EFFECTS OF SEROTONIN AND A PSYCHEDELIC DRUG ON EGG-LAYING BEHAVIOR IN *C. ELEGANS*

by

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Psychedelics have shown great promise in the treatment of mental health conditions such as treatment resistant depression, post-traumatic stress disorder, and substance use disorder. However, the mode of action of these drugs is largely unknown. Genetically tractable model organisms are particularly advantageous for identifying the genetic pathways involved in drug responses (Brundage et al., 1996). We characterized the behavioral effects of a psychedelic in one such organism, the nematode worm *C. elegans*. We began by creating a toxicity dose response curve that compared the percent survival 24 hours after drug exposure to the concentration of drug using the psychedelic drug 2,5-Dimethoxy-4-iodoamphetamine (DOI) (Aghajanian & Marek, 1999; de la Fuente Revenga et al., 2021; *DOI*, 2020; Trent et al., 1983) or the control buffer solution (M9). The data revealed that DOI does have toxic effects and the percent survival of worms following acute drug exposure was significantly decreased at higher drug concentrations. After determining the minimal toxic dose, we examined the effects of DOI on a behavior type. One critical behavior of *C. elegans* is egg-laying, which is regulated by serotonin and its corresponding receptors (Horvitz et al., 1982). Psychedelics have a particularly high affinity for serotonin receptors. We hypothesized that a psychedelic drug would have the same stimulating effect on egg-laying as serotonin (5-HT). As expected, we found that 5-HT-incubated animals laid more eggs than the control. Surprisingly, animals incubated in DOI laid

eggs at a similar rate to those incubated in the buffer solution. After completing these preliminary trials, a dose response curve was done for egg-laying compared to non-toxic doses. These results indicate that DOI does not stimulate egg-laying behavior, in a significant way, at any concentration.

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Introduction

A growing body of data (Aghajanian & Marek, 1999; de la Fuente Revenga et al., 2021) suggests that psychedelic drugs may be an effective treatment for mental health disorders such as treatment resistant depression, post-traumatic stress disorder (PTSD), and substance use disorder (SUD). The therapeutic effects of psychedelics have been observed within a day and have been shown to last up to several months (Carhart-Harris et al., 2021; Davis et al., 2021). It has also been discovered that psychedelics are psychoplastogens, meaning they induce neuronal plasticity in the form of increased dendritic complexity and density (Jones et al., 2009; Shao et al., 2021). The psychoplastic effects persist after the drug has been metabolized, therefore they could underlie the long-lasting therapeutic benefits of psychedelics (Shao et al., 2021). However, the mode of action of these drugs is not well understood. Previous studies with psychedelics have been done in rats and mice. These studies have demonstrated that psychedelics have a particularly high affinity for serotonin receptors (López-Giménez & González-Maeso, 2018). Serotonin (5-HT) is a neurotransmitter that acts on receptors called serotonin receptors. 5-HT has been highly conserved in its role and structure throughout evolution and is present phylogenetically in all organisms with a nervous system (Tecott, 2007; Whitaker-Azmitia, 1999). One study in mice found that the psychedelic drug lysergic acid diethylamide (LSD) induced behavioral changes via the 5-HT2A receptor, a specific type of serotonin receptor (Halberstadt et al., 2020). It was found that two psychedelic drugs, LSD and 2,5-Dimethoxy-4-iodoamphetamine (DOI), were agonists for these 5-HT2A receptors by causing an increase in locomotion at low doses, as locomotion is regulated by 5-HT2A receptors (Halberstadt et al., 2020). The effects of LSD on locomotion required functional expression of 5-HT2A receptors, as the effect was absent in 5-HT2A receptor deficient mice (Hanks & González-Maeso, 2012). This suggested that

psychedelic drugs are binding to this serotonin receptor to induce the observed behavioral effects (Hanks & González-Maeso, 2012). Another study concluded that the psychedelic drugs ibogaine and 3, 4-methylenedioxymethamphetamine (MDMA), can reopen a critical point of social reward learning during adulthood in mice (Nardou et al., 2023). The ex-vivo experiments confirmed an increase in dendritic spine density within 24 hours after exposure to drug (Nardou et al., 2023). Similar dendritic growth in length and density was shown during in-vivo experiments, specifically in the frontal cortex of mice (Shao et al., 2021). This indicates that psychedelics could have an effect on dendritic growth and neuroplasticity.

However, the molecular and genetic mechanisms underlying the effects of psychedelics can be difficult to study in more complex organisms like rats and mice.

In the present study, the nematode worm *C. elegans* was used to examine the behavioral effects of psychedelics. *C. elegans* is a well-established model organism that has a fully annotated genome and all 302 of its neurons mapped (Brittin et al., 2021; Cook et al., 2019; Hammarlund et al., 2018; Hobert, n.d.; Jarrell et al., 2012; White et al., 1986). These animals are also transparent, so the entire reproductive tract can be seen and used to determine age. *C. elegans* also have a rapid generation time of three days from egg to young adult. *C. elegans* mutants can be easily engineered due to the vast number of genetic tools that have been developed (Brundage et al., 1996). As the vast majority of *C. elegans* is hermaphroditic (less than 0.2% of the standard lab strain are male), self-fertilization is the main form of reproduction. *C. elegans* is also a model organism that offers a unique advantage in the ability to link behavioral changes to neuronal changes through their fully mapped nervous system. This enables an analysis of the proteins, signaling pathways, and genes that are likely responsible for causing observed behavioral changes.

While *C. elegans* is not be as closely related to humans as rodents, there is significant homology between *C. elegans* and mammals. Specifically, bioinformatics suggests that 60-80% of *C. elegans* genes are orthologous to human genes (Kaletta & Hengartner, 2006; Kim et al., 2018). The *C. elegans* nervous system also uses many of the same neurotransmitters as the mammalian nervous system. This includes the neurotransmitter serotonin, for which *C. elegans* expresses six types of receptors that share homology with mammalian serotonin receptors (Dag et al., 2023). Therefore, in this project we wanted to examine the effects of psychedelics on serotonin-regulated behaviors in *C. elegans*.

In the Lockery Lab, we are studying the effects of psychedelics on several serotonin-regulated behaviors in *C. elegans* to determine if *C. elegans* can serve as a useful model organism in which to study the molecular, genetic and neuronal mechanisms underlying the effects of psychedelic drugs. Nearly all psychedelics are classified as Schedule I under the Controlled Substances Act. We chose to begin our studies of psychedelics in *C. elegans* with the drug DOI because it is currently unscheduled and, therefore, accessible for research. DOI has also previously been used in several psychedelic experiments with mice (Halberstadt et al., 2020).

The lab has already identified one serotonin-regulated behavior in *C. elegans* that is affected by DOI: feeding (pharyngeal pumping). We had hypothesized that exposure to DOI would increase the rate of feeding, as was anticipated with egg-laying. The data show that DOI suppressed the rate of feeding and pumping, which was opposite of the expected result. However, the data does show that the drug has an effect on at least one kind of *C. elegans* serotonin-regulated behavior. This indicated that other serotonin-regulated behaviors may also be impacted. Another behavior that is regulated by serotonin in *C. elegans* is egg-laying, 5-HT is

known to stimulate egg-laying (Horvitz et al., 1982). Egg-laying behavior in *C. elegans* is particularly well characterized; there is a significant body of literature detailing the genes, neurons and receptors that are involved in stimulating and inhibiting this behavior. The egg-laying action is caused by the activation of the hermaphrodite-specific neurons (HSNs), which synapse onto the vulval muscles, releasing 5-HT, which causes contraction and egg expulsion (Dempsey et al., 2005; Teshiba et al., 2016). Of the six serotonin receptors expressed in *C. elegans*, *ser-1* is the receptor type that plays the largest role in regulating egg-laying behavior (Carnell et al., 2005; Dempsey et al., 2005). Therefore, in this project we examined the effects of exposure to serotonin and a psychedelic drug on egg-laying rate.

In order to more fully understand how DOI affects *C. elegans,* we wanted to determine the concentrations of DOI that should be included in our behavioral analysis. So, we began with a toxicity assay and created a dose response curve for rate of survival and DOI concentration. The toxicity assay examined the effect of DOI incubation on the percent survival of animals 24 hours after exposure to drug (Ornelas et al., 2024).

In the egg-laying experiments, *C. elegans* were incubated in either serotonin or the psychedelic DOI (Aghajanian & Marek, 1999; de la Fuente Revenga et al., 2021; *DOI*, 2020; Trent et al., 1983). DOI is pharmacologically similar to more commonly known psychedelics such as psilocybin and LSD.

Research Questions

1. How does DOI concentration affect survival 24 hours after exposure?
2. Do psychedelics affect egg-laying behavior in *C. elegans*?
3. How do the effects of 5-HT on egg-laying compare to the effects of DOI?

This project aimed to determine the non-toxic DOI concentrations to perform further behavioral experiments with that ensures observed effects are due to behavioral changes and not toxic effects. We also aimed to create a full dose response curve on egg-laying for DOI using serotonin as a positive control and a buffer solution (M9) as a negative control.

We aimed to learn if the psychedelic drug DOI affects egg-laying, as well as understand if the effect is dose-dependent. The results from this project will help us better understand the effects of DOI on egg-laying behavior, and how those effects compare to the effects of 5-HT. This will contribute to the collective understanding of psychedelics and the behavioral effects of DOI on *C. elegans*. We hypothesize that DOI stimulates egg-laying in *C. elegans* because it is known to act primarily on serotonin receptors and have a high affinity for 5-HT2A. We predict that DOI will increase the rate of egg-laying because exposure to 5-HT increases egg-laying and also primarily acts on serotonin receptors. These results will also contribute to our understanding of stimulating egg-laying behavior in *C. elegans*.

Materials and Methods

Reagents

M9, the control buffer solution, was prepared by combining 3 g KH_2PO_4, 6 g Na_2HPO_4, 5 g NaCl, and 1 ml of 1M $MgSO_4$ then adding H_2O to reach a final volume of 1 L. Drug incubation concentrations were made from either 2,5-Dimethoxy-4-iodoamphetamine (DOI) hydrochloride (Sigma Aldrich; St Louis, MO, USA) or serotonin creatinine sulfate monohydrate (5-HT) (Sigma Aldrich; St Louis, MO, USA). Each incubation solution was made by diluting an aliquot of 10 mM DOI to 0.1 mM, 0.3 mM, 1 mM, or 3 mM with M9 respectively. 5-HT 10 mM aliquots were diluted with M9 to 5 mg/mL.

Worm Strains and Cultivation

All experiments were performed on the reference strain N2 Bristol (SL1001). The *C. elegans* strain used in this study was obtained from the Caenorhabditis Center (CGC), which is funded by NIH Office of Research Infrastructure Programs (R35GM152169) (CGC; Minneapolis, MN, USA). Worms were maintained using standard techniques (Brenner, 1974), and plates were stored in incubators kept at 20 ^{o}C. Animals were grown on plates of nematode growth media (NGM) and seeded with *Escheria coli* strain OP50-1.

Animal Synchronization

All trials began with creating an age synchronized population of worms. Ten to twelve adult hermaphrodites were transferred to a plate that has been seeded with OP50-1, and left to lay eggs for 6-8 hours, then removed. The progeny was then allowed to hatch and mature over the next 3 days; this procedure created an age-synchronized population of worms.

Toxicity Assay

On the day of the experiment 20-25 adult hermaphrodite worms were picked from an age synchronized population and placed into one of two glass incubation tubes containing 50 µL of solution. Worms were incubated in either DOI or the control vehicle solution (M9) for 2 hours. Vehicle and DOI groups were run in parallel with the incubation start time for each group staggered by 10 minutes.

At the end of the incubation period, a 10 µL glass pipette was used to transfer 5 µL of solution, which included all worms, to an unseeded agar plate. The solution was allowed to soak into the agar for 5 minutes. After this acclimation period, all worms present on the plate were counted and the number of worms moving was also recorded. Each worm was also gently tapped on the nose using a platinum wire, and their behavior was recorded as either fully responsive to nose tap (executing a full reversal away from the stimulus), immobile (displaying only head bends in response to nose tap), or dead (displaying no head or body movement). Plates were then stored in incubators set at 20 ^{o}C. Observations were repeated 24 hours after worms had been removed from the incubation solution and transferred to the seeded plate.

This procedure was repeated for 5 doses of DOI with 3 replicates for each dose, each trial consisted of a drug and control pair. All observations were completed on a Zeiss Stemi SV 6 microscope attached to a 100IL-PS power supply (Spot Imaging: Diagnostic Instruments U.S.A.; Sterling Heights, MI, USA).

Egg-Laying Assay

On the day of the experiment, 12 young adult worms were picked from an age synchronized population and moved into one of three glass incubation tubes containing 50 µL of solution, 4 worms were placed in each tube. In the preliminary egg-laying experiments, worms

were incubated in either 5-HT, DOI, or the control vehicle solution (M9) for 30 minutes. The incubation start time for each group was staggered by 10 minutes, as shown in **Figure 1**.

At the end of the incubation period, a 10 µL glass pipette was used to transfer 5 µL of solution, which included all worms and laid eggs, to an unseeded agar plate. The solution was allowed to soak into the agar for 5 minutes. After this acclimation period, all eggs and worms present on the plate were counted and recorded. This procedure was repeated for 8 replicates of M9, DOI, and 5-HT. All data collection and animal behavioral observations were completed on a Zeiss Stemi SV 6 microscope attached to a 100IL-PS power supply (Spot Imaging: Diagnostic Instruments U.S.A.; Sterling Heights, MI, USA). Preliminary egg-laying data includes average eggs laid/worm after incubation of a DOI at 1mM and 5-HT concentration of 5 mg/mL, the standard dose (Corsi, 2015; Dempsey et al., 2005).

In our subsequent experiment, we repeated this procedure to generate a full dose response curve for the effect of DOI on egg-laying. Following a 30-minute incubation in M9 or DOI (0.1 mM, 0.3 mM, 1 mM, and 3 mM) and a 5-minute acclimation period, the average number of eggs laid per worm was counted. Then, the number of eggs laid per worm was averaged for each incubation concentration across all 8 trials for that concentration.

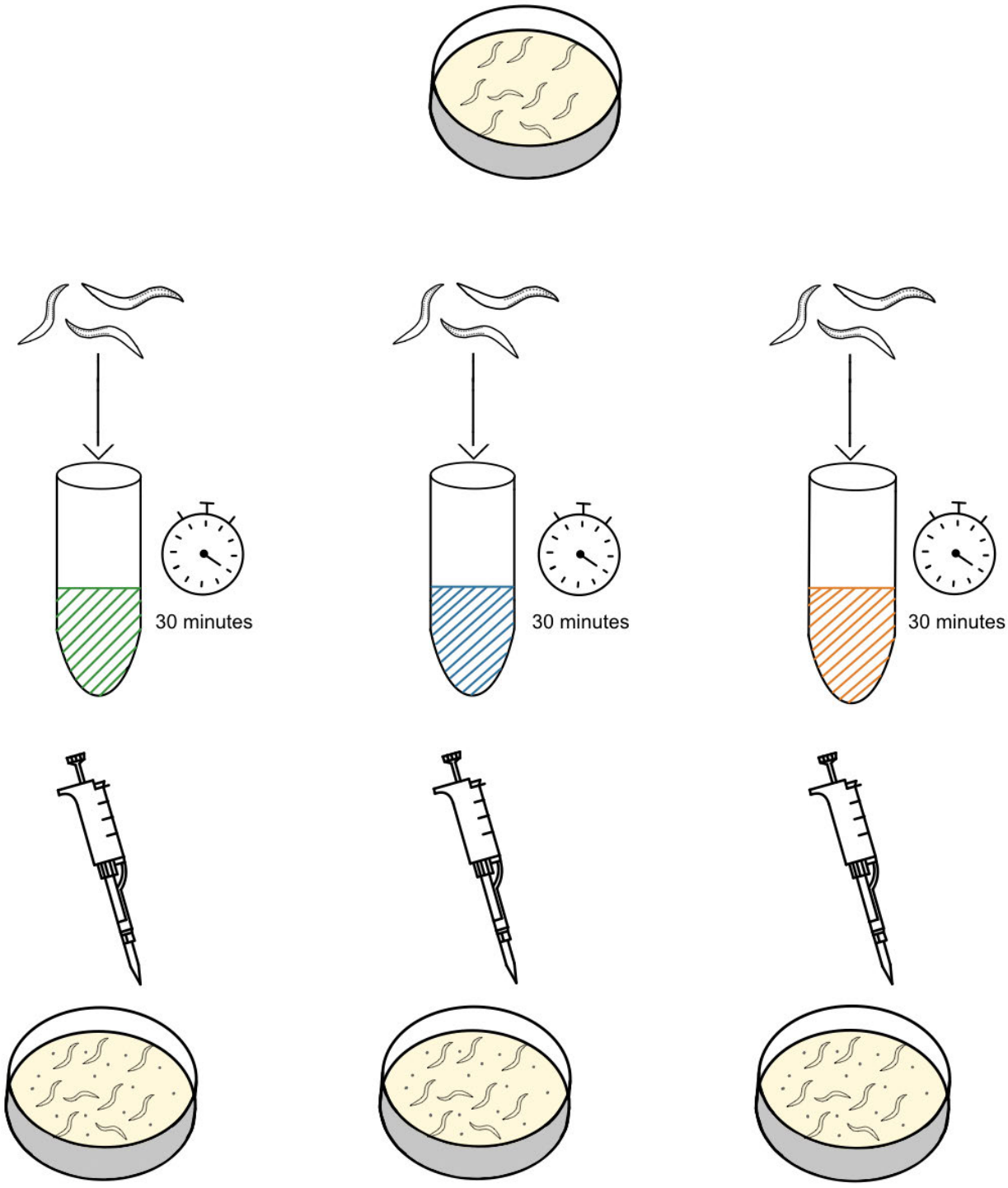

Figure 1: Egg-Laying Assay Procedure

Graphical representation of the egg-laying procedure. Experimental groups were run in parallel with incubation start times staggered by 10 minutes. One complete trial had a total duration of 55 minutes. Dots on plates are representative of eggs laid.

Data Analysis

First, egg-laying data was tested for normality using the Shapiro Wilks test. Then, a two-way analysis of variance (ANOVA) was used to compare multiple variable changes according to two categorical variables. In this study, the ANOVA compared the differences in average eggs laid between incubation types and each concentration. Data collected for the toxicity assay was analyzed using one-way ANOVA, to compare the differences in percent survival between concentrations, with Dunnett's post hoc tests. All analyses were performed in *Python* (Jupyter Notebook, Ver. 7.0.8).

Results

Toxicity Data

We began with the toxicity assay and created the dose response curve for the effect of DOI on percent survival rate. By using this dose response curve, we determined the drug concentrations that were affecting the survival of the *C. elegans* significantly. These toxic doses were then excluded from behavioral experiments so that toxic effects were not included in the analysis of drug effects on behavior. The toxicity dose response date is show in **Table 1**, and the curve is shown in **Figure 2**.

Drug & Dose	M9 (0mM)	0.1mM DOI	0.3mM DOI	1mM DOI	3mM DOI	10mM DOI
% Survival	92.892	94.324	95.159	90.239	93.629	12.742

Table 1: 24 hours % Survival – Toxicity Assay

Mean percent of worms alive 24 hrs. after acute drug exposure across all drug conditions and concentrations.

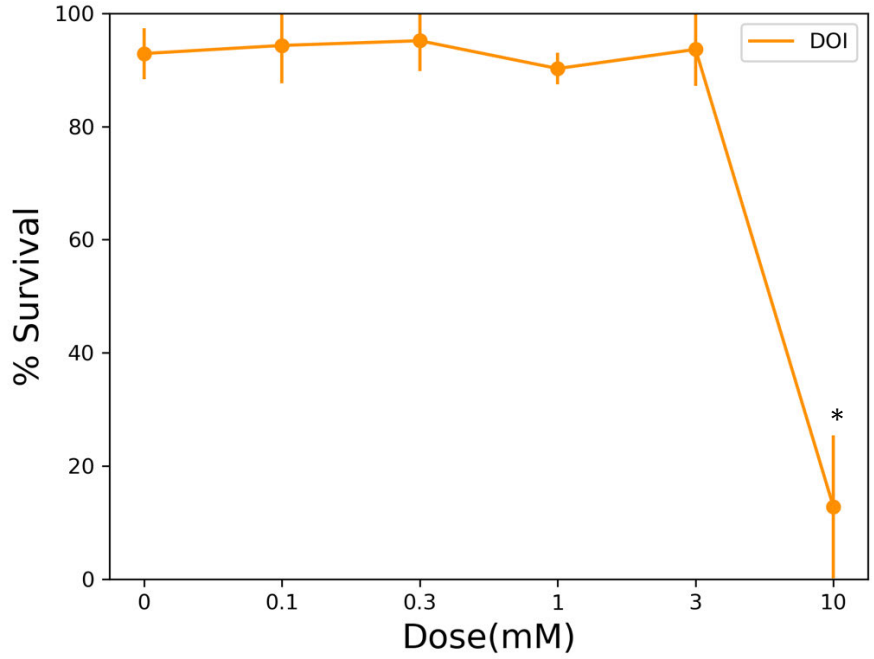

Figure 2: 24-hour Percent Survival – Toxicity Assay

Line graph of the percent survival at 6 doses with 0mM representing the control group and 10mM representing the highest drug concentration. A one-way ANOVA revealed a significant effect of dose on worm survival ($F(5,24) = 53.877$, $p = 2.895 \times 10^{-12}$). Survival was significantly diminished in the 10 mM group relative to vehicle control ($p = 8.31 \times 10^{-7}$; Dunnett's post hoc test). DOI concentrations below 10 mM did not significantly impact worm survival 24 hours later, (p's > 0.05). Significance is denoted with *. Error bars represent 95% CI.

From this data, we concluded that the toxic effects of DOI begin around the 10 mM concentration. Given that DOI appears to have toxic effects at the 10 mM concentration, we choose to test concentrations lower than 10 mM in the egg-laying assay. Data for egg-laying is shown in **Figure 4**.

Preliminary Data

These toxicity experiments were followed by a preliminary egg-laying assay. To determine whether we had an adequate protocol that accurately examines increases in egg-laying, we included a positive control group. Worms were incubated in a concentration of

serotonin that has been show in previous studies to elicit an increase in egg-laying (Brown & Luo, 2009; Dempsey et al., 2005; Schafer, 2005). In this preliminary experiment, we compared the effects of a control vehicle solution, a 1 mM concentration DOI, and a 5 mg/mL concentration of serotonin on egg-laying. Preliminary data is shown in **Figure 3**.

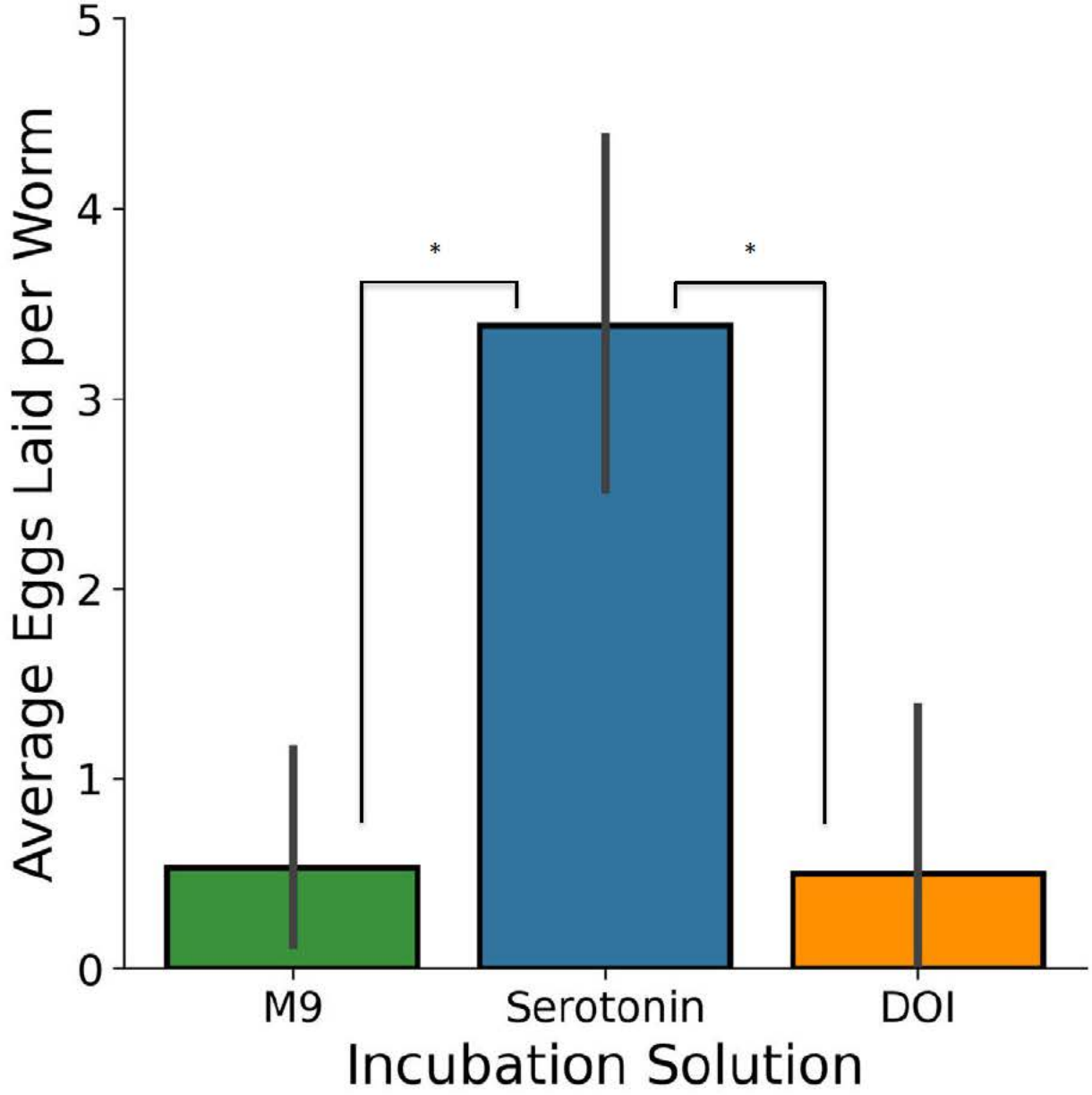

Figure 3: Preliminary Data – Egg-Laying Assay

Bar graph of the average number of eggs laid per worm across all 8 trials for each incubation type. A one-way ANOVA reveled that there was a statistically significant difference between at least two groups, ($F(3, 8) = 15.2694$. $p = (8.0517 * 10^{-5})$). * $p < 0.001$. Tukey's HSD Test for multiple comparisons found that the average eggs laid between M9 and 5-HT ($p < 0.001$, 95% C.I. = [-4.366, -1.343]) and 5-HT and DOI ($p < 0.001$, 95% C.I. = [-4.397, -1.374]) were significantly different. There was no statistically significant difference in average eggs laid between M9 and DOI ($p = 0.999$, 95% C.I. = [-1.480, 1.543]). Significance is denoted with *. Error bars represent 95% CI.

Egg-Laying Data – Dose Response Curve

After completing the preliminary experiment, we collected data to generate a full dose response curve. Each dose was averaged across 8 trials and graphed in **Figure 4**. Analysis began by performing a Shapiro-Wilk test to examine the normality of the data, which revealed that the distribution departed significantly from normality for each group *(W* = 0.898, p-value < 0.05). Based on this outcome, we performed a transformation for data normalization using the square-root function. The Shapiro-Wilk test on the transformed data, **Table 2**, showed that the distribution did not depart from normality, apart from the control groups *(W* = 0.878, p-value > 0.05). We decided to analyze and graph the transformed data, including the non-normally distributed control group, because the control group had a much larger pool (n=32), than each drug concentration (n=8).

	Solution	
Dose (mM)	**M9**	**DOI**
0.1	0.763035	0.897424
0.3	0.593236	0.689262
1	0.534954	1.069422
3	0.967419	1.154099

Table 2: Transformed Data – Egg-Laying Assay

Mean number of eggs laid per worm across all trials for each drug condition at each dose, after the data from each trial had undergone a square-root transformation to create a normal distribution of data.

The square-root transformed data was used for all graphing and statistical analysis; shown in **Figure 4,** which contains all doses and drug conditions.

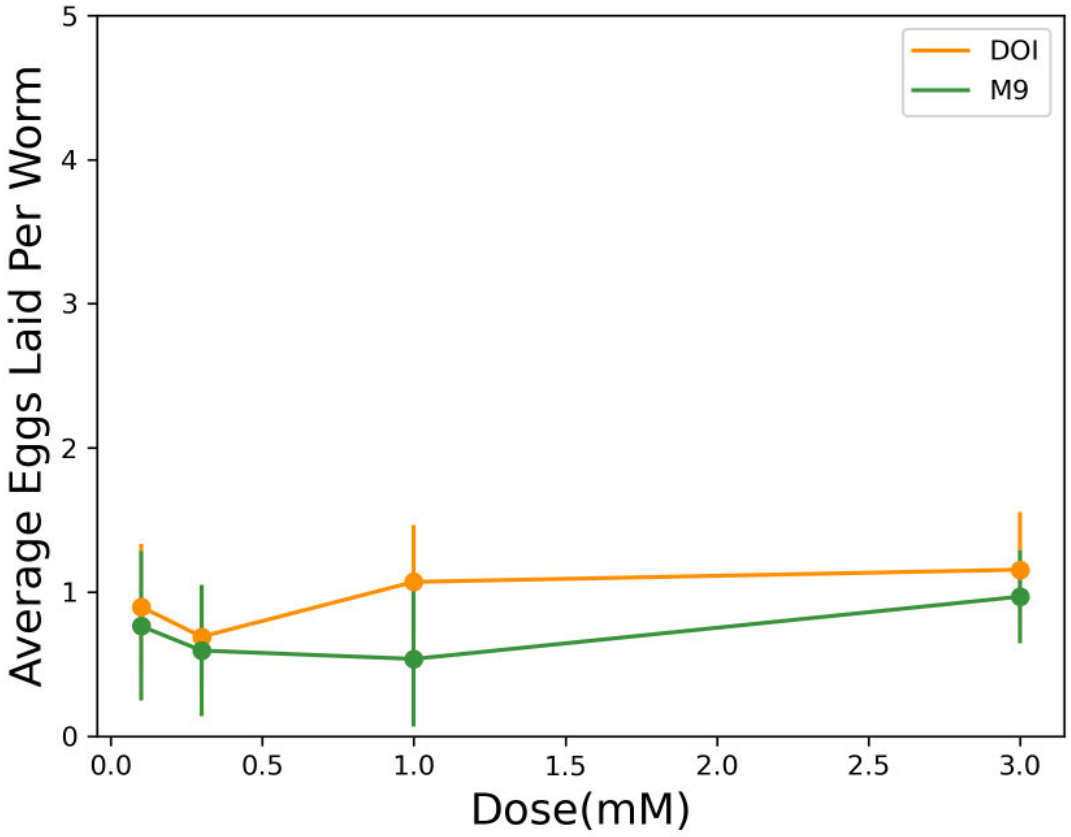

Figure 4: Dose Response Curve – Egg-Laying Assay

Line graph of the square-root transformed average eggs laid per worm at 4 doses, for both incubation conditions across all trials. A two-way ANOVA revealed that there was a no significant main effect from drug, ($F(1, 12) = 2.385$, $p = 0.1267$) or dose, ($F(4, 12) = 1.566$, $p = 0.1920$), and no significant interaction effects ($F(4, 12) = 0.772$, $p = 0.5469$). Error bars represent 95% CI.

An *a priori* power analysis was performed using G*Power which revealed that at a power of 0.8 at least > 200 trials would be required to detect a significant difference. Based on this analysis we conclude that there is no significant effect of DOI on egg-laying and the lack of effect is not dose dependent.

Discussion

Conclusions

Psychedelic research is rapidly growing due to the predicted positive effects in treatment of mental health. There has been an increase in interest to understand how and why psychedelics create these beneficial effects. The goal of this study was to contribute to the growing body of knowledge about the effects of psychedelics and determine if *C. elegans* are a useful model organism to use in further experimentation. Since psychedelics are hypothesized to act through serotonin receptors, we examined a behavior that is regulated by serotonin. Egg-laying behavior, one such behavior, is regulated specifically through the *ser-1* receptor in *C. elegans.* Through this experiment, we aimed to understand how DOI affects the rate of egg-laying behavior in *C. elegans.*

From the toxicity data, we can conclude that the toxic effects of DOI begin to be observed around the 10 mM dose as there is a statistically significant difference between the percent survival rate at 0 mM and 10 mM and a lack of significance at all other doses. This suggests that any behavioral effects that are observed at this dose are correlated with toxicity and cannot be used to explain any effect or lack of effect due to drug. The toxicity dose response curve provides context for the upper limit of this drug and allowed us to narrow down our range of experimental doses.

In our preliminary experiments, we found that 1 mM DOI did not have any significant effect on the egg-laying rate of *C. elegans.* This was likely not do to issues with methodology, since we were able to observe a significant increase in egg-laying rate with our positive control, 5-HT.

Following the preliminary data, we aimed to see if the effect of DOI on egg-laying rate was dose dependent. By comparing the average rate of egg-laying to increasing concentrations of DOI, we created a dose response curve of DOI on egg-laying. The dose response curve for egg-laying revealed that there is no effect of DOI on egg-laying. The data also shows that the lack of effect is not dose dependent and at all tested concentrations the drug treated animals behaved similarly to untreated animals. These effects could have been observed due to low affinity between DOI and the *ser-1* receptor in *C. elegans.* It has been demonstrated that of the six serotonin receptors that *C. elegans* expresses, the receptor *ser-1* plays the most critical role in simulating the egg-laying behavior (Carnell et al., 2005; Dempsey et al., 2005). There are eight total neurons that regulate egg-laying behavior, 2 are stimulatory HSNs that release 5-HT through *ser-1* receptors, and 6 inhibitory cholinergic neurons (Collins et al., n.d.). Inhibitory effect to egg-laying have been observed with cholinergic signaling (Teshiba et al., 2016); however, DOI was not inhibitory to egg-laying behavior and did not decrease the rate of egg-laying. In total, DOI had no significant effect on egg-laying, either stimulatory or inhibitory, and mimicked the results of our control buffer solution.

Overall, these results allow us to better understand the behavioral effects of psychedelics. These experiments mainly suggest that DOI is not the ideal psychedelic drug to use in behavioral experiments with *C. elegans* because of its inability to elicit significant and observable behavioral changes. By observing a lack of effect we have further characterized what does and does not induce egg-laying (Teshiba et al., 2016). These results reveal that there is further research to be done to determine if *C. elegans* is a good model organism and what behavior can reliably provide results on psychedelic effects.

Future Directions

In the future, assessing *C. elegans* behavior using other psychedelic drugs will provide more information on if *C. elegans* is an effective model organism to examine psychedelics in. We have begun experiments on locomotion, another serotonin regulated behavior. In this locomotion study we are using two new psychedelic drugs, lysergic acid diethylamide (LSD) and N, N-dimethyltryptamine (DMT). In these locomotion experiments we are recording changes in forward and reserve velocity along with the number of reverse and forward initiated movements. We also plan to repeat the pharyngeal pumping experiments with LSD and DMT and compare the effects of these drugs to the observed inhibitory effects of DOI.

Bibliography

Aghajanian, G. K., & Marek, G. J. (1999). Serotonin and Hallucinogens. *Neuropsychopharmacology*, *21*(1), 16–23. https://doi.org/10.1016/S0893-133X(98)00135-3

Brenner, S. (1974). The Genetics of CAENORHABDITIS ELEGANS. *Genetics*, *77*(1), 71. https://doi.org/10.1093/genetics/77.1.71

Brittin, C. A., Cook, S. J., Hall, D. H., Emmons, S. W., & Cohen, N. (2021). A multi-scale brain map derived from whole-brain volumetric reconstructions. *Nature*, *591*(7848), 105–110. https://doi.org/10.1038/s41586-021-03284-x

Brown, M., & Luo, Y. (2009). *Bilobalide modulates serotonin-controlled behaviors in the nematode Caenorhabditis elegans | BMC Neuroscience | Full Text*. BMC Neuroscience. https://bmcneurosci.biomedcentral.com/articles/10.1186/1471-2202-10-62

Brundage, L., Avery, L., Katz, A., Kim, U.-J., Mendel, J. E., Sternberg, P. W., & Simon, M. I. (1996). Mutations in a C. elegans Gqα Gene Disrupt Movement, Egg Laying, and Viability. *Neuron*, *16*(5), 999–1009.

Carhart-Harris, R., Giribaldi, B., Watts, R., Baker-Jones, M., Murphy-Beiner, A., Murphy, R., Martell, J., Blemings, A., Erritzoe, D., & Nutt, D. J. (2021). Trial of Psilocybin versus Escitalopram for Depression. *New England Journal of Medicine*, *384*(15), 1402–1411. https://doi.org/10.1056/NEJMoa2032994

Carnell, L., Illi, J., Hong, S. W., & McIntire, S. L. (2005). The G-Protein-Coupled Serotonin Receptor SER-1 Regulates Egg Laying and Male Mating Behaviors in *Caenorhabditis elegans*. *The Journal of Neuroscience*, *25*(46), 10671–10681. https://doi.org/10.1523/JNEUROSCI.3399-05.2005

Collins, K. M., Bode, A., Fernandez, R. W., Tanis, J. E., Brewer, J. C., Creamer, M. S., & Koelle, M. R. (n.d.). Activity of the C. elegans egg-laying behavior circuit is controlled by competing activation and feedback inhibition. *eLife*, *5*, e21126. https://doi.org/10.7554/eLife.21126

Cook, S. J., Jarrell, T. A., Brittin, christopher A., Wang, Y., Bloniarz, A. E., Yakovlev, M. A., Nguyen, K. c. Q., tang, L. T.-H., Bayer, E. A., Duerr, J. S., Bulow, H. E., Hobert, O., Hall, D. H., & Emmons, S. W. (2019). Whole-animal connectomes of both Caenorhabditis elegans sexes. *Nature*, *571*(7763), 63–71. https://doi.org/10.1038/s41586-019-1352-7

Corsi, A. K. (2015). A Transparent window into biology: A primer on Caenorhabditis elegans. *WormBook*, 1–31. https://doi.org/10.1895/wormbook.1.177.1

Dag, U., Nwabudike, I., Kang, D., Gomes, M. A., Kim, J., Atanas, A. A., Bueno, E., Estrem, C., Pugliese, S., Wang, Z., Towlson, E., & Flavell, S. W. (2023). Dissecting the Functional Organization of the C. elegans Serotonergic System at Whole-Brain Scale. *bioRxiv*, 2023.01.15.524132. https://doi.org/10.1101/2023.01.15.524132

Davis, A. K., Barrett, F. S., May, D. G., Cosimano, M. P., Sepeda, N. D., Johnson, M. W., Finan, P. H., & Griffiths, R. R. (2021). Effects of Psilocybin-Assisted Therapy on Major Depressive Disorder. *JAMA Psychiatry*, *78*(5), 1–9. https://doi.org/10.1001/jamapsychiatry.2020.3285

de la Fuente Revenga, M., Zhu, B., Guevara, C. A., Naler, L. B., Saunders, J. M., Zhou, Z., Toneatti, R., Sierra, S., Wolstenholme, J. T., Beardsley, P. M., Huntley, G. W., Lu, C., & González-Maeso, J. (2021). Prolonged epigenomic and synaptic plasticity alterations following single exposure to a psychedelic in mice. *Cell Reports*, *37*(3), 109836. https://doi.org/10.1016/j.celrep.2021.109836

Dempsey, C. M., Mackenzie, S. M., Gargus, A., Blanco, G., & Sze, J. Y. (2005). Serotonin (5HT), Fluoxetine, Imipramine and Dopamine Target Distinct 5HT Receptor Signaling to Modulate Caenorhabditis elegans Egg-Laying Behavior. *Genetics*, *169*(3), 1425–1436. https://doi.org/10.1534/genetics.104.032540

DOI. (2020, May 13). Psychedelic Science Review. https://psychedelicreview.com/compound/doi/

Halberstadt, A. L., Chatha, M., Klein, A. K., Wallach, J., & Brandt, S. D. (2020). Correlation between the potency of hallucinogens in the mouse head-twitch response assay and their behavioral and subjective effects in other species. *Neuropharmacology*, *167*, 107933. https://doi.org/10.1016/j.neuropharm.2019.107933

Hammarlund, M., Hobert, O., Miller, D. M., & Sestan, N. (2018). The CeNGEN Project: The Complete Gene Expression Map of an Entire Nervous System. *Neuron*, *99*(3), 430–433. https://doi.org/10.1016/j.neuron.2018.07.042

Hanks, J. B., & González-Maeso, J. (2012). Animal Models of Serotonergic Psychedelics. *ACS Chemical Neuroscience*, *4*(1), 33–42. https://doi.org/10.1021/cn300138m

Hobert, O. (n.d.). *Neurotransmitter Map ·*. Retrieved September 17, 2024, from https://www.hobertlab.org/neurotransmitter-map/

Horvitz, H. R., Chalfie, M., Trent, C., Sulston, J. E., & Evans, P. D. (1982). Serotonin and octopamine in the nematode Caenorhabditis elegans. *Science (New York, N.Y.)*, *216*(4549), 1012–1014. https://doi.org/10.1126/science.6805073

Jarrell, T. A., Wang, Y., Bloniarz, A. E., Brittin, C. A., Xu, M., Thomson, J. N., Albertson, D. G., Hall, D. H., & Emmons, S. W. (2012). The Connectome of a Decision-Making Neural Network. *Science*, *337*(6093), 437–444. https://doi.org/10.1126/science.1221762

Jones, K. A., Srivastava, D. P., Allen, J. A., Strachan, R. T., Roth, B. L., & Penzes, P. (2009). Rapid modulation of spine morphology by the 5-HT2A serotonin receptor through kalirin-7 signaling. *Proceedings of the National Academy of Sciences of the United States of America*, *106*(46), 19575–19580. https://doi.org/10.1073/pnas.0905884106

Kaletta, T., & Hengartner, M. O. (2006). Finding function in novel targets: C. elegans as a model organism. *Nature Reviews Drug Discovery*, *5*(5), 387–399. https://doi.org/10.1038/nrd2031

Kim, Y., Park, Y., Hwang, J., & Kwack, K. (2018). Comparative genomic analysis of the human and nematode Caenorhabditis elegans uncovers potential reproductive genes and disease associations in humans. *Physiological Genomics*, *50*(11), 1002–1014. https://doi.org/10.1152/physiolgenomics.00063.2018

López-Giménez, J. F., & González-Maeso, J. (2018). Hallucinogens and Serotonin 5-HT2A Receptor-Mediated Signaling Pathways. *Current Topics in Behavioral Neurosciences*, *36*, 45–73. https://doi.org/10.1007/7854_2017_478

Nardou, R., Sawyer, E., Song, Y. J., Wilkinson, M., Padovan-Hernandez, Y., de Deus, J. L., Wright, N., Lama, C., Faltin, S., Goff, L. A., Stein-O'Brien, G. L., & Dölen, G. (2023). Psychedelics reopen the social reward learning critical period. *Nature*, *618*(7966), 790–798. https://doi.org/10.1038/s41586-023-06204-3

Ornelas, I. M., Carrilho, B. de S., Ventura, M. A. V. de C., Domith, I., de V. Silveira, C. M., dos Santos, V. F., Delou, J. M., Moll, F., Pereira, H. M. G., Junqueira, M., Aguilaniu, H., & Rehen, S. (2024). Lysergic acid diethylamide induces behavioral changes in *Caenorhabditis elegans*. *Neuroscience Letters*, *837*, 137903. https://doi.org/10.1016/j.neulet.2024.137903

Schafer, W. R. (2005). Egg-laying. In *WormBook: The Online Review of C. elegans Biology [Internet]*. WormBook. https://www.ncbi.nlm.nih.gov/books/NBK19787/

Shao, L.-X., Liao, C., Gregg, I., Davoudian, P. A., Savalia, N. K., Delagarza, K., & Kwan, A. C. (2021). Psilocybin induces rapid and persistent growth of dendritic spines in frontal cortex in vivo. *Neuron*, *109*(16), 2535-2544.e4. https://doi.org/10.1016/j.neuron.2021.06.008

Tecott, L. H. (2007). Serotonin and the Orchestration of Energy Balance. *Cell Metabolism*, *6*(5), 352–361. https://doi.org/10.1016/j.cmet.2007.09.012

Teshiba, E., Miyahara, K., & Takeya, H. (2016). Glucose-induced abnormal egg-laying rate in Caenorhabditis elegans. *Bioscience, Biotechnology, and Biochemistry*, *80*(7), 1436–1439. https://doi.org/10.1080/09168451.2016.1158634

Trent, C., Tsung, N., & Horvitz, H. R. (1983). Egg-Laying Defective Mutants of the Nematode CAENORHABDITIS ELEGANS. *Genetics*, *104*(4), 619–647.

Whitaker-Azmitia, P. M. (1999). The Discovery of Serotonin and its Role in Neuroscience. *Neuropsychopharmacology*, *21*(1), 2–8. https://doi.org/10.1016/S0893-133X(99)00031-7

White, J. G., Southgate, E., Thomson, J. N., & Brenner, S. (1986). The structure of the nervous system of the nematode Caenorhabditis elegans. *Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences*, *314*(1165), 1–340. https://doi.org/10.1098/rstb.1986.0056