64]
0.1 mg/kg:Female	-0.38	0.42	59.12	-0.90	> .05	[-1.17, 0.41]
0.2 mg/kg:Female	-1.09	0.47	65.18	-2.34	< .05	[-1.98, -0.21]

Note. The median consecutive lever press variable was log-transformed and used as the outcome in a linear mixed model using a restricted maximum likelihood approximation.

Comparing the performance of rats across all treatment levels to the optimal value resulted in finding that the only optimal performances were those of male and female rats that received the 0.2 mg/kg dose (**Figure 3**). Males on this dose responded with 6.48 ± 1.67 median consecutive PD lever presses (t-ratio = 1.87, $p > .05$; $n = 8$), while females had a median consecutive lever press of 3.38 ± 0.87 (t-ratio = -0.66, $p > .05$; $n = 8$). All other performances across treatment levels were suboptimal (**Table 6**).

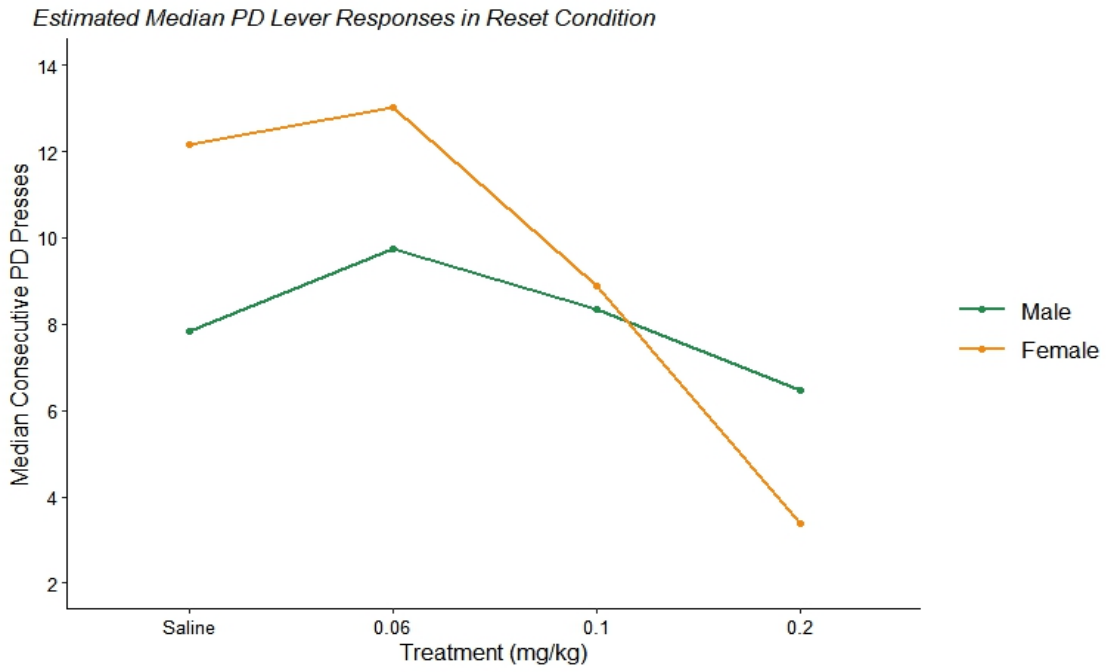
Table 6

Comparison of Median Consecutive PD Lever Presses to Optimal Values

Treatment	Sex	Estimate	*SE*	*z*-ratio	*p*
Saline	Male	7.82	1.63	3.21	< .01
0.06 mg/kg	Male	9.74	2.03	4.26	< .001
0.1 mg/kg	Male	8.34	1.74	3.52	< .001
0.2 mg/kg	Male	6.48	1.67	1.87	> .05
Saline	Female	12.15	2.54	5.32	< .001
0.06 mg/kg	Female	13.01	2.72	5.64	< .001
0.1 mg/kg	Female	8.90	1.86	3.83	< .001
0.2 mg/kg	Female	3.38	0.87	-0.66	> .05

Note. Estimated marginal means of median consecutive PD lever presses predicted from the linear mixed model on the log scale with four as the comparison value and using a Bonferroni adjustment. The *p*-values less than .05 indicate a significant difference from the optimal value.

Figure 3



Note. Median consecutive PD lever responses made by male and female rats across treatment levels in the reset condition. Optimal performance is four consecutive presses.

Measures of Impulsivity

Lastly, the dependent variables used to assess aspects of impulsive behavior were average response time and total lever presses. Female rats that received the 0.2 mg/kg dose took significantly more time to make a lever choice ($\beta = 0.96$, $SE = 0.29$, $t(61.96) = 3.31$, $p < .01$, 95% CI [0.41, 1.51]; $n = 8$). The other treatment levels and sex were not significant for their effect on increasing or decreasing the time in which rats responded on the levers (**Table 7**).

Table 7

Average Response Time for Rats to Choose a Lever in Reset

	Average Response Time					
Random Effects	Variance	*SD*				
Subject	0.08	0.29				
Residual	0.20	0.44				
Fixed Effects	*β*	*SE*	*df*	*t*	*p*	95% CI
Intercept	0.98	0.15	65.65	6.43	< .001	[0.68, 1.29]
0.06 mg/kg	-0.26	0.18	58.97	-1.46	> .05	[-0.58, 0.08]
0.1 mg/kg	-0.35	0.18	58.97	-1.97	> .05	[-0.74, 0.002]
0.2 mg/kg	0.06	0.21	61.96	0.27	> .05	[-0.37, 0.45]
Female	-0.19	0.21	65.65	-0.87	> .05	[-0.64, 0.19]
0.06 mg/kg:Female	-0.13	0.26	58.97	-0.50	> .05	[-0.59, 0.37]
0.1 mg/kg:Female	0.43	0.26	58.97	1.68	> .05	[-0.03, 0.95]
0.2 mg/kg:Female	0.96	0.29	61.96	3.31	< .01	[0.41, 1.50]

Note. The average response time data was log-transformed and used as the outcome in a linear mixed model using a restricted maximum likelihood approximation.

There was a significant effect of the 0.1 mg/kg dose on the total number of lever presses made including during intertrial intervals, suggesting the dose increased the total presses compared to saline ($\beta = 0.34$, $SE = 0.16$, $z = 2.11$, $p < .05$, 95% CI [0.02, 0.66]; $n = 24$). Female

rats on the 0.2 mg/kg dose also made significantly fewer lever presses (β = -1.00, *SE* = 0.27, z = -3.73, $p < .001$, 95% CI [-1.52, -0.47]; n = 8). Total lever presses across the other treatments were not significant (**Table 8**).

Table 8

Total Lever Presses Rats Made During Sessions in Reset

	Total Lever Presses				
Random Effects	Variance	*SD*			
Subject	0.14	0.37			
Fixed Effects	β	*SE*	z	p	95% CI
Intercept	6.77	0.16	42.95	< .001	[6.46, 7.08]
0.06 mg/kg	0.24	0.16	1.45	> .05	[-0.08, 0.55]
0.1 mg/kg	0.34	0.16	2.11	< .05	[0.02, 0.66]
0.2 mg/kg	0.20	0.19	1.05	> .05	[-0.17, 0.56]
Female	0.29	0.22	1.28	> .05	[-0.15, 0.72]
0.06 mg/kg:Female	0.09	0.23	0.39	> .05	[-0.36, 0.54]
0.1 mg/kg:Female	-0.27	0.23	-1.15	> .05	[-0.72, 0.19]
0.2 mg/kg:Female	-1.00	0.27	-3.73	< .001	[-1.52, -0.47]

Note. Results from the total number of lever presses made during a session including intertrial intervals. The model used a negative binomial distribution and a Laplace approximation.

No-Reset

Omissions

For the no-reset condition, female rats that received the 0.2 mg/kg dose had a higher occurrence of omissions during this condition as well (β = 3.36, *SE* = 1.01, z = 3.31, $p < .001$, 95% CI [1.37, 5.34]; n = 7). The other treatment levels did not significantly increase omissions

(**Table 9**), but the 0.06 mg/kg dose significantly decreased the occurrence of omissions compared to saline (β = -1.74, *SE* = 0.74, z = -2.35, $p < .05$, 95% CI [-3.18, -0.29]; n = 22).

Table 9

Omissions by Treatment and Sex in No-Reset

	Omissions				
Random Effects	Variance	*SD*			
Subject	0.30	0.55			
Fixed Effects	β	*SE*	z	p	95% CI
Intercept	0.99	0.65	1.53	> .05	[-0.28, 2.28]
0.06 mg/kg	-1.74	0.74	-2.35	< .05	[-3.18, -0.29]
0.1 mg/kg	-0.78	0.65	-1.2	> .05	[-2.05, 0.50]
0.2 mg/kg	-0.66	0.79	-0.84	> .05	[-2.21, 0.89]
Female	0.01	0.86	0.01	> .05	[-1.68, 1.70]
0.06 mg/kg:Female	1.33	0.98	1.36	> .05	[-0.59, 3.25]
0.1 mg/kg:Female	1.72	1.03	1.67	> .05	[-0.30, 3.74]
0.2 mg/kg:Female	3.36	1.01	3.31	< .001	[1.37, 5.34]

Note. The model used a negative binomial distribution and a Laplace approximation.

Proportion of PD to FD Responses

The average percent PD lever presses for all treatment levels except 0.2 mg/kg ranged from 31.6% ± 4.9% to 48.2% ± 5.6%, while the range of averages for 0.2 mg/kg was 56.5% ± 7.2% for females to 57.3% ± 6.4% for males (**Figure 4**). This demonstrates that rats were making more choices on the FD lever in this condition, except after receiving the 0.2 mg/kg dose which resulted in a higher proportion of PD lever presses. It was found that there was a significant effect of the 0.2 mg/kg dose on the lever response probability in this condition, with rats making more choices on the PD lever than the FD lever compared to saline (β = 1.07, *SE* = 0.26, z = 4.14, $p < .001$, 95% CI [0.55, 1.58]; n = 14). A pairwise comparison of the estimated

marginal means suggested a significant difference between all treatment levels (n = 11) and the 0.2 mg/kg dose (n = 7) for male rats (saline – 0.2 mg/kg: z-ratio = -4.14, $p < .001$; 0.06 mg/kg – 0.2 mg/kg: z-ratio = -3.72, $p < .01$; 0.1 mg/kg – 0.2 mg/kg: z-ratio = -3.39, $p < .05$) as shown in **Figure 5**. The effects of the other treatment levels and the difference between sexes were not significant for their effect on the proportion of lever presses (**Table 10**).

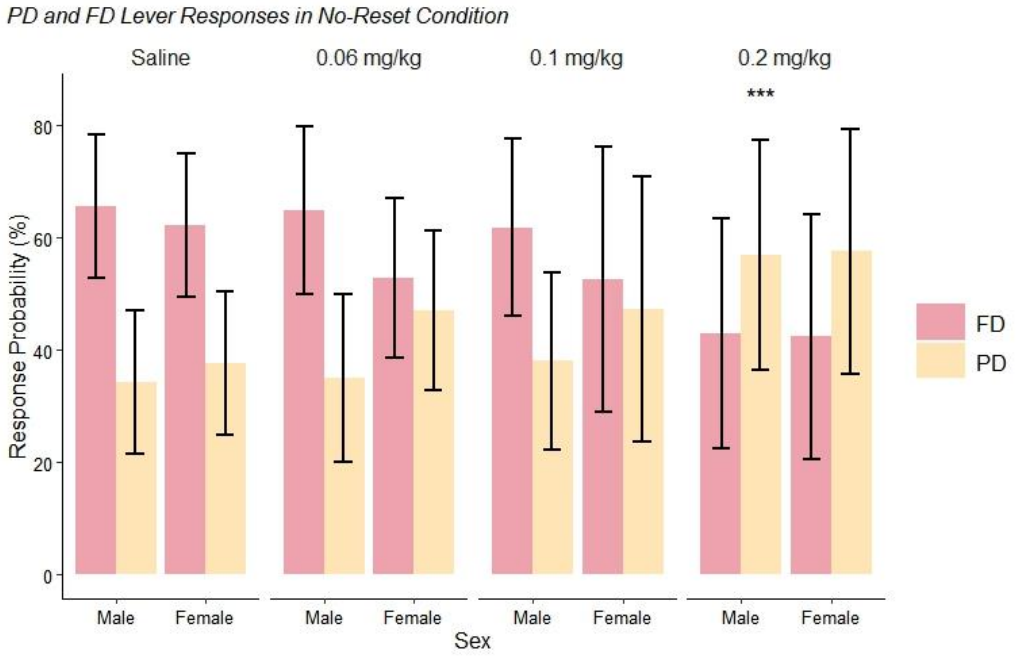
Table 10

Proportion of PD to FD Lever Presses in No-Reset

	PD to FD Response Probability				
Random Effects	Variance	*SD*			
Subject	0.32	0.57			
Observation-level	0.19	0.44			
Fixed Effects	*β*	*SE*	*z*	*p*	95% CI
Intercept	-0.77	0.23	-3.40	< . 001	[-1.23, -0.32]
0.06 mg/kg	0.11	0.22	0.51	> .05	[-0.32, 0.54]
0.1 mg/kg	0.20	0.22	0.89	> .05	[-0.23, 0.62]
0.2 mg/kg	1.07	0.26	4.14	< .001	[0.56, 1.57]
Female	0.17	0.32	0.54	> .05	[-0.46, 0.80]
0.06 mg/kg:Female	0.42	0.31	1.35	> .05	[-0.19, 1.02]
0.1 mg/kg:Female	0.32	0.31	1.03	> .05	[-0.29, 0.93]
0.2 mg/kg:Female	-0.20	0.39	-0.53	> .05	[-0.96, 0.55]

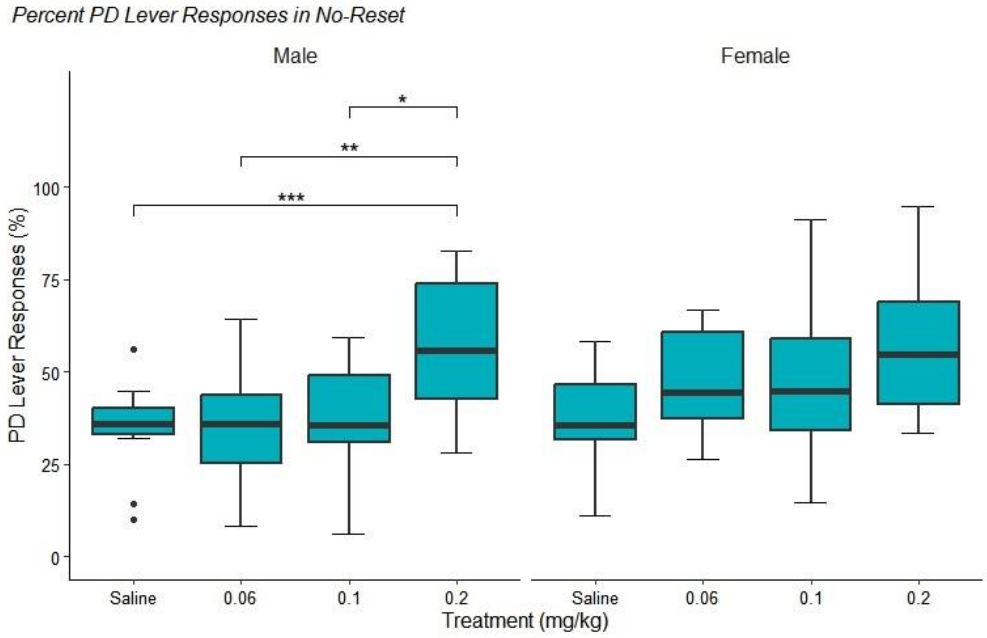
Note. The model used a binomial distribution with a Laplace approximation and an observation-level random effect to account for overdispersion.

Figure 4



Note. Proportion of PD and FD lever responses male and female rats made across treatment levels in the no-reset condition. ***; $p < .001$, male PD presses on 0.2 mg/kg compared to saline.

Figure 5



Note. Proportion of PD lever presses made by males and females across treatment levels in the no-reset condition. ***; $p < .001$, PD lever presses made by males on saline compared to 0.2 mg/kg. **; $p < .01$, PD lever presses made by males on 0.06 mg/kg compared to 0.2 mg/kg. *; $p < .05$, PD lever presses made by males on 0.1 mg/kg compared to 0.2 mg/kg.

Rewards

We found a significant interaction of the 0.2 mg/kg dose with female rats, suggesting they obtained significantly less rewards compared to receiving saline (β = -0.84, SE = 0.10, z = -8.74, $p < .001$, 95% CI [-1.03, -0.65]; n = 7). The other treatment levels were not significant in how their effects resulted in more or less rewards compared to saline (**Table 11**). Though male rats on the 0.2 mg/kg dose responded significantly differently, they still obtained a statistically similar number of rewards on average (70.40 ± 3.35) as when they received saline (74.01 ± 2.67).

Table 11

Rewards Obtained by Rats in No-Reset

	Rewards				
Random Effects	Variance	*SD*			
Subject	0.001	0.04			
Fixed Effects	*β*	*SE*	*z*	*p*	95% CI
Intercept	4.30	0.04	119.13	< . 001	[4.23, 4.38]
0.06 mg/kg	0.06	0.05	1.16	> .05	[-0.04, 0.15]
0.1 mg/kg	0.03	0.05	0.62	> .05	[-0.07, 0.13]
0.2 mg/kg	-0.05	0.06	-0.86	> .05	[-0.16, 0.06]
Female	-0.02	0.05	-0.32	> .05	[-0.12, 0.08]
0.06 mg/kg:Female	-0.04	0.07	-0.59	> .05	[-0.18, 0.09]
0.1 mg/kg:Female	-0.14	0.07	-1.92	> .05	[-0.28, 0.003]
0.2 mg/kg:Female	-0.84	0.10	-8.74	< .001	[-1.03, -0.65]

Note. The model used a negative binomial distribution with a Laplace approximation.

Optimal PD Responses

The optimal values for no-reset were obtained as described earlier. These values were based on trials that each rat from both sexes completed after receiving each treatment. When the optimal values were compared to performance, all rodent decision-making was suboptimal with rats across treatment and sex performing significantly differently than optimal including those that received saline (**Table 12**). Rats that received saline had the lowest average percent PD with males choosing it 31.6% ± 4.9% of the time and females choosing it 35.5% ± 5.2% of the time, while those that received the 0.2 mg/kg dose reversed the ratio of PD to FD lever selection (**Figure 6**). Due to female rats completing less trials after receiving the 0.2 mg/kg dose, the optimal percent PD response was 33.3%.

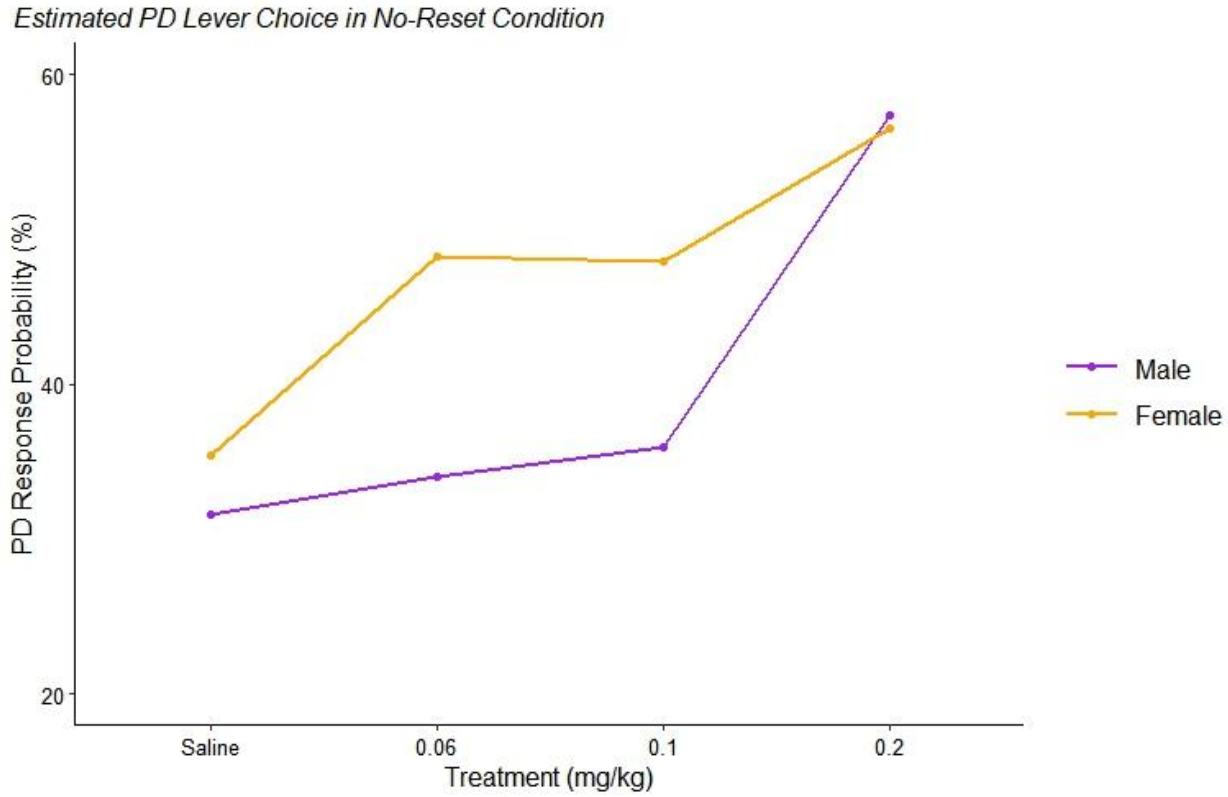
Table 12

Comparisons of Performance to the Optimal Values in No-Reset

Treatment	Sex	Estimate	*SE*	*z*-ratio	*p*
Saline	Male	0.32	0.05	4.58	< .001
0.06 mg/kg	Male	0.34	0.05	5.09	< .001
0.1 mg/kg	Male	0.36	0.05	5.52	< .001
0.2 mg/kg	Male	0.57	0.06	7.55	< .001
Saline	Female	0.36	0.05	5.01	< .001
0.06 mg/kg	Female	0.48	0.06	7.45	< .001
0.1 mg/kg	Female	0.48	0.06	6.98	< .001
0.2 mg/kg	Female	0.57	0.07	3.27	< .01

Note. Estimated marginal means of PD lever response probability predicted from the GLMM on the logit scale and using a Bonferroni adjustment. The optimal values for comparison were 0.141, 0.141, 0.139, 0.157, 0.151, 0.149, 0.157, and 0.333 in that order from top to bottom. The *p*-values less than .05 indicate a significant difference from the optimal value.

Figure 6



Note. Response probabilities of male and female rats across treatment levels in the no-reset condition. Optimal performance is unique to each rat but ranges from 13.9% to 33.3%.

Measures of Impulsivity

As for the other variables for aspects of impulsive behavior, it was found that all drug doses significantly decreased average response times (**Table 13**). However, females that received the 0.2 mg/kg dose were significantly slower compared to when they received saline (β = 1.20, *SE* = 0.32, $t(55.85) = 3.77$, $p < .001$, 95% CI [0.60, 1.80]; $n = 7$). There was not a significant difference between sexes ($p > .05$).

Table 13

Average Response Time for Rats to Choose a Lever in No-Reset

	Average Response Time					
Random Effects	Variance	*SD*				
Subject	0.07	0.26				
Residual	0.20	0.45				
Fixed Effects	*β*	*SE*	*df*	*t*	p	95% CI
Intercept	1.32	0.16	65.16	8.45	< .001	[1.03, 1.62]
0.06 mg/kg	-0.60	0.19	51.72	-3.10	< .01	[-0.97, -0.24]
0.1 mg/kg	-0.46	0.19	51.72	-2.39	< .05	[-0.83, -0.10]
0.2 mg/kg	-0.46	0.22	55.85	-2.07	< .05	[-0.89, -0.04]
Female	-0.13	0.22	65.16	-0.59	> .05	[-0.55, 0.29]
0.06 mg/kg:Female	0.21	0.27	51.72	0.77	> .05	[-0.31, 0.73]
0.1 mg/kg:Female	0.45	0.27	51.72	1.63	> .05	[-0.07, 0.97]
0.2 mg/kg:Female	1.20	0.32	55.85	3.77	< .001	[0.60, 1.80]

Note. The average response time variable was log-transformed and used as the outcome in a linear mixed model using a restricted maximum likelihood approximation.

Similar results were found for the total number of lever presses in this condition where all doses of MK-801 increased lever presses (**Table 14**). The 0.2 mg/kg dose significantly increased total lever presses to the greatest extent ($\beta = 0.65$, $SE = 0.22$, $z = 2.91$, $p < .01$, 95% CI [0.21, 1.09]; $n = 14$), next was the 0.1 mg/kg dose ($\beta = 0.51$, $SE = 0.20$, $z = 2.59$, $p < .01$, 95% CI [0.13, 0.90]; $n = 22$), and third in order of magnitude was the 0.06 mg/kg dose ($\beta = 0.50$, $SE = 0.20$, $z = 2.52$, $p < .05$, 95% CI [0.11, 0.88]; $n = 22$). There was a significant interaction of the 0.2 mg/kg dose with female rats where they made significantly fewer total lever presses ($\beta = -1.48$, $SE = 0.32$, $z = -4.68$, $p < .001$, 95% CI [-2.10, -0.86]; $n = 7$).

Table 14

Total Lever Presses Rats Made During Sessions in No-Reset

	Total Lever Presses				
Random Effects	Variance	*SD*			
Subject	3.46e-9	5.89e-5			
Fixed Effects	*β*	*SE*	*z*	*p*	95% CI
Intercept	6.43	0.14	45.97	< .001	[6.15, 6.70]
0.06 mg/kg	0.50	0.20	2.52	< .05	[0.11, 0.88]
0.1 mg/kg	0.51	0.20	2.59	< .01	[0.13, 0.90]
0.2 mg/kg	0.65	0.22	2.91	< .01	[0.21, 1.09]
Female	0.29	0.20	1.45	> .05	[-0.10, 0.67]
0.06 mg/kg:Female	-0.13	0.28	-0.46	> .05	[-0.68, 0.42]
0.1 mg/kg:Female	-0.24	0.28	-0.85	> .05	[-0.78, 0.31]
0.2 mg/kg:Female	-1.48	0.32	-4.86	< .001	[-2.10, -0.86]

Note. The total number of lever presses made during a session including intertrial intervals.

The model used a negative binomial distribution and a Laplace approximation.

Chapter IV: Discussion

Sex Differences

The article by D'Souza et al. (2002) concluded that there is a sex-dependent effect of MK-801 on rats where females exhibited stronger effects of the drug after receiving a 0.2 mg/kg dose. This was confirmed by our results which found that female rats receiving the high dose of MK-801 (0.2 mg/kg) demonstrated a significantly higher occurrence of omitted trials in both the reset and no-reset conditions. This implied that the drug caused a strong enough effect to result in a higher number of omitted trials, which is an important consideration for the results pertaining to female rats on this dose. Since fewer decisions were made, the rest of the results were consistent in that they obtained significantly fewer rewards, had significantly longer latency periods, and made significantly fewer total lever presses. We also observed more behavioral effects such as head weaving, hyperlocomotion, and ataxia, which have all been well-documented (D'Souza et al., 2002; Kovacic & Somanathan, 2010). The other doses did not produce significantly different results than saline in terms of how they affected female rats, so the effect appeared to be dose-dependent where over 0.1 mg/kg affects females to a greater extent.

Another difference between sexes appeared in the reset condition in rats that were injected with saline. It appeared that in the control condition, females responded at a higher proportion on the PD lever than males. As this task was designed to model decision-making related to foraging behavior, this could represent differences in how males forage versus females. A preprint article by Garcia et al. (2023) found that female rats were more likely to leave a patch of resources before male rats while both sexes overharvested patches in a spatial foraging task.

The Diminishing Returns task uses the ratio of PD to FD lever presses to simulate whether rats choose to switch "patches" when the return of rewards begins to diminish (Schuweiler et al., 2021). Perseverance on either lever past the optimal point would be akin to overharvesting a patch. Therefore, in the current study, it appeared that female rats did not tend to switch patches as readily as male rats after receiving saline during the rest condition. Ultimately, this difference in decision-making was not significantly less rewarding as the female and male rats obtained a statistically similar number of rewards, but it can indicate differences in how rats across sex make foraging-related choices.

Lever Response Probability

It is interesting to observe that the difference in the control treatment occurred during the reset condition but not in the no-reset condition. As the movement from one patch to another is indicated by the ratio of lever presses, the rats should intersperse FD presses to reset the PD at the optimal rate during the reset condition. In the no-reset condition, optimal responding is when rats respond only on one lever and then the other for the duration of the session. The no-reset scenario seems to put the rat in a situation of having to overharvest a patch, but perseverance in the patch is a more optimal decision than switching patches too readily because the PD only becomes longer. It is possible that is why we observed such differences between the two conditions for how they challenge a rat's decision-making and foraging behavior.

In the reset condition, rats should respond more on the PD lever than the FD lever. The results indicated that rats responded appropriately in this condition as the minimum average PD response probability was no less than 78.5%. In the no-reset condition, rats should respond more on the FD lever than the PD lever, especially after the delay associated with the PD lever is equal to that of the FD lever. In general, rats did achieve this, but the range was much larger than that

of the reset condition. Additionally, after receiving the 0.2 mg/kg dose, rats actually exhibited opposite response probabilities, making more selections for the PD lever than the FD lever, which was most significant for male rats (**Figure 5**). This suggests a significant effect of this dose on the decision-making males employed in the no-reset condition, which could possibly be due to the difference in how these conditions require rats to make foraging-related decisions. Male rats did not have a significantly greater occurrence of omissions like females did. By completing more trials, the male rats on the high dose still successfully obtained a substantial number of rewards that did not differ significantly from the other treatment levels. Therefore, the male rats were not making the most optimal decisions after receiving MK-801, but they were still able to achieve as many rewards.

Optimal Performance

Furthermore, the primary goal was to find out whether the rats obtained their rewards by performing optimally under the effects of saline or the doses of MK-801. In the reset condition, the optimal proportion of lever presses to obtain the most rewards by the end of a session was 80% PD to 20% FD (Schuweiler et al., 2021). The results indicated rats receiving all treatment levels, including saline, had suboptimal response probabilities, except for male and female rats that received the 0.2 mg/kg dose. This is especially interesting as female rats had more omissions and fewer completed trials, but of the trials they did complete, their responses were more optimal. It appeared that female rats on this dose started the sessions by making more efficient lever decisions before there was a more global effect of the drug on their faculties. Though for males and females on the high dose, the overall lever proportion was close to optimal.

When the median consecutive PD lever presses were compared to the optimal value of four, the results further confirmed that male and female rats on the 0.2 mg/kg dose made more

optimal sequences of choices of the trials that they completed. In both overall percentage and in the sequences of their choices, female rats were performing optimally despite experiencing a greater effect of the drug. It cannot really be said that female rats on this dose were more successful in the task since they obtained fewer rewards, but with male rats also performing close to optimally, it appears there could be pro-cognitive effects of MK-801 improving optimal decision-making in this condition of the task.

Conversely, no rats on any of the treatments performed optimally during the no-reset condition. This further supports that there are important differences between the two conditions and how they influence the performance of the rats. Due to female rats completing less trials after receiving the 0.2 mg/kg dose, the median optimal percent PD response was 33.3%, and their responses were still significantly higher. As reported by Schuweiler et al. (2021), most of the time, rats did not perform optimally in this condition, as we similarly found here. It is possible the rats did not learn the condition well enough to perform optimally or there were other factors affecting them, but most rats in both conditions had suboptimal performances while rats that received the high dose in the reset condition did not.

Based upon prior research, there are complex mechanisms through which MK-801 affects delay processing. Miller et al. (2006) found that rats on a 0.2 mg/kg dose of MK-801 exhibited impaired temporal processing so that they overestimated time delays, which suggested increased processing speed, as opposed to other results that MK-801 slowed processing. Similarly, Tsukada et al. (2005) concluded that acute MK-801 treatments impair working memory via increased dopamine in the prefrontal cortex. According to Dudchenko (2004), working memory handles temporal information that influences behavior within a session of a task and not between sessions. The results from the current study indicate that female rats on the 0.2 mg/kg dose

demonstrated slower processing speed as they had longer response latency in both conditions. Furthermore, the optimal performances on the high dose in the reset condition do not suggest that working memory was impaired as rats were choosing levers that would result in more rewards when tracking the temporal delays associated with their decisions. Although, in the no-reset condition, the 0.2 mg/kg dose decreased average response time when controlling for sex, suggesting increased processing speed, and the rats did not perform optimally. Thus, the effect of MK-801 in this task may be condition-dependent.

Specifically, rats that received 0.2 mg/kg of MK-801 in the reset condition, performed more optimally, meaning they chose the FD lever more often than on other treatments. This would be more indicative of MK-801 increasing a tolerance for waiting through 10 s delays from FD lever presses to receive more rewards than the accumulating, and at times shorter, delays from repeated PD lever presses. While in the no-reset condition, rats on the 0.2 mg/kg dose responded more on the PD lever than the FD lever compared to the other treatments, a less optimal decision. This suggests that rats were more tolerant of the accumulated delays from PD lever presses. In both conditions, these rats had to tolerate a delay. It is possible there is a mix of effects occurring as a result of the differences between the two conditions, influencing how rats respond while affected by MK-801.

There are also foraging behaviors to consider. Animals should be more motivated to make optimal decisions while foraging to obtain more rewards without using excess effort. Li et al. (2016) explained that MK-801 affected decision-making in a competitive foraging scenario whereas non-competitive foraging was unaffected. Despite whether or not MK-801 impaired memory in this task, foraging, in terms of the number of rewards rats obtained, was largely

unaffected by MK-801. It is even a possibility that it improved foraging decision-making in the reset condition.

Impulsivity

Lastly, we also assessed variables of impulsive behavior as average response time and total lever presses. Previous research has found that MK-801 increased impulsive behavior in the form of decreasing response latency and increasing premature responses (Higgins et al., 2016; Leite-Almeida et al., 2013; Renda et al., 2018). Our results indicated that the doses of MK-801 (besides the effect of 0.2 mg/kg on females) did not affect response time in the reset condition. The 0.1 mg/kg dose did significantly increase the total lever presses in reset. Meanwhile, in the no-reset condition, all doses outside of 0.2 mg/kg with females significantly decreased response times and increased total lever presses. Though the findings were not consistent between the two conditions, the significant measures in the no-reset condition all provide support for MK-801 increasing impulsive behavior, which was further confirmed only for the 0.1 mg/kg dose in the reset condition. Overall, these results suggest a role for MK-801 increasing activity in general, which provides support for prior research finding that MK-801 increases impulsivity in tasks more sensitive to behavioral measures.

Limitations and Future Directions

There was a possible limitation in the training the rats completed before testing in the Diminishing Returns task. It was surprising that rats receiving saline did not perform optimally, and this could be due to how they were trained. In this study, we made the decision to train rats in each task until their responses were statistically consistent. This was because we did not desire for the rats to become too familiar with a memorized pattern of responses to obtain the most rewards. Yet, their performance was generally suboptimal upon analysis. It also could have been

that rats still became well-learned in the task so that they were perseverant in how they responded after training. Despite this possibility, we observed significant differences in lever choices made after drug injections. As more studies utilize the Diminishing Returns task, it would be beneficial to attempt different training schedules to better define the learning and memory that the task exercises.

As for other future research studies, the Diminishing Returns task presents a valuable method for analyzing complex decision-making and lever-choice behavior related to foraging. Future research using it for similar studies with NMDA receptor antagonists could pair them with NMDA receptor agonists to compare how those may affect optimal decision-making. For MK-801 and other models of psychosis, a deeper investigation into the neurological and cognitive components they affect and how they alter foraging decision-making would be valuable for better understanding schizophrenia and other related disorders. Also, modifying the Diminishing Returns task to implement voluntary delay-based drug intake could present a useful model for research using addictive drugs.

Conclusion

As NMDA receptor antagonists are growing to become a more popular treatment method with humans, there are still unknown effects they have on our cognitive processes. Gaining more insight into these effects is beneficial, especially as it relates to how we weigh costs versus rewards. The NMDA receptor antagonist MK-801 and differences between sex in rats present complex effects on cognitive and behavioral functions related to optimal foraging. Our research sought to investigate whether MK-801 would diminish the cognitive processes employed in the Diminishing Returns task, specifically optimal decision-making. This was not ultimately indicated by the results. There is a potential finding that MK-801 improved optimal decision-

making through the 0.2 mg/kg dose while the other doses of 0.06 mg/kg and 0.1 mg/kg largely did not produce effects that differed significantly from saline. As for the role of NMDA receptors, it is likely that they are not as involved in this decision-making process as much as other cognitive mechanisms. Therefore, the findings suggest inhibiting NMDA receptors may not have a detrimental effect on either optimal decision-making or foraging behavior as they are measured in this task.

The goal of this research was also confirmatory. The dose-dependent effects of MK-801 on female rats were confirmed as they expressed a significantly stronger effect of the 0.2 mg/kg dose. We also confirmed that MK-801 generally increases behavioral activity as demonstrated by response time and total lever presses, further supporting findings that MK-801 increases impulsive behaviors.

Lastly, our research has found validity and support for the usefulness of the Diminishing Returns task in measuring critical psychological and biological functions using rodent models. As a result of using it in this research, another step has been taken toward having a more thorough understanding of the effects of the NMDA receptor antagonist MK-801 and how NMDA receptor inhibition in general contributes to several cognitive and behavioral processes.

References

Bates, D., Mächler, M., Bolker, B., & Walker, S. (2015). Fitting linear mixed-effects models using lme4. *Journal of Statistical Software*, *67*, 1–48. https://doi.org/10.18637/jss.v067.i01

Bolker, B. M. (2015). Linear and generalized linear mixed models. In G. A. Fox, S. Negrete-Yankelevich, & V. J. Sosa (Eds.), *Ecological Statistics: Contemporary theory and application* (pp. 309-333). Oxford University Press. https://doi.org/10.1093/acprof:oso/9780199672547.003.0014

Bolker, B. M., Brooks, M. E., Clark, C. J., Geange, S. W., Poulsen, J. R., Stevens, M. H. H., & White, J.-S. S. (2009). Generalized linear mixed models: A practical guide for ecology and evolution. *Trends in Ecology & Evolution*, *24*(3), 127–135. https://doi.org/10.1016/j.tree.2008.10.008

Bolker, B., & R Development Core Team (2022). bbmle: Tools for general maximum likelihood estimation (R package version 1.0.25) [Computer software]. The Comprehensive R Archive Network. Available from https://CRAN.R-project.org/package=bbmle

Brooks, M. E., Kristensen, K., van Benthem, K. J., Magnusson, A., Berg, C. W., Nielsen, A., Skaug, H. J., Maechler, M., & Bolker, B. M. (2017). glmmTMB balances speed and flexibility among packages for zero-inflated generalized linear mixed modeling. *The R Journal*, *9*(2), 378-400. https://doi.org/10.32614/RJ-2017-066

Charnov, E. L. (1976). Optimal foraging, the marginal value theorem. *Theoretical Population Biology, 9*(2), 129–136. https://doi.org/10.1016/0040-5809(76)90040-X

da Matta, A., Gonçalves, F. L., & Bizarro, L. (2012). Delay discounting: Concepts and measures. *Psychology & Neuroscience, 5*(2), 135–146. https://doi.org/10.3922/j.psns.2012.2.03

D'Souza, D. N., Harlan, R. E., & Garcia, M. M. (2002). Sexually dimorphic effects of morphine and MK-801: Sex steroid-dependent and -independent mechanisms. *Journal of Applied Physiology*, *92*(2), 493–503. https://doi.org/10.1152/japplphysiol.00565.2001

Dudchenko, P. A. (2004). An overview of the tasks used to test working memory in rodents. *Neuroscience & Biobehavioral Reviews*, *28*(7), 699–709. https://doi.org/10.1016/j.neubiorev.2004.09.002

Figner, B., Algermissen, J., Burghoorn, F., Held, L., Khalid, A., Klaassen, F., Mosannenzadeh, F., & Quandt, J. (2020). *Standard operating procedures for using mixed-effects models* (version 1.0.0). Decision, Development, and Psychopathology (D2P2) Lab. Retrieved from http://decision-lab.org/resources/

Fix, A. S., Horn, J. W., Wightman, K. A., Johnson, C. A., Long, G. G., Storts, R. W., Farber, N., Wozniak, D. F., & Olney, J. W. (1993). Neuronal vacuolization and necrosis induced by the noncompetitive N-methyl-d-aspartate (NMDA) antagonist MK(+)801 (dizocilpine maleate): A light and electron microscopic evaluation of the rat retrosplenial cortex. *Experimental Neurology*, *123*(2), 204–215. https://doi.org/10.1006/exnr.1993.1153

Floresco, S. B., Tse, M. T. L., & Ghods-Sharifi, S. (2008). Dopaminergic and glutamatergic regulation of effort- and delay-based decision making. *Neuropsychopharmacology, 33*(8), 1966–1979. https://doi.org/10.1038/sj.npp.1301565

Fox, J., & Weisberg, S. (2019). *An R companion to applied regression* (3rd ed.). Sage. https://socialsciences.mcmaster.ca/jfox/Books/Companion/

Garcia, M., Gupta, S., & Wikenheiser, A. M. (2023). *Sex differences in patch-leaving foraging decisions in rats*. BioRxiv. https://doi.org/10.1101/2023.02.19.529135

Hartig, F. (2022). DHARMa: Residual diagnostics for hierarchical (multi-level/mixed) regression models (R package version 0.4.6) [Computer software]. The Comprehensive R Archive Network. Available from https://CRAN.R-project.org/package=DHARMa

Henter, I. D., Park, L. T., & Zarate, C. A. (2021). Novel glutamatergic modulators for the treatment of mood disorders: Current status. *CNS Drugs, 35*(5), 527–543. https://doi.org/10.1007/s40263-021-00816-x

Higgins, G. A., Ballard, T. M., Huwyler, J., Kemp, J. A., & Gill, R. (2003). Evaluation of the NR2B-selective NMDA receptor antagonist Ro 63-1908 on rodent behaviour: Evidence for an involvement of NR2B NMDA receptors in response inhibition. *Neuropharmacology*, *44*(3), 324–341. https://doi.org/10.1016/S0028-3908(02)00402-1

Higgins, G. A., Silenieks, L. B., MacMillan, C., Sevo, J., Zeeb, F. D., & Thevarkunnel, S. (2016). Enhanced attention and impulsive action following NMDA receptor GluN2B-selective antagonist pretreatment. *Behavioural Brain Research*, *311*, 1–14. https://doi.org/10.1016/j.bbr.2016.05.025

Higgins, G. A., Silenieks, L. B., MacMillan, C., Zeeb, F. D., & Thevarkunnel, S. (2018). Effects of the NMDA receptor antagonists dizocilpine and Ro 63-1908 on delay-discounting and risky decision-making in a gambling task. *Behavioural Brain Research*, *348*, 201–210. https://doi.org/10.1016/j.bbr.2018.04.028

Kalia, L. V., Kalia, S. K., & Salter, M. W. (2008). NMDA receptors in clinical neurology: Excitatory times ahead. *The Lancet Neurology, 7*(8), 742–755. https://doi.org/10.1016/S1474-4422(08)70165-0

Kamil, A. C., & Roitblat, H. L. (1985). The ecology of foraging behavior: Implications for animal learning and memory. *Annual Review of Psychology, 36*(1), 141–169. https://doi.org/10.1146/annurev.ps.36.020185.001041

Kassambara, A. (2023). ggpubr: 'ggplot2' based publication ready plots (R package version 0.6.0) [Computer software]. The Comprehensive R Archive Network. Available from https://CRAN.R-project.org/package=ggpubr

Kassambara, A. (2023). rstatix: Pipe-friendly framework for basic statistical tests (R package version 0.7.2) [Computer software]. The Comprehensive R Archive Network. Available from https://CRAN.R-project.org/package=rstatix

Kearney, M. W. (2018). tfse: Various useful functions (R package version 0.4.1) [Computer software]. The Comprehensive R Archive Network. Available from https://tfse.mikewk.com

Kovacic, P., & Somanathan, R. (2010). Clinical physiology and mechanism of dizocilpine (MK-801). *Oxidative Medicine and Cellular Longevity*, *3*(1), 13–22. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2835885/

Kubanek, J. (2017). Optimal decision making and matching are tied through diminishing returns. *Proceedings of the National Academy of Sciences of the United States of America*, *114*(32), 8499–8504. https://doi.org/10.1073/pnas.1703440114

Kuznetsova, A., Brockhoff, P. B., & Christensen, R. H. B. (2017). lmerTest package: Tests in linear mixed effects models. *Journal of Statistical Software*, *82*, 1–26. https://doi.org/10.18637/jss.v082.i13

Leite-Almeida, H., Melo, A., Pêgo, J. M., Bernardo, S., Milhazes, N., Borges, F., Sousa, N., Almeida, A., & Cerqueira, J. J. (2013). Variable delay-to-signal: A fast paradigm for

assessment of aspects of impulsivity in rats. *Frontiers in Behavioral Neuroscience*, *7*, Article 154. https://doi.org/10.3389/fnbeh.2013.00154

Lenth, R. V. (2023). emmeans: Estimated marginal means, aka least-squares means (R package version 1.8.5) [Computer software]. The Comprehensive R Archive Network. Available from https://CRAN.R-project.org/package=emmeans

Li, F., Cao, W.-Y., Huang, F.-L., Kang, W.-J., Zhong, X.-L., Hu, Z.-L., Wang, H.-T., Zhang, J., Zhang, J.-Y., Dai, R.-P., Zhou, X.-F., & Li, C.-Q. (2016). Roles of NMDA and dopamine in food-foraging decision-making strategies of rats in the social setting. *BMC Neuroscience*, *17*(1), 3. https://doi.org/10.1186/s12868-015-0233-8

Lodge, D., & Mercier, M. S. (2015). Ketamine and phencyclidine: The good, the bad and the unexpected. *British Journal of Pharmacology*, *172*(17), 4254–4276. https://doi.org/10.1111/bph.13222

Long, J. A. (2022). jtools: Analysis and presentation of social scientific data (R package version 2.2.0) [Computer software]. The Comprehensive R Archive Network. Available from https://cran.r-project.org/package=jtools

Lüdecke, D. (2023). sjPlot: Data visualization for statistics in social science (R package version 2.8.14) [Computer software]. The Comprehensive R Archive Network. Available from https://CRAN.R-project.org/package=sjPlot

Lüdecke, D., Ben-Shachar, M. S., Patil, I., Waggoner, P., & Makowski, D. (2021). performance: An R package for assessment, comparison and testing of statistical models. *Journal of Open Source Software*, *6*(60), Article 3139. https://doi.org/10.21105/joss.03139

Milkman, K. L., Chugh, D., & Bazerman, M. H. (2009). How can decision making be improved? *Perspectives on Psychological Science*, *4*(4), 379–383. https://doi.org/10.1111/j.1745-6924.2009.01142.x

Miller, J. P., McAuley, J. D., & Pang, K. C. H. (2006). Effects of the NMDA receptor antagonist MK-801 on short-interval timing in rats. *Behavioral Neuroscience*, *120*, 162–172. https://doi.org/10.1037/0735-7044.120.1.162

Moore, T. J., Alami, A., Alexander, G. C., & Mattison, D. R. (2022). Safety and effectiveness of NMDA receptor antagonists for depression: A multidisciplinary review. *Pharmacotherapy*, *42*(7), 567–579. https://doi.org/10.1002/phar.2707

Newcomer, J. W., Farber, N. B., & Olney, J. W. (2000). NMDA receptor function, memory, and brain aging. *Dialogues in Clinical Neuroscience*, *2*(3), 219–232. https://doi.org/10.31887/DCNS.2000.2.3/jnewcomer

Olney, J. W., Labruyere, J., & Price, M. T. (1989). Pathological changes induced in cerebrocortical neurons by phencyclidine and related drugs. *Science*, *244*(4910), 1360–1362. https://www.jstor.org/stable/1704400

R Core Team (2023). R: A language and environment for statistical computing (version 4.3.0) [Computer software]. The Comprehensive R Archive Network. Available from https://www.R-project.org/

Renda, C. R., Rung, J. M., Hinnenkamp, J. E., Lenzini, S. N., & Madden, G. J. (2018). Impulsive choice and pre-exposure to delays: IV. Effects of delay- and immediacy-exposure training relative to maturational changes in impulsivity. *Journal of the Experimental Analysis of Behavior*, *109*(3), 587–599. https://doi.org/10.1002/jeab.432

Réus, G. Z., Abelaira, H. M., Tuon, T., Titus, S. E., Ignácio, Z. M., Rodrigues, A. L. S., & Quevedo, J. (2016). Glutamatergic NMDA receptor as therapeutic target for depression. In R. Donev (Ed.), *Advances in protein chemistry and structural biology* (Vol. 103, pp. 169–202). Academic Press. https://doi.org/10.1016/bs.apcsb.2015.10.003

Schuweiler, D. R., Rao, M., Pribut, H. J., & Roesch, M. R. (2021). Rats delay gratification during a time-based diminishing returns task. *Journal of Experimental Psychology: Animal Learning and Cognition*, *47*, 420–428. https://doi.org/10.1037/xan0000305

Shapiro, M. L., & Caramanos, Z. (1990). NMDA antagonist MK-801 impairs acquisition but not performance of spatial working and reference memory. *Psychobiology*, *18*(2), 231–243.

Tsukada, H., Nishiyama, S., Fukumoto, D., Sato, K., Kakiuchi, T., & Domino, E. F. (2005). Chronic NMDA antagonism impairs working memory, decreases extracellular dopamine, and increases D1 receptor binding in prefrontal cortex of conscious monkeys. *Neuropsychopharmacology*, *30*(10), 1861–1869. https://doi.org/10.1038/sj.npp.1300732

Vezzani, A., Serafini, R., Stasi, M. A., Caccia, S., Conti, I., Tridico, R. V., & Samanin, R. (1989). Kinetics of MK-801 and its effect on quinolinic acid-induced seizures and neurotoxicity in rats. *The Journal of Pharmacology and Experimental Therapeutics*, *249*(1), 278–283.

Wickham, H. (2016). *ggplot2: Elegant Graphics for Data Analysis* (2nd ed.). Springer-Verlag. https://doi.org/10.1007/978-0-387-98141-3

Wickham, H., Averick, M., Bryan, J., Chang, W., McGowan, L. D., François, R., Grolemund, G., Hayes, A., Henry, L., Hester, J., Kuhn, M., Pedersen, T. L., Miller, E., Bache, S. M., Müller, K., Ooms, J., Robinson, D., Seidel, D. P., Spinu, V., … Yutani, H. (2019). Welcome to the tidyverse. *Journal of Open Source Software*, *4*(43), Article 1686. https://doi.org/10.21105/joss.01686

Wickham, H., François, R., Henry, L., Müller, K., & Vaughan, D. (2023). dplyr: A grammar of data manipulation (R package version 1.1.2) [Computer software]. The Comprehensive R Archive Network. Available from https://CRAN.R-project.org/package=dplyr

Xu, J., Li, Y., Tian, B., Liu, H., Wu, S., & Wang, W. (2022). The effects and mechanism of environmental enrichment on MK-801 induced cognitive impairment in rodents with schizophrenia. *Frontiers in Cellular Neuroscience*, *16*, Article 1024649. https://doi.org/10.3389/fncel.2022.1024649

Yates, J. R., Batten, S. R., Bardo, M. T., & Beckmann, J. S. (2014). Role of ionotropic glutamate receptors in delay and probability discounting in the rat. *Psychopharmacology*, *232*(7), 1187–1196. https://doi.org/10.1007/s00213-014-3747-3

Yates, J. R., Day, H. A., Evans, K. E., Igwe, H. O., Kappesser, J. L., Miller, A. L., Murray, C. P., Torline, B. T., Ellis, A. L., & Stacy, W. L. (2019). Effects of d-amphetamine and MK-801 on impulsive choice: Modulation by schedule of reinforcement and delay length. *Behavioural Brain Research*, *376*, Article 112228. https://doi.org/10.1016/j.bbr.2019.112228