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Usage of Psilocybin to Treat Huntington's Disease: A Research Protocol

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Abstract

Introduction: Huntington's Disease (HD) is a progressive, neurodegenerative disease that causes significant amounts of neuron death in the brain. It is a genetic disorder, resulting from the over-repetition of the CAG sequence in the gene that codes for the huntingtin protein. Currently, there are no viable cures or treatments to slow or stop the progression of this disorder, making it a target candidate for treatment research. However, given the difficulty and complexity of in treating the genetic cause of HD in adults, a more viable approach may involve treating the resulting neurodegeneration with neuroprotective compounds, such as psilocybin. As such, our study proposes the usage of psilocybin to treat HD due to its neuroprotective, neurotrophic, and neuroplastic effects, resulting in a decreased rate of neuron loss and increased synaptic density.

Methods: We propose an *in-vivo* experiment using several groups of zQ175 knock-in (KI) mice, which will mimic HD in the mice. Following 8 weeks, the mice's brains will be extracted at different time intervals to analyze the progression of neuronal death using histology and immunohistochemistry, which should inform us about the progression of HD in the different groups of mice. Moreover, throughout this experiment, the motor control of the mice will be observed using the rotarod test, the raised beam test, and the footprint test. Data from these tests will act as behavioral markers for HD, providing an alternate source of information on the progression of HD in the mice.

Expected Results: KI mice are expected to have lower rates of neuronal death, higher amounts of synaptic density, and higher scores on average across the three motor behavior tests, compared to the non-treated KI mice.

Discussion: These results could provide insight into potential treatments for slowing the progression of HD. If successful, possible next steps could be to determine the efficacy of psilocybin in clinical trials for HD.

Conclusion: This study is expected to provide information on the usage of psilocybin as a treatment for HD. If the expected results are obtained, psilocybin may help improve the quality of life for those afflicted with HD.

Keywords: Huntington's disease; psilocybin; synaptic density; 5-HT_{2A} receptor

Introduction

Huntington's Disease (HD) is a progressive, neurodegenerative disease that is characterized by significant neuronal death in the brain [1]. HD has a genetic basis, and is caused largely by one defective gene, found on chromosome 4 [1, 2]. HD follows an autosomal dominant inheritance pattern, and the defect in the gene involves the over-repetition of a specific trinucleotide sequence (CAG) in the gene that codes for the huntingtin protein [1, 3]. Huntingtin exists normally in humans and is coded for by the repeating trinucleotide sequence, however in individuals without the defect, it repeats only 10-35 times, whereas in HD, it repeats 36 to 120+ times, resulting in a defective protein that is responsible for the symptomatology of the disease [1, 3]. Symptoms can include, but are not limited to, issues with movement, swallowing, speaking, breathing, concentrating, memory, personality/mood swings, jerky movements, clumsiness, depression, and stumbling. Individuals with over 39 repeats almost always develop the disease, which usually becomes fatal after a certain period, up to 20 years [4]. To date there are no approved cures/treatments to slow down or stop the progression of HD, making it an important candidate for treatment research, which, in addition to the neurodegenerative nature of the disease, is why we chose to explore the viability of psilocybin-based therapies to treat it [5, 6].

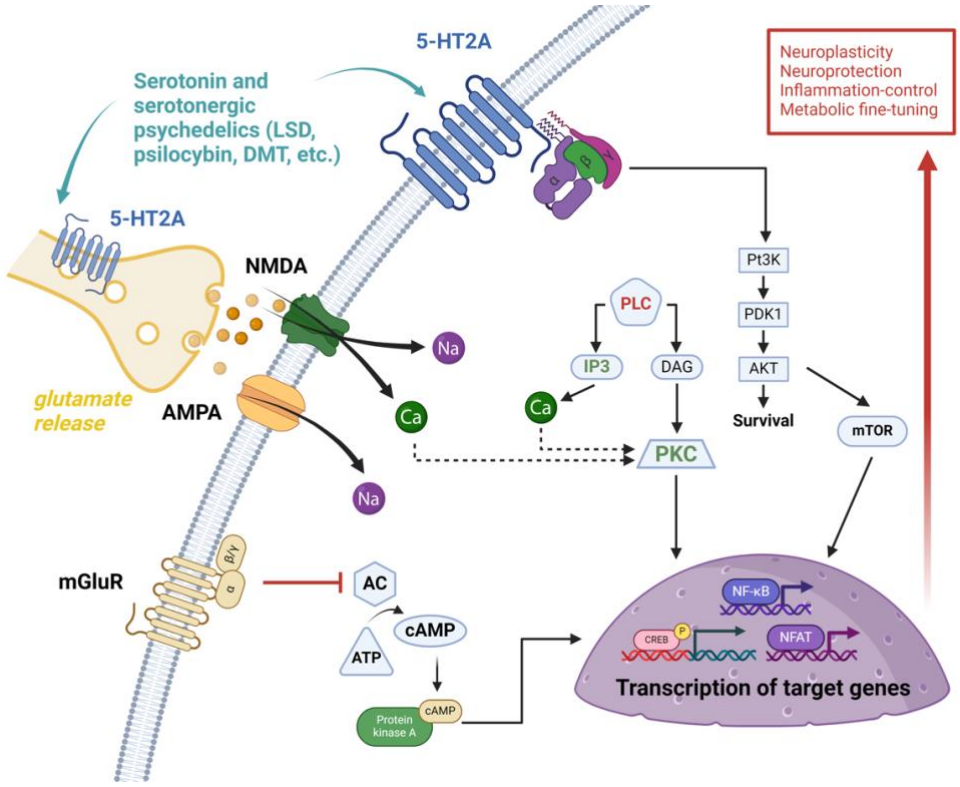

Figure 1. This diagram depicts the mechanism behind how psilocin, which is the active form of psilocybin, works in the brain (Created with BioRender.com).

Psilocybin is a psychotropic alkaloid that is commonly derived from fungi in the *Psilocybe* genus (most commonly *Psilocybe cubensis*) [7, 8]. This drug, when converted to its active form (psilocin) upon ingestion, binds primarily to the 5-HT_{2A} receptor and causes a variety of effects, including, but not limited to, increased synaptic density, neurogenesis, neuroprotection, and neuroplasticity through stimulation of glutamate release (which then triggers such effects through downstream activation of various receptors, including NMDA, AMPA, and mGluR), and protective, pro-neurotrophic pathways involving the PI3K/AKT/mTOR pathway, PLC/PKC pathway, and protein kinase A associated activity (see Fig. 1) [9, 10]. The potential of psilocybin as a neuroplastic, neurotrophic, and neuro-protective agent has been explored previously and may show promise, with the latter two attributes being primarily in animal trials and the first being in both animal and human trials [9-11]. These attributes of psilocybin have made it a compound of interest for treating neurodegenerative illnesses such as Alzheimer's Disease or Dementia. There is evidence that suggests psilocybin can slow or even reverse some of the damage that is characteristic of Alzheimer's and Dementia [10].

The neuroprotective and neurotrophic activity of psilocybin, along with its prior efficacy for other neurodegenerative diseases, may offer some much-needed hope for individuals afflicted with HD. These attributes may also help control and give structure to the rapid neurogenesis that occurs in an attempt to compensate for HD damage [12, 13]. It has also been shown that the onset and progression of HD symptoms in mice can be partially prevented by the pathways and proteins, notably brain-derived neurotrophic factors (BDNF), that are stimulated by psilocybin therapy [14].

This research protocol explores the potential of using psilocybin therapy to achieve similar results, in hopes that such therapies may improve the length and quality of the lives of those afflicted with HD.

Methods

Mice Conditions

192 zQ175 knock-in (KI) mice, which have a median survival of 90.1 weeks [15], and 48 wild-type (WT) mice, separated into 120 males and 120 females, will be housed in same-sex pairs in standard mouse cages under controlled temperature and humidity. They will be exposed to a 12-hour light/dark cycle and will be held at 23ºC (± 1ºC). Moreover, they will be given access to unlimited water, will be fed a controlled chow diet, and will be monitored every day for signs of cage aggression, disease, and overall wellness.

Drug Conditions and Administration

Psilocybin will be kept at -20ºC for storage throughout the experiment [16]. The compound will be dissolved in a saline solution and diluted to a concentration of 1mg/ml.

Experimental Protocol

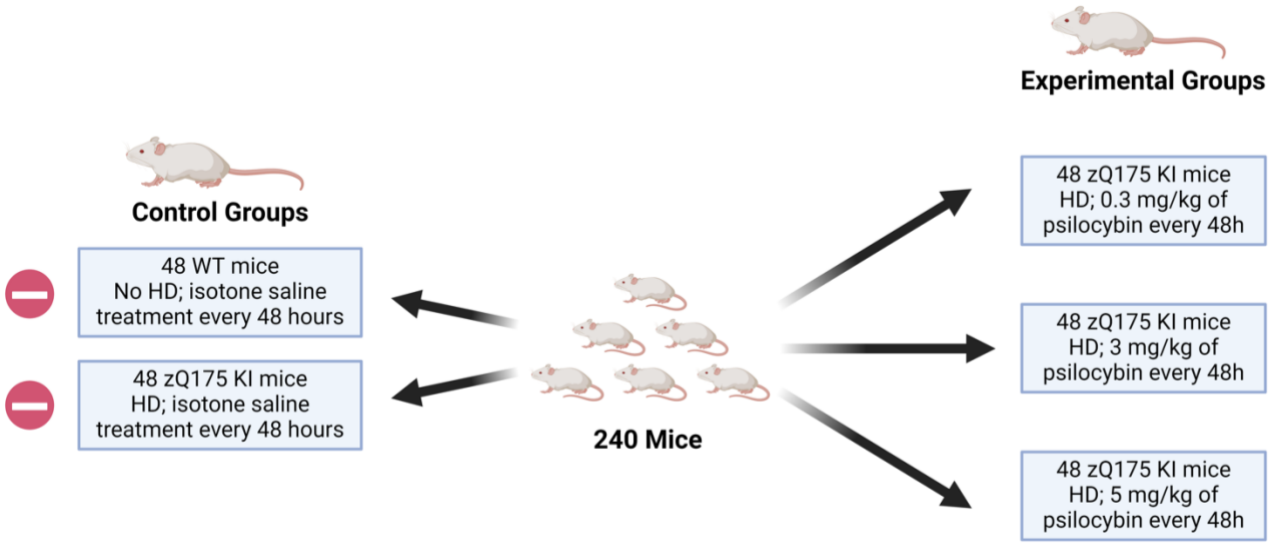

Figure 2. This diagram depicts how the 240 mice will be separated into 5 groups, 2 of which are the control groups and 3 of which are the experimental groups. The control groups will receive isotonic saline, while the experimental groups will receive psilocybin at varying concentrations. All mice will receive their respective treatment every 48 hours (Created with BioRender.com).

The 240 mice will be randomly assigned and are separated into 5 groups of 48 mice (24 male and 24 female per group) by a third party who will not be involved in data analysis, with 3 experimental groups and the other two acting as negative control groups [17]. The negative control groups include the 48 WT mice and a set of 48 zQ175 KI mice. The zQ175 KI mice were selected due to their phenotype being of close resemblance to human HD and their long life span, indicating their suitability for our protocol. Moreover, the WT mice will act as a point of comparison, helping us determine the disease baseline for HD in our mice. It will demonstrate behavioral and molecular differences for analysis. Starting from 8 weeks old, the experimental groups will receive psilocybin intraperitoneally via a cannula every 2 weeks and the control groups will receive isotonic saline in the same manner, given by the same third party who randomly assigned the mice [17]. The mice in the 3 experimental groups will receive the following dosages of psilocybin: 0.3 mg/kg, 3 mg/kg, and 5mg/kg (see Fig. 2) [18, 19].

Behavioral Observations

Three motor behavioural tests will be used to measure HD progression: rotarod test, raised beam test, and footprint test. For each test, the mice will undergo training, detailed below, so that they may complete each behavioral task. While they are receiving some exercise as a result, they are not receiving extensive motor training, allowing us to model our design and number of control groups off of [17, 20]. It is also interesting to note that when HD mice were given extensive exercise, there was no impact on BDNF levels when comparing the non-exercised and exercised HD mice. As such, any motor training given during this study should not be of concern when analyzing results.

For the rotarod test, which measures forelimb and hindlimb motor coordination and balance, all mice will undergo training where they are placed on the rotarod apparatus at a constant speed of 24 rpm for 60 seconds [21]. The latency for the mice to fall off the rotarod within the period is then recorded and the process is repeated 4 times per day for 3 days to establish a baseline performance [21]. Following this period, the mice will be tested every 2 weeks in a single session of 2 trials on an accelerating rotarod (5-44 rpm), where the mean latency will be recorded [21].

For the raised beam test, which measures motor coordination and balance, all mice will undergo initial training where they are placed on an inclined beam that starts wider on one side and progressively narrows [22]. The mice will be placed on the wider section of the beam and will be trained to cross the beam in under 20 seconds with their final time being recorded [21, 22]. Following this period, the mice will be tested every 2 weeks in a single session of 2 trials, where the time taken to traverse the beam and the number of times the hind feet slipped off the beam will be recorded. The mean score will then be calculated.

For the footprint test gait analysis, which is used to compare the gaits of the mice and determine any abnormalities in their gait, the hind feet and forefeet of the mice will be coated in non-toxic purple and orange paint, respectively [21]. The mice will then be prompted to walk along a 50 cm long, 10 cm wide, and 15 cm tall runway that has a sheet of white paper placed on the floor [21]. The

mice will be given 3 runs to establish a baseline performance, with the footprint patterns being analyzed for 4 parameters: stride length, hind-base width, front-base width, and amount of overlap between the left or right front footprint/hind footprint [21]. If the center of the hind footprint and the preceding front footprint completely overlap, a score of 0 will be given [21]. If the footprints do not overlap, the distance between the center of the footprints will be calculated [21]. Three scores will be calculated for each parameter: one immediately following the beginning of the run, one in the middle of the run, and one immediately before the end of the run [21]. The three scores will be averaged throughout the three trials [21]. Following this period, the mice will be given one run every 2 weeks, where the average scores will be taken for each parameter. It is also important to note that following each run, the sheet of paper on the floor will be replaced [21].

Molecular Analysis

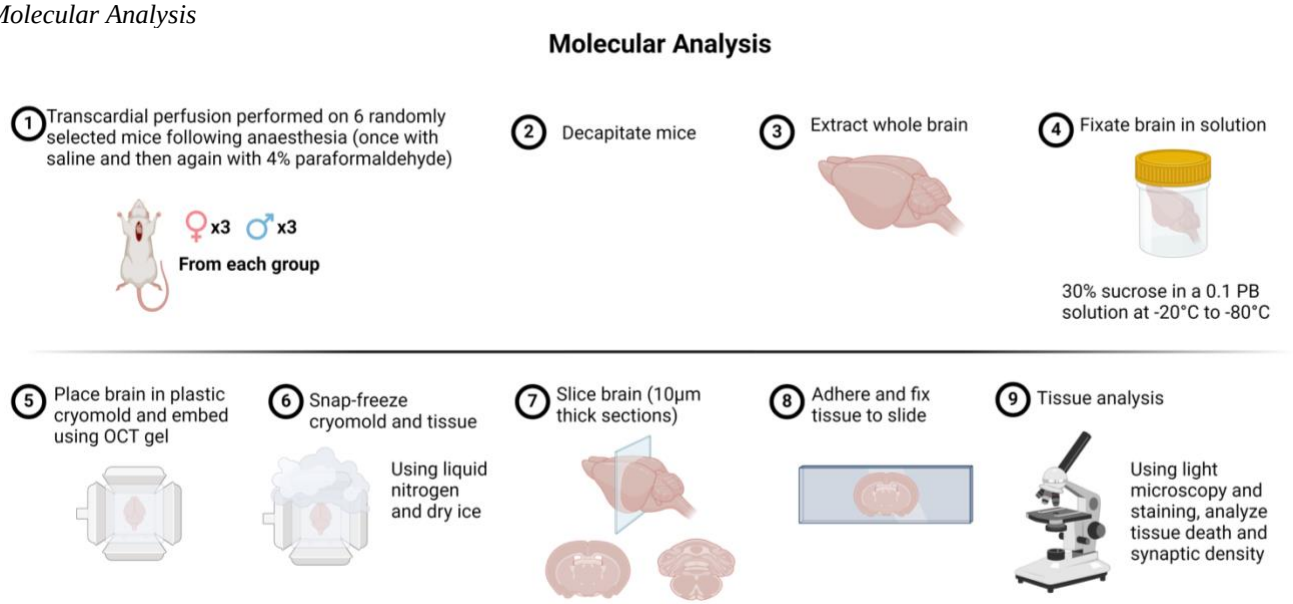

Figure 3. This diagram depicts the steps used to analyze the mice brains, which will provide information on synaptic density and rate of neuron death (Created with BioRender.com).

Before tissue collection, 6 mice, 3 female, and 3 male, randomly selected from each group will undergo anesthesia every 8 weeks from the start of the protocol [23]. Following this, transcardiac perfusion using saline will be performed to clear out any blood from the samples, using enough saline so that the fluid flowing out of the mice is clear of blood [23]. The mice will then undergo the same procedure but with roughly 15-20 ml of 4% paraformaldehyde instead to preserve the brains for histology staining [23]. The mice, 30 in total at each extraction point, will then be decapitated before having their brains extracted whole and fixated by storing them in a 30% sucrose in a 0.1M PB solution at minus 20-80 ºC, which will act as a cryoprotectant and dehydrate the tissue to improve microscopy results [24]. Tissue samples will then be placed in plastic cryomolds and embedded using OCT gel at minus 80ºC, which will be snap-frozen using liquid nitrogen and dry ice. Next, the tissue will be sliced into 20 µm thick sections using a cryostat before being adhered and fixed to slides [24]. Using light microscopy, Golgi staining, and Nissl staining, neuron death, and synaptic density can be observed [25-27]. This process will repeat until no mice are remaining, indicating that the protocol will last for approximately 64 weeks following the initiation of the protocol with 8 time points for data collection, specifically at the 56th, 112th, 168th, 224th, 280th, 336th, 392nd, and 448th postnatal days of the mice (see Fig. 3).

Results

By comparing the stains in the experimental mice and the control mice in each collected set, it is possible to see the difference in the amount of neuronal death and synaptic density in each mouse at each collection date. In particular, we will focus on regions of the hippocampus and neocortex, as these are the locations where both psilocybin and HD have significant impacts [11, 28]. In addition to these regions, we will also look at regions specific to psilocybin or HD, despite there being a lack of activity overlap, such as the basal ganglia (specifically the striatum, as it is heavily implicated in HD), and some areas of the amygdala, thalamus, brainstem, claustrum, locus coeruleus, and lateral habenula [11, 28]. Specifically, for Golgi staining, which is used to determine synaptic density, the number of spines per micrometer of dendrite observed in the stain will be used to quantitatively represent synaptic density [26]. As for Nissl staining, which is used to determine the rate of neuron loss,

the images of the brain slices will be analyzed using the "Measure" and "Analyze Particles" tools in the Fiji-ImageJ software [27]. This will allow us to measure the brain area and determine the number of total neurons in the area, allowing us to calculate neuron density [27]. When looking at these stains at each collection date, we expect to see and measure a denser array of nerve fibers and spines per micrometer of dendrite for the psilocybin-treated mice compared to the KI control mice at each time point, indicating increased synaptic density and decreased neuronal death. Additionally, when comparing the progression of neuronal loss throughout the treatment, there should be a general increase in synaptic density and a decrease in neuron death. This prediction is due to psilocybin's ability to induce rapid and persistent growth of spinal density, an indicator of synaptic density, for at least a month, as well as the overall ability of psychedelics to increase BDNF mRNA levels and neurogenesis after repeated administration for up to a month following treatment [8, 29]. These results demonstrate that there should be an increased therapeutic effect over time as psilocybin is being given every 48 hours.

Regarding the impact of dosage on the results, we expect to see notable differences between the 0.3, 3, and 5mg groups. Biologically, we expect to see a dose-dependent increase in neuroplasticity-related markers and synaptic density in the neocortex based on the significant neuroplasticity-related gene expression increases seen with psilocybin therapy in a study by Jefsen and colleagues. In the hippocampus, however, there may be a decrease in such markers, as the same study by Jefsen and colleagues found much less genetic regulation of the same genes in the hippocampus compared to the cortex, and another study by Catlow et al. found that low doses (0.1 mg/kg) may increase neurogenesis, but higher doses (1mg/kg) significantly decrease it [30]. With this in mind, the best results in the neocortex are expected to come from the higher doses, whereas the best results in the hippocampus are expected to come from the lowest dose.

Moreover, by analyzing the average scores of each behavioral test of each group of mice across the different collection points, the progression of HD symptoms between the 6 groups may be quantified. From this, we expect to see that the psilocybin-treated mice have higher scores compared to the control KI mice at each collection date, demonstrating a slowed progression of HD. As for determining the trend of the scores over the time course of the treatment, we expect to see a plateau in scores with a slight increase due to the practice effect for the first 33 weeks, as body tremors, indicative of motor abnormalities, begin to be apparent in mice starting from this date [15]. Following this, there should be a general decrease in motor scores but with smaller decreases between each set of scores as the treatment goes on due to the neuroplastic and neuroprotective effects of psilocybin. Finally, regarding the influence of dosage on behavioral tests, the changes in competence should correspond to the degree to which the treatment has been effective, which, in theory, will correlate to the effect of the drug at differing doses as mentioned in the previous paragraph.

Discussion

Analysis and Interpretation of Results

Analysis of the results obtained from histology and immunohistochemistry and the behavioral tests should yield information on the progression of HD using both biological and behavioral markers. The biological markers (spinal density and neuronal death) provide information on the effects of psilocybin in the brain with an expected increase in spinal density and a decrease in neuronal death. These results are predicted given that psilocybin, when converted into psilocin in the body, acts as an agonist on the 5 - HT_{2A} receptor, leading to effects such as an increase in neuroplasticity and synaptic density [9]. While the exact mechanism behind these therapeutic effects is unknown, an animal study by Raval and colleagues has shown that giving a single dose of psilocybin to the animals drastically increased the SV2A protein with a continuing increase even seven days after [9]. This protein, which is expressed in synaptic vesicles, is thought to reflect presynaptic density [9]. As such, using the results presented by Raval and colleagues, it is likely that Golgi staining would reflect higher spinal densities, correlated with higher synaptic densities, in psilocybin-treated mice brains [9]. Moreover, a study by Ly and colleagues demonstrates that the usage of psychedelics, including DMT, LSD, and DOI, all can to increase neuritogenesis and spinogenesis, largely due to their high affinities for the 5-HT_{2A} receptor [10]. As such, given that psilocin also has a high binding affinity for the same receptor, it can be predicted that the same effects will be seen in the mice brains [9]. Finally, the same article by Ly and colleagues mentions the ability of psychedelics to increase the amount of BDNF, which plays a role in neuronal survival, growth, and plasticity by activating downstream signaling mechanisms that increase the expression of pro-survival genes [10, 31]. Given that low BDNF is associated with HD, there may be a therapeutic benefit in using psychedelics, such as psilocybin, to increase the concentration of this neurotrophic factor in the brain [31]. A potential result of this treatment may be a decreased rate of neuron loss, which is hypothesized to occur in our study, due to the elevated expression levels of pro-survival genes.

Regarding behavioral markers, the rotarod test, the footprint test, and the raised beam test will be used to determine the progression of HD in the mice, which are among the most common tests to assess motor control and have been proven to be effective in assessing motor skills for HD research in experimental mice [22]. Results from these tests will provide further evidence on the potential efficacy of psilocybin as a treatment for HD and it is expected that there will be an increase in the average scores of the psilocybin-treated mice in comparison to the control mice. These scores indicate improved motor coordination and balance, which

should indirectly support the hypothesis of the psilocybin-treated mice having an increase in neuronal density and a slowed progression of neuronal death. As such, given that these are common symptoms of HD, these observations should signify that psilocybin has a therapeutic effect.

All quantitative data obtained through this study will be analyzed by comparing the different experimental groups to determine which variables are influencing what outcomes. We will compare all experimental groups to the disease baseline, which will be represented by the KI mice that receive isotonic saline. In addition to baseline comparison, it would also be beneficial to compare within and between the experimental groups, which is most optimally achieved through 3 comparisons. First is the completely variable-isolated within-group comparison, where individual mice within a group will be compared to each other at the same dose at the same point in time, to identify any individual inconsistencies in their performance that must be noted before comparing to other groups. Next is the dose-based between-group comparison, where we will isolate the time variable, and look at how different dosage groups compare to each other at the same point in time. Finally, there is the temporal within-group comparison, where we will isolate the dosage variable, and look at how the same dose group compares to itself at different times. The baseline comparison will tell us if our treatment has any effect and will yield a more general, binary result. The variable-isolated within-groups comparison will ensure that we have accounted for the possibility of individual differences being the primary contributor to the changes seen. The temporal within-groups comparison will tell us how the time variable affects the results independent of dosage. The dose-based between-groups comparison will tell us how dosage acutely affects the results. For this particular comparison, it is important to consider the results of the variable-isolated within-groups comparison to ensure that each group did, on average, start at the same level both in terms of biology and behavior so that the dosage variable is completely isolated.

These trends will be observed for behavioral results and biological results, and the quantitative results will be plotted and compared using analysis of variance (ANOVA) and the Kruskal-Wallis test. The endpoint (outcome variable) of each plot is continuous, but in some cases (notably with the time variable, but also potentially with the dosage variable as we do not have enough experimental groups to observe a clean normal distribution) may not be normally distributed, so our analysis will utilize a combination of tests that are suited for normally distributed data (ANOVA) as well as tests suited for non-normally distributed, but still ordinally scaled data (Kruskal-Wallis) depending on the outcomes observed [32]. The time and dosage variables will also be compared with Spearman's correlation test, to establish if there is a relationship between them. All of this information combined will offer a thorough look into how time and dosage may be optimally adjusted in psilocybin therapies so that the maximum benefit is given to the recipient for the minimum cost.

Error Mitigation

The validity of the results drawn from this study depends on the quality of data that can be obtained via the aforementioned methodology. This quality depends on the mitigation of error throughout the procedure, which may be achieved through control of environmental factors like temperature and humidity, materials (i.e. ensuring reagent freshness and contamination control via sterilization procedures), and experiment (i.e. standardizing animal care, collection procedures, staining/imaging procedures, and any other processes involved in the methodology).

Limitations and Strengths of Study

This proposal demonstrates several strengths that make it a quality candidate for experimentation. Firstly, and most notably, it would be the first study on utilizing psilocybin as a treatment for Huntington's Disease, which, given the lack of current treatments and unfavorable prognosis, could improve the quality of life for the millions of people afflicted with HD. Aside from the premise of the study, the details of the experimental procedure also present numerous strengths, including rigorous control of variables to ensure quality results (i.e. temperature, humidity, diet, drug concentration/administration control), examination of biological and behavioral markers to establish a holistic view of the treatment and its efficacy, and the fact that this is an animal study, which allows for the observation of global symptomatology without causing unnecessary risks to humans.

Though there are notable strengths, it is also important to consider limitations and next steps to further the impact of this study and those that follow it. This study is largely limited by its significant resource requirements. This is primarily a function of the number of mice, which greatly contributes to the cost and time needed to complete the study as each mouse requires housing, feeding, drug dosages, cannulas, etc. Aside from cost, there are also limitations within the experimental procedure that restrict the generalizability of the results to clinical trials. This is notably a result of the psilocybin administration method. The mice are receiving the treatment intraperitoneally, which is incredibly invasive for a human, especially considering that psilocybin can be absorbed readily through other methods. However, since the route of administration is changing, and mouse models are imperfect approximations of humans, there is no indication that the treatment will still be effective to the same degree, or at all. Finally, and most notably for human purposes, are the significant side effects that come with the therapeutic administration of psilocybin at the specified dosage. Psilocybin is a powerful classical hallucinogen, and, in addition to the neuroprotective attributes that come with this class of drugs, also demonstrates the hallucinations,

paranoia, confusion, fear, headache, nausea, and high blood pressure side effects that are characteristic of such drugs [33]. Psilocybin usage also has potential cardiovascular implications and has been linked to cardiotoxicity, platelet aggregation issues, and arrhythmia [34].

Future Steps

The expected findings will have significant implications for furthering the treatment for HD. As such, a potential next step would be to transfer this study to clinical trials. However, the intraperitoneal route of administration causes uncertainty about whether such results from animal testing will translate to clinical testing, where intraperitoneal administration is not possible. Therefore, before moving to clinical trials, another round of animal testing should be done to determine if the treatment remains effective through oral administration. If the expected results are obtained, we will proceed to Phase 1 of clinical testing where 20-80 subjects will participate to test for the safety, side effects, and safe dosage range of the compound, when administered orally [35]. If the drug is proven to be safe and clinically tolerated, then Phase 2 of clinical testing will test 100-200 HD patients to determine the efficacy and safety of the treatment and the optimal dosage in a larger group of people [35]. In Phase 3, the compound will be tested on a larger population of ideally 1000+ patients; however, due to the rarity of HD, these numbers will depend on the number of patients available for testing [35]. In this phase, we will be monitoring long-term effectiveness and side effects in a larger population, and comparing the compound to pre-existing treatments to collect enough data for regulatory approval of Health Canada [35].

Ethics Approval

Due to the nature of the proposal, this study did not require ethics approval and/or participant consent; it is an experimental proposal and analysis of existing research. If this study is carried out, animal experimentation guidelines should be followed, and ethics approval should be obtained from the appropriate authorities corresponding to the location wherein the study is completed.

Conclusion

Huntington's Disease is a debilitating, genetic illness that dramatically decreases the quality and length of one's life, and currently has no effective treatments [5,6]. As such, it is necessary to explore novel avenues of treatment to find a way to diminish its impact. Psychedelic substances have demonstrated remarkable efficacy in other degenerative diseases like Alzheimer's and Dementia, which makes this category of therapeutics one of particular interest for treating HD [10]. Our study explores this use case for one of the most studied psychedelic therapeutics, psilocybin, in hopes of getting closer to a quality, effective treatment for HD. We predict that psilocybin's effects on plasticity and neurogenesis will slow the progression of the disease, and also possibly assist with the organization of the new neurons that form once a certain level of degeneration has occurred. Such effects would be revolutionary in the field of HD research and would offer a basis for other psychedelic therapies to be explored in this context. Future studies could focus on other types of classical psychedelics, such as LSD, DMT, or mescaline, in addition to those with alternative mechanisms of action, such as Salvinorin A, DOI, and the 2C family. Results from such studies, including this one, may offer some much-needed hope for those who suffer from HD, and bring us a few steps closer to understanding and treating not only HD but neurodegenerative illnesses as a whole.

List of Abbreviations Used

5-HT_{2A}: 5-hydroxytryptamine 2A receptor
AKT: protein kinase B
AMPA: α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor
BDNF: brain-derived neurotrophic factor
DMT: N,N-dimethyltryptamine
DOI: 2,5-dimethoxy-4-iodoamphetamine
HD: Huntington's disease
KI: knock-in
LSD: lysergic acid diethylamide
mGluR: metabotropic glutamate receptor
mTOR: mammalian target of rapamycin
NMDA: N-methyl-D-aspartate receptor
OCT: optimal cutting temperature (gel)
PI3K: phosphoinositide 3-kinase
PKC: protein kinase C
PLC: phospholipase C
SV2A: synaptic vesicle membrane protein
WT: wild type

Conflicts of Interest

The authors declare that they have no conflicts of interests.

Ethics Approval and/or Participant Consent

Due to the nature of the proposal, this study did not require ethics approval and/or participant consent; it is an experimental proposal and analysis of existing research. However, animal experimentation guidelines and ethics should be followed when completing this study.

Authors' Contributions

CD: Contributed to the production of the abstract, methods, results, discussion, citations, and abbreviations; made substantial contributions to study design, drafted/revised the manuscript, and approved final publication.
NF: Contributed to the production of the background, discussion, conclusions, citations, and abbreviations; made substantial contributions to study design, drafted/revised the manuscript, and approved final publication.
VS: Contributed to the production of the methods and discussion; made substantial contributions to study design,

drafted/revised the manuscript, and approved final publication.
EY: Contributed to the production of the discussion and figures; made substantial contributions to study design, drafted/revised the manuscript, and approved final publication.

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