Specific Aims

Amyloid beta-42 ($A\beta_{42}$) peptide is a common target of therapeutics, either directly or indirectly due to its accumulation in Alzheimer's disease(AD) patients—a neurodegenerative disorder that severely reduces quality of life in millions of older individuals. However, this approach has had low success in clinical trials with growing concern that the approach is too narrow. While tau fibrils are another notable hallmark, interest is growing in treating the disease by considering other causative factors like synaptic dysfunction. Despite growing recognition of synaptic dysfunction in AD, a gap of knowledge remains to systematically test molecules that reverse synaptic dysfunction and restore neuronal circuitry lost in AD. Serotonergic molecules are known to induce synaptic plasticity, particularly, psychoplastogens are able to produce rapid and sustained neuritogenic effects after a single dose. Dosing a psychoplastogen like DOI on a proven *Drosophila* AD model, and measuring its effects through behavioral and molecular assays would quickly expand the approaches to the treatment of AD.

My long-term goal is to establish various lines of AD *Drosophila* as high-throughput drug repurposing screens to efficiently and systematically inform future therapeutic strategies to address AD. The overall objective of this application is to characterize the phenotypic effects after a single dose of the psychoplastogen DOI, to *Drosophila* that express $A\beta_{42}$. My central hypothesis is that given the neurodegenerative phenotypic effects of $A\beta_{42}$ in *Drosophila*, synaptic plasticity induced by DOI will restore neuronal circuitry thus rescue lifespan and motor skill deficits(figure 1). The rationale behind this is that mammalian optogenetic studies have shown psychoplastogens can reverse dendritic atrophy and restore the activity of neuronal populations previously disrupted by chronic stress, suggesting a potential for rescuing neuronal circuitry disrupted in neurodegenerative contexts. Additionally, previous neuronal imaging studies with *Drosophila* and DOI show increased dendritic spine formation after a single dose, 5-HT2 receptor in aggression models provide a tractable system to test serotonergic modulation *in vivo*, and expression of $A\beta_{42}$ can be induced in *Drosophila* using the GAL4-UAS system and wide variety of tissue specific drivers which has shown deficiencies in longevity, motor skills, and eye morphology–highly indicative of the neurodegenerative pathology. Therefore, I propose the following aims.

AIM 1: Rescue the lifespan deficits of $A\beta_{42}$ *Drosophila* after single DOI dosage

Expression of $A\beta_{42}$ with the GAL4-UAS and Appl pan-neuronal driver results in a significant decline of lifespan in *Drosophila* measured in a longevity assay and Kaplan-meier survival analysis. I hypothesize that a single early life DOI dose will alleviate neurodegenerative lifespan defectits.To characterize this effect, I will generate, maintain, and administer DOI to $A\beta_{42}$ *Drosophila*,14 days after eclosion(DAE). Their lifespan will be monitored daily until natural death to generate survival curves to compare to controls.

AIM 2: Improve motor skill deficits over the lifespan of $A\beta_{42}$ *Drosophila* after single DOI dosage

Expression of $A\beta_{42}$ in *Drosophila* with the GAL4-UAS and Appl pan-neuronal driver results in a significant decline of their motor skills over their lifespan. I hypothesize that a single early life DOI dose will rescue climbing distance, climbing time, and climbing velocity deficiencies caused by $A\beta_{42}$. I will measure and characterize DOI's effects by administering it at 15 DAE then measuring motor abilities at 20 DAE and 40 DAE by recording their performance in the Rapid Iterative Negative Geo-taxis (RING) assay. Afterwards, video tracking software will automate data analysis to generate relevant plots.

a) Significance:

There is currently no cure for AD, a progressive neurodegenerative disorder which affects millions of people, and is the 7th leading cause of death in the United States [1]. Symptoms of the disease include lifespan deficits, motor dysfunction, and memory loss [1]. The amyloid cascade hypothesis has been the focus of millions of dollars and decades of pharmaceutical research to develop drugs that inhibit, clear, or reverse precursors or enzymes that give rise to cytotoxic $A\beta_{42}$ plaque formations [2,3,4]. However, despite FDA approval of well throughout candidate drugs for clinical trials, none have led to high efficacy treatment without major side effects—necessitating further studies into alternate therapeutic strategies and approaches [2,4,5]

A critical knowledge gap exists regarding early synaptic dysfunction and the mechanisms underlying phenomena such as terminal lucidity. In the early stages, the degeneration of synapses precedes the degeneration of neurons given the accumulation of cytotoxic $A\beta_{42}$ in the synapses [6]. Additionally, terminal lucidity episodes clue into therapeutic targeting of synaptic dysfunction, wherein, late-stage AD patients briefly regain mental faculties, hypothesized to be caused by sporadic neural bypass formation which restores neuronal circuitry [7].To date, no studies have tested the neuritogenic and synaptogenic properties of psychoplastogens in an *in vivo* neurodegenerative disease model which could restore neuronal circuitry and behavioral deficits. Thus, it is significant to test a psychoplastogen for the first time in an established *in vivo* AD model [7,8,9,10].

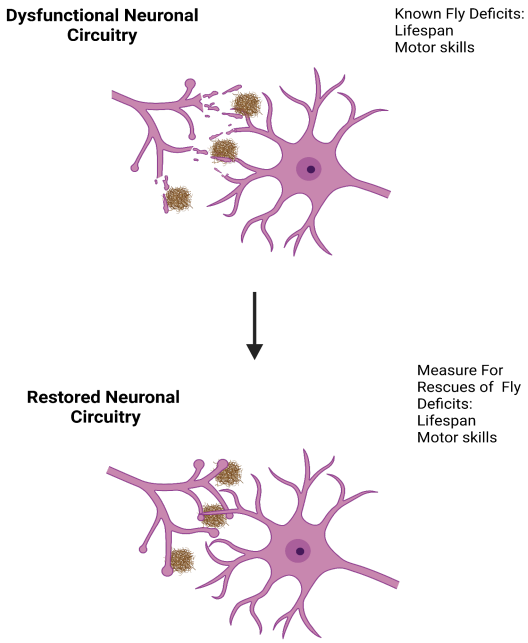


Figure 1: General neuronal regeneration at the cellular level after DOI administration. DOI's ability to induce synaptogenesis through neurogenesis and increase of dendrites would circumvent neurons degenerated by $A\beta_{42}$ plaques or restore synapses $A\beta_{42}$ destroyed. The outcomes of DOI will be measured through measure of known behavioral outcomes due to $A\beta_{42}$.(Made with Biorender)

Psychoplastogens include psychedelics and 5HT2 agonists that induce neuronal restructuring and restore functionality by increasing dendrites and synapses with long lasting changes [11,12]. DOI–the psychoplastogen I plan to test—is a psychoplastogen and 5HT2 agonist. It has been shown to increase dendritic arbor of class I neurons in fruit fly larvae first instar[12]. Psychoplastogens have been studied in depression and PTSD studies in mice and humans, resulting in positive effects and promising findings [13,14,15,16].

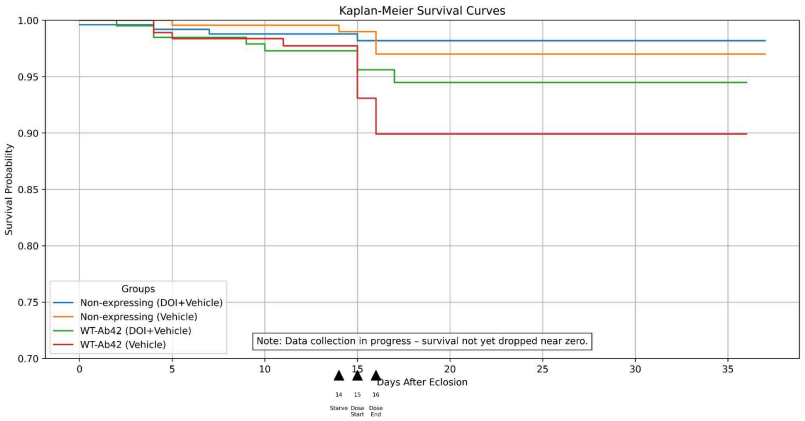
This proposed project is significant because the field demands it[4,5,8,21]. I will provide the first *in vivo* evidence for the use of psychoplastogens to rescue AD-related synaptic dysfunction, paving the way for new therapeutic strategies. My results will deepen the understanding of biological and molecular mechanisms underlying AD. Ultimately, I will illuminate alternative therapeutics that are potentially more cost-effective due to their natural and synthetic availability.

b)Innovation:

This project is innovative because it applies psychoplastogen screening to an established *in vivo* Drosophila model of Alzheimer's disease for the first time. While Drosophila has been used to study $A\beta_{42}$-induced neurodegeneration, no studies to date have explored the potential of psychoplastogens to treat this neurodegenerative disease model [17,18]. Leveraging the GAL4-UAS genetic toolkit, short generation time, and high-throughput capacity of Drosophila, this work establishes a scalable, cost-efficient platform for evaluating psychoplastogen compounds in a neurodegenerative context [19,20]. This approach not only introduces a novel application of existing models but also has the potential to uncover fundamentally new therapeutic strategies for enhancing synaptic resilience in AD.

c) Approach

Preliminary Data:

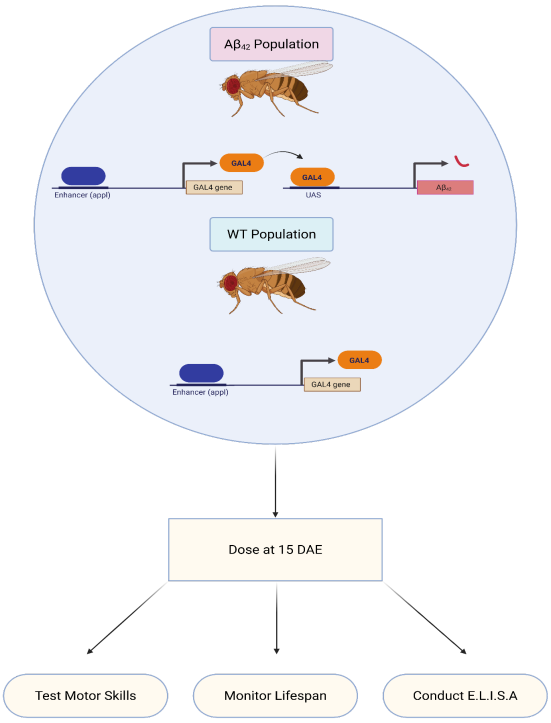


Early trends in my longevity assay described in Aim 1 section seem to support my hypothesis. Flies dosed with DOI have higher probabilities of survival in both the $A\beta_{42}$ and wildtype flies compared to not dosed populations. This suggests a positive effect similarly described in my hypothesis. This is still very early in the assay as the last fly is yet to die in any of my crosses, making data analysis and interpretation inconclusive.

Figure 2: In progress longevity data generated 5/8/25. Data analysis is inconclusive until the last fly passes away.

AIM 1: Rescue the lifespan deficits of *Drosophila* expressing $A\beta_{42}$ through DOI dosage treatment

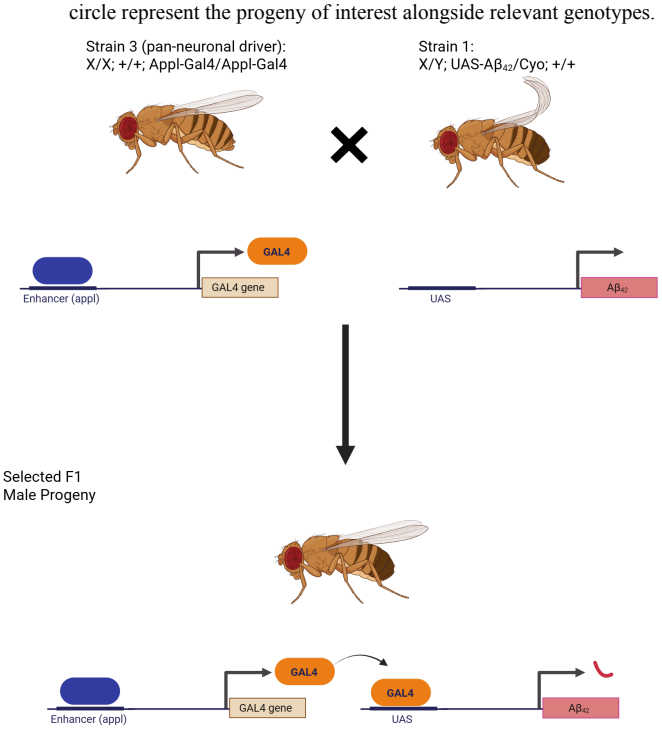
Introduction: The *objective* of this aim is to rescue the longevity deficit in fruit flies that express the neurodegenerative $A\beta_{42}$ by administering a psychoplastogen, DOI. My *working hypothesize* is that given the neuritogenic effects of DOI, its dosage will rescue lifespan deficits due to the neurodegenerative $A\beta_{42}$ in adult fruit flies. I will accomplish this aim by generating, maintaining, and administering DOI to $A\beta_{42}$ *Drosophila* 14 days after eclosion(DAE) and proceed to track population numbers until death of natural causes.



Research Design:

Fruit Flies: This aim will be completed with the male progeny of crosses made with 3 parental strains of flies that carry relevant genes and selection markers shown in figure 3. The parental strains shown in figure 4 are as follows, strain 1 (UAS-$A\beta_{42}$) contains the $A\beta_{42}$ gene with a UAS activated by Gal4 alongside a Cyo allele balancer to prevent crossovers and serves as a selection marker through curly winged flies. Strain 2 (w;+;+) contains all wildtype genes except for a white eyed phenotype which when crossed with a driver(appl) line that carries a wildtype eye color allele will result in selectable orange eyed progeny. Strain 3 is a pan-neuronal driver using the appl promoter found in all fly neurons to express gal-4 for UAS expression—in our case the $A\beta_{42}$ gene. Male progeny generated from 2 crosses, strain 1 x strain 3(experimental) and strain 2 x strain 3(experimental control), will be used to conduct the longevity experiment.

Figure 3: Overview of experimental work flow for the 3 aims in this proposal. Flies in circle represent the progeny of interest alongside relevant genotypes.



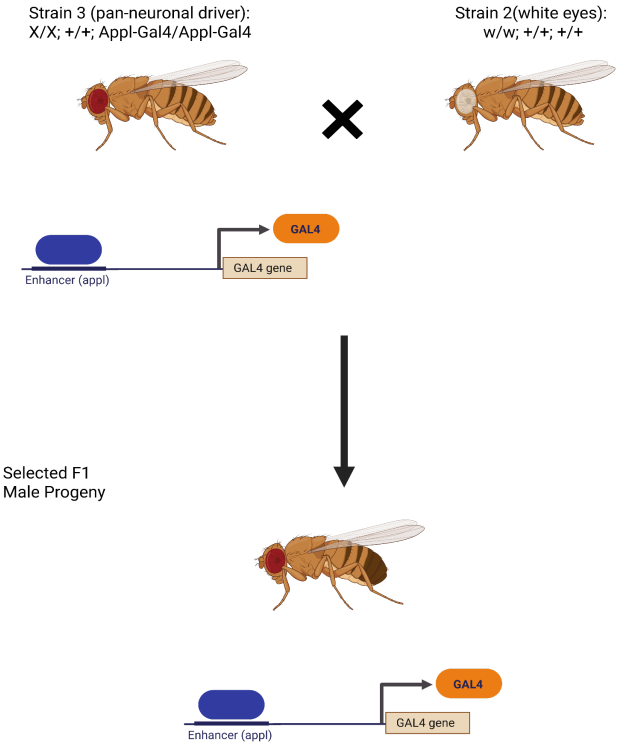
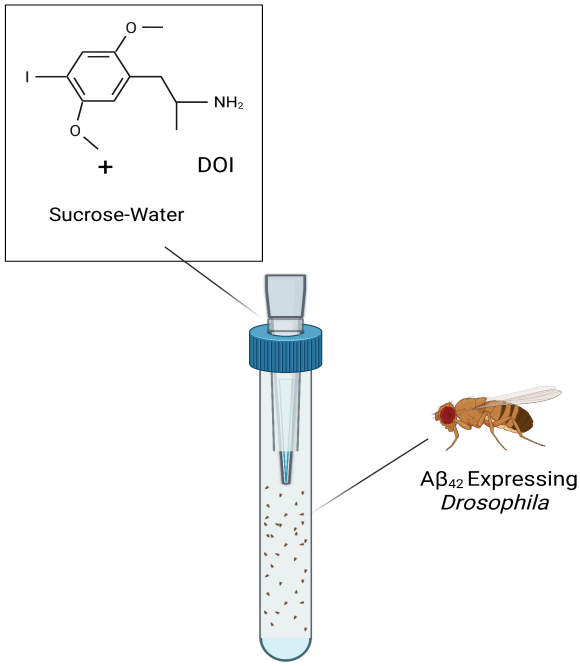


Figure 4: Experimental strains and crosses to be tested in the 3 aims of this proposal.

Crosses: The progeny of the 2 crosses will be separated from parentals, grouped into vials with food not exceeding 10 individual flies per vial. Each of the crosses's progeny will be split into 2 groups, DOI dosage group and vehicle dosage group for a total of 4 groups. 3 controls are used in this study: 2 vehicle groups—non-expressing and $A\beta_{42}$ expressing—and 1 DOI control for non-expressing. My experimental is $A\beta_{42}$ expressing with DOI dosage

Longevity: At least 100 male progeny collected into food vials for 4 groups will be maintained until death from natural causes. All vials will be swapped every 3 days until the conclusion of the experiment to maintain consistent quality of food, which affects fly lifespan[22]. No anesthesia protocols such as CO_2 knockout will be used after collection of progeny into food-vials; CO_2 exposure can decrease lifespan[22]. Progeny will be raised in a 25°C environment, 12 hr dark/night cycle, and constant humidity for consistent Gal4-UAS expression and circadian rhythm. Data will be collected everyday to note the number of flies alive or dead. Flies that get stuck in food, fly away, or squished during data collection and food swaps will be censored to account for accidental deaths. Following the completion of the experiment, Kaplan-Meier survival curves will be generated to visualize the survival probability over time of the genotypes and treatments. A Mental-cox(log-rank) statistical test will measure the significance of the data and a pairwise test will be used to show significance between the groups.



Dosing during longevity: At 14 days after eclosure (DAE) from the flies' pupal form during the longevity protocol, they will be removed from food vials into agar vials for a starvation protocol of 24 hrs. The starvation period allows for a more efficient dosing protocol. After the 24 hr starvation period, flies will be transferred to a glass test tube with agar for a modified capillary feeding (CAFE) assay which uses micropipette tips to drip feed a 20% sucrose water vehicle solution or a 3mM DOI-vehicle solution for a 24 hr dosing period as shown in figure 5. 3mM has shown considerable effects in previous fly research concerning circadian behaviors that are linked to the same receptors in neuronal plasticity[15]. Dosing test tubes will hold no more than 10 flies, and all dosing tubes will be outfitted with 10 ul of DOI-vehicle or vehicle. The meniscus will be ticked off at the beginning and end of the dosing period to be compared to evaporation controls to ensure flies are ingesting a given solution.

Detailed Expectations: I expect to obtain the lifespan probabilities of non-expressing and $A\beta_{42}$ expressing flies treated or not treated with DOI over time. This experiment can run from anywhere from 60 to 150 days given the average lifespan of lab reared fruit flies in our lab. Statistical analysis between the groups will reveal whether there is a significant difference in DOI treated flies that express $A\beta_{42}$. A significant lifespan increase in $A\beta_{42}$ DOI treated flies compared to not treated $A\beta_{42}$ flies will prove that DOI has positive lifespan effects in a neurodegenerative disease *in vivo* model(figure 6).

Figure 5: Drip feed apparatus containing 3mM DOI dissolved in 20% sucrose-water vehicle solution for modified CAFE assay.

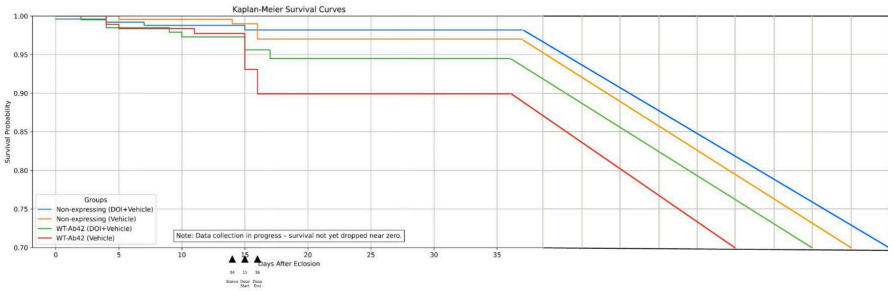


Figure 6: Expected longevity trends wherein significance in treatment groups is observed.

Potential Pitfalls & Alternative Strategies: Dosage with DOI could result in the opposite effect, wherein flies that received the treatment lived less than those that didn't(figure 7). It would be significant to see this effect only in flies that express $A\beta_{42}$ rather than

the controls. This would still provide valuable insight into the nature of $A\beta_{42}$'s cytotoxicity combined with neuroplasticity, necessitating further studies. There is also the possibility that the dosage makes the poison or cure, necessitating a study into generating a dosage response curve.

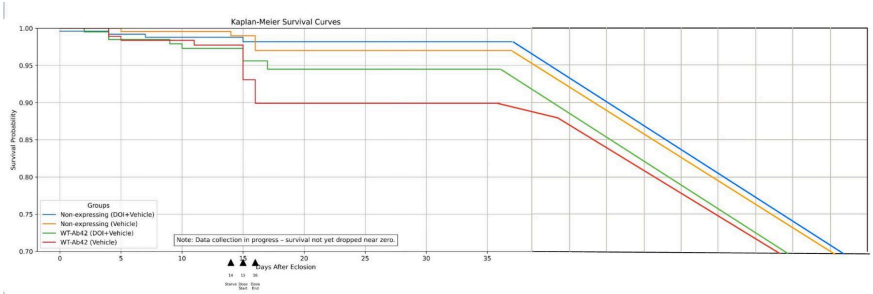


Figure 7: Unexpected longevity trends wherein no significance in treatment groups is observed.

AIM 2: Improve motor skill deficits over the lifespan of *Drosophila* expressing $A\beta_{42}$ through DOI dosage treatment

Introduction: The *objective* of this aim is to rescue the motor skill deficits in fruit flies that express the neurodegenerative $A\beta_{42}$ by administering a psychoplastogen, DOI. My *working hypothesize* is that given the neuritogenic effects of DOI, its dosage will restore motor neuronal circuitry that the neurodegenerative $A\beta_{42}$ previously eliminated in fruit flies. I will accomplish this aim by generating, maintaining, and administering DOI to $A\beta_{42}$ *Drosophila* at an early and late life time point after eclosion. After a recovery period, a rapid iterative negative geotaxis (RING) assay will video record their motor ability performance before video movement analysis.

Research Design:

Fruit Flies: This aim will be completed with the male progeny of crosses made with 3 strains of flies that carry relevant genes and selection markers shown in figure 3. The parental strains shown in figure 4 are as follows, Strain 1 (UAS-$A\beta_{42}$) contains the $A\beta_{42}$ gene with a UAS activated by Gal4 alongside a Cyo allele balancer to prevent crossovers and serves as a selection marker through curly winged flies. Strain 2 (w;+;+) contains all wildtype genes except for a white eyed phenotype which when crossed with a driver(appl) line that carries a wildtype eye color allele will result in selectable orange eyed progeny. Strain 3 is a pan-neuronal driver using the appl promoter found in all fly neurons to express gal-4 for UAS expression—in our case the $A\beta_{42}$ gene. Male progeny generated from 2 crosses, strain 1 x strain 3(experimental) and strain 2 x strain 3(experimental control), will be used to conduct the RING experiment.

Crosses: The progeny of the 2 crosses will be separated from parentals, grouped into vials with food not exceeding 10 individual flies per vial. Each of the crosses's progeny will be split into 2 groups, DOI dosage group and vehicle dosage group for a total of 4 groups. 3 controls are used in this study: 2 vehicle groups for non-expressing and $A\beta_{42}$ expressing and 1 DOI control for non-expressing. My experimental is $A\beta_{42}$ expressing with DOI dosage

RING assay: At various distinct time points, flies will be tested to measure their motor skills over their lifespan. The first time point will measure their skills at 25 DAE for an early life test and 39 DAE for a late life time point. More time points will be measured upon the completion of the longevity assay for a more apt comparison of early, mid, and late lifespan points given the broad range of lab reared fruit flies(60-100 days). Nonetheless, flies will be starved and dosed over a 2 day period, 7 days before the RING test. Flies will be given 5 days of recovery after dosing so they don't adapt to vial tapping during the dosing protocol that induces negative geotaxis. 1 day before testing, flies will be anesthetized with CO_2 to sort into fresh food vials not exceeding 5 flies per vial. On the day of testing, these flies will be knocked out again for an equal amount of time as the previous CO_2 exposure for sorting into empty vials again not exceeding 5 flies per vial. These vials are then loaded on to a RING test contraption to raise the vials to a set height before being released into freefall to induce negative geotaxis. A camera at level with the landing height will record the flies in the vial for later video analysis of fly movement in computer software. Analysis with ANOVA will reveal significance before proceeding with a Tukey-Kramer analysis.

RING video analysis: Ctrax video tracking software is specially designed to track fruit fly movement on a light background. This will automate tracking analysis to generate position time graphs for the different groups. From this, time-velocity and time-acceleration graphs will be produced for further insight into the motor abilities of the flies.

Detailed Expectations: I expect to obtain data for position, velocity, and acceleration over time for non-expressing and $A\beta_{42}$ expressing flies treated or not treated with DOI for motor ability analysis over their lifespan. The major expectation is that flies expressing $A\beta_{42}$ and that are treated with DOI will reach target lines more often and faster than $A\beta_{42}$ flies not treated with DOI(figure 8). Statistical analysis between the groups will reveal whether there is a significant motor ability improvement in DOI treated flies that

express $A\beta_{42}$. A significant increase in $A\beta_{42}$ DOI treated flies compared to not treated $A\beta_{42}$ flies will prove that DOI has positive motor ability effects in a neurodegenerative disease *in vivo* model.

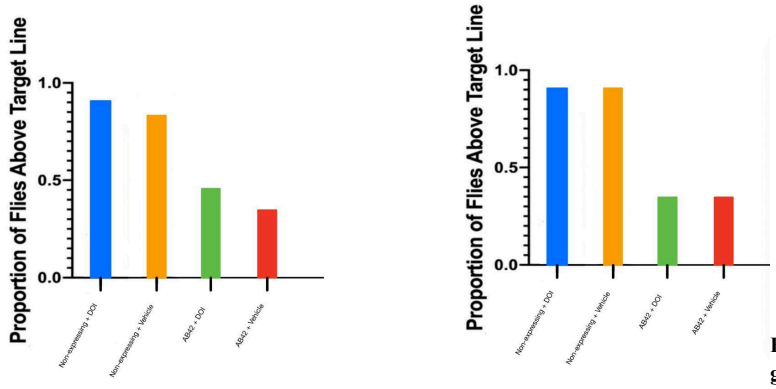


Figure 8: Expected(left graph) RING data and unexpected (right graph) RING data when considering each group's ability to reach a target line.

Potential Pitfalls & Alternative Strategies: Dosage with DOI could result in the opposite effect, wherein flies that received the treatment are less mobile than those that didn't(figure 8). Again, this effect would be highly intriguing in conjunction with the longevity outcomes. If my longevity results as hypothesized but my RING doesn't—and vice versa—it would provide valuable insight into the nature of $A\beta_{42}$'s cytotoxicity combined with neuroplasticity, necessitating further studies. Furthermore, not all psychoplastogens behave the same so testing others within this class of molecules would exhaust my hypothesis to completion[11,12].

Potential Difficulties, Limitations and Alternative Strategies

Limitations: Many limitations exist in this project given the lack of preliminary studies and technological access. I plan to observe male progeny to reduce genetic contamination females carry after copulation. This raises a lingering doubt that my results would be due to a bias found in males. Furthermore, our Gal4-UAS system starts expression during the larval stage which fails to mimic the progressive nature of Alzheimer's disease (AD) in humans[23]. Furthermore, our lab only expresses the $A\beta_{42}$ peptide directly instead of the APP pathway that produces $A\beta_{42}$ as a cleavage product which limits the complexity of my model. Tau pathology is another protein commonly associated with AD that my model does not capture in the Gal4-UAS. Investigating $A\beta_{42}$ levels overtime doesn't directly evidence a synaptogenesis mechanism. Testing only one psychoplastogen limits the scope of this investigation. Antagonists are also not studied in this proposal. Finally, the major limitation of *Drosophila* study is confidently informing clinical outcomes in humans given the vast difference in both organisms. That said, they do provide valuable investigation into notorious agents of AD by producing preliminary data to launch plausible and worthwhile new investigations into increasingly complex *in vivo* studies with mouse models or other higher organisms.

Alternative Strategies: GeneSwitch technology exists for temporal control of the Gal4-UAS system by adding RU486 to fly food at a desired time point in the fly's life[24]. This would allow for a more accurate AD model with our model, in terms of disease progression observed at later time points[1]. Furthermore, models that mimic the APP pathway to produce $A\beta_{42}$ exist in fruit flies and produce similar deficits in lifespan, motor skills, and memory allowing for a more complex system for psychoplastogen study[25]. Similarly, optogenetic studies would be better suited to primarily investigate the synaptogenesis mechanisms that would rescue lifespan and motor deficits in my hypothesis. The Gal4-UAS system could drive green fluorescence protein (GFP) expression with a chosen neuronal driver to visualize neuronal shape at the synapses for neuritogenesis with confocal microscopy.

Expanding the molecules tested is a bottleneck given the controlled status of these substances [26]. Tabernantholog (TBG) is another psychoplastogen of interest given its use in pre-existing studies and easier obtainability directly from Dr. Olson at UC Davis without state or federal oversight given its non-controlled status[27]. Furthermore, antagonists could be used in flies for a deeper insight into the role of the targeted 5HT2 receptor in our neurodegenerative fly model.

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