±DOI Attenuates Spontaneous Recovery in a SEFL Extinction Paradigm

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Table of Contents

Abstract 2
Introduction 2
Post Traumatic Stress Disorder, Major Depressive Disorder, and Exposure Therapy 2
Pharmacological Treatment 5
Methods 7
Subjects 7
Apparatus 7
Pre-SPT 8
SEFL Protocol 8
Post-SPT 8
Statistical Analysis 9
Results 9
SEFL Training 10
Sucrose Preference Test 15
Discussion 16
SEFL Training 17
Sucrose Preference Test 19
References 21

Abstract

This study investigates how the psychedelic drug DOI with fear extinction affected rats' generalization and potentiation in a novel context as well as spontaneous recovery. 66 Long-Evans rats underwent Stress Enhanced Fear Learning (SEFL) to condition aversive memory. DOI was injected prior to undergoing fear extinction. Anhedonia was assessed with the Sucrose Preference Test (SPT). We saw that rats that went through extinction following shock froze

significantly less when exposed to a mild stressor in a novel context. However, when placed back into that context the next day, shock/extinction and shock/no extinction rats froze similarly. Results from spontaneous recovery showed 1mg/kg DOI in shock/extinction rats froze significantly different from 2.5mg/kg DOI rats and no significant results from sucrose preference test.

Keywords: post-traumatic stress disorder, stress-enhanced fear learning, sucrose preference test, psychedelics, extinction, fear generalization, spontaneous recovery

Introduction

Post Traumatic Stress Disorder, Major Depressive Disorder, and Exposure Therapy

It is estimated that 3.9% of individuals worldwide experience post-traumatic stress disorder (PTSD) in their lifetime (World Health Organization, 2024). This disorder can occur after an individual experiences an intensely traumatic event, which results in re-experiencing said event through flashbacks as well as avoiding any triggers related to the event, as it can cause an amplified emotional response (Careaga et al., 2016, Kelmendi et al., 2016). PTSD has both associative and non-associative learning components that can trigger flashbacks of the aversive event and create exaggerated fear in mild, and sometimes innocuous, stimuli.

Furthermore, major depressive disorder and PTSD are highly comorbid. Rosen et al., (2020) found that 80% of individuals in the United States suffer from PTSD with a comorbid psychological disorder, and 50% of those individuals have major depressive disorder as the

comorbid disorder. Major depressive disorder is characterized by a loss of interest in typically pleasurable activities, as well as depressed mood and social, physical, and cognitive symptoms (Cui et al., 2024; Marx et al., 2023). O'Donnell et al., (2004) found in their study that individuals with comorbid PTSD and depression often develop depression after the initial trauma which caused their PTSD, and PTSD and comorbid depression may have the same trauma which causes both disorders.

The associative learning component of PTSD involves a conditioned stimulus (context) (CS) paired with an unconditioned stimulus (foot shock) (US). This association is often reworked through exposure therapy—direct, safe confrontation with stimuli that triggers the individual until anxiety is reduced and allows them to learn that the environment is nonthreatening (Rothbaum & Schwartz, 2002). Fear extinction is the mechanism behind exposure therapy, helping disconnect the relationship between the CS and the US (Zaretsky et al., 2024) and reduce their emotional response through inhibitory learning (Norrholm et al., 2011; Long & Fanselow, 2012). The effects of exposure therapy, however, are mixed. While some populations find improvements in symptoms following refined and prolonged exposure therapy, others, such as veterans, are unable to find improvement. In a review by Eftekhari et al. (year), 40% of people who went through exposure therapy did not see a significant reduction in symptoms (Markowitz & Fanselow, 2020). Furthermore, in some instances it has been shown to worsen symptoms (Brown et al., 2018; Markowitz & Fanselow, 2020).

The non-associative learning component creates fear generalization (Lis et al., 2020), where a fear reaction expands beyond the original conditioned stimulus to stimuli, similar to the conditioned stimulus, regardless of whether that stimulus is actually threatening (Lommen et al., 2024). Whether or not exposure therapy works for an individual, generalization and potentiation

still occur (Markowitz & Fanselow, 2020). Spontaneous recovery, where fear re-emerges after extinction with the passage of time, is also seen (Schiller, 2008), even during successful exposure therapy treatment—a review by van Dis et al., (2021) cites a study where fear was found to recur even after successful exposure therapy (Kodzaga et al., 2025).

Stress-enhanced fear learning (SEFL) is effective at modeling the associative and non-associative aspects of PTSD using rodents and Pavlovian fear conditioning (Long & Fanselow, 2012). In SEFL, the protocol typically involves the aversive event (15 1mA shocks) in context A and then assessments for fear potentiation with a singular shock in a new context, as well as fear generalization, to see if fear is carried over into the new context (Rajbhandari et al., 2018). Fear is measured through freezing, or behavioral inhibition with a complete absence of movement aside from breathing (Roelofs, 2017). Following exposure to the aversive event, Long & Fanselow (2012) investigated whether extinction could reduce fear generalization, potentiation, and spontaneous recovery. They found that extinction was not effective—even as freezing decreased during extinction trials, when placed into the new context or receiving the singular foot shock, rats who were extinguished froze at levels comparable to rats who did not go through extinction at all. Spontaneous recovery of fear was also seen in rodents following exposure to the paradigm. With this issue in mind, pharmacological treatments have been paired with psychotherapy to help improve these effects.

Pharmacological Treatment

There are few pharmacological treatments available for individuals with PTSD. The only treatments available are not developed directly for PTSD, which are paroxetine and sertraline. These are selective serotonin reuptake inhibitors (SSRIs) and originally developed for individuals with major depressive disorder (Kelmendi et al., 2016; Zaretsky et al., 2024). While

PTSD and major depressive disorder are often comorbid and overlap in their neurochemistry, they are fundamentally distinct and thus should not be treated the same (Zaretsky et al., 2024). When treated with these drugs, there has been minimal improvement in symptoms, comparable with the improvement seen in placebo groups (Hoskins et al., 2015; Cipriani et al., 2018). Furthermore, individuals taking these drugs often experience a 'numbing' to their emotional experience and are therefore unable to process their trauma (Zaretsky et al., 2024). Because of this, other pharmacological treatment options are being explored for PTSD to relieve symptoms and prevent inability from trauma processing.

A treatment shown to have effectiveness for PTSD seen in both rodent and human studies has been psychedelics. Most psychedelics are similar in mechanism, working as agonists with the serotonin 2A (5-HT2A), 1A (5-HT1A), and 2C (5-HT2c) receptors. They have also been found to promote neuroplasticity through action in brain sites such as the infralimbic cortex, amygdala, dorsal hippocampus, and frontal cortex, promoting fear memory extinction and facilitating reconsolidation of new learning (Werle & Bertoglio, 2024). In many studies reviewed by Werle & Bertoglio (2024), psychedelics have shown to be effective in enhancing fear extinction and promoting extinction retention, such as Du et al., (2023), where a single administration of psilocybin in mice was found effective.

1-(2,5-Dimethoxy-4-iodophenyl)-2-aminopropane (DOI) is like these drugs in its mechanisms and has been shown to facilitate extinction. DOI is a psychedelic that has an exceptional level of affinity for 5-HT receptors, comparable to serotonin itself (Glennon & Dukat, 2024). A study conducted by de la Fuente Revenga et al., (2021), reviewed in Werle & Bertoglio's paper (2024), found that DOI reduced freezing over the course of fear extinction trials, as well as fear generalization assessments at the 2.0mg/kg dose. A study by Pędzich et al.,

(2022) found reduced freezing in fear extinction, but no significant results in fear consolidation. We hope to find results like those in de la Fuente Revenga's study (2021), where a dose of DOI supports fear extinction during the test and after the test during generalization.

The same stressor that may cause PTSD may also cause major depressive disorder. With this in mind, we measured a key feature of depression: anhedonia, or the inability to enjoy typically pleasurable activities, following exposure to the SEFL protocol. In a study completed by Kim et al., (2017), mice exposed to unpredictable and inescapable electric shocks like SEFL produced anhedonia and reduced sucrose intake during sucrose preference assessment. Enkel et al., (2010) also found that unpredictable foot shocks can produce anhedonia in rats, reducing the intake of sweetened condensed milk following the foot shocks (Bali & Jaggi, 2015).

In our study, we first expect vehicle rats to show the SEFL effect. We would also expect pre-extinction DOI to facilitate fear extinction, resulting in lower freezing during the potentiation test. We would expect rats who go through extinction alone without DOI to display generalization and potentiation, as well as rats who do not do extinction at all. For SPT, we would expect vehicle rats to display anhedonia symptoms, as well as rats who are shocked and do not go through extinction.

Methods

Subjects

This study used 66 Long-Evans rats (m = 48, f = 18) from Charles River Laboratories. ±DOI was purchased from Cayman Chemical.

Rats were on a reverse light-cycle with 12 hours of dark (5 A.M. – 5 P.M.) and 12 hours of bright light (5 P.M. – 5 A.M.). At the start of the experiment, rats ranged from 2 to 4 months old, with the average male rat being 426g and the average female rat being 235g. In our no

shock/no extinction group, we had five males and three females receive 1mg/ml 1mg/kg ±DOI (low dose), two males and three females receive 1mg/ml 2.5mg/kg ±DOI (high dose), and six males and two females receive 1mg/ml 1m/kg saline vehicle. In our shock/no extinction group, we had seven males and three females receive low dose, five males and no females receive high dose, and six males and two females receive vehicle. In our shock/extinction group, we had six males and three females receive low dose, five males and no females receive high dose, and six males and two females receive vehicle.

Apparatus

In our SEFL procedure, we had two distinct contexts. Context A was distinguished with a 50% vanilla scent in the operant chamber pan, as well as being run with bright lights on. Context B was distinguished with a plexiglass insert, 5% vinegar scent in the operant chamber pan, and was ran in red light, with red cellophane placed over the lights inside of their chamber. During transport for context B, rats were placed into individual cages and covered with a dark cover to minimize light.

Pre-SPT

Rats were given a bottle of 1% sucrose water with regular water on their home cage for four days, four hours each day, to prevent neophobia during post-SPT assessment (Primo et al., 2023).

SEFL Protocol

Rats underwent the SEFL protocol, which spanned over a series of four days. For rats who were shocked, 15 unpredictable 1mA shocks occurred over the course of 90 minutes.

Twenty-four hours later, rats received either an intraperitoneal injection of vehicle, low dose ±DOI, or high dose ±DOI, with both doses of ±DOI producing head-twitch response in rodents, an indicator for proper drug administration (Canal & Morgan, 2011). Thirty minutes later, experimental rats were returned to context A to undergo five 30-minute context extinction sessions spaced five minutes apart (Long & Fanselow, 2012). Forty-eight hours later, all rats were placed into context B and received one shock following a three-minute baseline period. The next day, rats underwent a 10-minute context B test with no foot shocks administered (Rajbhandari et al., 2018). Two weeks after the context B test, rats underwent a 10-minute spontaneous recovery test in context A with no foot shocks administered. Freezing behavior was recorded using ANY-Maze software and was measured to determine fear.

Post-SPT

Following the SEFL and extinction, SPT was conducted. All rats were deprived of water for four hours, then were individually housed and received a bottle with 1% sucrose concentration and a bottle with regular water. Side preference was controlled for by alternating sides (left versus right) of the sucrose bottle and the control bottle daily. Bottles were weighed before and after assessment to determine water intake, with bottle leakage accounted for, to determine anhedonia (Primo et al., 2023).

Statistical Analysis

IBM SPSS Statistics Software (Version 31) was used to run statistical analyses. Extinction data was analyzed using a multivariate ANOVA, comparing how doses (saline, low, and high dose) affected freezing during the five extinction trials.

SEFL training was analyzed using univariate ANOVAs, assessing for main effects of dose (saline, low dose, and high dose), condition (no shock/no extinction, shock/no extinction, and shock/extinction) and/or sex (male and female) on freezing during context B baseline, test, and spontaneous recovery. Fischer's LSD post-hoc-tests compared condition, and *a priori* planned comparisons compared drug dose and sex.

SPT was assessed using a repeated measures ANOVA, comparing how dose (saline, low dose, and high dose), condition (no shock/no extinction, shock/no extinction, and shock/extinction) and/or sex (male and female) impacted 1% sucrose water versus regular water consumption.

Results

SEFL Training

A multivariate ANOVA was used for extinction, where average freezing was taken over the five trials and compared based on whether vehicle, low dose, or high dose were received.

A multivariate ANOVA for extinction trials revealed a significant main effect in extinction ($p = 0.013$) and extinction*dose interaction ($p = 0.004$). Fischer's LSD post-hocs revealed a significant difference between vehicle and low dose ($p = 0.002$) and vehicle and high dose ($p = 0.003$), but not low and high dose ($p = 0.693$) for extinction trial 1 for freezing. We also found significant differences for extinction trial 2 for vehicle and low dose ($p = 0.004$) and vehicle and high dose ($p = 0.028$), but not between low and high dose ($p = 0.704$) for freezing. During extinction trial 3, we see a significant difference between vehicle and low dose ($p = 0.038$) and vehicle and high dose ($p = 0.026$), but not between low and high dose ($p = 0.611$) for

freezing. Trials 4 and 5 saw no significant difference in freezing between any drug group ($p >$ 0.05).

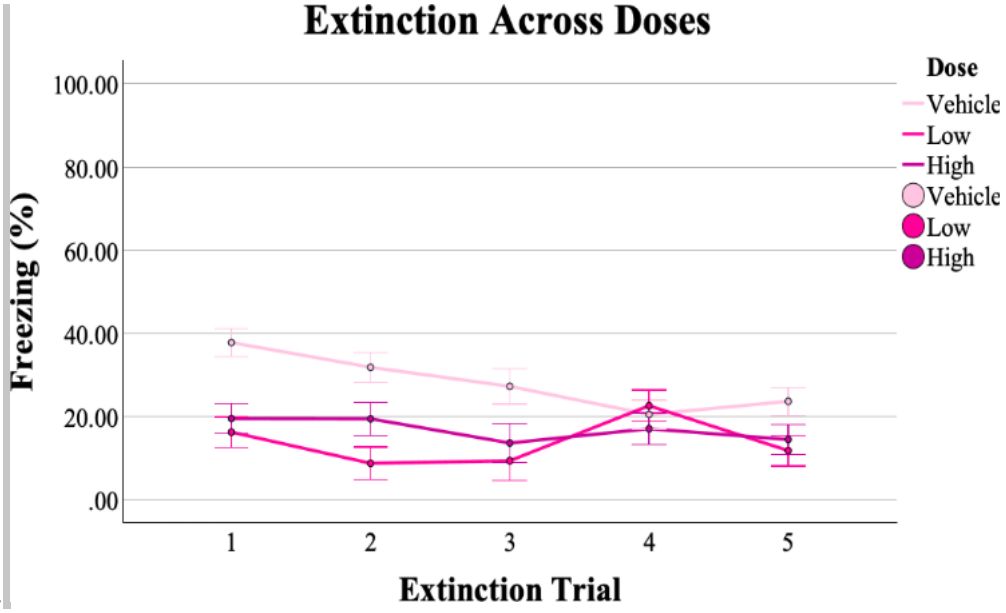


Figure 1: Extinction across doses – Data represents average time freezing across each 30-minute session, +/- 1 SEM. Freezing is significantly lower for low and high dose of DOI compared to vehicle during trials 1 through 3.

A univariate ANOVA for context B baseline, context B test, and spontaneous recovery assessed for main effects and/or interactions of dose, condition (no shock/no extinction, shock/no extinction, and shock extinction) and/or sex (female/male) on freezing. Fischer's LSD post-hoc-tests were used to investigate any significant main effects. *A priori* planned comparisons were conducted to compare dose and condition groups. ANY-Maze videos were reviewed to ensure proper tracking of freezing behavior, and any videos that appeared to have errors in determining freezing were removed from statistical analysis, which included three rats in context B baseline, and one rat in spontaneous recovery.

Context B baseline had no main effect for sex, dose, or interaction effect of sex*condition, or condition*dose ($p > 0.05$). We found significant main effects for condition

($F(2, 47) = 8.665$, $p < 0.001$, ηp2 = 0.269), and interaction of sex*dose ($F(2, 47) = 4.115$, $p = 0.023$, ηp2 = 0.149), and sex*condition*dose ($F(2, 47) = 4.883$, $p = 0.012$, ηp2 = 0.172).

Fischer's LSD post-hoc-tests showed no shock/no extinction and shock/extinction groups froze less than shock/no extinction (both $p < 0.001$). No shock/no extinction and shock/extinction had no significant difference ($p = 0.490$). There was no significant difference between vehicle or either DOI dose for any condition ($p > 0.05$). Sex*dose comparisons showed a marginally significant difference of freezing, where females ($M = 16.67$, $SD = 22.33$) froze more with vehicle dose compared to males ($M = 4.83$, $SD = 9.53$) ($p = 0.084$). Finally, in context B baseline, we see a sex*dose*condition effect, where in context B test, female rats in no shock/no extinction with low dose ($M = 25.54$, $SD = 11.84$) froze significantly less than high dose ($M = 2.90$, $SD = 1.02$) ($p = 0.030$). *A priori* planned comparisons showed no significant difference between vehicle and either DOI dose for any condition ($p > 0.05$).

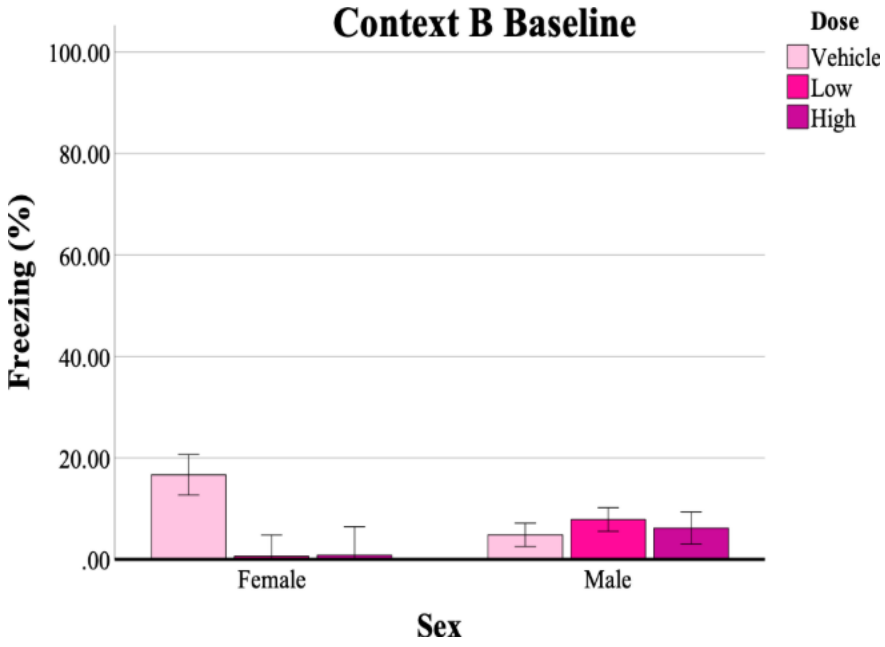


Figure 2: Freezing in context B baseline between condition and dose. Data represents average freezing time across 220-second baseline period, +/- 1 SEM. Shock/no extinction and shock/extinction groups froze less than shock/no extinction (both $p < 0.001$).

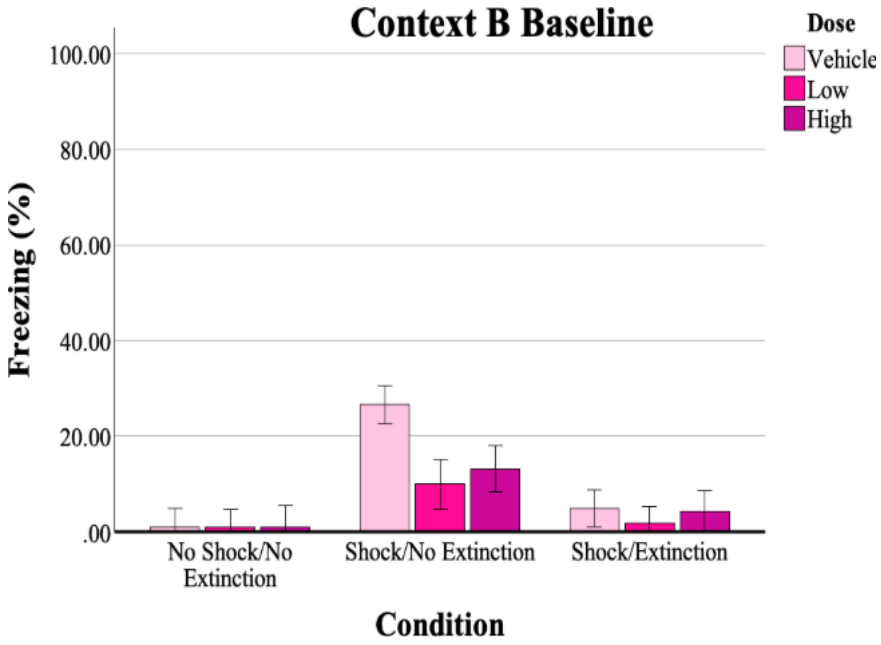


Figure 3: Freezing in context B baseline between dose and sex. Data represents average freezing time across 220-second baseline period, +/- 1 SEM. Females injected with vehicle froze marginally more compared to males ($p = 0.084$).

For context B test, we found significant main effects of condition ($F(2,50) = 17.324$, $p < 0.001$, $\eta p2 = 0.409$), and marginal interaction effects for sex*dose ($F(2,50) = 3.155$, $p = 0.051$, $\eta p2 = 0.112$) but no significant effects of sex, dose, sex*condition, condition*dose, or sex*condition*dose ($p > 0.05$). Fischer's LSD post-hoc tests showed no shock/no extinction and shock/extinction groups froze less than shock/no extinction (both $p < 0.001$). Shock/no extinction and shock/extinction did not significantly differ ($p = 0.822$). Sex*dose comparisons revealed significantly lower freezing in context B test ($t(13) = - 6.36$, $p < 0.001$) in females ($M =$

2.90, *SD* = 1.02) compared to males (*M* = 46.09, *SD* = 11.43) in high dose. There was no significant difference between vehicle or either DOI dose for any condition ($p > 0.05$). *A priori* planned comparisons showed no significant difference between vehicle and either DOI dose for any condition ($p > 0.05$).

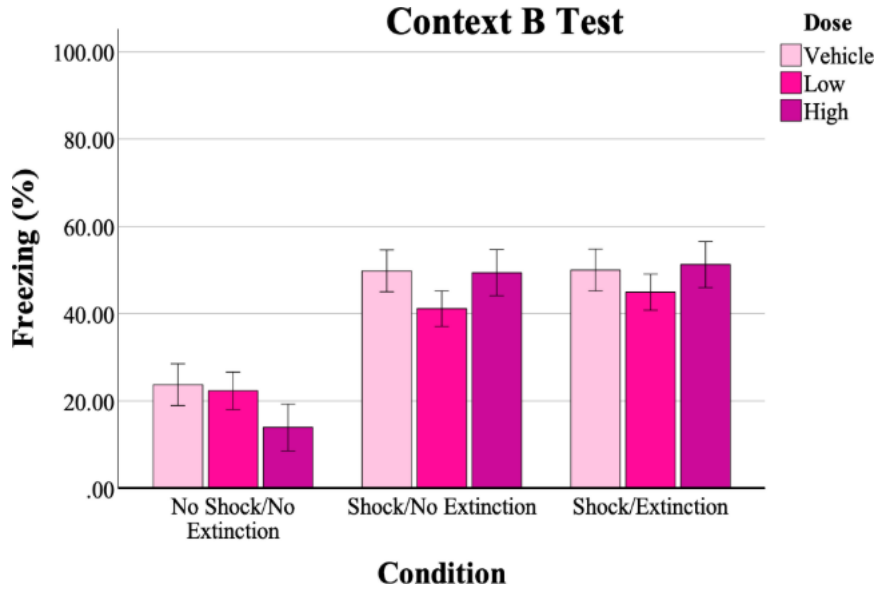


Figure 4: Freezing in context B test between dose and condition. Data represents average freezing time across 10-minute test period, +/- 1 SEM. Post-hoc tests showed no shock/no extinction froze less than shock/no extinction and shock/extinction (both $p < 0.001$).

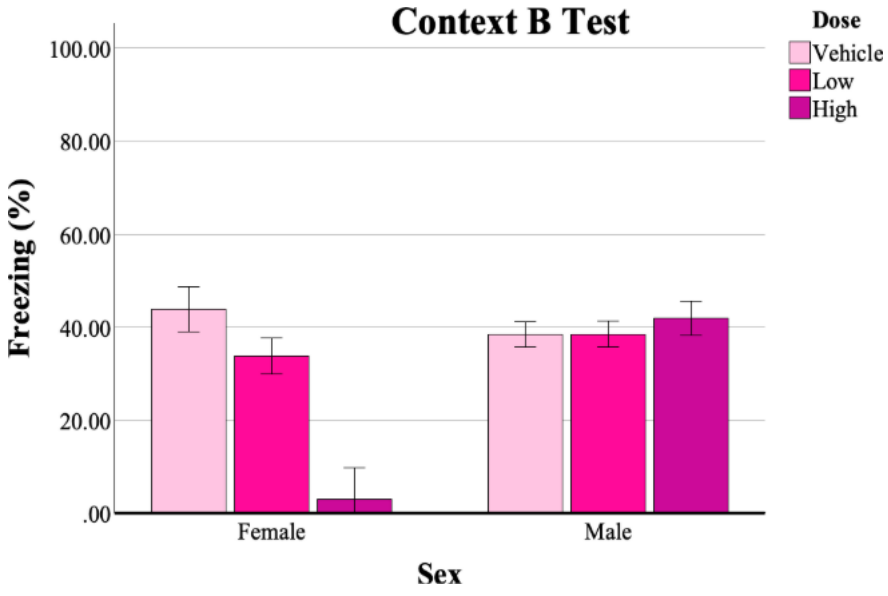


Figure 5: Freezing in context B test between sex and dose. Data represents average freezing time across 10-minute test period, +/- 1 SEM. Freezing was significantly lower in females compared to males for high dose ($p < 0.001$).

For spontaneous recovery, we had a significant main effect of condition (**$F(2,49) = 27.900$, $p < 0.001$, $\eta p2 = 0.532$**) but no significant effects for sex, dose, sex*condition, sex*dose, condition*dose, or sex*condition*dose ($p > 0.05$). Fischer's LSD post-hoc tests revealed no shock/no extinction froze higher than shock/no extinction and shock/extinction ($p < 0.001$). Shock/no extinction and shock/extinction had a marginal significant difference ($p = 0.062$). Sex*dose comparisons showed a significantly lower freezing in spontaneous recovery in females ($M = 1.07$, $SD = 1.41$) compared to males ($M = 62.54$, $SD = 31.42$) for high dose ($t(13) = - 3.30$, $p = 0.006$). There was no significant difference between vehicle or either DOI dose for any condition ($p > 0.05$). *A priori* planned comparison showed a significant difference between low and high doses of DOI for the spontaneous recovery shock/extinction group ($t(12) = - 2.39$, $p = .034$).

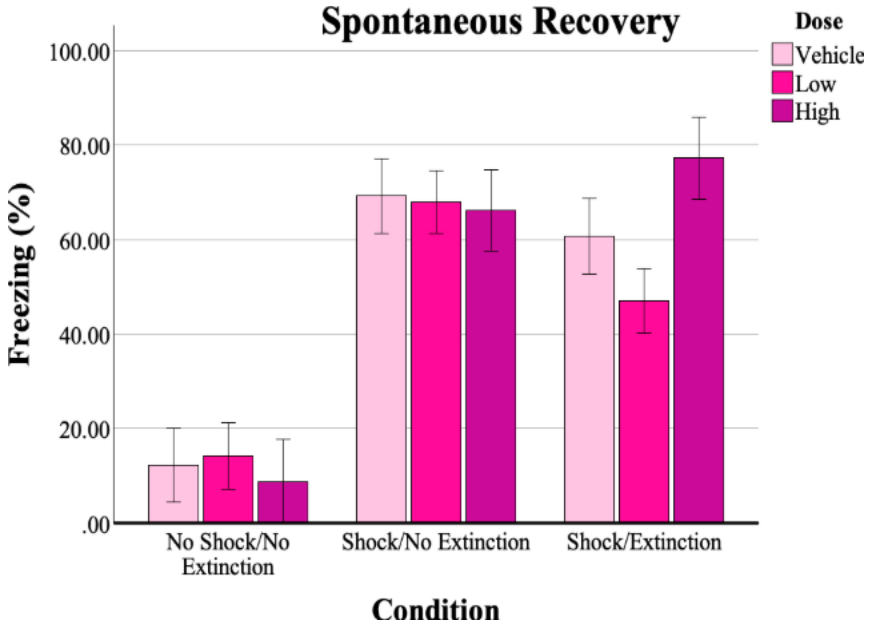


Figure 6: Freezing in spontaneous recovery between dose and condition. Data represents average freezing over 10-minute test period, +/- 1 SEM. Shock/no extinction and shock/extinction had a marginal significant difference ($p = 0.062$), and a significant difference between low and high doses of DOI for the spontaneous recovery shock/extinction group ($p = .034$).

Sucrose Preference Test

A repeated measures ANOVA for SPT compared how dose (vehicle, 1mg/kg, and 2.5mg/kg), condition (no shock/no extinction, shock/no extinction, and shock/extinction) and/or sex (male, female) impacted 1% sucrose water versus regular water consumption. Results found no significance between dose ($F = 1.297$, $p = 0.262$), condition ($F = 1.356$, $p = 0.236$) or sex ($F = 0.106$, $p = 0.956$) by day, nor any interaction effects between these groups ($p > 0.05$). Water or sucrose intake that was considered abnormally high had scores from the previous day and day after averaged to make up for the excessive intake.

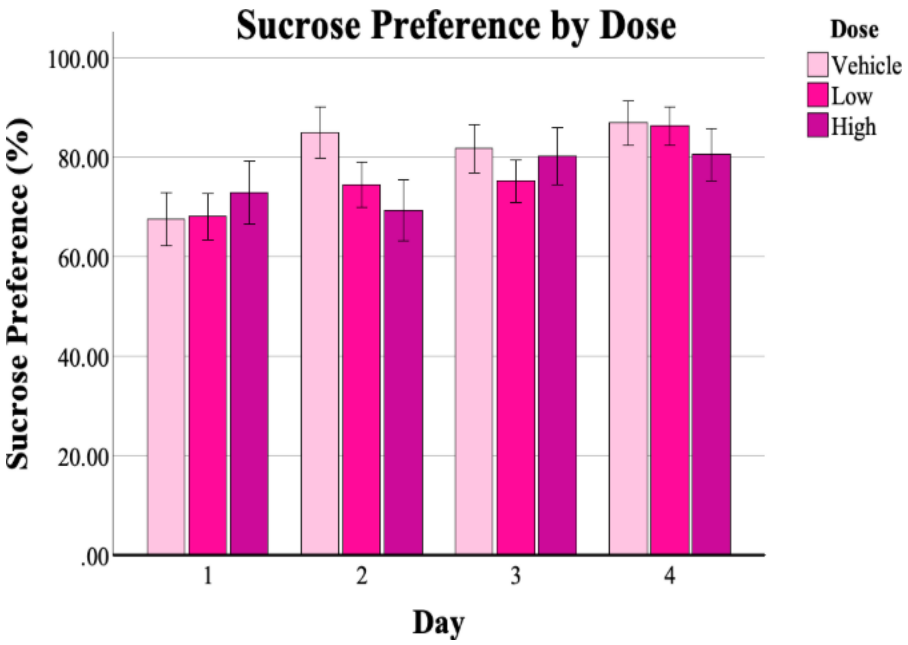


Figure 7: Sucrose preference by day based on dose. Data represents average sucrose consumption compared to regular water across a four-day period, +/- 1 SEM. No significant effects between doses.

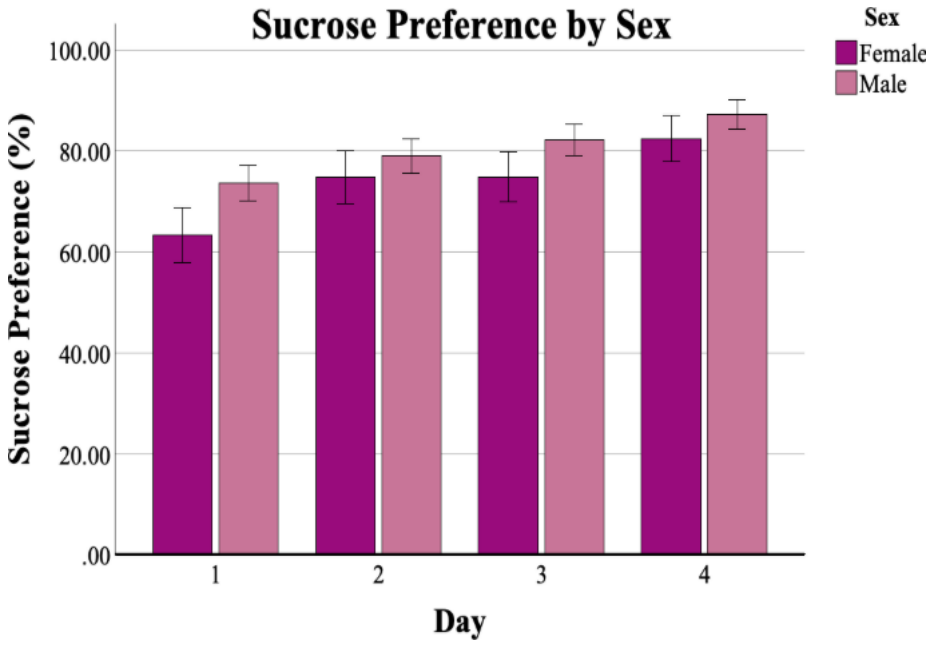


Figure 8: Sucrose preference by day based on condition. Data represents average sucrose consumption compared to regular water across four-day period, +/- 1 SEM. No significant effects between conditions.

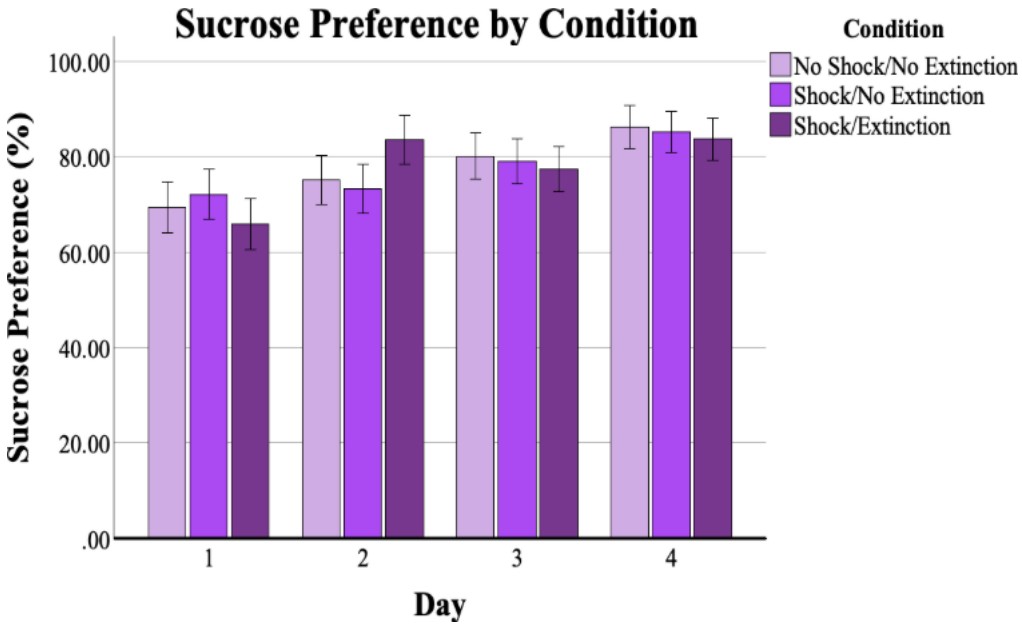


Figure 9: Sucrose preference by day based on sex. Data represents average sucrose consumption compared to regular water across a four-day period, +/- 1 SEM. No significant effects between sexes.

Discussion

This study aimed to investigate how SEFL was impacted by psychedelic DOI and whether exposure to the SEFL procedure could produce anhedonia in rats. To do this, rats experienced SEFL and either went through extinction or not, with drug or not. Afterward, rats were assessed for fear potentiation and generalization in context B, then assessed for anhedonia with sucrose preference testing. Finally, rats were put through a spontaneous recovery assessment in context A two weeks after the context B test.

SEFL Training

Our results showed significantly less freezing during the first three extinction trials with either drug dose. We also saw significant effects of condition throughout our three tests. In context B baseline, no shock/no extinction and shock/extinction froze significantly different from shock/no extinction, indicating that extinction may help in the initial exposure to a novel context, and to a mild stressor single shock. In context B test, we saw that shock/no extinction and shock/extinction froze at similar levels, showing that extinction alone does not prevent generalization and potentiation into a novel context.

In spontaneous recovery, we saw that shock/no extinction and shock/extinction froze at similar levels as well, showing that extinction alone does not prevent generalization and potentiation into a novel context.

Like results seen in Pedzich et al.'s study (2022), we do see an acute decrease of freezing in rats during the first three extinction trials with both doses of DOI. Extinction does also seem to benefit rats in baseline assessment; it does not benefit during test or spontaneous recovery, however. This indicates that extinction is not enough to reduce SEFL effects, like results seen in Long & Fanselow's, (2012) study.

For dose, we saw no significant effects of dose during context B training or test, regardless of condition. While we see results consistent with Long & Fanselow, (2012) and Schiller et al., (2009) that extinction without drug produces spontaneous recovery following SEFL, we did find our low dose of DOI in our shock/extinction group produced significantly less freezing, but only when compared to the high dose of DOI. This is contrary to other studies, where a dose of 2.0mg/kg or 2.5mg/kg is seen as most effective (de la Fuente Revenga et al., 2021, Pędzich et al., 2022, Plaznik et al., 1994). Our results may be due to the timing of our administration for our drug. We administered our drug 30-minutes prior to extinction to ensure peak effects, however, the study conducted by de la Fuente Revenga, (2021) administers their drug 24 hours before conditioning the aversive memory. Perhaps administering a low dose of DOI prior to extinction may prevent spontaneous recovery in that same context, but administering before beginning the paradigm may allow for the psychedelic benefits of promoting fear memory extinction and facilitating reconsolidation of new learning to set in (Werle & Bertoglio, 2024). But this should be explored more with greater power in our groups, as our low dose was only significantly different from our high dose, and not from our vehicle group.

We also saw interaction effects of sex and dose in context B baseline, and marginally in context B test, which indicate higher freezing in females when receiving vehicle compared to

males during initial introduction to novel context and being exposed to a single shock, and marginally lower freezing in females when receiving high dose compared to males during test, indicating high dose is effective at significantly decreasing freezing during generalization assessment for females compared to males. There are noted sex differences in drug dose when it comes to classic psychedelics such as psilocybin, which work similarly to DOI. Woodburn et al., (2024) found that a narrower range of doses for psilocybin were effective for females compared to males. However, our results should be taken lightly, as our powering for females, particularly in high dose, was exceptionally weak. Some high dose groups had no females at all, which is the true reason for our effects. However, sex differences in psychedelic dose should be considered in future directions for this study.

We also see sex, dose, and condition interaction, where no shock/no extinction females in context B test froze significantly different between low and high doses. Since there was no traumatic experience introduced to these rats, and this context being introduced the previous day to rats, this difference in freezing may be because of heightened sensitivity females have to psychedelics in general. As mentioned, females are much more sensitive to psychedelics, due to serotonin 5-HT1A having higher binding affinity (Sahoo et al., 2026), estrogen levels potentially influencing 5-HT2A expression (Shadani et al., 2026), and females tending to have a higher response in general to ±DOI at lower doses (McGriff et al., 2025). However, again, these results should be taken lightly due to the low number of females in our study

Sucrose Preference Test

We saw no significant difference in sucrose preference across condition, dose, or sex in our study. We investigated sucrose preference to see if experience with the SEFL model would cause anhedonia, a key symptom of depression. While the sucrose preference test has not been

paired with SEFL before, it has been paired with paradigms like it, such as learned helplessness, where rats receive numerous unescapable, unpredictable foot shocks. With this logic, we assumed that rats who are shocked and not extinguished may exhibit a decreased sucrose preference, like the effects seen in learned helplessness studies mentioned before, such as Kim et al., (2017). However, this was not the case, and this may be because learned helplessness tends to use many more foot shocks, up to 100 1mA shocks over a two-hour period (Conoscenti & Fanselow, 2019) — and may indicate that SEFL may not be robust enough to produce the anhedonia symptom. But this should be investigated further, and other depression assays should be used alongside the SEFL model to give more dimension into whether SEFL can produce comorbid depression with other key symptoms beyond anhedonia, such as assessing for despair in a forced swim test.

Limitations & Future Directions

One of our limitations was the powering of our sex effects in our study. While we see significant results in sex*dose and sex*dose*condition interaction effects, these significant results are rooted in our low number of females in these groups rather than a true significant difference of freezing. However, this trend should be considered for future investigation, and females should be investigated more closely for potential differences in freezing during SEFL depending on condition and/or dose.

We found that some generalization and potentiation occurred in our study regardless of condition, and while this may have been in part due to SEFL effects, this may have also been caused by how we discriminated contexts. We made context B as novel as possible; however, one thing of note was the use of the same floor insert between context A and context B. Studies that involve contextual discrimination often use distinct grid floors, either different ones entirely

(Duarte et al., 2024) or adjusting the grid spacing bars to simulate a unique floor (Esmorís-Arranz et al., 2008). Regardless, this is a primary contextual feature rodents encode (Curzon et al., 2009). A study by Luyten et al., (2016) found that grid floors influence contextual learning and as a result, may contribute to generalization when used across contexts.

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