Welcome to the Huberman Lab Podcast where we discuss science and science-based tools for everyday life.
I'm Andrew Huberman and I'm a professor of neurobiology and ophthalmology at Stanford School of Medicine.
Today we are discussing psilocybin.
Psilocybin is a psychedelic, meaning it modifies the psyche.
And in doing so, it changes our level of consciousness.
Psychedelics such as psilocybin change the way that we perceive the outside world and our internal world, our memories, our thoughts, our feelings, etc.
Not just while one is under the influence of psilocybin, but it can also fundamentally change all of those things afterwards and for a very long period of time afterwards as well, which is one of the reasons why there's growing excitement about the application of psilocybin and other psychedelics for the treatment of various mental health issues such as depression, alcohol abuse disorder, and addictions of various kinds, as well as things like OCD and eating disorders.
Today we will discuss psilocybin, talking about what it is.
In fact, you may be surprised to learn that psilocybin basically is serotonin.
Now, for those of you that are familiar with psilocybin and serotonin, you might think, wait, that's not true.
But in fact, psilocybin's main effect is to mimic serotonin, but it does it in a very specific way because it activates a subset of serotonin receptors in a very strong fashion leading to neuroplasticity at the level of the neural circuits, that is the brain areas and connections that serve things like memory and perception.
So if any of that is confusing at this point, I promise to make it all clear in just a few minutes.
Psyllocybin is one of many psychedelics, of course.
There are things like LSD, DMT, 5MEO, DMT, even MDMA will not consider it a classic psychedelic, is considered a psychedelic in the general sense.
This episode is going to focus on psilocybin in particular.
I will tell you what psilocybin is, how it works at the molecular and cellular level.
I'll talk about how it changes brain circuitry.
I'll talk about the clinical effects, what's been demonstrated in controlled laboratory studies.
I'll talk about dosages and translating from psilocybin mushrooms to actual psilocybin and the compound that actually exerts the effects of psilocybin, which it turns out is not psilocybin, but something called psilocin.
Psyllocin is the actual compound that goes into the brain to create all the changes in consciousness and all the rewiring effects that we associate with psilocybin.
So understanding how psilocybin is converted to psilocybin has tremendous impact on the duration of a psilocybin journey, whether or not that psilocybin journey is going to lead to a short or longer window for neuroplasticity.
In fact, many people don't realize this, but much of the positive changes that are possible with proper, and I do want to underscore proper psilocybin therapeutic approaches takes

place after the session in which one feels all the typical or typically associated effects of psilocybin like hallucinations and changes in thought patterns, et cetera.
So today we are going to talk a little bit about chemistry, but I promise to make it accessible to anyone and everyone, regardless of whether or not you have a background in chemistry or biology, we're going to talk about some cell biology, the actual neuronal changes that occur when one takes psilocybin, and we're going to talk about how neural circuits change over time and how all of that impacts the changes that most people are interested in when they go on a psilocybin journey, things such as longstanding improvements in mood, things such as tremendous insight into themselves and to others, into their past, their present and their future, and even changes in their levels of creativity or their ability to experience joy from music or their ability to dissociate in a positive way from things that formerly were depressing or triggers for depression. In fact, we're going to talk quite a lot about the conditions inside of a psilocybin journey that make it actually positive and therapeutic.
This is a very important point that I'll make several times throughout today's episode, which is that just because something invokes neuroplasticity, changes in brain circuitry, does not mean that it's therapeutic, or I should say does not necessarily mean that it's therapeutic. For neuroplasticity to be therapeutic, it has to be adaptive. It has to allow someone to function better in life than they did previously. So today we will talk about how the conditions of a psilocybin journey, including whether or not it's done with eyes closed or eyes open, or whether or not people alternate between eyes closed and eyes open phases of that journey, as well as whether or not music is played during that journey and even what types of music are played will dictate whether or not somebody will feel better or worse in the days and weeks and years following that psilocybin journey, as well as the dosage level, because as you'll soon learn as well, there are clinical studies showing that just one psilocybin journey can improve mood in a long-standing way, but most clinical trials involve two dosages spaced in very precise ways from one another with appropriate follow-up. But in both of those particular journeys, the structure of the journey, who's present, who's not present, eyes open or eyes closed, the particular music that's played, all of those features make up part of a larger neuroplasticity trigger of which psilocybin is critical, but psilocybin is not the only variable. So whether or not you're interested in participating in a clinical study or whether or not you're interested in psilocybin for other reasons, this is critical information to understand. So today we're going to talk about nearly every feature of psilocybin possible, including what psilocybin is, how it works at the level of chemistry, cell biology, and neural networks, and neuroplasticity. We'll talk about the clinical studies, we'll talk about dosages, we will talk about conditions of clinical studies, and we will talk about the post psilocybin journey period in which neuroplasticity and the various activities, including therapy or perhaps not therapy, can contribute to positive therapeutic changes from psilocybin. Now, as we go into this discussion, I do want to underscore the fact that at the time of recording this episode, meaning now, May 2023, psilocybin is still a schedule one drug, it is considered illegal in the United States. There's perhaps just one exception to that, maybe a few others, but the main exception is in the state of Oregon, psilocybin has been approved in particular therapeutic settings for use in particular conditions, namely depression and some forms of addiction. So in Oregon, it's more or less in the domain of decriminalized as opposed to actually legal in other areas of the country,

including Oakland, California, there's some areas in which it has been decriminalized and perhaps there are a few others that I'm not aware of. But in general, psilocybin and other psychedelics are still considered illegal. And this is very important. I'm not just saying this to protect me, I'm saying this to protect you, possessing or certainly selling psilocybin, except for rare instances such as clinical studies and these decriminalized areas that I talked about a moment ago is still very much not allowed under the law. Today, I'll also discuss safety issues. I'll talk about whether or not young people, meaning people 25 or younger, should consider psilocybin given that their brain is still in a rampant period of naturally occurring neuroplasticity. I will also talk about dosages as it relates to people who have formerly been on or may currently be on different forms of antidepressants. And I will talk about people who are at risk for psychotic episodes, either because they know they themselves have a propensity for psychosis or they have close family members who have psychosis, which includes things like schizophrenia, bipolar depression, as well as things like borderline personality and some related psychiatric conditions. So today's episode really will be a deep dive into psilocybin.
So whether or not you think you're already familiar with psilocybin and its effects, or whether or not you're just curious about them, I do encourage, if you're willing, to try and ratchet through some of the understanding of how psilocybin works and what it is, leading up to some of the therapeutic applications and different patterns of dosing, spacing of different sessions, etc. Because I do believe that with that knowledge in hand, you will be able to make far better, much more informed decisions about whether or not psilocybin is right for you. Before we begin, I'd like to emphasize that this podcast is separate from my teaching and research roles at Stanford. It is, however, part of my desire and effort to bring zero cost to consumer information about science and science-related tools to the general public. In keeping with that theme, I'd like to thank the sponsors of today's podcast. Our first sponsor is 8Sleep. 8Sleep makes smart mattress covers with cooling heating and sleep tracking capacity. Sleep is the foundation of mental health, physical health, and performance. Everything goes far better when we are sleeping well on a consistent basis. One of the key things to getting a great night's sleep is to make sure that the temperature of your sleeping environment is correct. In fact, your body temperature has to drop by 1 to 3 degrees in order to fall asleep and stay deeply asleep, and waking up involves a heating up of your body by about 1 to 3 degrees. With 8Sleep, you can program your mattress to be a specific temperature at the beginning, middle, and towards the end of your sleep night. Ever since I started sleeping on an 8Sleep mattress, I've slept far better than I ever have, so it's an all-around great tool that has tremendous functionality, not just for measuring, but for improving your sleep. If you'd like to try 8Sleep, you can go to 8Sleep.com slash Huberman and save $150 off their Pod3 cover. 8Sleep currently ships in the USA, Canada, UK, select countries in the EU, and Australia. Again, that's 8Sleep.com slash Huberman. Today's episode is also brought to us by Roka. Roka makes eyeglasses
and sunglasses that are the absolute highest quality. I've spent a lifetime working on the biology, the visual system, and I can tell you that your visual system has to contend with an enormous number of challenges in order to make sure that you can see clearly under any conditions. Roka understands all of that and has designed their eyeglasses and sunglasses so that regardless of whether or not you're in a very brightly lit area or a more shady area, or you go from

brightly lit to shady areas, you can always see with tremendous clarity. Now, even though they were initially designed for sport, Roka eyeglasses and sunglasses come in a tremendous number of different aesthetics. So they have the kind of what I call cyborg versions that most people associate with triathlon glasses and sports related glasses, but they also have a tremendous number of frames that you feel perfectly comfortable wearing to work or out to dinner, etc. If you'd like to try Roka eyeglasses and sunglasses, you can go to Roka. That's Roka.com and enter the code Huberman to save 20% off your first order. Again, that's Roka. Roka.com and enter the code Huberman at checkout. Today's episode is also brought to us by HVMN Ketone IQ. Ketone IQ is a ketone supplement
that increases blood ketones. Now, I know most people are familiar or at least have heard of the so-called ketogenic diet, which is essentially a very low carbohydrate diet. It's designed to get your brain and body functioning off ketones, which are a great source of fuel for the body and brain. However, most people, including myself, are not ketogenic. That is, I'm not in a ketosis state, pretty much ever, as far as I know. Nonetheless, with ketone IQ, you can increase your blood ketones and thereby improve things like cognition and physical performance. I find that when taking ketone IQ, even if I'm eating a standard omnivore diet, which is the diet that I follow, by taking ketone IQ prior to workouts, sometimes on an empty stomach, and especially prior to doing any kind of cognitive work, so researching podcasts or doing work related to my lab or teaching, et cetera, that I can maintain mental clarity for a longer period of time. And it does seem to enhance my mental clarity as well. If you'd like to try ketone IQ, you can go to hvmn.com and use the code Huberman to get 20% off. Again, that's hvmn.com and use the code Huberman to get 20% off. Let's talk about psilocybin. And again, today, we're going to focus specifically on psilocybin, and we're going to set aside all the other psychedelics for future episodes. psilocybin is what's called a tryptamine. That refers to its chemical composition, not to the so-called psychedelic trip. In fact, it's spelled differently. Tryptamine is T-R-Y-P, trip, T-R-I-P, of course. Tryptamines include psilocybin, but also things like DMT and 5MEO DMT. The tryptamine psychedelics very closely resemble serotonin itself. That's right. Most of you have probably heard of the chemical serotonin, and serotonin is what's called a neuromodulator, which means your brain and body naturally make it, and that it modifies or changes the activity of other neurons and neural circuits. And it does that generally by either increasing or decreasing the activity of those neural circuits. If I were to show you a picture of the chemical structure of psilocybin or its active derivative, psilocin, and I were to also put right alongside an image of the chemical structure of serotonin, provided that you weren't a chemist who really likes to focus on the detailed differences between things, you would say those look very similar. And indeed, psilocybin and its active form, psilocin, are very similar structurally and chemically to serotonin itself. Now, as I mentioned before, serotonin is something that you naturally make. And yes, it's true that about 90% of the serotonin in your brain and body is manufactured in your gut. However, contrary to popular belief, the serotonin in your brain is not manufactured from the serotonin in your gut. You have separate independent sources of serotonin. That is, you have particular neurons that make serotonin in your brain. You also have serotonin in your gut, and those work more or less in parallel separately. Now, what does serotonin do? This is really important to understand because of the similarity between psilocybin and its active form, psilocin and serotonin. Serotonin, in that it's a neuromodulator,

changes the activity of other neurons. And the net effects of those changes are things that you're familiar with. For instance, satiety or the feeling that we've had enough of various things such as food or a social interaction or sex or pleasure of any kind. Serotonin is involved in all of that and an enormous number of other things, such as mood regulation, such as our sense of pleasure itself or lack of pleasure, such as whether or not we feel motivated or not motivated. It works in concert with other neuromodulators such as dopamine and epinephrine and norepinephrine. In fact, if this were an episode about serotonin, which it is not, you would soon realize that serotonin is involved in so many different functions that impact our daily life. And that is one reason why certain antidepressant medications, which alter, either increase or decrease, the amount of serotonin transmission in the brain will often have a lot of side effects related to things like mood, libido, appetite, sleep, et cetera. It's because serotonin is involved in so many different things. And serotonin is involved in so many different things because there are a lot of different so-called serotonin receptors. Serotonin is a chemical that we call a ligand. And the chemical ligand is simply the thing that plugs into the receptor for that chemical or ligand. The receptors, in this case, serotonin receptors, have the opportunity to do all sorts of different things. They can change the activity of neurons, making them more active or less active. They can cause growth factors to be released, making sure that those neurons reinforce or even build up stronger connections so that they're more likely to be active in the future. Serotonin binding to particular receptors can even change the gene expression in particular cells, making those cells proliferate, so make more of them, making those cells more robust, making those cells interact with new elements of the brain and body.

Basically, serotonin and all these different receptors that it binds to has dozens, if not hundreds and maybe even thousands of different functions. So the fact that psilocybin so closely resembles serotonin leads to a very important question that we should all be asking ourselves, which is why is it that psilocybin, which looks so much like serotonin, when one takes it in the form of magic mushrooms or some other form, maybe the synthetic form of psilocybin itself, which nowadays is manufactured in laboratories and placed in different psilocybin containing foods and pills, et cetera, why that leads to complex yet fairly circumscribed sets of experience like visual and auditory hallucinations, changes in particular thought patterns and neuroplasticity that in many cases in the clinical setting provided things are done correctly, improvements in mood relief from depression, relief from various compulsive disorders, et cetera. This is really what you need to understand if you want to understand psilocybin and how it works and how to make it work optimally for a given condition or goal.

You have to understand what it's actually doing and what allows psilocybin to do fairly specific things in comparison to serotonin, even though psilocybin and serotonin are so similar, is that psilocybin mainly binds to and activates the so-called serotonin 2A receptor. The serotonin 2A receptor is one of, again, many different serotonin receptors, but serotonin 2A is expressed in particular areas of the brain and even on particular areas of neurons in the brain that allow for very specific types of changes in neural circuitry to take place, not just when one is under the influence of psilocybin, but afterwards as well.

Really, in order to have a useful discussion about psilocybin, we need to talk a lot about the serotonin 2A receptor. Fortunately for you, unless you're somebody really interested in

structural biology or cell biology, that discussion is not going to be about the binding pocket for serotonin on serotonin 2A receptor or a lot of the downstream signaling of the serotonin 2A receptor. We'll talk a little bit about that where it's relevant, but more importantly, at least for sake of today's discussion, we're going to talk about how the serotonin 2A receptor is really the one responsible for triggering all the changes in neural circuitry that lead to the changes, that is the improvements in mood, the relief from compulsive disorders in many case, but really it's the serotonin 2A receptor selectivity of psilocybin that is leading to all the excitement that you hear about in terms of psilocybin as a therapeutic tool.
Let me say that from a slightly different angle. There are data that I'll talk about today which show that one, although in most cases, two psilocybin journeys done with particular dosages of psilocybin lead to maximal binding or occupancy of those serotonin 2A receptors in ways that lead to significant and unprecedented relief for major depression. In fact, you'll soon learn that the clinical trials for psilocybin are outperforming standard therapy and outperforming so-called SSRIs and various other antidepressants in terms of providing depression relief in ways that are frankly staggering, not just to me, but to the psychiatric community at large. And this is what so much of the excitement is coming from. Now, that statement could be taken one way, which is to just say, okay, well, here's a compound psilocybin that outperforms SSRIs and therefore all the attention should be on psilocybin. But SSRI stands for selective serotonin reuptake inhibitor. In other words, the SSRIs of which there's now a lot of controversy, things like Prozac, Zoloft, et cetera. I'm sure you've heard some of this controversy. There are people who are very pro SSRIs, although there are a growing number of people who really feel that the SSRIs are probably most appropriate for things like obsessive compulsive disorder where they, in fact, can be very beneficial. But there's a lot of kind of leaning back from SSRIs as the be all end all for the treatment of depression nowadays because of the side effect profiles and the fact that it's not even really clear that serotonin deficiencies are the major cause of depression in the first place. Now, again, we're talking about psilocybin, not about SSRIs, but you should be thinking, wait, how is it that two molecules, psilocybin and some particular SSRI, both of which look like and or increase serotonin transmission in the brain, are leading to either incredibly positive and interesting outcomes or to kind of troubling side effect riddled outcomes. And again, it all boils back down to the selectivity of psilocybin to bind that serotonin to a receptor. And so in order to understand how psilocybin works and in order to
understand proper dosing profiles and spacing of sessions, aka journeys, we really need to talk a little bit more about the serotonin to a receptor, where it is in the brain, what sorts of things happen when psilocybin binds the serotonin to a receptor and how those things set in motion, the various changes, the neuroplasticity that allows people to feel better in terms of their mood. And as you'll soon learn, can experience more pleasure and joy from things like music and enhanced creativity, all the things that I do believe whether or not people are thinking about or maybe even exploring psilocybin for recreational or therapeutic purposes, all the things that people
want and are really talking about and perhaps even doing psilocybin in order to obtain. So before going any further, I just want to place an image in your mind. You can place an image in your mind whereby when serotonin is released in the brain naturally, not having taken any compound, any

drug,
anything, it's getting released a lot of different sites binding to a lot of different
serotonin receptors doing a lot of different things. When somebody takes an SSRI, the net effect
of that selective serotonin reuptake inhibitor is that there's more serotonin around to exert
its effects because it's a reuptake inhibitor at the synapse, the connections between neurons,
the serotonin can do its thing more extensively and for longer periods of time, but it's doing it
kind of non specifically. So when you think about standard anti-depressant treatments,
at least for sake of this discussion, you kind of think of a sprinkling or a kind of, you know,
spraying of serotonin at different locations in the brain and binding to lots of different
receptors. Whereas when you think about psilocybin, even though the subjective effects are pretty
diverse, we'll talk about those in a few moments, what you're really talking about is a molecule
psilocybin that looks a lot like serotonin that is selectively and very strongly binding to and
activating that serotonin 2A receptor. So that's the image I'd like you to embed in your mind,
and then the next image I'd like you to embed in your mind is where these serotonin 2A receptors
are located in the brain. Now, the serotonin 2A receptors are located in multiple brain regions,
but they have a tremendous amount of expression in the so-called neocortex, the outside of the brain
that includes things like our prefrontal cortex, which is involved in understanding context,
which behaviors, thoughts, and speech patterns are appropriate for certain circumstances,
how to switch context and category switch when you go from playing sports to hanging out with
friends to being in a professional setting, you change your behavior in the way that you speak,
and perhaps even the way that you think, you might think some things that are out of context,
we probably keep those to yourself, and your ability to keep those to yourself
are dependent on a functional prefrontal cortex. There are a lot of 5HT 2A, and by the way 5HT
is the abbreviation for serotonin, so there are a lot of serotonin 2A receptors in the prefrontal
cortex, also in other areas of the cortex that are associated with sensation and perception,
that is hearing of sounds, that is seeing of particular things, and in particular,
there is a very, very, very high expression of serotonin 2A receptors in the visual cortex,
and that is one of the reasons why psilocybin triggers visual hallucinations, and provided
psilocybin is present at sufficient enough concentration that is taken at a sufficient
dosage, one will experience profound visual hallucinations regardless of whether or not
their eyes are open or their eyes are closed. Now that is an important fact because it explains
one of the major effects of psilocybin that people experience while they are on the drug.
Now as I will talk about a little bit later in terms of what constitutes a useful psilocybin
session, useful meaning that it is leading to adaptive improvements in mood, adaptive
improvements in creativity and cognition, etc., is that people not have their eyes open for at
least the majority of the psilocybin session. This is something I have discussed with several
experts who are running clinical studies on psilocybin in their laboratories, some of whom
are going to be guests on the Huberman Lab podcast in upcoming episodes, and I can't underscore
this
enough because your visual cortex contains so many of these serotonin 2A receptors,
and because psilocybin binds so strongly to that serotonin 2A receptor, you're going to experience
a lot of visual hallucinations when you are under the influence of psilocybin. There's no surprise
there. This has been known for hundreds if not thousands of years. It's one of the main reasons

why people take psilocybin. However, as I mentioned earlier, these hallucinations occur even when the eyes are closed, and it's now fairly well established that if people are to take psilocybin and have their eyes open, much of their cognition, much of their thinking, much of the time spent in that psilocybin journey is focused on the altered perceptions of things in the outside environment. Sometimes this looks like a sort of a fracturing of the outside world into kind of geometric shapes. Sometimes it appears as a kind of melting of things in the visual environment, including people's faces or a morphing of people's faces. All of that has a strong, let's just call it a draw for a lot of people who are looking for a highly unusual experience inside of the psilocybin journey. But I think if one's goal is to derive the long lasting benefit from the psilocybin experience, it's very clear that having an eye mask or some other eye covering or something that ensures that one's eyes are closed for the majority, if not the entire psilocybin session, is going to be very useful because it's going to limit the extent to which one is focused on those outside changes in visual perception, aka hallucinations, and rather will allow the person to go inward to combine whatever it is that they happen to be seeing in their mind's eye with the different thoughts and memories and changes in their emotions that are occurring. And that going inward by staying in the eye mask, at least for the majority of the time, seems to be a very, if not the critical feature of making the psilocybin journey effective in the therapeutic sense. Now, once again, I want to cue to some of the safety precautions here. I'm going to say this at least three times throughout today's episode. As I'm talking now in various other times throughout today's episode, you may get the impression that I'm all for everybody doing psilocybin, and that is simply not the case. In order for a psilocybin journey to be therapeutically useful, it does require certain conditions and supports, and there are certain people for which psilocybin use is going to be contraindicated, meaning they should not do psilocybin, in particular, people who have existing or have a predisposition to psychotic episodes or bipolar episodes, even having a first relative who has bipolar or schizophrenic or schizotypal issues can be a rule out condition. That is, can get someone eliminated from a clinical study on psilocybin for fear of triggering psychotic episodes, not just during the psilocybin journey, but potentially in a longstanding way. So again, that's really critical. The other thing is that everything I'm talking about today, unless I say otherwise, is really focused on adults, meaning people who are 25 years old or older, that is, their basic wiring and rewiring of the brain that we call developmental neuroplasticity is completed. Most of the studies today that I'll talk about involve subjects ranging from 25 years of age out to about 70 years of age, but no one younger. So again, psilocybin and its use is certainly not for everybody. It's still illegal. It's being used in the clinical setting and research setting. They're these pockets of decriminalized areas and potentially suing legalization of psilocybin, but again, only in the proper clinical setting. Okay. Again, I say that not just to protect myself, but I say that also to protect all of you. Psilocybin is a powerful, powerful drug, not just to be under the influence of, but also in terms of its longstanding changes after the effects of psilocybin have worn off. I'd like to take a quick break and acknowledge one of our sponsors, Athletic Greens. Athletic Greens now called AG1 is a vitamin mineral probiotic drink that covers all of your foundational nutritional needs. I've been taking Athletic Greens since 2012. So I'm delighted that they're sponsoring the podcast. The reason I started taking Athletic Greens and the reason I still

take Athletic Greens once or usually twice a day is that it gets to be the probiotics that I need for gut health. Our gut is very important. It's populated by gut microbiota that communicate with the brain, the immune system, and basically all the biological systems of our body to strongly impact our immediate and long-term health. And those probiotics and Athletic Greens are optimal and vital for microbiotic health. In addition, Athletic Greens contains a number of adaptogens, vitamins, and minerals that make sure that all of my foundational nutritional needs are met. And it tastes great. If you'd like to try Athletic Greens, you can go to athleticgreens.com slash huberman, and they'll give you five free travel packs that make it really easy to mix up Athletic Greens while you're on the road and the car on the plane, et cetera. And they'll give you a year's supply of vitamin D3K2. Again, that's athleticgreens.com slash huberman to get the five free travel packs and the year's supply of vitamin D3K2. Let's talk a little bit about dosing of psilocybin and also about micro dosing of psilocybin. Now, this is an area that I wouldn't say is controversial, but that there's a, how should we say this? There's a lot of loose thinking around this in the non-clinical, non-research communities, but within the clinical and research communities, there's a lot of data that's come out indicating what effective and safe doses provided all other things are considered safe. Safe doses of psilocybin actually are. And here we really can go back to our discussion of psilocybin as quote unquote magic mushrooms or mushrooms. And if one were to translate from the mushroom form of psilocybin to the psilocybin that's
actually used in various studies, because frankly, in these studies, people aren't eating mushrooms, they're typically taking synthetic psilocybin either intravenously injected into a vein or orally. And that's how the researchers are able to tightly control the amount of psilocybin. And the typical dosage that's used in clinical studies ranges from one milligram,
often given repeatedly from day to day over long periods of time, so-called micro dosing. And really that one milligram per day or even up to three milligrams per day, repeatedly over time is what people generally think of as micro dosing. As compared to say a 10 milligram dose given once,
maybe twice in two separate sessions, or a 25 to 30 milligram dosage that's given once or twice. Now, those amounts of one to three milligrams or 10 milligrams or 25 to 30 milligrams might not mean much to those of you that don't think about these things in the research terms. Perhaps you've heard of micro dosing and you've also heard of macro or quote unquote heroic dosing.
Okay, that's sort of a common or I should say popular nomenclature for psychedelics. And I'll circle back to that in a few minutes. But I think one of the questions that I hear a lot is how much psilocybin is present in a given amount of mushrooms. And so the way this typically works is that mushrooms are often discussed in terms of grams or ounces. So an eighth of mushrooms refers to an eighth of an ounce of mushrooms or X number of grams of mushrooms. The breakdown is actually quite simple. 1000 milligrams equals one gram. And the concentration of psilocybin in most so called magic mushrooms is about 1%. So one gram of mushrooms being 1000 milligrams means that it contains approximately and again, it's approximately 10 milligrams of psilocybin. And in most of the clinical studies, it's been shown that the dosage of 25 to 30 milligrams given or I should say taken once or twice, we'll talk about the spacing of sessions a little bit later taken once or twice is what's leading to the most pronounced therapeutic outcomes.

But of course, with enhanced therapeutic outcomes, one also observes enhanced side effect profiles or what are called adverse events. So there's an important nuanced conversation that has to take place. But right now we're talking about the conversion of grams of mushrooms to psilocybin. So one gram of mushrooms being 1000 milligrams containing 1% psilocybin means that it contains 10 milligrams of psilocybin. Now the so called heroic doses that you've heard about and this is something that's discussed more with the let's call them traditional or classic psychonauts. These are people that may have an advanced degree but typically are not running laboratories exploring the effects of psilocybin and controlled clinical trials. These are people who have been longtime explorers and often writers and people who have been spokespeople for psilocybin and other psychedelics
and they will often refer to the so called heroic doses. It's a little bit hard to translate from that informal community to the scientific data. But in discussing that topic with various researchers who run laboratories at major universities focused on psychedelic therapies. What I was told is that the quote unquote heroic dose that's often discussed really refers to a five gram or so dose of mushrooms. So what that translates to is 50 milligrams of psilocybin. So when you hear someone talk about a quote unquote heroic dose, they're probably referring to ingestion of 50 milligrams or so of psilocybin but in its mushroom form. So about five grams of mushrooms. And again, it's important to point out that the concentration of psilocybin in different strains of mushrooms and in different batches and depending on the age of those mushrooms and how
they've been stored, et cetera, can vary tremendously from batch to batch. In fact, there are some laboratories that have explored the range of psilocybin concentration in different mushroom strains and different so called magic mushrooms. And that range is pretty broad. It's anywhere from a half percent all the way up to two percent. What that means is that someone might get a hold of one gram of mushrooms thinking that they're taking 10 milligrams of psilocybin in those mushrooms when in fact they're actually taking 20 or somebody could take three grams of mushrooms
thinking they're taking 30 grams of psilocybin. And in fact, they're only taking 10 or 15 milligrams of psilocybin. So the sourcing is really key. Obviously, as things become more legal and more regulated and more used in the therapeutic setting, or, and this is what's happening more and more, or as people start to rely on synthetically made psilocybin as opposed to using mushrooms to ingest psilocybin, then certainly the dosaging is going to be more consistent from batch to batch because we're not talking about batches of mushrooms. We're talking about batches of psilocybin itself. So now I'd like to take a step back from all this chemistry and cell biology and talk a little bit about the structure of a psilocybin journey itself and relate that to what we now know about what's happening in the brain during the psilocybin journey. And then a little bit later, we will return to that serotonin 2a receptor when we talk about some of the more lasting changes in brain chemistry and brain wiring that occur after the psilocybin journey is over. So let's take a couple of minutes and just discuss the various components of an effective therapeutic psilocybin journey. And here I'm not detailing a menu of things that people should do in order to pretend that they are a psilocybin assisted therapy coach or to do self-administered psilocybin therapy. That is not what I'm doing. What I am trying to do is to share with you the consistent components that are present in the clinical trials that have demonstrated the

effectiveness of psilocybin for the treatment of depression and for other compulsive and addictive disorders. And those data, meaning the specific data related to those trials and the references themselves, we'll get into a little bit later. But we can't really have a conversation about psilocybin and what it does without talking about the so-called set and setting, as it's often referred to, that is known to at least bias the probability of the journey being beneficial and not a so-called bad trip. So what are the variables that make up an effective and safe psilocybin journey? And again, when we say safe, we're referring to people who are not prone to psychotic episodes. I don't even have a first relative that's prone to psychotic episodes. We're talking about people that are 25 years or older. We're talking about people that, for instance, are not taking antidepressants that impact the serotonin system. This is very important to understand. I think a lot of people don't know this, but as far as I know, all of the studies that have explored psilocybin for its ability to positively impact brain chemistry and mood and function have required that people either not be on or abstain from antidepressants in the weeks leading up to the psilocybin journey. Now, that is not to say that if you are currently taking SSRIs or something similar, that you should cease taking them and do psilocybin. I'm absolutely not saying that. That could be very, very, very dangerous if not catastrophic. Anytime you're going to take anything or stop taking anything for that matter, you do need to consult with your physician. Let's get a psychiatrist as well.

So let's talk about psilocybin journeys from the subjective side and from the structural side. And when I say the structural side, what I mean is, what does a psychedelic journey actually include? And here are the words set and setting become extremely important. Some of you may have heard that set and setting are the foundation of a well done or even therapeutically beneficial psychedelic journey. And all of that really hinges on safety and outcomes. So set refers to mindset, the mindset of the person taking the psychedelic and setting refers to, as the name suggests, the setting in which they're taking it in and the people that are present there.

So let's talk about setting first. The setting for a psychedelic journey needs to be one in which the person under the influence of the psilocybin or other psychedelic is safe. That means no windows they can jump out of. That means no streets of moving cars they can run out into. That means no opportunity for getting lost. That means no opportunity for getting into bodies of water. In other words, it requires that there be at least one and perhaps even two or more other individuals who are not also taking psychedelics, who are not also taking psychedelics present in that setting to ensure that the person taking the psilocybin is not going to harm themselves or others. I say this not to sound like a school teacher, even though technically I'm a school teacher, but because of course I don't want anyone to get harmed. And I'm also aware that there's a lot of interest nowadays in psychedelics such as psilocybin becoming legal or decriminalized for their therapeutic applications. And if we look back to the late 1960s and early 1970s when the controlled substances act was invoked to make psychedelics like psilocybin illegal, one of the bases for that was not just the geopolitical unrest at the time and things like the Vietnam War, but also some highlighted instances in which people did not take set and setting into consideration, took things like LSD, stared at the sun when blind, or took psilocybin, went out and harmed somebody else. Again, these are very, very isolated instances, but these are the exact sort of instances that lead to criminalization or the fact that things like psilocybin and LSD and MDMA for that matter are considered illegal. Again, I completely acknowledge that

there are a number of different factors making them illegal. We could have a whole discussion about that. We talked about the drug trade, the war on drugs, but right now is such a critical time in the history and the use of psychedelics for therapeutic and other reasons. And getting setting correct, meaning making it absolutely as safe as possible for the person taking the psychedelic, is absolutely key. And one of the best ways to ensure that it's safe is to have responsible individuals who are not under the influence of psychedelics present in that environment.
So that's one component of setting. The other component of setting that we talked about earlier, which turns out to be very important is the opportunity and perhaps even
the bias toward the person on the psychedelic being seated or ideally lying down and being in the eye mask or at least having their eyes covered so that they can combine any spontaneous visual hallucinations that occur with the various thought processes that are occurring while under the influence of psychedelics. This is far and away different than quote, unquote, taking mushrooms and going into the woods or taking mushrooms and going to the beach. What we're talking about today
is the use of psychedelics for particular brain rewiring outcomes that, yes, can involve things like changing one's relationship to nature or changing one's relationship to somebody else by interacting with nature or somebody else. And while I'm not trying to diminish the potential value of those sorts of psychedelic journeys, if we look at the scientific data, the vast majority of it, not just in the clinical setting, but in terms of understanding the safety and efficacy and positive rewiring of brain circuitry that allows people to feel better, to understand themselves better and to interact with life in more adaptive ways, going forward out of the psychedelic journey, involve these very, let's say, subdued settings that are typically in one room, a closed environment with one or two other individuals acting as sort of guides or helping the individual by talking to them from time to time if they feel like they have to sort through a particular aspect of the psychedelic journey that's creating anxiety. And we'll talk about the contour of the psychedelic journey that almost everyone who takes psilocybin at somewhere between
20 and 30 milligram dosages tends to experience. But the setting that I'm describing is not just a list of things to make sure you're safe, but they're really the list of things that also ensure that one can get the maximum benefit out of the psilocybin journey. Now, other things included in setting that are known, again, from scientific literature to be very influential in terms of the experience that one has and to bias things towards a positive experience are, again, safety, eye mask, but also the presence of music. Now, when I first heard about this from one of the premier researchers on psilocybin and other psychedelics, which is Robin Cardard Harris, he's a professor at University of California, San Francisco, who's one of the major pioneers in the studies of psychedelics. And when he first started telling me about the critical role that music plays, I thought, okay, that makes sense. Music can impact our emotion, impact the way that we think, and could therefore impact what one experiences during the psychedelic
journey. But he really underscored for me the extent to which music is not just a sort of incidental feature of the setting in psychedelic set and setting, but that it is one of the, but that it is one of the major drivers of the actual cognitive and emotional experience that somebody has on something like psilocybin that allows the psilocybin journey to be looked at

or viewed, not just as beneficial, but, and this is quoted in the scientific literature as one of the most profound and important positive experiences that one ever experienced in their life.
So let's talk about the sorts of music that have been used in these clinical studies.
First of all, we need to think about how long the psilocybin journey itself is going to be.
And the typical duration of the psilocybin journey is anywhere from four to six hours.
It's going to depend somewhat on dose. It's going to depend somewhat on variability in people's liver metabolism. And it's also going to depend somewhat on how much food people have in their gut.
In all the clinical studies that I read, it was advised that people not have any food in their gut at the time at which they ingest or injected with the psilocybin.
It's particularly true if people are going to be taking psilocybin mushrooms in order to get their psilocybin. And that has been done in a few studies. Most studies, however, use synthetic psilocybin taken orally. Again, that's converted to psilocin in the gut by the acidity of the gut.
And the acidity of the gut is going to be impacted by the various foods that people eat.
And so that's one of the major reasons why people are advised to not eat for at least four hours prior to the psilocybin journey. So here we've got this six hour, what we're calling journey, because that's what everyone calls it, or trip, that people start experiencing about 30 to 45 minutes after ingesting psilocybin or taking psilocybin. There's a peak component in which there's a maximal intensity of emotion and often that's also associated with anxiety.
And this is very important to understand the anxiety component is part of what in the therapeutic setting they refer to as ego dissolution and that anxiety around the peak. And I think most people would probably hear peak experience and think, Oh, we're talking about a peak positive experience. But no, we're referring to a peak experience and anxiety that people stay with and then come down from gradually as one goes from the second or third hour after taking psilocybin and that tapers off slowly toward the six hour mark, what sometimes people refer to as parachuting back in. Of course, they're not hopefully, I would very much hope people aren't actually parachuting back in while on psilocybin. But I think you get the idea.
The music that's typically played in the clinical studies using psilocybin for the treatment of depression or for compulsive disorders or addiction tends to have a particular contour that matches with and can also drive that contour of the psilocybin journey that I just described.
Again, we're talking about people wearing an eye mask with guides present. So people who are not taking psilocybin there as well to ensure that the person feels supported and is safe.
The person is typically lying down, sometimes sitting down, but more often than not lying down wearing an eye mask. And the music that's played at the beginning of the psilocybin session tends to be music that doesn't have a lot of vocalizations. It tends to be things like classical music. It tends to be fairly low volume, but that then transitions into music that has a lot of percussion. So often drums that tends to be higher volume that has a lot of intensity at about the time that one would be experiencing the peak in emotion and in perception, the so called peak of the journey. That intense music tends to be played for about 45 minutes to 90 minutes, depending on the study one looks at, and then tends to transition into softer music. Again, sometimes choral type or more melodic music, often female voices in particular, and then transition into nature sounds and things that more or less mimic the outside natural world and less so synthetic things like drums or instruments and vocalizations and things of that sort.

So why would it be so important that music match and even contribute to the subjective experience that people have on psychedelics? And here we should probably take a couple of moments and just talk about what those subjective experiences are like. So for people that haven't done psilocybin or any psychedelics, it's a little hard to describe. But one way to describe it is that there's a lot of so called perceptual blending. So for instance, people in the eye mask will report seeing some geometric shapes and colors, but perhaps the music they're listening to will then start to change the intensity or the movement of whatever it is that they're seeing hallucinating inside of the eye mask in ways that are linked. This is referred to as synesthesia or the merging of different senses that are not ordinarily merged. In addition, people under the influence of psilocybin or other psychedelics for that matter often will report that their pattern of breathing becomes linked to the perceptions of things that they are hearing or seeing or feeling.
So for instance, if they take a big deep breath in and then a long exhale out, they may find that during the long exhale out that the notes of music that they're hearing in those moments are also drawn out for the duration of the breath and they'll inhale and that they're getting at least what they perceive as control over the music, which of course they are not actually controlling by using their breath. And that perhaps their visual perceptions are also being merged with that.
So those are just a couple of examples of how perceptual blending, aka synesthesia, can occur while under the influence of psilocybin. And this really is highly individual from one person to the next. Some people, for instance, will find that if they take their fingertips and rub them across the couch or the chair that they happen to be lying down or sitting on, that they will experience a change in the music. Maybe even if they move their hand up, they hear an increase in frequency of sound, they move their hand down, they hear a decrease in frequency of sound and that all of this is linked to their emotional state at the same time and vice versa. So we're talking about a lot of perceptual and emotional blending and some sense of control over one's perceptions and emotions in a way that's
very unordinary, even extraordinary. Now we can step back from all of this very subjective description of the psychedelic journey and ask, what is going on that would allow these sorts of things to occur? And there you are already equipped with an understanding of the cell biology and the
chemistry that makes all of this possible. And that is that when psilocybin is ingested and then converted to psilocin, that's the psilocin that crosses the blood brain barrier and then even though psilocin looks a lot like serotonin, psilocin has this incredible ability to predominantly activate the serotonin 2A receptor. Well, we can understand much of what's happening at a subjective level during the psychedelic journey, even right down to the sorts of emotions and perceptual blending, the synesthesia, we can understand a lot of that by understanding where the serotonin 2A receptors are expressed on neurons and what those particular neurons are doing. And the simplest way to describe this is that there's a category of neurons that we call pyramidal neurons. Paramidal neurons are found lots of places in the brain, but they're called pyramidal neurons because they're shaped like a pyramid. They have a cell body, which is the part of the cell that has the DNA in it, a lot of other important things like the organelles, mitochondria, etc. And then they also have what are called dendrites. Dendrites are the little branches or processes that reach out both from the bottom of these cells. And then

these pyramidal cells are interesting because they also grow a branch up, up, up, up, up into layers of neural tissue above them. And they have what's called an apical branch. That's the part that grows up. And then they fan out at the top. And that fanning out at the top allows them to communicate
with other neurons in their environment. Okay, so if you're not getting a good picture of this in your mind from my description, I apologize, but simply think about putting your arms out to the side. And by doing that, you're able to interact with things that are some distance from your body, sort of an obvious thing in that case. These cells are effectively doing the same thing by extending little processes out into layers above them and to the sides. And this is really important because much of the serotonin to a receptors that are present on neurons in the brain are present in those apical dendrites, those branches of these pyramidal neurons that are above and that extend out to the side of those neurons. And so when somebody is under the influence of psilocybin, that means that psilocin has bound to the receptors on those apical dendrites, and it's increasing lateral communication across brain areas. In fact, this is perhaps one of the most well documented effects of psilocybin and other psychedelics, which is that there's a shift from the brain being more modular, meaning more segmented, like auditory neurons are communicating electrically and chemically, largely with other auditory neurons. Of course, they'll communicate with other types of neurons too, right? When I hear something off to my right, you know, like a snap of fingers off the right, I'll turn my head and my ability to do that depends on my auditory neurons being linked up with things like my motor system and my visual system. But the key thing to understand is that when there is psilocybin present in one system, that the communication of any of these pyramidal neurons, the ones involved in hearing, the ones involved in thinking, the ones involved in memory, the ones involved in visual perception, or in the generation of visual hallucinations with eyes closed, those are all talking to many, many more other neurons more extensively. So what happens effectively is that there's a reduction in the modularity, the separateness of function in the brain and an increase in what's called integration of communication across what would otherwise be disparate brain regions.
We can say that really simply by saying psilocybin increases communication across the brain.
Now, in addition to that, there's a reduction in what's called the hierarchical organization of the brain. Typically, sensory information comes in from the outside environment. So we hear something,
we see something, we taste something, we smell something. And in what's called a bottom up fashion,
meaning bottom from the periphery, up, meaning it propagates up through the eyes, through the nose,
through the ears, through the skin, or the senses in those regions, I should say,
up into areas of the brain that sit deep to the cortex, like the thalamus.
And then the thalamus is sort of a way station. It's like a switchboard that sends visual stuff to the visual centers and auditory stuff to the auditory centers and touch stuff to the touch centers and things that maybe trigger a memory off to the memory centers of the brain, etc.
That's the typical organization. It's hierarchical because it goes from the periphery
up to the more complex processing regions of the brain that make decisions,
that link all of that stuff to prior experience, maybe plans about the future.

When psilocybin is present in the system, there's a broadening of the flow of that information from the bottom up as well. And that has to do with what's called thalamic gating. The thalamus is a very interesting structure. We probably don't want to go into it in too much detail right now. But it really is like a switchboard in a way station saying, Hey, pay attention to the visual stuff. Pay attention to the auditory stuff or just to the visual and auditory stuff and ignore, you know, touch sensation for the time being or vice versa.

When psilocybin is present in the system and when serotonin 2a receptors are activated very strongly, there's a tremendous broadening of the flow of information up and through the thalamus. So not only is there more communication of so-called higher order brain centers, we refer to them as higher order because they're involved in thinking and decision making and emotion, et cetera. But there's also a shift in the flow of sensory information into the brain that can generally be described as broader and including more blending of the different senses. And when I say blending of the senses, I'm also referring to blending of the sense of interoception of our sense of our body and what's happening inside of our body. And this without question, at least partially explains why when under the influence of psilocybin, one's breathing can be linked to a sound and then suddenly the sound one thinks is being controlled by one's breathing or that the sound itself can be linked to something that we see in our mind's eye while in the eye mask. Essentially what I'm describing here is that serotonin 2a receptor activation allows for more broad, less precise and less hierarchical activation of brain circuitry. And when I say hierarchical, what I mean is that normally things go from periphery from eyes to thalamus to visual cortex. However, when under the influence of psilocybin, as I mentioned before, even in the eye mask, the visual cortex is going to be very activated even in the absence of any visual input. So then if one hears a sound, perhaps from music, a particular motif or voice, and that's linked to a particular emotional state, that is now being blended with visual phenomenon occurring within the brain that have no external stimulus. And so while the patterns of activation in the brain while under the influence of psilocybin aren't random, they are far less channeled, far less modular, and far less hierarchical than would ever be the case when not under the influence of psilocybin. I'd like to just take a brief break and thank one of our sponsors, which is Element. Element is an electrolyte drink that has everything you need and nothing you don't. That means plenty of salt, sodium, magnesium, and potassium, the so-called electrolytes, and no sugar. Now salt, magnesium, and potassium are critical to the function of all the cells in your body, in particular to the function of your nerve cells, also called neurons. And we now know that even slight reductions in electrolyte concentrations or dehydration of the body can lead to deficits in cognitive and physical performance. Element contains a science-backed electrolyte ratio of 1000 milligrams, that's one gram of sodium, 200 milligrams of potassium, and 60 milligrams of magnesium. I typically drink Element first thing in the morning when I wake up in order to hydrate my body and make sure I have enough electrolytes.

And while I do any kind of physical training and after physical training as well, especially if I've been sweating a lot, and certainly I drink Element in my water when I'm in the sauna and after going in the sauna because that causes quite a lot of sweating. If you'd like to try Element, you can go to DrinkElement, that's lmnt.com slash Huberman to claim a free Element sample pack with your purchase. Again, that's DrinkElement lmnt.com slash Huberman. Now in all fairness to

the scientific literature, there are not one, not two, not three, but four prominent theories of which brain networks are most activated during a psilocybin or other psychedelic journey. And so for those of you that are interested in those different models, first of all, please know that they are not competing models. While some of them disagree about some of the details, it's very likely that all of these models are true. They include things like changes in the so-called default mode network. There's a lot of interest in this. I've talked about it before on this podcast, the default mode network, because the network in the brain, that's thought to be responsible for spontaneous imagination, for daydreaming, and that reflects sort of the base activation state of the brain when there's no drugs in our system. And the default mode network is one of the systems or networks, rather, that is thought to be rewired under conditions of psilocybin or other psychedelics. Again, if you're interested in these models and comparing and contrasting them, there's a very nice review from Brian Rothslab at Duke entitled The Neural Basis of Psychedelic Action. We'll provide a link to this in the show note captions. And again, I just want to emphasize that all of these models have been shown to be true in different studies. And what they all point to is more extensive communication between areas of the brain that normally are not as active at the same time, while under the influence of psychedelics such as psilocybin. The controversy in the field relates to which of these networks is the one that changes the most to explain the therapeutic outcomes that have been discovered in recent years. So again, check out that review if you're interested in that sort of thing. In the meantime, we can cut a broad swath through all of those models and just say that psilocybin expands the functional connectivity of the brain while one is under the influence of psilocybin. And it does seem that some of that expanded functional connectivity persists after the effects of psilocybin have worn off. And that statement about the functional connectivity of the brain being more expanded, not just during the psilocybin session, but after as well, has been substantiated in a number of papers. But one of the key papers in this area is one that I recommend people check out if they're interested in this sort of thing is entitled the effects of psilocybin and MDMA on between network resting state functional connectivity and healthy volunteers. And I like this paper for a number of reasons. First of all, it's a very high quality paper carried out in the laboratory of Robin Cardard Harris at UCSF. Again, one of the premier researchers
in this area of psychedelics and their function, what they do in the brain and also their therapeutic applications, but also because it focused on healthy volunteers. They explored using brain imaging, what brain areas are active in a resting state. So things like default mode network, then they had people take psilocybin or MDMA. And then they looked at the connectivity between those brain areas in those same individuals when they were not under the influence of these drugs and found more extensive connectivity, all of which pointed to an enhanced lateral connectivity, less hierarchical organization, effectively more interconnection and communication between different brain areas. I think not only is the fact that they looked at healthy volunteers very interesting and important, but also that they looked at this resting state of the brain. They weren't providing a particular auditory or visual stimulus for people to hear or look at while they were in the brain imaging scanner as it's called. Rather, they were simply looking at how the brain was behaving at rest. And so it's very clear that for people that do two or even just one of these psilocybin journeys at a particular dose, that the brain is actually getting rewired. We hear this a

lot, psilocybin or other psychedelics lead to plasticity. They rewire your brain. Let's go back to what we said at the beginning. Rewiring of the brain is not the goal. Adaptive rewiring of the brain is the goal. Rewiring that leads to new ideas that are interesting, that are accessible after the psychedelic journey. New ideas and new ways of thinking are feeling that allow people to function better in their lives. That's the goal of effective psychedelic therapies, not simply rewiring of the brain. A brain injury for that matter will lead to rewiring of the brain, but that's maladaptive rewiring. The use of things like amphetamines or methamphetamines in particular
will lead to rewiring of the brain, but that is strongly maladaptive rewiring. So now there are really dozens of studies conducted in humans using brain imaging and other techniques have evaluated how things like psilocybin change connectivity in the brain. I think the take-home message is it expands that connectivity. However, it seems to do so in ways that still allow people to function in their daily lives. One of the key things that I gleaned from the literature on the therapeutic use of psilocybin for the treatment of depression is that very seldom do people who take psilocybin experience long-term issues with memory. Why is that so critical? Well, you could imagine that increasing connectivity in the brain, reducing modularity, reducing hierarchical organization of the brain would lead to disruptions in memory. It's as if you're shuffling books on the bookshelf, so to speak, but that doesn't seem to be the case. Rather, it seems that the increase in connectivity is leading, provided set and setting are correct, provided safety protocols are followed to positive rewiring or adaptive rewiring of neural tissue. So that's one of the things that makes psychedelics and psilocybin in particular very exciting from the therapeutic standpoint. And of course, we have to acknowledge it's also what has a lot of people excited about psychedelics, not just for the treatment of depression, but for expanding the brain's capabilities more generally. So along those lines, I want to touch on the issues of creativity and the experience of life outside of psychedelic journeys is impacted by psychedelic journeys. And here this relates to a question that I heard a lot when I put the call out on social media that I was going to do this episode, and I asked people, what do you want to know about psilocybin? And one of the more common questions that I got was, does it increase creativity? Does it increase our experience of life in ways that are beneficial, aside from its now documented positive effects in treating depression and compulsive disorders and addiction? And the short answer to this is yes, but that the positive effects of psychedelics, psilocybin in particular, on creativity and our experience of life have only been explored in a fairly narrow set of dimensions. However, where it's been explored, there's some really interesting findings. So one of the more interesting findings, I think, is a paper entitled, increase low frequency brain responses to music after psilocybin therapy for depression. I think this is a really interesting paper because what the authors did is they took advantage of the fact that in these therapeutic psilocybin sessions that are carried out for the treatment of depression, music is being played. And there are prior studies
showing that when music is played, you activate different brain areas, depending on what sort of music is being played. That's somewhat obvious, perhaps, you know, sad music versus, you know, intense, you know, you could think about heavy metal versus choir music versus Gregorian chants versus punk rock music and on and on. It makes sense that different brain areas would be activated when different patterns of music are played. However, there do seem to be some universal

features of brain activation in response to music. This should probably be the topic of an entire episode of the Huberman Lab podcast. And indeed, it will be. For instance, there are areas of the auditory cortex that are activated, no surprise there, and areas of the brain's reward circuitry, the so-called ventral striatum and the so-called mesolimbic reward pathway. I talked a lot about these in the episodes about dopamine that I've done previously. These are brain areas that lead to the release of dopamine in other brain areas and that reinforce certain experiences and that tend to give us the subjective feeling of, yes, I like this, I want more. So in this particular paper, what the authors did is they took advantage of the fact that people are in the clinic, they're on psilocybin, they're listening to music. And as you recall, the music played at different stages of the psilocybin journey are different. They have a different emotional component and music is a really nice stimulus in the laboratory, as we say, because like with visual stimuli, you can break it down into high frequency, low frequency, right? Sounds like these kinds of things. That was my attempt at low frequency versus high frequency auditory stimuli. Or at the spatial frequency, or what in the auditory domain would be called the temporal frequency, is it boom, boom, boom, or is it boom, boom, boom, boom. All we've changed there is the temporal frequency. The sound was somewhat the same, but the distance between those sounds
was different. You get the idea. So they have access to these people and these different conditions and they can put them in the brain scanner and they can do that before and after having taken psilocybin. And the long and short of this study is that psilocybin changes one's experience of music not just during the psilocybin journey itself, but thereafter. And in fact, it changes one's emotional response to music in very interesting ways. For instance, one of the more common features
of major depression is that people don't derive as much pleasure from different types of experiences, whether or not it's food or sex or social experiences, to the point where sometimes they just stop trying to seek out those experiences. People with depression often feel as if music no longer has the same impact. It just doesn't really lift them up very much. This study found that people who have taken psilocybin, according to the parameters we talked about earlier, can get a return of the elevated emotionality, the positive emotions associated with music that formerly made them feel good. In other words, they can feel music again. They can feel good in response to music again. Now, this is interesting because in theory, it could be that psilocybin simply allowed them to access the emotions around music again more generally, but that's actually not what this paper and some other papers that have been published report. Rather, it seems that taking psilocybin can increase one's positive perception of music that one likes and can tone down or reduce the depressiveness or the sadness of music that tends to make one sad even after the psilocybin has worn off and for a long period of time afterwards, maybe even forever, although no study, of course, can be carried out forever because forever is forever.
What we do know, however, is that psilocybin can rewire the connections between the emotion centers in the brain and the networks that control auditory perception of music and leads to this condition in which people who felt like I was depressed or I couldn't feel the music, I just wasn't getting the same lift and joy from it again. They can start to experience more joy from that music again and that music that made them feel sad and depressed has a diminished capacity to make them feel sad and depressed. There's a lot of neuroimaging data in this paper that point

to the specific brain areas that include areas like the ventral tegmental area that can explain why these sorts of effects would occur. This isn't just subjective reports of people saying, oh yeah, I was depressed and then music didn't feel really good and now it feels great or that used to make me feel so sad and now I feel like I have a capacity to listen to that without being crushed by feelings of sadness. The paper included some subjective reports of that sort, but then was able to link those to changes in brain circuitry and brain activation in response to music using neuroimaging. In that way, it really points to both the subjective and structural and functional changes that psilocybin can bring about through that expanded connectivity between brain areas because remember during the psilocybin session, it's not as if music or the perception of music is specifically being looked at or focused on in these studies, rather music is playing, people are in the eye mask, they're feeling all sorts of things, they're breathing, they're hearing, they're touch, it's all happening all at once. There's a peak, it's long, there's a long taper, the music's changing. Okay, all of that took place in this study as well, but it is after the session when comparing brain activation states to music of a particular type, sad or happy and comparing that
to the patterns of brain activation that occurred before the psilocybin journey that they discover that people's brains have rewired during the psilocybin session in a way that allows them to experience joy in response to music again. So that's one of the more rigorous studies I was able to find that addresses this question of whether or not psilocybin really does rewire the brain in ways that allows us to be more creative and experience life differently after the psilocybin session. Now that paper didn't focus specifically on creativity, I did an entire episode on creativity that talked about different types of meditation like open monitoring meditation, it talked about different patterns of thinking that one can actually practice to increase creativity. We had arguably one of the most creative people on the planet, Rick Rubin came on this podcast, talked about the creative process from the perspective of music and his role in producing music so you can check out those episodes if you're interested in the neural circuitry related to creativity. At least at the time of recording this episode, there haven't been a lot of studies looking specifically at the brain networks that we think are involved in creativity and how those change in response to psilocybin and other psychedelics. I imagine those studies are either happening now or will happen in the future, but the studies I just described referring to the changes in emotionality and responses to music, I think provide a nice template for what's likely happening, both during psilocybin journeys and after those psilocybin journeys, when we talk about less hierarchical organization, more connectivity between brain areas. What it's pointing to is the fact that during the psilocybin journey, people have the opportunity to learn new relationships between different sensory and emotional states. And those new relationships seem to persist long after the psychedelic journey has been finished. And a lot of people researching psilocybin in the clinical setting think that that's one of the major reasons why psilocybin and other psychedelics can rewire our relationship to things more broadly. It allows for new learning, new contingencies. And when we look at depression, we often think, you know, diminished mood, people now have an appetite, they're not interested in social relationships or romantic relationships, they're really struggling. And all of that, of course, is true. But another lens to look at depression through is that a lot of that thinking and a lot of those emotional states that are negative are somewhat habitual. They relate to a sort of implicit understanding

and living out of the idea that A leads to B leads to C. Okay, you seek out a relationship, it doesn't work out. Try a new job, you don't get the job, you get the job, it's no good. All these negative outcomes of if A then B, then C. And it does seem that psilocybin can have this effect of invoking new patterns of learning, new considerations about what might be possible. And indeed may even lead to actual rewiring of the emotion centers in the brain with these other brain areas and vice versa, in ways that eject people from the psilocybin session, thinking, oh, you know, yeah, I used to feel this way about something, work, relationships, myself, etc. But I'm willing to consider this other possibility or this other possibility seems at least partially true to the extent that I'm willing to go out and evaluate that. Now here I'm speaking very subjectively, but remember, we have to tie back the subjective experiences and changes of things like music and emotion in our relationship to life and jobs and relationships back to the cell biology and chemistry of psilocybin, because ultimately, it really is just a chemical activating receptors, those receptors changing networks in the brain. And the journey itself seems to be the time when all of those changes are put in motion. It's like a boulder that gets rolling. In fact, I think the best way to think about psilocybin and other psychedelics is that they initiate the neuroplasticity process, but they are not the neuroplasticity process itself. And the journey itself is not where all the neuroplasticity occurs. We know that for sure. In fact, if you want to imagine how psilocybin and other psychedelics work to change the brain, think about them as a wedge that gets underneath the boulder that is the neuroplasticity that gets rolling forward. And then think about whether or not the plasticity is adaptive or maladaptive, whether or not it actually serves you in your life on a daily basis or not, depending on whether or not you're using your conscious brain to move that boulder in a particular direction, right? Not just bulldozing through things and destroying them, but clearing a path through old, ineffective, maybe even destructive patterns of thoughts or emotions, etc. I give you that analogy because I think it more accurately captures what psychedelics like psilocybin are doing rather than the typical discussion around psychedelics that we tend to hear, which is that, oh, it creates plasticity and plasticity is what you want. For the next couple of minutes, I'd like to focus on some of the key and stereotype that is characteristic experiences that people tend to have during a psilocybin journey because there's some really interesting research on this. These are phrases that perhaps you've heard before, things like letting go, ego dissolution, feelings of connectedness. Well, all of that is very subjective on the one hand. Those words are heard often enough
and repeatedly enough in psilocybin sessions and after psilocybin sessions, along with this description of the psilocybin experience as one of the most profound of one's life or one of the most positive in the ideal case of one's life that they are worth exploring. We should also, of course, explore the so-called bad trip, the possibility that someone will have a not a good time or even very frightening time while under the influence of psilocybin. There have been some scientific studies that have explored what sorts of subjective experiences that is thoughts and feelings, insights that people have that relate to positive therapeutic outcomes and more generally with the sense that the psilocybin journey was positive or maybe even tremendously positive in one's life. So while there's a century or more of writings about psychedelics that describe things like enhanced feelings of connectedness or dissolution of the ego, the loss of one's sense of self and then the regaining of one's sense of self and so on, there's a particular paper that

describes some of those things in terms of rating scales. That is the sorts of tests that people can take in which they answer particular questions and that link back to things like feelings of connectedness and ego dissolution that allows us to put some numbers to those experiences and to look at some of the statistics associated with those experiences. And this is really what's important about scientific studies, whether or not a measure is subjective, so someone's self reporting how they felt or feel or whether or not it's measure of blood pressure or of a chemical in the bloodstream, et cetera. It's the use of numbers and statistics that allows comparison between different groups and that can be compared between studies that allows us to make some firm
conclusions about what sorts of things psilocybin may or may not be doing when it's effective or not. So the paper I'd like to highlight is entitled quality of acute psychedelic experience predicts therapeutic efficacy of psilocybin for treatment-resistant depression. I'll put a link to this paper in the show note captions, but the basic contour of this paper is that they looked at subjects that underwent two different psilocybin sessions, one at a relatively low-ish dose of 10 milligrams of psilocybin, and that would be equivalent to about one gram of psychedelic mushrooms, more or less. And a second session involving subjects taking 25 milligrams of psilocybin or what's roughly equivalent to somebody taking two and a half grams of psilocybin mushrooms. Those people then answered what's called the altered states of consciousness questionnaire, which allowed them to address, and here I'm paraphrasing, the quality of experiences in the 25 milligrams psilocybin session. So without going into too much detail, it's often the case in these sorts of two-session studies that subjects will take a slightly lower dose of psilocybin to familiarize themselves with the experience and then the higher dose that leads to the more intense experience, intense meaning a bigger, more intense peak, a longer session overall, greater distortions in emotionality and perceptual experience, all the stuff we talked about before. So what this study found is that one of the key features, if not the key feature of a positive quote unquote psychedelic experience is this sense of oceanic boundlessness occurring at some point during the psychedelic journey. Now oceanic boundlessness doesn't necessarily mean anything to any of us. It probably means different things to different people. It's this idea that one is experiencing something extremely unusual, even mystical, beyond this world and one's normal experience, but that it's not aligned with any specific outcome in the moment. It's not directly attached to anyone feeling or memory or thought process. It's this, it's a little bit tough to describe because I can guarantee you I'm not on psilocybin or any psychedelics right now. And I can only imagine that you're not, although some of you might be, I can't even imagine what this podcast would be like for somebody on psilocybin at this moment, but in any case, oceanic boundlessness, a feeling of the experience being mystical and not really heading in any one particular direction, just a feeling of massive connectedness with one's environment, both in the room and session, perhaps with the guides, with oneself, with one's past, with one's present, people outside the room, with the entire world, maybe even the universe, that sort of thing. The intensity of that experience of oceanic boundlessness, the mystical experience seems to be positively correlated with positive therapeutic outcomes. That is relief from major depression. Now, during the psychedelic journey, as we talked about before, there are a number of steps that one typically goes through. So there's the build up to first experiencing the effects of the drug about maybe 20 to 45 minutes into the journey or trip,

then the peak. And it is during that peak that people often feel the sense of oceanic boundlessness. However, it's also often the case that it is during the peak with a maximum intensity of emotion. And we know based on direct measurements, also increases in blood pressure and heart rate,
often very significant increases in anxiety and fear as well, that people will experience things like ego dissolution. And the guide's role at that point is, of course, to keep the person safe, make sure they don't run out of the room, jump out of a window, run into traffic. Sadly, these are things that have happened outside of a strong, healthy, safe set and setting. But the guide's role is to keep the person safe, but also to encourage them to let go and move through that experience, to experience the anxiety, allow it to peak, allow them to see that they're not going to die from that anxiety, they're not going to dissolve, they won't lose their sense of self completely, or they may temporarily feel as if they lose their sense of self, but then they feel it restored at various intervals during the peak or as they exit that peak and move toward the, say, second, third, fourth, fifth hour of the session. So when exactly these feelings of oceanic boundlessness and ego dissolution occur, varies from person to person, but typically it's during the peak that the ego dissolution, the fear and the need to quote unquote, let go is most typical.
I think perhaps the best way to describe the data in this paper in a way that's meaningful to everybody
is to refer you to figure two, which if you're not looking at the paper, won't mean anything to you, but I'll describe it. And if you do want to take a look at figure two, again, you can access the paper in the show note captions. What they did is they looked at a number of different subjective measures, things like experience of unity, the feeling that one is connected to others into the world, things like spirituality, whether or not the whole thing felt like a spiritual experience, whether or not it was a blissful state, whether or not there were insights, whether or not somebody felt disembodied, out of body, whether or not somebody had a lot of anxiety, whether or not they had these synesthesia, these blending of visual auditory touch and breathing and things of that sort. And they addressed which of those measures related to the positive clinical outcomes that were observed later after the psilocybin wore off. And while I'm not going to go point by point through each one of these measures, there's a general feature to emerge from the study,
which is that the experience of unity, the sense that the psilocybin journey was spiritual,
an experience of bliss at some point inside of the psilocybin journey,
the sense that there were insights, that there were learnings about one's life and one's self.
When those things were experienced very strongly, that correlated with the person being what was called a responder to the psilocybin treatment, meaning they got relief from their depression.
Whereas people who felt less of that, okay, so the non-responders, as they're called,
the people who do not benefit so much in the long run from the psilocybin treatment,
tended to report less of an experience of unity, less of a spiritual experience,
less of a blissful state, less insightfulness, and so on. Whereas there were very few differences between the people that derived benefit from the psilocybin treatment, and those did not,
along the divensions of synesthesia, this blending of different perceptions that ordinarily doesn't occur for most people, or complex imagery, right? Put simply, everyone who took psilocybin in this study at 25 milligrams saw a complex imagery. They saw a lot of hallucinations, but just seeing

hallucinations did not lead to the positive clinical outcomes in terms of mood. Anxiety was a very interesting measure here, because ordinarily we think of the ego dissolution, the letting go is such a key component of the psychedelic journey in terms of the positive therapeutic outcomes. This has been discussed quite a lot, and in full disclosure, Robin Carter at Harris has already come on to record an episode of the Huberman Lab podcast. That episode hasn't been released yet, but it will be released soon. He talks about the importance of this letting go in terms of the positive clinical outcomes of the psilocybin journey. Indeed, that is true. I should also mention that Dr. Matthew Johnson from Johns Hopkins, who also runs a laboratory exploring psychedelics and their role in treating things like eating disorders and depression, etc., also doing incredible work, also talked about the importance of letting go during the psilocybin journey, this ego dissolution, this ability to move through the anxiety. And again, I can't underscore this enough because it's been told to me over and over again by the top researchers in this area that people will head into that peaking phase of the psilocybin journey. And oftentimes, it is not pleasant for them. They're feeling like it's uncomfortable, it's scary, and their heart rate is up, and their blood pressure is up, and they're having a hard time calming down, then they want to calm down. But it does seem that while the guides should not ramp them up and get
them more stressed, that the ability to move through that stressful period to somewhat guide oneself or to be encouraged to guide oneself through that peak and that anxiety and the fear of losing oneself and the so-called ego dissolution that occurs is an important feature for an effective therapeutic session. In this study, anxiety itself was inversely correlated with a positive therapeutic outcome. Okay, so this is important and somewhat nuanced. On the one hand, I'm telling you that the letting go, the ego dissolution does seem to be important in terms of reporting a psychedelic experience as effective as having accomplished something and perhaps even
explaining some of the long-term positive effects to emerge from that psychedelic journey, in this case, psilocybin journey. However, non-responders, that is people who did psilocybin, but did not have
a positive therapeutic outcome in comparison to the responders. Those non-responders tended to have
higher subjective ratings of anxiety than did the responders. So this is important. And what it speaks to is the fact that, well, yes, letting go during the session, experiencing some anxiety, perhaps even ego dissolution and the dissolving of self and then the return of self is important. It is also important, it seems, that anxiety not be so, so high or subjectively experienced as so high that one does not experience the positive neuronal rewiring that leads to a more pervasive elevated mood. Okay, so I'm definitely saying two things at once because I'm trying to capture the data accurately. It would not be fair for me to say just let go, experience as much anxiety as is possible, and that's part of the process. Yes, letting go, again, an air quote seems to be important for one's experience of the psychedelic journey, in particular around the peak that occurs about two hours in or so. However, extreme levels of anxiety seem inversely correlated or negatively correlated, would be the better way to put it, with the positive therapeutic outcome or relief from depression. So this takes us back to all of the things we've been talking about thus far, not just the chemistry and biological action of psilocybin, but the key importance of getting

dosage right, the key importance of making sure that you're in a safe environment, but also one in which the guides really know what they're doing. I think this is one of the biggest and most important reasons for having well-trained guides who really understand the contour of the psychedelic
journey, but are also trained in how to help somebody with their anxiety in real time while they're under the effects of psilocybin. And of course, to help people integrate those feelings of high anxiety and maybe guide them back down to a calmer state during the psychedelic session itself. Here I can just mention some unpublished data and studies, and again, this is very preliminary,
but through discussions with Dr. Matthew Johnson, who is running these psilocybin and other sorts of psychedelic trials at Johns Hopkins, he and I discussed the importance of having a real-time tool to adjust anxiety while under the influence of psychedelics like psilocybin. And there he asked and they've started to incorporate, is my understanding, some of the real-time respiration tools, that is breathing tools that we know based on work in my laboratory, Dr. David Spiegel's laboratory, can reduce anxiety very quickly in real time. And that involves the use of the so-called physiological sigh. I've talked a lot about this before on previous podcasts. So rather than explain it to you again here now, we'll put a link to the physiological sigh. I do a demonstration of it in the show note captions. I'll also link to a recent paper that we published in Cell Reports Medicine. This was a collaborative work that my laboratory did with Dr. David Spiegel's laboratory at Stanford School of Medicine, showing that the physiological sigh is among the different deliberate respiration techniques, one of the fastest and most effective ways to reduce levels of autonomic arousal, aka anxiety or stress. And Dr. Matthew Johnson's laboratory has started to incorporate physiological sighs within these psychedelic sessions as a tool that the guides can refer people to before the session begins, teaching it to them so they realize they can calm themselves down, if necessary, in real time. It works the first time. It works every time. This is not because it's some magic breathing technique that I created. It certainly is not. This is a naturally occurring pattern of breathing that occurs in sleep and in waking, but that when done deliberately leads to very rapid and quite significant decreases in stress and anxiety. And then when people are inside of the psychedelic session, if they feel their anxiety levels are going too high, they're heading toward what might be called a quote unquote bad trip. They're starting to panic or really think they're going to have a panic attack or die. Again, the subjective experience is going to be layered on top of the physiological experience of one's heart rate being really elevated. So a stress and agitation by using the physiological sigh inside of the psychedelic session. Dr. Johnson's laboratory and I believe at least one other laboratory are starting to use breathing techniques such as the physiological sigh as a way for these people who are under the influence of psilocybin to self direct their own calm and to bring that level of anxiety down so that they can continue to move through the peak and move through the other
phases of the psychedelic journey in ways that could be most beneficial for them. So to close out the description of this really wonderful study. And by the way, it's another one from the Harris laboratory about the subjective experience of ego dissolution or oceanic boundlessness, this mystical state as so key as a component of a positive psilocybin journey. I'll just

read for you the final sentence of this paper because it captures it so well quote, it seems vital that appropriate consideration is paid to the importance of promoting a certain kind of experience as the quality of that experience may be the critical determinant of therapeutic success. Now, before we move into what will be a very brief description of some of the other rewiring phenomena that psilocybin can induce and then into some of the therapeutic applications of psilocybin as they relate to these recent really exciting clinical trials for depression and addictive disorders and things of that sort. I just want to cue everybody to a paper that I think many people will want to take a look at in thinking about psilocybin. And I'll provide a link to this paper as well in the show note captions. This paper is entitled therapeutic use of psilocybin practical considerations for dosing and administration. And this is a wonderful paper because it really goes step by step through the pharmacology of psilocybin of which you now understand a bit, but it goes into a bit more detail. But then it also really nicely describes the contour of a psilocybin session and what's happening at the level of chemistry, early, middle, peak and toward the end of the psilocybin session. And then also importantly gets into issues of dosage and translating from mushrooms to psilocybin itself to psilocin. Things I talked about earlier, but in a bit more detail if you'd like to see that detail. And then perhaps most importantly, there's a section on contraindications where it points out that of course women who are pregnant or breastfeeding people who have a predisposition to psychosis, those people should really avoid the use of psilocybin and other psychedelics entirely. It also talks about where the evidence is strong, moderate and weak for the use of psilocybin for treatment of various disorders. And I can just summarize that very quickly because it's where we're going to head in a few minutes, which is that the most evidence for positive therapeutic outcomes response to psilocybin taken and conducted in the manner that we've been describing today in terms of dosage and journey set and setting is for cancer related depression, cancer related anxiety and treatment resistant depression. That's where most of the evidence resides. There's also some evidence for the use of psilocybin journeys. And again, this is typically one or two psilocybin journeys spaced in the cases of two journeys anywhere from one to two weeks apart. And again, with all of the same contour of supports and set and setting that we've been talking about today. And there there's some evidence for improvement in terms of outcomes in alcohol use disorder independence and tobacco addiction. And then finally, there's the least amount of evidence although there is clinical trial support for relief or partial relief for obsessive compulsive disorder cluster headaches and migraines and demoralization due to AIDS diagnosis. So this paper has a lot of really interesting information in terms of different conditions in terms of dosage and again, contraindications and what's called adverse events, what sorts of bad things can and do happen as a consequence of psilocybin and other types of psychedelic journeys both during and after those psilocybin or psychedelic sessions. We'll talk a bit more about this when we go into some of those clinical studies because adverse reactions is always a key measure in any clinical study. So very soon we'll get into the more recent clinical studies related to psilocybin for the use of treating depression and some other conditions. But before we do that, I'd be remiss if I didn't talk about how psilocybin does and does not change the brain, what is and what is not known about that. In fact, when I put out the call for questions about psilocybin, many of the questions related to these issues. The first thing to understand is that a psilocybin journey is really a way to try and put that wedge under the

boulder, as I described it, to try and invoke neuroplasticity of our particular kind. And in that way, it's kind of remarkable, if you think about it, that everyone has different lives, different experiences, psychedelics, in this case psilocybin, are activating these brain networks that each of us has more broadly than they would normally be activated. These are very abnormal patterns of thinking and perceiving and experiencing our emotional and physical life, et cetera. And yet, so often, the outcomes are positive, not always, but the outcomes are positive, the experience is positive, even though it might have these anxiety moments or components within them. It's very important to understand that psilocybin and the journey, while important, are not really what all of this is about. It's really about neuroplasticity. So researchers, in particular, neuroscientists, are very intensely interested in understanding what sorts of neuroplasticity psilocybin creates, because it turns out there are lots of different types or processes involved with neuroplasticity. For instance, brain networks, behavior, thinking, emotion, et cetera, can change because of the addition of new neurons. That's one form of neuroplasticity that's referred to as neurogenesis, the production of new neurons, most typically in the so-called dentate gyrus or other subregions of the hippocampus, a brain area involved in learning and memory. Neurogenesis in other regions of the adult human brain are exceedingly rare, and to be honest, may not occur at all. This is a debated area. We could do an entire episode about this, but for the most part, neuroscientists don't really believe that your neocortex, your striatum, your cerebellum has that much neurogenesis that's related to learning and memory of new things or new experiences, and we don't actually think that occurs as a consequence of taking psilocybin either. Now, some of you who are familiar with, for instance, the cerebellum, might be saying, wait, what about granular cell proliferation in the cerebellum? Or what about the rostral migratory stream from the subventricular zone where there are neuroblasts spitting out little new neurons that migrate into the nose to replenish the olfactory neuron population? Yes, that's all true. That does occur. It's been observed in mice, it's been observed in monkeys, and to some extent, it's been observed in humans, but it's not, again, I repeat, it is not a prominent feature of learning and acquisition of new skills, new ideas, or new emotional states. Perhaps the best supported evidence for neurogenesis underlying new thoughts, experiences, abilities, emotions, et cetera, is the production of new neurons in that dentate gyrus subregion of the hippocampus. And that probably does occur in humans. But neurogenesis is not really the dominant
mode of changing neural circuitry in adult humans. It might be a player in adolescence, in young childhood. It is certainly a player before we are born when we are still in utero, but then the brain is being wired up in many different ways, including the addition of new neurons and changing of connections. All this is to say that while neurogenesis is a really sticky idea and it makes great headlines, the addition of new neurons is not really the way that the brain changes under psilocybin, other psychedelics, or just generally. It's perhaps responsible for maybe one to 2% and I'm being generous there of the rewiring events that are going to be most important for all of us. So we need to set that down and kind of cement that there until further evidence comes out to the contrary. That's certainly where I, and here I feel comfortable speaking for the majority of neuroscientists out there, professional neuroscientists that is. The papers showing adult neurogenesis are interesting, but they don't really explain most of the plasticity that occurs in the adult human brain. So if neurogenesis ain't it, what is?

Well, it's very clear that psilocybin, other psychedelics, and any sort of behavioral or drug intervention that can induce neuroplasticity does so largely through the addition or strengthening of new neural connections or through the elimination or weakening of other neural connections. And if you look at the data exploring the mechanistic basis for psilocybin induced neuroplasticity, it's mostly focused on animal brains, animal models, mice and rats in particular, a little bit on primates, but mostly mice and rats because that's where the interventions can be done of knockout animals of imaging the brain in real time. Of course, there are the beautiful studies of Robin Cardart Harris and others exploring neuroplasticity at the level of brain imaging, at the level of ultrasound measurements of how active are certain brain areas in humans, and how extensive is the modularity or not extensive is the modular, etc. The stuff we talked about earlier. So in other words, there are neuroplasticity studies with the effects of psilocybin in humans. But in terms of underlying mechanisms of neuroplasticity, I think the predominant theory is that psilocybin induces neuroplasticity through the addition of novel connections in those pyramidal neurons of the frontal cortex elsewhere in the cortex and certainly also in the visual cortex, probably also subcortically as well below the cerebral cortex in areas like the thalamus, maybe even in the brainstem as well. And that those neuroplasticity events are structural and functional. And they involve a couple of basic events, the most prominent of which is the growth of dendrites. Dendrites are those little branches or processes that come out of the neurons, not just the pyramidal neurons, but other neurons as well. But since we're talking mainly about pyramidal neurons today, both the apical, those ones that top, they're called the apical tufts are the ones that reach laterally to connect with other neurons, communicate with other neurons that we talked about before, as well as the dendrites that come out of the base of those pyramidal neurons, those processes grow in response to psilocybin, as well as the addition of what are called dendritic spine. So the dendrites are the branches, the spines are these little protrusions that grow out. They actually in here, I don't know if this is coincidence or not. Again, I always say, I wasn't consulted design phase, but these little protrusions actually look like little mushrooms. They have a little stalk and they have a little head, a little spine head and those little spine. So think of these as like little tiny mushroom appearing. Okay, they aren't actual mushrooms. Okay, the first person that puts in the comments, Oh my goodness, I learned today that mushrooms grow out of our neurons when we take magic mushrooms. That is not what I'm saying. What I'm saying is that these little mushroom shaped protrusions that we're calling dendritic spines do in fact grow out of dendritic branches of neurons when animals ingest psilocybin or are injected with psilocybin and that those little mushroom shaped protrusions are the sites of new excitatory connections, new locations for input from other neurons to activate those neurons that have those little mushroom shaped protrusions. If you'd like to see examples of this, both movies and still shots, it's pretty remarkable. There's a paper that I'll provide a link to in the show note captions. This was published in the journal neurons cell press journal, excellent journal entitled psilocybin induces rapid and persistent growth of dendritic spines in the frontal cortex in vivo. So these measurements were done in the mouse equivalent more or less of the prefrontal cortex. There's some interesting details in this paper. For instance, that those new connections persist. So they don't just grow out during the psilocybin being active in the bloodstream and brain of

the animal. They persist. Okay. So this may again may explain some of the persistent changes that occur in people after psilocybin journeys. They may to grow new spines. I should also mention that a reduction in the number of dendritic spines, these little mushroom shaped protrusions in the frontal cortex neurons of humans occurs in depressed patients. We know that from postmortem
tissue and that drugs that relieve depression or that treatments including behavioral treatments that provide some relief from depression do seem to be correlated with increases in spine growth in frontal cortex neurons as well. So this raises a very interesting idea, which is perhaps it's the growth of new connections, these new dendritic spines in particular neurons that's created by administration of psilocybin that explains the relief from depression that people experience. So this is just one paper, but it's one paper of a growing body of work showing that yes, indeed psilocybin induces both structural and functional plasticity in the human and animal brain. It does that in the human brain at therapeutic doses of anywhere from 10 to 25, perhaps even 30 milligrams per session, one or two sessions. I should mention that the mouse studies
tended to use quite high doses of psilocybin. I was actually, I wasn't shocked, but I was somewhat wide eyed for a moment to realize that most of the studies looking at changes in plasticity in the mouse brain in response to psilocybin use the equivalent of one milligram per kilogram of body weight, which is if you do the math and you translate what we were talking about before in terms of dosages, I'll just spare you all the time. It's about double the sorts of dosages that are typically used in humans, maybe even triple in some cases. Now it's often the case in animal studies because of the metabolism of animals being different, but also because seeing effects of drugs in animal studies can be difficult. They did use a dose response anywhere from zero to 0.25 to half to one to two milligrams per kilogram of psilocybin in the study, so they had a dose response curve, but focused mainly on this one milligram per kilogram dosage. In any event, the point is that many of the studies that describe these pretty dramatic structural changes in the animal brain, most typically the mouse brain in response to psilocybin, use dosages of psilocybin that if translated to humans would be about double the human therapeutic dose. So that is something that we need to take into consideration. Nonetheless, it's very clear that in both animal studies and humans psilocybin is inducing both structural and functional changes in brain circuitry and that in humans, the network connectivity is being changed dramatically. We talked about those data earlier and that the underlying basis for that might be again might be we don't know for sure the addition of new genetic spines on these pyramidal neurons that we've been talking about repeatedly throughout today's episode, although neurogenesis perhaps and other modes of neuroplasticity such as the elimination of certain connections perhaps related to unhealthy maladaptive thoughts or our feeling that a particular sad song is overwhelmingly sad, it could be the case that those sorts of things change subjectively because of the removal of neural connections. If you're going to think like a neurobiologist or scientist for that matter, you don't ever want to think that one mechanism can explain all the effects of a given drug or a given experience is almost certainly likely to be the consequence of multiple mechanisms acting in parallel. And because I know there are people out there who would like to know even more about the neuroplasticity induced by psychedelics, including psilocybin, there's a wonderful review that I provide a link to in the show note captions entitled

psychedelics and neuroplasticity, a systematic review unraveling the biological underpinnings of psychedelics. This review is great because it goes a step beyond just psilocybin, psilocin, binding to the serotonin 2a receptor and things like brain derived neurotrophic factor. It actually talks a lot about the intracellular signaling and exactly how neurons change their excitability patterns based on this activation of the serotonin 2a receptor. It's probably more detailed than most of you out there are interested in, but if you are interested in that level of detail, this is a wonderful open access review. So a few minutes ago, I talked about where there is strong, modest and somewhat weak or rather, I should say minimal evidence for the therapeutic use of psilocybin to treat various disorders. And across the board, it really appears that major depression and so-called intractable depression in some cases is where we're seeing the most exciting research to date. Now keep in mind that because of the controlled substance act being invoked in 1970 in the United States and because it was only just a few years ago really only about five years ago that psychedelics, including psilocybin, received what's called breakthrough status at the FDA, that there are now a lot of clinical trials exploring how psilocybin can impact various things like mood disorders, addictive disorders, and so on. Prior to 2018, when that therapeutic breakthrough potential was established in the United States, I think a lot of people in the so-called psychedelics community had the sense and really the belief that these drugs had enormous potential, but they just weren't being explored that extensively. So I do want to give a nod to the incredible researchers, such as Robin Cardard Harris, but also Matthew Johnson, Roland Griffiths, Nolan Williams, and many others. Okay, I'm certainly not listing off everybody that would take hours, but those researchers have really pioneered both the legal efforts and the funding efforts and most importantly, the research efforts defining the clinical data that I'm about to describe. And here I'm going to summarize the clinical data in a bit of a top contour fashion, just giving you the kind of highlights. We will, of course, provide links to the papers if you'd like to look into it further, but I'm only giving you the top contour because I've had the great fortune of having Matthew Johnson on this podcast before. You can find that episode at hubermanlab.com. Just simply put Matt's name or psychedelics into the search function. It'll take you to that episode in all formats or links to all formats rather. I've also had the great fortune of sitting down recently with Dr. Robin Cardard Harris to talk about his work at University of California, San Francisco, on psilocybin, LSD, ayahuasca, and DMT as it relates to depression and other disorders. And that episode, which also will be released at hubermanlab.com and on all platforms, YouTube, Apple, Spotify, really goes in depth into these clinical studies and what those studies really look like. You know, who's in the room, whether or not people just get one dose or two doses, how far apart those are separated. All of that is covered in extensive detail in that what I found to be wonderful discussion with Dr. Robin Cardard Harris. So if you're interested in all of the details as it relates to clinical application of psychedelics, stay tuned for that episode soon. Again, you can find that at hubermanlab.com and on all platforms. In the meantime, I would be remiss if I didn't include a bit of discussion about what has been observed in terms of using psilocybin journeys as a way to treat depression because the data are just oh, so exciting. Again, these data really started to surface as the consequence of studies that were initiated around 2006 in just a few select laboratories and then really picked up in terms of the number of laboratories and number of studies between 2018 and now. So what you'll

notice is that most of the papers I'm about to describe were published in, for instance, phenomenal journals, New England Journal of Medicine in 2021, New England Journal of Medicine November 2022, Journal of the American Medical Association and Psychiatry just very recently, 2021. So these are very recent papers. Essentially, all of these clinical studies involve either one or two psilocybin sessions. The dosages that were explored range from zero milligrams, so placebo, if you will, 10 milligrams, some cases 25 milligrams, in some cases 30 milligrams. And most typically, people received the same dosage for both sessions if indeed they did both sessions. However, there's at least one study looking at just one single episode of psilocybin administration. So this is the paper entitled, no surprise, single dose psilocybin for treatment resistant episode of major depression. This was published in the New England Journal of Medicine in November of 2022. I'll just summarize the results of this single application study. They randomly assigned subjects who had treatment resistant depression. So they'd resisted treatment to other things to receive a single dose of a synthetic formulation of psilocybin. So they're not eating mushrooms. They're getting a synthetic dose of psilocybin. But the dose is known of either 25 milligrams, 10 milligrams, or one milligram, which was the control. And they received psychological support. There were a number of different tests, subjective tests of depression taken before and after the psilocybin journey. They had about 75 to 79 participants in each group, again at the three different doses, 25, 10, or one milligram. And they looked at the changes in these scores, these depression related scores on these tests. There are many results from this paper one could summarize, but among the most important results I can summarize from the discussion in here, I'm paraphrasing that the change in baseline levels of depression that is at week three, following the psilocybin session was significantly better. That is people experienced more relief or more people experienced more relief from the 25 milligram dose than from the one milligram dose. And this is important. There was no significant difference between the 10 milligram dose and the one milligram dose. This really points to the fact that the 25 to 30 milligram dose that's used in the largest numbers of studies exploring treatment resistant depression really seems to be, I don't want to say the best dose, but the most effective dose at least in this clinical context, in this set and setting, and with this particular patient population. So we want to be careful to say that so that one doesn't just translate the 25 milligrams is better than 10 milligrams, although in this study it was for sake of treatment resistant depression relief. There were a number of other key aspects of this paper, in particular the exploration of so-called adverse events. So things like headaches, propensity for self harm, actual self harm, anxiety, and so on. It's worth mentioning that there were adverse events in essentially every group. The number of adverse events was highest in the 25 milligram dose group. This is observed in other studies as well. With higher dosages, there tends to be greater relief from depressive symptoms, but also a greater chance for adverse events. Some of those adverse events can be quite severe. So feelings of suicidal ideation, et cetera. Some of them, one could consider a little less severe, mild headache or severe headache that was transient or anxiety that was transient. Again, highly individual responses. We could go line by line by table through this paper, which we won't because there's a lot of data. Again, we'll provide a link to this paper if you'd like to peruse it yourself. It's fairly straightforward to read. That's one thing that's nice about these clinical trials is they tend to be written in fairly non-technical language, although there's a little bit of technical language. The important point is that a single dose

of 25 milligrams of psilocybin provided significant relief from treatment resistant depression in this particular patient population, but it is not the case that 100% of the people who took 25 milligrams of psilocybin experienced that relief. However, the majority of them did. Now, when you say majority in science, you really need to look to numbers. And the reason I'm not telling you, oh, it was 75% or 60% or 50% is because it depends on which time point people were analyzed. People were asked about their level of depression relief immediately after one week after two weeks after three weeks after. And the degree of relief tended to change over time. In fact, it tended to diminish over time, but it was also stable or remarkably stable, I should say, at least by my read, in the 25 milligram dose group. And that is summarized nicely in figure two of the paper because they explored these people's levels of depression out to week 12. And they still saw a significant degree of depression relief 12 weeks after the single 25 milligram psilocybin dose session. So as I mentioned earlier, there are now about a dozen or so excellent studies, clinical trials, exploring the use of single or two sessions psilocybin treatment in that 25 to 30 milligram range, which seems to be the most effective dose for long lasting relief from depression. Each one of those studies explored something different, as is important. Replication is also important, of course, in order to validate previous studies. But for instance, there have been comparisons of psilocybin versus SSRIs or other antidepressants.

There have been comparisons of psilocybin plus psychoanalysis or cognitive behavioral therapy versus cognitive behavioral therapy alone or psychoanalysis alone. And so there's a lot of evaluation now of the clinical outcomes and the statistical outcomes of these subjective measures and even some objective measures of neurochemistry where that's possible in terms of trying to understand if and how psilocybin is effective for the treatment of depression. And the major takeaway is that indeed it does seem to be the case. And the numbers that I feel comfortable not throwing out there, but putting out to you reflect my conversation with Robin Cardhart Harris. Again, that will be released soon at hubermanlab.com, as well as takeaways from what I would say are the six broadest studies, meaning they have the widest range of age groups, the broadest demographic in terms of the subjects, their backgrounds, their levels of education, men, women, ethnicity, et cetera. And a lot of that can be summarized in the paper entitled effects of psilocybin assisted therapy on major depressive disorder. This was a particular randomized clinical trial. But in the discussion, I think they summarize it quite well, which is that if you look at the number of people who take this 25 milligram dose twice in sessions spaced about a week apart, what you will find is that anywhere from 60 to 75% of the people who have major depressive disorder who do these psilocybin sessions in the proper setting, report a good experience with it, have minimal adverse events coming out of those sessions and in the weeks following. Those people experience substantial positive relief from major depression in ways that other treatments that they had explored, including antidepressant drugs, cognitive behavioral therapy, and other types of therapy alone could not provide. Now it's a general feature of these clinical trials focusing on psilocybin that people are asked to stop taking their antidepressants prior to participating in the trial. It's also a general feature of these trials that people are encouraged to not suddenly start their antidepressant treatment immediately afterwards because, of course, that could confound the results of the psilocybin treatment.

However, and this is a very important thing to note, all subjects were encouraged not to

avoid taking those antidepressant medications if, in fact, their clinician felt that it was important for their immediate and long-term survival. So no one should be reckless in thinking about what to add or delete from their drug protocol when dealing with depression, all right? The outcomes could be very severe in that case. Nonetheless, we can paraphrase from the discussion of the paper I just mentioned because it really highlights the incredible results that psilocybin applied in these particular therapeutic settings are providing.
And here, again, I'm paraphrasing. The present trial showed that psilocybin administered in the context of supportive psychotherapy, consisting of approximately 11 hours of psychotherapy. So this is going to be two sessions of the psilocybin with proper therapeutic support, produced large, rapid and sustained antidepressant effects. The effect sizes reported in this study were approximately 2.5 times greater than the effects sizes found in psychotherapy.
And more than four times greater than the effect sizes found in psychopharmacologic depression treatment studies. In other words, four times the positive effect observed with typical SSRIs or other pharmacology of that sort.
These findings are consistent with the literature that showed that combined pharmacotherapy and psychotherapy were more efficacious in the treatment of major depressive disorder than either intervention alone. So again, this points to the fact that combining drug therapy with talk therapy, as it's often called, is going to be more effective than either treatment alone. Here the drug therapy is psilocybin therapy. And again, please don't take the fact that in these studies, they tended to ask people to not take their antidepressant medication heading into the study as a sign that one should stop taking their antidepressant medication. Rather, I think this study and other studies like it again, which we'll provide links to in the show note captions that are discussed extensively in the episode with Dr. Cardard Harris soon to come, really point to the incredible role that psilocybin can have in creating an experience inside of the session, the journey or the trip as it's called, as well as initiating neuroplastic events, perhaps the addition of dendritic spines, maybe even some new neurons, maybe, although I don't think that's the predominant mode. But that leads to these more extensive conductivities in the brain, so-called reduction in modular networks, enhanced activity in brain areas that normally wouldn't be talking to one another, but not doing that in any kind of haphazard way. It really does seem that the one or two sessions of psilocybin that induce these feelings of ego dissolution, that induce these feelings of oceanic boundlessness, right? So mystical. And in many ways, it's what I find so incredible about psilocybin and other psychedelics is that despite the highly mystical, highly subjective and still at this time, somewhat top contour understanding of how they might exert their effects, you can highlight boldface and underline might there, right? Because it hasn't really been firmly established what the exact cell biological rewiring events are. But there is now what I would refer to as a center of mass of data that point to the fact that psilocybin, when taken in the appropriate set and setting at the appropriate dosages, can invoke the sorts of neuroplasticity and changes in emotionality, in perceptual experience, not just during the psychedelic session, but for long periods of time after the psychedelic session, they can provide really remarkable relief from things like major depression and perhaps other psychiatric issues as well. And of course, I realize that many of you are listening to and are watching this episode, and you're not necessarily depressed or thinking about psychedelics like psilocybin in the context

of depression. I hope today's discussion allowed you to better understand how psychedelics and psilocybin in particular, because that's what we've been talking about, are able to exert these incredible effects that they seem to exert. This is not a call for everyone to run out and do psilocybin. It is absolutely not that it is. However, my attempt to really put a magnifying lens on this incredible area of research that's happening, not just in the context of clinical trials, but in the context of trying to understand how serotonin and how drugs like psilocybin, which in many ways mimics serotonin, and more particularly the activation of particular receptors in the brain, like the serotonin 2A receptor. I mean, just sit back and think about that. The selective activation of this receptor, which is, by the way, associated with the expansion of the neocortex across evolution, didn't mention that before, but indeed it is, how that can lead to enhanced ways of thinking, changed ways of thinking, actual learning inside of this short four-hour or six-hour session that we call the psilocybin journey. As is often the case, perhaps as is always the case here on the Huberman Lab podcast, we did a deep dive into a topic today into the topic of psilocybin, what it is, how it works, the different ways in which it changes brain circuitry, how it creates the experiences that we think of as the psilocybin journey, what the safety issues are, what the so-called set and setting are that can lend themselves to positive therapeutic outcomes. And in doing so, my goal was really to highlight several things. First of all, I am very excited about the potential for psychedelics such as psilocybin to provide relief for mental health issues that to date have been very hard for people to access. In addition to that, I'm just fundamentally interested in the brain and how it works and how it can change this thing we call neuroplasticity. To me, neuroplasticity is the holy grail of the human nervous system. As far as we know, we are the animal that can have long-lasting neuroplasticity
throughout the lifespan. And if it requires the use of compounds in a safe and controlled way, such as psilocybin, in order to achieve maximal plasticity in a short amount of time, that's exciting. But of course, that also needs to be considered with all of the safety precautions in mind that we talked about earlier, including the fact that people who have a predisposition or who have psychosis or bipolar disorder or a relative that has psychosis or bipolar disorder, younger people, meaning people 25 years of age and younger, and really anyone who's not working with a dedicated and highly trained physician needs to be very cautious about these compounds as well. They're very exciting. I think psilocybin is an exciting and super interesting compound for basic and clinical reasons and for other reasons as well. But they are sharp blades, as we say. And with sharp blades, you can do incredible things, but you can also cut yourself very badly. So all those considerations need to be taken to mind. So I consider the science and use of psilocybin to be an exciting but still preliminary area that I certainly am paying a lot of attention to. And I know there's a lot of excitement about. So stay tuned for the episode with Dr. Robin Carter at Harris, and we will probably revisit psilocybin and we will certainly revisit the other psychedelics and non classical psychedelics, including LSD, DMT, 5MEO, DMT, ketamine, MDMA, mescaline, and all the rest in future episodes as well. If you're learning from and or enjoying this podcast, please subscribe to our YouTube channel. That's the best zero cost way to support us. In addition, please subscribe to the podcast on both Apple and Spotify. And on both Apple and Spotify, you can also leave us up to a five star review. If you have questions for me or comments about this or any other podcasts or topics that you'd like me to cover or guess you

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Lab podcast, but much of which is distinct from the content covered here on the Huberman Lab podcast. So again, it's Huberman Lab on Instagram, Facebook, Twitter and LinkedIn. Thank you once
again for joining me for today's discussion all about psilocybin. And last but certainly not least, thank you for your interest in science.