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Predicting the Efficacy of Psilocybin in Treating Mental Health and Addiction

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Courtney: Hello, my name is Courtney Ledford. I am a rising Junior at Portland State University. For the past 8 weeks, I have been apart of the altREU Computational Modeling program offered by Dr. Christof Teuscher, and have been working with Dr. Joe Fusion as my faculty Advisor.

My project is on Predicating the Efficacy of Psilocybin in treating mental health and addiction. Through the use of Machine Learning, a Random Forest: Classification model is used. This model intended to see if the model could predict if the experimental study involved healthy participants or participants with a DSM Diagnosis. I will refer to the experiments with participants diagnosed with a mental disorder as the clinical experiments versus the healthy participants.

To get started a brief introduction to what Psilocybin is. It is a psychoactive compound found in fungi. Upon ingestion, the psilocybin is converted to psilocin, which binds to the serotonin receptors. This is what causes individuals to undergo an altered state of consciousness and hallucinations. Psilocybin was first synthesized in 1958 and marked and sold for research purposes as Indocybin. Throughout this time and until now this psychoactive compound, psilocybin has been researched to aid in treating mental health and addiction.

The data was pulled from the Altered States Database, and from that 31 experiments were chosen to predict if the Random Forest could differentiate between a healthy experiment or clinical. All of these experiments contained results from 5 subjective questionnaires to access consciousness. The participants filled these out after the administration of psilocybin. My model focuses on the 5-Dimensional Altered States of Consciousness (5D-ASC) questionnaire. It is composed of 94 questions on a sliding YES or NO scale and is broken down in to 5 dimensions categorized as Auditory Alterations, Dread of Ego Dissolution, Oceanic Boundlessness, Vigilance Reduction, and visionary restructuralization. These subjective responses result in the values inputted in to the model.

Due to the legality of Psilocybin being classified as a Schedule I drug, this has limited the number of research experiments that have been conducted. There are a couple of studies that perform a meta-analysis on past psilocybin administrations to healthy participants. I am more so interested in how psilocybin affects participants who have been diagnosed with a mental disorder. For instance, my model included 4 clinical experiments involving patients with a diagnosis of Obsessive-compulsive disorder (OCD), alcohol dependency, and two studies involving anxiety induced by a cancer diagnosis. A limitation of my model is it is biased towards healthy participants as I compared 31 experiments, and only four of those included the clinical experiments.

This is where a random forest, Machine Learning algorithm is used to make these predictions. As there are several variables to compare within the small sample size of the 31 analyzed experiments. The model created 1,000 decision trees that make up the forest, and as it is a Classification model it works off a majority votes. The dependent variable of this model is whether or not the experiment was classified as healthy or clinical. The values of the 5 categorized dimensions from the questionnaire will determine if the experiment consisted of healthy or clinical participants.

The intent is to continue adding more data and variables to make better predictions as to whether an individual may benefit from treatment involving psilocybin. The model was able to predict out of the 5 categories which variable is the most important in determining if the experiment used clinical participants. From this prediction, Oceanic Boundlessness was the most important variable accounting for nearly 25% of the model in making these predictions.

Going further into machine learning process I will be interviewing my mentor, Dr. Joe Fusion, who has helped me learn what is required to create a Random Forest as well as how machine learning may benefit pharmaceutical research.

Courtney: Hello, Dr. Joe Fusion, so you are working at Portland State University. If you don't mind giving a brief introduction of yourself .

Dr. Fusion: Sure, so I'm an adjunct at Portland State in the system science department. I have my PhD in system science from Portland State a background in computer science before that. I've worked in any industry in computer science as a developer and a software engineer and I've worked as a data scientist and analyst and the modeler different senses before and after my degrees at PSU and I teach classes in data science, machine learning, systems theory, artificial life, few different things here at Portland State.

Courtney: And how long have you been working in the field?

Dr. Fusion: I've been doing well depending on which field I've been doing machine learning and data science work since maybe 2004-2005.

Courtney: Okay, and you've been helping me, and you've been my mentor in this computational modeling program here at PSU. And in regards to pharmaceutical research. Where do you see the field of machine learning going and what are the benefits of using machine learning?

Dr. Fusion: Well, there's that there's a whole lot. There's a lot going on in pharmaceuticals. There's a lot of it's been one of the promising areas for a while or are it's got a lot of tension because there's a lot of data. There's a lot of unknowns a lot of good to be done. A lot of money involved running to be made or your money for research some of the main there are things going on at like sort of you know molecular, you know pharmaceutical design level of having machine learning predict what molecules might do based on their structure as a sort of a way to guide research to look at certain molecules. There's a lot of work to be done.

So like this stuff that you're looking at. I think some of the interesting stuff is in looking at looking at how drugs are high treatments affect people when there's a very complex system involved and it's not easy to see just what a drug is doing or just which people are helped by it this idea of having a having treatments and drugs tailored to individuals based on their genome or their experience their particular way a condition presents in them. There's a lot of benefit there. A lot of ways we could improve dealing with difficult or long term conditions some of the

harder problems. So I think there's a lot of potential there for modeling in machine learning to help out.

Courtney: Okay, and where does neural networks tie into that?

Dr. Fusion: Neural networks. Are there one of a number of methods that do a nice job of potentially of handling a lot of data handling the complex system. Where the goal isn't necessary to understand necessarily to understand exactly how the system works. There are cases where we can't understand everything about how a system works.

But we know that we can learn some of its structure we can learn the patterns and and make the some some predictions some someone to get some understanding of it neural networks, you know part of the principle of them is that we know that we know that human brains are pretty good at some of this pattern finding brains in general a good at it. So we've designed algorithms that act like brains and are different in you know certain ways and can be fed a whole lot of data can be experimented on different ways. So and neural networks have a big push behind them in in technology and in the tools available in the research done for a number of different fields. So it makes them it makes it kind of exciting to apply neural networks to a new problem because people are doing so much with it. They've got a lot of tools and a lot of excitement available around it.

Courtney: Okay, and then going into the model we were working on as the data was limited to a small sample size and 31 experiments. What are the advantages of using a random Forest compared to other machine learning models?

Dr. Fusion: Let's see using specifically about having a small amount of data. If you approach this kind of standard ways to get a significant risk significant result or something. You're really confident in with a small amount of data. You're going to get a very simple model like if you if you approach that model with linear regression you're going to do you'll get a pretty good model of it sort of

That is kind of simple and conservative kind of safe and what it does to get you a significant response if we use something so something like the random forest or you know, a bigger sort of more robust model. Maybe if we used like a multivariate regression or used a neural network or use something else. We may not get as much we're not going to get as much significance.

Or confidence in the result, but what we can get is an idea of how complex the system might be or we can we if there are more interactions among the variables. There are nonlinear relations if there are different kinds of complexity and we'll get an idea of what might be there and then that that maybe drives a hypothesis or for what you might get if you got more data.What you might look for or what how you might model this one of the questions you might ask in the future.

Courtney: Okay, and what were some of the biggest disadvantages working with the limited data set for our random Forest?

Dr. Fusion: Well, the one challenge is that we really like to beside significance. Like I was talking about of your confidence in results. We like to do these kinds of methods. We'd like to have enough data that we split it up into a training and test split. So we have a we use most of the data to train our model so that the model learns everything in the train set. Maybe that's you know, 80% of your data and in most

Is typically like the method can get really really good at the training data and then once it has trained once it's drained to some as long as we want to train or to some performance level then we give it the test data to look at and see is it actually that good does it does it generalize to data that it hasn't seen before so that's a nice part of the process that we typically do and when so we didn't do that step with this limited amount of data.

And the other the other issue here is that in this could be an issue with larger data sets as well. But the issue here is that the these 31 samples were biased in this variable. We're interested in of what kind of what kind of subjects were used in it. This was a binary variable and only four of the of those 31 samples had one of the values and 27 have the other so in those cases it can be your machine learning method might pick up on some quirk in the data to separate those four from the others instead of finding the real pattern that we're interested in. Hopefully with the random Network. Maybe it does a little better than some in not getting caught up on quirks in the data since its sampling the 31 as in different subsets.

Courtney: Right now we currently have the variable importance that you found through the random Forest through the data sets. What other information can we learn from these 31 experiments from this model?

Dr. Fusion: Let's see, so we did this prediction of looking at the looking at the aggregate survey results from these studies and said can the survey results, you know, tell us whether they were the study used healthy patients or patients have been clinically treated and it was able to separate them. And then it we looked at how it did that and that gave us this importance of the variables. So which variables were used most often in the decision trees in the random Forest?

So we could, there's some other things we could get, you know from that same random Forest perhaps of looking at how they say. It's a look at the importance of the variables may be in different ways or looking at which variables made the decision were involved in more decisions or we might look at two particular cases from the 31 from our third runner-up is like taking one case and run it through the random forest and seeing how particular decisions are made.

But there's the maybe more to be done in taking that data and training a different training and the random Forest on it or skip some of the method but taking doing another another machine learning method to ask a different question of it where they were so as well as survey responses. There are other variables in this data set for parameters of the study design such as how long until how long after treatment until the questions were asked or the dosage used of the treatment whether there was another treatment used at the same time so seen whether any of those may be predicted survey responses could be interesting seeing what other patterns whether connections are in the data. There's a number of different questions. You could ask just in the even that small set so the ability to ask different.

Courtney: With the ability to train the model on different questions asked, would you still recommend continuing using the random force or at this point looking at the data? Do you have another machine learning method in mind?

Dr. Fusion: I think the random Forest is nice for sure and it does it has this built in the fact that it's making it bunch of decision trees based on different subsets of the data is is a very nice built-in thing to the method with some other methods other algorithms. You can do that. You do some sort of bootstrapping or something, but it's kind of an extra step and maybe you do it or you don't it's but it's kind of a core to the random forest and that's great. Nice. One of the things that I would do typically working with data like this is I would I would start with really simple Methods at first I would do, you know just do the linear regression do look at correlations between variables and we did some visualizations. You did some visualizations with data at the start which is some of the first steps I would do just to understand like you want to know if there's a like really obvious correlation between some variables and then you expect that. Those are a little bit conflated or maybe you need to drop one or something. But you want to get a baseline of like, okay how good can I do with with a linear regression or logistic regression or something because you want the Random Forest to do better than that in some way either to find something different or to get no better performance or something.

So what I might do is go back and do some of the simpler methods or you spend more time with those and then yeah, there are some other methods you could apply to this. This is for like I wouldn't necessarily use a neural network with the small amount of data because I would expect it to to train perfectly on it. Just like the random Forest did but then there wouldn't be as much sort of inspection that I could do other results. Like we're talking about this variable importance and so on if I wouldn't get as much out of neural network, maybe or anything different than that, so I think that might be interesting would be to do some sort of clustering analysis.

Which would be so instead of asking like we've been talking about questions in the form of what do these you know X many variables say these input variables say about one other variable. So we're asking this predictive or classification question, maybe a clustering method doesn't have that dependent variable that you're asking about instead. You would be saying based on these variables which of the samples are similar to each other and in what way and that might give you so if we did a cluster analysis of these it might say these seven studies were similar to each other and these 12 are similar to each other and these other five were similar to each other and then and the others were not really similar to any of them and you'd get this sort of diagram of the clusters of them and how close they are to each other in a sense. And that gives you a very different picture of what's going on between them potentially.

Courtney: Well, thank you for answering my questions and for all your assistance throughout this project. It's been a great learning experience.

Dr. Fusion: Sure, it's been really fun.

Courtney: Thank you.

Courtney: The second interview will be with Dr. Alin Ledford who has experience working with patients and prescribing medications for individuals suffering from poor mental health. As he is on the front line of working with patients, it is important to know more about the current treatments and their potential for abuse, and where psilocybin therapy may fit in to this.

Hello. Dr. Alin Ledford. Thank you for joining me today for this podcast discussing the efficacy of using psilocybin in treating mental health and addiction. Do you mind giving us a brief introduction to your experience working in the Navy as a doctor as well as in Nome, Alaska in the emergency room?

Dr. Ledford: Okay. My name is Dr. Alin Ledford. I'm a MD went to John A Burns School of Medicine and did residency at Camp Lejeune in North Carolina. Got the military scholarship paid for my way to medical school. Did my time in the Navy with the Marines then when I got out of the Navy I went to Alaska and I've been there in the emergency room for approximately 12 years working in the emergency room there as well in in-patient. Then I returned back home to Hawaii where I'm currently working in Outpatient Clinic my own Outpatient Clinic

Courtney: So you have worked with a wide range of population groups and you've been practicing medicine since 2004. Can you briefly describe your experiences prescribing medications while working in the ER or what is the process when a patient comes in and is having a difficult experience with their mental health.

Dr. Ledford: It all varies depending on what condition you have versus you know, depression, anxiety, PTSD or schizophrenia bipolar disorders or even alcoholism drug abuse, altered mental status is like that. So basically when they come in we do an assessment. I'll typically get a urine drug screen and an alcohol level to see if they're on any mind-altering substances that could lead to depression anxiety disorder, PTSD or even kick off a schizoaffective disorder based off in that it was come back in their normal then you know, my thought process is okay, you know.

They're acting bizarre to this be asked is schizoaffective disorder. Now I am limited in the emergency room because I usually don't have the patience for medical history nor do I have their psychiatric history. So I do not diagnose schizophrenia because they're acting bizarre or strange. I'll diagnose schizoaffective disorder because again, I don't know if this is just a psychotic break that the patient is having or what in those cases. Yes. I do prescribe medications and I have a follow up with their primary care provider within you know, the next two to three days so that they can get seen hopefully by their Specialist or psychiatrist or their primary care provider that could you know further the cause or continue with their treatment.

And when they come anxiety or depression. Obviously, we try to get down to what's going on by whether it's depression, anxiety, PTSD and we go that way that direction as far as giving medications for anxiety and depression. I do give medications from the emergency room. If the patient has already been on medications and even if they have been on medications to calm them down, I usually will give a benzodiazepine usually a short acting in the emergency room as well as a long-acting in the emergency room. That way I can get the patient calm down and relaxed and then be able to talk to them more in-depth or call the psychiatrist to come down and take a

look at the patient. But yeah, the emergency room like the main goal is to address the emergency and quick resolutions so that we can resolve a bigger problem at hand.

In the outpatient setting it is a little different as I have been working out patient for the past year and a few months. So the process outpatient setting being the primary care provider now there's a little different. I'm more apt to put them on an SSRI or any type of MAO inhibitors, I'll do that in the office and in the outpatients and this because I have I should have more follow-up and it should be easier for me to do that. But again my experience is in the emergency room, and I don't have enough data and I can only go based off what I've seen in a 15-minute period basically

Courtney: So what would you use for your patients that need long-term assistance with these diagnosis related to anxiety or depression?

Dr. Ledford: Being that I'm an Emergency room doctor anything long term that has to be deferred to their primary care provider and maybe even a specialist if the primary care doesn't feel comfortable tackling that on. Now that I'm working in primary care, I do prescribe medications for people that need it, but I also want them to do counseling because basically these medications that we give is just a bridge they are not the cure for any of these elements. It's just a means to help the patient get to a cure. Really the medications in my opinion is not the cure, the cure is within the patient. Finally what's causing the depression finding what's causing the anxiety or PTSD and addressing those issues and learning how to better cope with that situation whether the offending agent of their depression and PTSD is completely removed or they learn techniques to better cope with their feelings and thoughts when they creep up in the middle of the night.

Well, I really do believe in physical exercise. Is he going to be moving to that be sweating? And in my opinion? I think if you know eat healthy diet heavy exercise workout, run, do sports, do something and I think that can really help with a lot of depression anxiety and PTSD issues.

Courtney: As psilocybin is being studied as a treatment for mental health and addiction. Can you talk briefly about the current medications as you mentioned benzodiazepines? How is that related to addiction?

Dr. Ledford: So it depends on the benzodiazepine. I had mentioned earlier in the emergency room setting I do use a quick-acting benzodiazepine everybody's familiar with Xanax. Everybody knows that its highly abused. So the shorter acting benzodiazepine or the faster the acting the medication is usually the more addictive it is so yes, Xanax is highly addictive and do I use it in the emergency room, yes I do. But do I send the patient home of the prescription of that? No, I don't. I actually change them over to a long acting benzodiazepine such as Klonopin. Now Klonopin is also highly addictive any type of mind altering substance can be highly addictive so any of the benzodiazepines are highly addictive the longer-acting are less addictive and that's this is where the patient will need, you know to see their physician see a counselor again, if we can get people off these medications and just be able to cope better. Better coping mechanisms, whether it's exercise or work or whatever the better it would be for them.

Courtney: So on that note, how would you feel about a new medication such as psilocybin and including your patients in a clinical treatment study?

Dr. Ledford: So I have heard of Psilocybin and it's been around since the 50 60 s not a lot of research has gone into it me personally for my patients. I think anything that could give hope to a patient is better than nothing. I think hope for patients that have no hope with anxiety, depression, or PTSD. I think hope is key to help these patients who get better.

So would I be interested in a kind of clinical trial for my patients, absolutely I ask my patients if they'd be interested in. I would definitely participate if my patients were willing to do something like this.

Courtney: Well, thank you for answering all my questions. It was a pleasure interviewing you Dr. Ledford.

Dr. Ledford: No problem. Glad I could help.

Courtney: As Psilocybin continues to be researched as an alternative treatment, individuals must be thoroughly accessed prior to being involved in these studies. Machine learning provides an option to create predictions based on the available data, to best prepare future research as well as determining if an individual may be a good candidate for this therapy. Mental health is an issue that every community faces. Predicting the efficacy of psilocybin through the use of machine learning will benefit future therapies and overall health of individuals.

Thank you for joining me in this discussion on using machine learning to predict the efficacy of psilocybin as a mental health and addiction treatment.