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 my guest is Dr. Nolan Williams. Dr. Williams is a medical doctor and professor of psychiatry and behavioral sciences at Stanford University School of Medicine. His laboratory and clinic focus on depression and other mood disorders. They focus specifically on the use of transcranial magnetic stimulation, which is a brain stimulation technique that can either activate or quiet specific brain circuits as well as circuits within the body in order to treat depression and other mood disorders. Other laboratories and clinics use TMS. What sets apart the work of Nolan Williams and colleagues is that they combine TMS with other treatments and some of those treatments are among the more cutting edge that you've probably heard about these days including eye-bagging, psilocybin, MDMA, cannabis, DMT and other drugs that at this point in time are experimental in terms of clinical trials but that at least the preliminary data show hold great promise for the treatment of depression and other mood disorders. In the course of my discussion with Dr. Williams we covered things such as the history of each of these drugs. How they can to be and their current status in terms of their clinical use and legality. We also talk about their safety profiles both in children and in adults. And we talk about what the future of psychedelic research and clinical use really looks like. For instance, we discuss how a number of laboratories and clinics are modifying psychedelics to remove some of their hallucinogenic properties while maintaining some of their antidepressant or antitroma properties. You'll also learn about some fascinating research in Dr. Williams' laboratory focused on ketamine which is a drug that is increasingly being used to treat depression. And contrary to common belief, the effects of ketamine in terms of relieving depression may not actually arise from its dissociative effects. One thing that you'll find extraordinary about Dr. Williams is that not only does he have vast knowledge of the various treatments for depression but that he and his laboratory are really combining these treatments in the most potent way. That is combining psychedelic treatments with brain machine interface or combining brain machine interface with particular learning protocols. That is neuroplasticity protocols which can directly change the brain in specific ways. So today you're going to learn a tremendous amount about the neural circuitry underlying depression as well as positive moods. You'll also learn about all the various drugs that I described and you're really going to learn about the current status and future of the treatment of mood disorders. Today you'll also learn about a number of ongoing studies in Dr. Williams' laboratory. I should mention that they are recruiting subjects for these studies. If you go to BSL which stands for brain stimulation laboratory so that's BSL.stanford.edu. You have the opportunity to apply for one of these clinical trials for the treatment of depression and other mood disorders. I confess that the conversation with Dr. Williams was for me one of the more stimulating and informative conversations I've ever had about psychedelics which is simply to say that he is a drug that is used to treat depression. Simply to say that his breadth and depth of knowledge on that topic is incredible and his breadth and depth of knowledge in terms of the underlying brain science and how it can all be combined with clinical applications is also extraordinary. I'm sure that by the end of today's episode you're going to come away with a tremendous amount of knowledge about the clinical and non-clinical uses of those substances and you're going to understand a lot more about how the healthy and diseased brain work. I'm pleased to announce that the Hubertman Lab podcast has now launched a premium channel. I want to be very clear that the Hubertman Lab podcast will continue to be released every Monday at zero cost to consumer and there will be no change in the format of these podcasts. The premium channel is a response to the many questions we get about specific topics and it will allow me to really drill deep into specific answers related to those topics. Once a month I'm going to host and ask me anything so called AMA where you can ask me anything about specific topics covered on the Hubertman Lab podcast and I will answer those questions. Those of course will be recorded. There will also be other premium content available to premium subscribers such as transcripts and short videos of new tools and unique tools for mental health physical health and performance. If you want to check out the premium channel you can go to Hubertman Lab.com slash premium. There is a $10 a month charge or $100 per year and I should mention that a large portion of the proceeds from the Hubertman Lab premium channel will go to support scientific research that develops the very sorts of tools that we talk about on the Hubertman Lab podcast. The rest of the support from the Hubertman Lab podcast premium channel will go to supporting the regular Hubertman Lab podcast again that Hubertman Lab.com slash premium. 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. Now for my discussion with Dr. Nolan Williams. Thanks for joining today. I'm really excited to have this conversation. It's been a long time coming and I have a lot of questions about different compounds psychedelics in particular. But before we get into that discussion I want to ask you about depression broadly speaking intractable depression how common depression is or isn't. I heard you say in a wonderful talk that you gave that depression is perhaps the most debilitating condition worldwide and yet in contrast to other medical conditions like cancer. We actually have a fairly limited number of tools to approach depression and yet number of tools in the potency of those tools is growing so you could educate us on depression. I really appreciate it. Yeah absolutely so depression is a condition that it has a lot of a lot of manifestations you know so you can have kind of a depression that's primarily loss of interest. You can have folks who feel very anxious and they're kind of overactive. You can have people who don't have any anxiety at all and they're very underactive and they have low motivation to do anything. You know so you have this huge range of symptoms that are in that umbrella of depression and some of our work is to actually work with with folks that Connor listen in Cornell and try to actually get bio types based off of neuro imaging to see if we can kind of parse out the different depression kind of presentations in the end. See that clinically and also see that in the brain depression is the most disabling condition worldwide what's interesting about depression is it's both a risk factor for other illnesses and it makes other medical and psychiatric illnesses worse right so recently the American Heart Association added depression is the fourth major risk factor for coronary artery disease right so alongside the risk factors that we know hyperdiproton. There's that we know hypertension high blood pressure hyperlipidemia high cholesterol and diabetes high blood sugar those three have been on the list for a long time and depression and to you know being added to the list is the fourth one and you know really interesting right so in addition to taking medications to address those other three risk factors we really have to be thinking about how do you treat folks with depression to reduce the risk of having a heart attack in the future. And you know there's some of that's being worked on now but we don't have a complete solution to thinking about that at this time and then the other thing that's interesting is once you have our heart attack into the in in the individuals and of having a heart attack the risk of having depression after the heart attack is higher than the normal population right and so a lot of what we're doing in the lab actually is is measuring kind of brain heart connections and we can actually with trans cranial magnetic stimulation a form of brain stimulation we can actually decelerate the heart rate and capture that heart rate deceleration over the mood regulatory regions and so actually a direct probe of that connection. So it's it's interesting and so you know as you said a second ago you know it's a it's a very disabling condition moderate depressions about is disabling is is having a heart attack acutely having a heart attack severe depressions is disabling is having cancer without treatment. You know and dying from from a cancer without treatment and so you know it's it's kind of under appreciated just how disabling depression is in that way and I think important as stigma is consistently kind of being reduced over the years for mental illness for mental illnesses than the idea that we can start really putting more funding and putting more focus the federal level you know foundation level whatever it is at a given university to to thinking about developing treatments we've been very interested in a very particular clinical set of problems around the the most severe and the most high acuity settings that folks with depression end up being in and that's in you know emergency settings where they go into in patient units and you know in the rest of medicine if it's talking about heart attacks if I start having chest pain right now and and you bring me to a primary care doctor's office are going to have a certain number of tests and treatments right but very limited because it's an outpatient facility if you bring me to the emergency room after that there are more tests and more treatments if you put me in the ICU or in the cath lab where they do invasive procedures the heart there are more tests and more treatments in psychiatry as we elevate the acuity of an individual you go from being just depressed to being depressed and now thinking about into your life the number of treatments actually go down on average I mean some scenarios they go up but on average they go down and there are no tests right and so we've been very focused on that particular problem somebody that maybe was doing you know fairly okay with a pretty moderate depression and the depression gets worse and then they end up in an emergency setting and the field really hasn't developed a way of you know consistently being able to treat that problem and folks end up getting the same standard oral antidepressants that they've been getting outpatient and I came to this because you know dual trained as a neurologist and psychiatrist went back and forth between neurology and psychiatry saw that in neurology we have all these ways of treating acute brain based problems and really wanted to emulate that in psychiatry and find ways to develop an engineer new you know brain based solutions. There's a lot to impact there one thing that you said is I'd like to focus on a bit more because I think we hear that the brain and the heart are connected but you described I believe a direct relationship between areas of the brain associated with emotion and heart rate yes and that makes perfect logical sense to me but I think I'm not going to be able to do that. But I think at the same time many people out there probably think of the relationship between the heart and the mind as kind of who are kind of a soft biology but here you're talking about an actual physical connection between what area of the brain is it. The you know the first place where the stimulation goes is called the door salateral prefrontal cortex it's kind of the sense of control kind of governor of the brain and then it'll and then what we know is that when you use a magnet use kind of what we call fair days law this idea of using a magnetic pulse to induce an electrical current and electrically conducting substances so in this case. Brain tissue but not skull or skull for any of that or hair you avoid all that just the brain tissue then you have a direct depolarization of cortical neurons you know the surface of the brains neurons in this door salateral prefrontal. And if you do that in the actual scanner which we can do you can see that that distributes down into the enter singulate in the insula and the amygdala and ultimately the tract goes into something called the nucleus tract of solitarius and ultimately into the vagus nerve into the heart so that the heart very consistently seems to be the end organ of the door salateral prefrontal cortex. If you measure heart rate in standard ways that cardiologist measure heart rate and you stimulate over this left or lateral you get a disseleration of the heart rate it's very. Time lock to the stimulation so it's a two second train of stimulation at one second you see the acceleration it goes down about ten beats per minute and then it'll drift back up moves a break rate seconds on the stimulation drifts back up in the stimulation goes back in and then the heart rate goes back down so you see the heart rate just do this. Ten beats per minute every train and so we know if you do that over visual cortex you don't get that or motor cortex you don't get any of those findings it's really specific to this kind of control region of the brain and so yeah it seems to you know it's our work other other folks work martinards and in in Europe and other ones work showing the same connection so I think it's been replicated like four or five times. So you mentioned left door salateral prefrontal cortex anytime I hear about lateralization of function I get particularly curious because obviously we have two mirror symmetric sides of the brain there are you know rare exceptions to this like the pineal and things of that sort that are only there is only one pineal. So what is special about the left door salato prefrontal cortex does this have anything to do with handedness right hand or left hand because we know right hand in left handedness has a lot to do with lateralization of function for language. A topic for another time but why do you think that left door salato prefrontal cortex would be connected to the heart in this way yeah yeah I think so so left or lateral. It's thought to be the side that when you excite it when you kind of do excitatory stimulation, potentiating sort of stimulation that you can reduce depressive symptoms and guy by the name Mike Fox at Harvard demonstrated that if you have strokes in the brain that that caused depression you put them on the human connect them 100,000 patient map and you ask the question what they're all functionally connected to left door salateral. If you take lesions it caused mania in individuals and you put those all in the human connect them map and ask what they're all the one common area they're all connected to it's the right door salateral and so there seems to be a hemispheric you know balancing of mood between these two brain regions and we know this from an experimental standpoint too because you can take individuals with depression and you can excite the left or you can inhibit the right and they they're both in the right. And they're both antidepressant you can excite the right and that's anti manic in some studies and so this idea that there is this hemispheric balancing of mood is quite interesting right it's incredibly interesting and just so people know if you're curious what the connect home is a connect home is a term that was built out of this notion of genomes of being a large collections of sequencing and mapping of genes their proteomes of proteins. Of connect homes is a so called connect home X of connections between neurons of the human connect home project is ongoing and I find that incredible that within the connect home project that can identify these regularities of right versus left or salateral prefrontal cortex especially since I've looked at a fair number of brains from humans not certainly not as many as you have and if you look at the architecture the layers the same as the other. The layers the cell types and even the neuro chemicals of which cells are expressing say dopamine or serotonin or receiving input from areas that make dopamine or serotonin. Look at that different on the right and left side and yet here we're talking about a kind of an accelerator in a break if you will on depression and mania using what at least by my eye and I think other people's eye look to be basically the same set of bits the same parts list more or less. So what gives that these properties to the right and left or salateral prefrontal cortex is that the inputs they receive is this something that we learn during development or do you think that we come into the world with these hemispheric biases. Yeah, it's a great question and you know it hasn't been worked out with your original question was around in a left handed individual which as you know 25% of those folks end up having a right brain dominance or 1% of right handed people have a right brain. If it's flipped right and that you know unfortunately that study still hasn't been done at the level because that would be probably pretty helpful for teasing some of this out. But you know it's it's still you know it's still being sorted out right we know enough to know this phenomenon exists because we can use TMS as a probe and do this sort of these sorts of manipulations but to my knowledge there hasn't been anybody that's got to be a good example. It's not been anybody that's gotten so interested in it that they've been able to get a mechanism of why that is but but it you know it's kind of empirically true in the sense that you can push and pull on those systems or in this in the case of strokes that folks have and then you kind of get their brains and their brain images and look at where the strokes landed. So that's a little bit of information point to this this asymmetry interesting well. In that case going with what we do know that stimulation of Dorsal Adore prefrontal cortex slows the heart rate down transiently but slows it down and seems to alleviate at least some symptoms of depression leads me to the question of why would that be the case is it does it tell us anything fundamental about depression that anxiety is inherent to depression I think of faster heart rate is you know part of that. It is you know part and parcel with with with anxiety in my laboratory we've studied fear a bit in animals and in humans and we often observe brachycardia where somebody or an animal is afraid of something and rather than the heart rate speeding up it actually slows down something that most people don't think about or recognize but given that stimulation of Dorsal Adore prefrontal cortex slows the heart rate down and can alleviate depression. And then there are other ways to slow the heart down I have two questions what do you think this tells us about the basic architecture of depression and its physiology at the level of the heart and does the circuit run in the opposite direction to if one were to have or find other ways to slow the heart rate down say with a beta blocker. Does that help alleviate depression. Yeah, that's a great question. So the I'll answer the second question first so we know that and they're ongoing trials of this if you stimulate in the Vegas nerve and an implanted Vegas nerve stimulator you can actually have this the a parent parts of the Vegas project ultimately up to the DLPFC the single it through these anterior insula so that same obviously the same track right and you can stimulate there and alleviate depression which seems very unusual right you're stimulating a cranial nerve down on the neck but if you can get up into the brain you actually can improve depressive symptoms and so you know more evidence that this is a kind of a whole track and system and if you stimulate in part of that system it appears that you can improve mood. What if I were somebody who did not have a stimulating electrode in my Vegas nerve and I was dealing with minor depression and I decided I wanted to take some other approach to slow my heart rate by the Vegas for instance exhale emphasized breathing or deliberately slow cadence breathing things of that sort is there any evidence that behavioral interventions of those kinds can. Alive eight depression or some symptoms of depression and is there any evidence that it does indeed feedback to the door salato prefrontal cortex to achieve some of that alleviation absolutely yeah so there's a number of studies implicating DLP the door salato and say you know meditation. Mindfulness that sort of thing and in their small studies but but pretty well designed studies suggesting that behavioral interventions in mild depression actually work quite well there seems to be a volitional threshold for depression where at some point you start losing it you go from being completely in total volition to having kind of semi volition you have thoughts that you really have a hard time controlling and that sort of thing and you. Go through that threshold at some point it gets harder and harder for those sorts of things to kind of kick in and work in the extreme form that is catatonia right where people in a very severe form of depression get kind of stuck motorically right and they obviously can't they have no control and so or very limited control and so you know I think there's a threshold in which these sorts of interventions will work exercise seems to really be a good. Treatment for for mild depression and it may work through the mechanism you're describing right as we all know you know athletes hold a lower resting heart rate. Then folks that are you know if you're you were an athlete you had a lower resting heart rate you stopped. You know exercising and a couple years later you're resting heart rate in many cases goes up right and so maybe that's maybe that's part of the process I'm not aware of any. Studies specifically looking at door salateral prefrontal physiology pre post exercise but it would be a great study I think that would be really helpful to understanding this especially if you had a correlation of changes and kind of lowering of say heart rate with. Move improvements there's been a lot of work with heart rate variability and in depression and you know studies are kind of point towards it it's not not every study is is you know positive for this but. But quite a few studies say basically that lower heart rate variability is associated with you know moderate to severe depression and that may be part of that mechanism of that heart brain. Risk so I'm both intrigued and a little bit perplexed by this relationship between heart rate and depression. On the face of it I think of depression as depressed so lower heart rate might make somebody more depressed even mention catatonia or somebody that just. Doesn't seem motivated or excited to do anything I think a mania is elevated heart rate and being excited on the other hand I realize that anxiety which. You know brings about ideas is elevated heart rate is also built into depression which brings me back to what you said earlier which is that when we say depression are we really talking about four or five different. Disorders yeah that's right lack of a better word and for what percentage of people that have depression does. Some approach to reducing heart rate work whether or not stimulation of the door select left door selectile prefrontal cortex. By way of transcranial mind stimulation or by taking a beta blocker or by stimulating the Vegas can we throw out a number a rough number does that help 30% 50% how pervert how long lasting is that that relief and to be clear the. The acceleration of the heart rate is in the moment when the stimulation is happening but it's not something that's necessarily maintain chronically it's more of an indicator that you're in the right network more than it's. Then it appears to be itself you know central mechanism the heart rate variability piece may be in there's some studies that link the tube the actual deceleration seems to be much more of a marker that you're in. The right system but you know very well could be that the heart rate system in the mood system to sit next to each other in the stimulation hits both if you look at. How much of the variance in the mood is explained by the heart rate deceleration it's not it's not a huge you know it's not a huge amount right so it only explains a small percentage and so it's. It's unlikely that simply dis you know simply reducing the heart rate and in fact you know for many years per panel all these sorts of drugs actually were implicating causing depression and so that that's been kind of debunked but it's unlikely it's simply decelerating the heart rate can improve depression. But what it does tell you is that if you're in that area that is the mood regulatory area there's some parasympathetic cortical kind of process that's going on that gets in and causes this to happen and it's. You know it's independent of mood you can take a normal healthy individual and you can do this and they're going to decelerate their heart rate. I'm so glad you mentioned the parasympathetic nervous system which of course is the most people think of is the rest and digest or the kind of calming side of the autonomic nervous system as I'm hearing you say all this and in particular what you just told me which is that it's not as if having a lower heart rate protects you against depression or a higher heart rate is associated with depression although I think streams that might be true. But rather it's something about the regulatory network the ability to control your own nervous system to some extent and when I think about the autonomic nervous system I like to think about as a seesaw of you know alertness and calmness and when you're sleep it's for a lot of calmness and when you're panicking it's a lot of alertness to the but that. But that and I don't think this has ever been defined and when I teach medical students at Stanford or anatomy I my wishes that someday I'll be able to explain what the hinge in that process would be right not the ends of the seesaw we know what the sympathetic nervous system is and what it's to wake us up and make us panic or make us feel nicely alert and calm we know what puts someone into sleep or a coma or make some feel relaxed. But what shifts from one side of the seesaw to the other and the tightness of that hinge seems to be what you're describing that that depression is sort of a lack of control over interstate so that when I'm stressed I can't get myself out of it when I'm feeling completely collapsed with exhaustion I can't get out of bed and you're motivated to do the very things that would help me get out of depression like a workout or social connection or think the quality meal these kinds of things so this is perhaps the first time that I've ever heard about a particular disease. But about a potential circuit for the hinge as I'm referring to it does it make absolutely absolutely I just want to make sure that I'm framing this correctly in my mind. Yeah, absolutely and in some studies if you do the same identical stimulation on the right door slatter we can get an acceleration. You know just kind of further confirming this idea of lateralization right that that even it appears that even the prefrontal quarter you know cortical areas seem to be lateralized in this in this way and I you know it's it's less. The right finding is more variable depending upon the study the left's very consistent in this way so. So we've talked about churns cranio man net stimulation for getting into these networks and I also just want to take a brief tangency I because I've heard you say this before I think it's so vital what you're saying that it's really not about stimulation of areas it's or any specific brain area or Vegas nerve being important. And per se it's really about a network connection a series of connections I think that's really important for people to understand and is a kind of a new emerging theme really the other thing that to me seems extremely important for us to consider is what is. What are these lateral prefrontal courtesies doing are they involved for instance in sensation sensing the heart rate are they involved in thinking and planning. And this gets down to a very simple question that I know a lot of people have which is can we talk ourselves out of depression if it's mild can we talk ourselves into a manic state or an excited state a positively excited state that doesn't qualify as many of you know other areas of the brain I think of the is responsible for perception or for for motor control but here we are in this mysterious frontal cortex area which people say executive function planning etc are we talking about thoughts are we talking about. Are we talking about structured thoughts are we talking about dream like thoughts what in the world is going on in the prefrontal court is yeah now I spent my career you know in neuroscience and I still I still can't really understand what it's doing and maybe it's doing 50 things yeah that's a great it's a great question so you know to so one of the one of the studies that we've been working on addition to the depression work is actually trying to change trait hypnotizability so David speed a lot I have been working on. This is a lot of people that I have been working on this and you know he's found and publishes 10 years ago that a different part of the left or lateral is functionally connected with the inter the door slantier single it with a lot of functional connectivity and high hypnotizables and not much in low hypnotizables and that's a different kind of a different sub region within this bigger brain region we call left or moody and so the left or lateral seems to have connections that are locations specific within the overall kind of named brain region that connect to various parts of the single it and seem to regulate it. And so if you knock out the left or a lateral prefrontal cortex and you have people do the strup task for instance which is a task where you have it's a simple task. But I know this you have people name the color of words and so if I if I look at up with you know if I look at one of the cards that they'll show you it'll have the word red and red and that's very easy and that's a called a congruent. And then the incongruent is red in the color blue and you have to name you have to say the the word you don't name the color to have to suppress a response yeah yeah exactly and so I'm sorry you do the you name the color and you and you see the word written in a different way and so basically. If you if you stimulate in a way that inhibits the left or a lateral prefrontal cortex or either one you can actually knock out the ability to do that well and it'll take longer for people in the incongruent cards to be able to name it and so they have a they have a kind of a time delay that's greater than they had before they got stimulated so that's a part of the prefrontal cortex that's different than the part of the prefrontal cortex that's involved in mood regulate. And the nice thing about TMS is that you can go through you can find these areas that are functionally defined through brain imaging and you can perturb them and answer the question you're talking about how do I understand this part of the prefrontal cortex and its function this part and so we were able to stimulate and inhibitory way within the left doorcell lateral prefrontal cortex that's involved with. You know this sort of cognitive control area and we were able to knock that area out and increase trait hypnotizability so people had greater hypnotizability after they got active stimulation versus when they got sham and so it suggests that that brain circuit is involved in the in the process of what hypnotherapy to hypnosis ends up being but it's a very different region. Within the left doorcell lateral and say we do we do these very intensive stimulation approaches to treat severe depression and we're able to get people out of depression. You know with the part of the doorcell lateral it seems to be lower in the you know kind of more lateral. And in fear on the DLPFC and connected with the subgenual anterior singlets of the part of the anterior singlet that processes emotion. I'd like to take a quick break and acknowledge one of our sponsors athletic greens athletic greens now called AG one 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 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 got 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 like to try athletic greens you can go to athletic greens dot 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 in the car on the plane etc. And they'll give you a year supply of vitamin D 3 K to again that's athletic greens dot com slash Huberman to get the five free travel packs and the year supply of vitamin D 3 K to based on what you told us about the strup task and the role of the prefrontal cortex and strup task to me the strup task is a rule switching game. Yeah, and one moment the rule is you read whatever the word says and then then you switch and then you say the rule now is you tell me what color the word is written in and you suppress whatever is the word says. That's right. So a rule in some sense is a like that is a transiently adopted belief system. So I could imagine that in depression which has all sorts of backstory to it that of course the psychiatrist or psychologist or friend can pull on that thread like for instance somebody might believe that they are bad or that they don't deserve love. I'm trying to bring this into the typical language that they will tell about or that they will never succeed or that even if they keep succeeding it's just going to get harder and harder and it will never feel good. These are sort of rules like the strup task at some level it's their rules that are more pervasive over time unfortunately. But I could imagine that if the PFC is also contains some sort of maps or algorithms related to rules of emotionality or self representation or things that we've heard I think there must be data out there the saying that you know whatever we heard in middle school when someone made fun of us we can remember that because I can remember things that people said about a jacket I wore one day or something in the fourth grade crazy I didn't even like the jacket. Now I think it was kind of cool but anyway the point being that we have an intense memory for these things set up a sort of rule or a question like maybe I don't really know how to dress for instance maybe that's why I always wear the same black shirt. But in all seriousness it seems like the door-to-low prefrontal cortex is in this amazing position to access rules which are beliefs and beliefs are rules and then for moments or longer to switch those rules. And so for somebody who's depressed to just simply look themselves in the mirror and say you are great you are fantastic that's it feels like a lie if you feel like garbage to say that it doesn't fit with the rule it's like saying that card is not red that card is green when your eyes tell you that it's that it's red and that's right and it seems like there's something about prefrontal cortex that that in principle gives flexibility to rules based on what we know on the strup task. So given its connectivity can we assume that the talk therapy that occurs in a the psychiatrist office or with a friend or through journaling out something. Because we do know that reporting things about trauma or difficult circumstances or the rules that we contain and attend to hide inside of us about how we feel miserable about ourselves or anything really that in re scripting that that somehow it allows us to do a sort of strup task on our beliefs is that is that a tremendous sleep. So I try to frame this in the context of what what I and most people think of as depression yeah totally because the network components are vitally important but I guess what I'm trying to figure out is like what are the what are the algorithms that govern yeah prefrontal cortex yeah absolutely so in a kind of standard cognitive behavioral therapy session right what what the therapist is trying to do is identify those beliefs and and you know kind of determine how how fixed they are you know if they're flexible. As you're saying and then and then help folks to find another explanation for them and to and to kind of re integrate that potential other explanation into their their memory system right. So I think where I think TMS is really interesting actually we had a lot of patients who've told me like my my therapist told me that I wasn't trying hard enough in therapy and and you know and I really am trying hard but I'm these are you know moderate pretty severe depressed patients. And as soon as we get them well with with the TMS approach is you know kind of rapid you know five day approach next week we come in and see them and they'll say you know what I did all weekend as I looked at my therapy books and now I can understand it. And so you know I actually see TMS is a way of having kind of exogenous sorts of cognitive functions that in milder forms of depression we can pull off with psychotherapy you know this idea being able to kind of turn that prefrontal cortex on and have it govern these deeper regions and depression the deeper regions govern the prefrontal cortex they they precede the prefrontal cortex timing. We've got some data and in review now we're we're seeing that in depressed individuals that are responsive to our rapid TMS approach we call Stanford accelerated intelligent neuromodulation therapy or S&T or saying if you look at the brain before people get this they will they will have a temporal delay where the single is in front of the DLPFC. And in people that are normal healthy controls no depression the door salateral prefrontal cortex is temporarily in front of the anterior singulate with effective treatment we can flip the timing of things so the door salateral is in front of the anterior singulate just like in a normal person. So you're not talking about obviously physically moving these structures talking about in time time their activation so in one case it's like the coach telling the player what to do exactly a player telling the coach what to do and you you restore order to the game you restore order to the game and and what it looks like is depression to your point is a bunch of kind of spontaneous content that's semi-evolution all that's being kind of generated out of this conflict detection system the singulate seems to. To to to sense conflict and kind of feed that information gets over active in depression and and then in depression it looks like the left or a lateral does not sufficiently clamp down on it and what therapy appears to do is to kind of restore that what we see with TMS over that region is that we just exogenously do the same sort of thing we restore the governance of the left or salateral over the singulate area and that is correlated with treatment improvement so the degree in which you can re time re regulate in time the left or salateral over the singulate the more of an antidepressant effect you have. Can we therefore say in crude terms that the dorsal lateral prefrontal cortex really is the governor of how we interpret physiological signals and spontaneous thoughts it is it places a lens that the rest of the brain sees things through. And you can you can do these experiments where you you can put a normal healthy control person in the in the scanner and you can make them feel like they have a loss of control and you can see that region come offline right so you experimentally manipulate the system and so. Can you buffing it up it's like almost TMS is almost like exercise for the brain right you're kind of exercising this region over and over again with a physiologically relevant signal and kind of turning that system on and what's interesting we're I think really interesting for this show is to you know we had a couple of folks you know probably five or six folks that have actually told me this where if they were meant early enough in the week we have this very dense stimulation approach where we can stimulate people really rapidly over a five day block we don't discriminate when they get better to when they stop so if they they get better on day one we still give them the other four days because it's in the protocol to do that we can't we're getting to a point where we can tell how long it's going to take we're not there yet. And so you know every time somebody gets better at day one or two at the beginning when we first started doing this we'd say you know we're not sure. You know we think this is safe to keep going but you know what do you want to do and everybody was like no I want to keep going and so you know they're by Wednesday they're like totally zero down the depression scales you know even better than most people walking around like really no anxiety no no depression anything by Thursday the first guy that the told me this he came in and he said you know I was driving back to my. I was driving back to my hotel and I decided to go to the beach and I just sat there and I was totally present in the present moment for an hour and he's like I read about this in my mindfulness books but I experienced it last night I've never experienced anything like this before and I was like that's interesting but kind of wasn't sure and then and then I didn't tell any you know obviously any more patients about that and then about five over the last couple of years when they get they were meant early in the week by the end of the week they're like going to the beach and they're like totally having a what. People describe as a pretty mindful present moment sort of experience is really interesting you know what that is I mean I don't have full on scientific data to tell you but it's just it's an interesting anecdote right that that folks when you push them through this point of feeling kind of clinically well that some people end up reporting this additional set of features so you mentioned the singular and the enter singular in particular because I'm not sure if you can see that. Because now I feel like for the first time in my career I have some sense of what prefrontal cortex would actually be doing besides providing a bumper for the rest of the brain is the singular it seems is a more primitive structure in the sense that it's under the ideally it's under the regulation of this top down control from prefrontal cortex but what's mapped in the singular in and for the non neuroscientist out there when I say mapped if we were to put someone in a single or put an electrode in there what what makes the neurons in their fire what what sorts of things in the body and in the mind and out in the world light up for lack of a better phrase the singular what does the singular like yeah yeah so that's true task those incongruent word color associations the the dorsal part of that for obsessive compulsive disorder patients certain you know certain kind of triggers you'll see some some of their imaging studies will point to to enter a single it in the kind of very crude psychosogery world 50 years ago the inter single out of me was a way of treating obsessive compulsive disorder right because that area seems to be overactive in people who are experiencing obsessive compulsive disorder you can kind of walk the singular wraps around you know this white matter track like bundles it wraps around that and so there's a part that's above that around that and below that and depending upon how much of the the conflict task has an emotional component the more the more ventral and subgenual that that activation is so the dorsal part of the anterior single it seems to be kind of more of a pure cognitive maybe obsessive compulsive disorder sort of area whereas when you start getting into mood sorts of triggers like facial expression like for your supposed to they you know there's an emotional strip task where you show the word happy and then you have a face of a person that looks mad then that's another way of having the same sort of strip conflict that seems to be more periginual subgenual areas right so you can kind of you can trigger the singular based off the level of emotional valence from none down to a lot and that seems to be how the how it's distributed there are you know heart rate kind of components to an autonomic components in there to there's something called a kinetic mutism you know you know I'm a board certified neurosurcuitive behavioral neurologist and I've seen you know a lot of these what we call zebra cases and neurology where people have you know these unusual neurological presentations and one of them is a genetic mutism so you have a glioma sitting in the inner hemispheric fissure and having kind of having pressure on the singular people can get into an almost catatonic looking state where they kind of get stuck and they don't speak and so that tells you something about how the how the singular works as well right it's it's like if it's if it's not functioning then you have a hard time kind of connecting with reality it seems to need to be constantly on you know online to be able to interact with the exterior world is it involved in some of the dissociative states that sometimes people who are very stressed or depressed experience you said catatonia being an extreme one but I know someone for instance that when they get really can even be if someone yells at them or someone's angry even if someone's angry with them or they perceive someone's angry with them there's a developmental backstory to why they they likely feel this way they sort of just kind of can't this is a high high functioning individual normally and they they just sort of can't function they can't complete simple things like email or groceries or things for for a short while it's it's almost like a catatonia and they refer to as a dissociative state do you see that in depression and I mean we're speculating here as to whether or not that involves a singular but what you're saying it has holds a lot of salience for me and thinking about this example. Yeah yeah there's so you see you see catatonia is an extreme outcome of depression and of and sometimes it gets afraid and other illnesses dissociation is an extreme outcome or even in some cases a less extreme outcome of PTSD and trauma and you know and it's also a phenomenon that happens naturally in some people that are highly hypnotizable and so if you ask David Spiegel I'd say that you know some of the work that he's been working on is around posterior singulate and in the capacity to dissociate but yeah you know with our stimulation approach to to DLPFC Dorsal anterior singulate one of the subscales that moved the most was the dissociative subscale for hypnotizability so even in a normal individual you know you see that that change in that kind of experience of dissociation. I am highly hypnotizable but David's hypnotized me a number of times I mean we have a clip of that on our human life channel. I've always well always it was starting it early teens I started exploring hypnosis I'm extremely hypnotizable and self hypnosis or assisted hypnosis. I don't know that I ever go into the dissociative states I'll try and avoid forcing you into running a clinical session right now but to assess anything like that but this brings about something really interesting I think which is I'm aware that some of the more popular emerging treatments for depression include things like ketamine which is a dissociative anesthetic is that right? Yep. And yet and my assumption is that as a dissociative anesthetic that it leads to dissociative states where people can sort of third person themselves and be so feel somewhat distanced from their emotions. Yes. I've also been hearing that there are emerging treatments, psilocybin being one of them but some other treatments MDMA etc that will parse each of these in detail that lead to the exact opposite state during the effect of the drug which is a highly engaged emotionality and heart rate and sense of self and can also lead to relief of depression. Now whether or not this again reflects that depression is many conditions as opposed to just one or whether or not somehow tickling or in some cases pushing really hard on the opposite ends of the scale really matter I am absolutely fascinated and again also perplexed by this why would it be that a drug that induces dissociative states and a drug taken separately that induces hyper associative states would lead to relief of the same condition. Yeah. That's a great question. Yes. So for ketamine you know the level of dissociation appears to be correlated with the therapeutic effect. It appears to be necessary but not sufficient to produce an antidepressant effect and so folks that don't have any psychological change from the ketamine or don't experience any dissociation typically tend to have less potent antidepressant effects from ketamine. We did a study a couple of years ago it was really interesting so we gave folks Naltrexone which is an opiate antagonist, mu and capo opiate receptor antagonist and we gave folks the same individuals a pill of that or a pill of placebo and they had no idea which one they were getting. Was this low dose Naltrexone? 50 milligrams so it's pretty high dose. Okay. Yeah and so we gave a typical ketamine therapeutic dose and then we gave 50 milligrams of Naltrexone or placebo and then in the same individuals we gave two infusions, one with each of those conditions and if they had an antidepressant effect we waited until they relapsed and then we gave them the other condition and then we looked to see what effect of blocking the opioid receptor, what effect would you see on the antidepressant effect of blocking the opioid receptor? With the idea that if ketamine works the way that a lot of researchers at the time thought that it completely worked in which is the glutamate system then you would have no effect of Naltrexone because Naltrexone just interacts with the opiate system. It doesn't do anything with any other systems. ketamine has a lot of effects over, you know, it has clear opiate effects in mice and various ways of looking at that and NMDA receptor antagonism and glutamate effects and so if it's just that the glutamate part is the part driving the antidepressant effect you shouldn't have any difference in the antidepressant effect between the two conditions. If however the antidepressant effect is primarily the opioid properties of ketamine are necessary for the antidepressant effect then you should have a loss of antidepressant effect during the ketamine plus Naltrexone condition that you observed in the ketamine plus placebo condition and what we saw was that there was a dramatic blockade of the antidepressant effect when Naltrexone was present in the people that had an antidepressant effect with ketamine plus placebo alone and then some friends of mine did a TMS study with pain and they stimulated over the left or a slattle prefrontal cortex and they gave Naloxi, I mean Naloxi, which works basically the same way as Naltrexone and they were able to block the anti-pain effects of TMS with an opiate blocker. So this idea that another kind of convergent point right, this idea that the opioid receptor may have a role in mood regulation, what's also interesting is if you look at people that are getting a total knee operation, it's a very painful operation, total knee replacement and you age sex, everything match the individuals that are going through that but you have a group of people that don't have depression and a group of people that do have depression. The presence of depression triples the oral opioid dose by day four. That's required. That's required to cover the pain but what may be happening is it's not just treating physical pain, maybe treating emotional pain as well, right, at least transiently it seems to have an antidepressant effect chronically, it seems to have a very pro-depressant effect and can make people treatment resistant but you know it's an interesting phenomenon but yeah, the opioid system seems to be pretty involved but what's interesting there with the ketamine trial is that we didn't see any effect on the dissociation and so the dissociation was the same each time so the psychological effect of what we call the trip or the kind of dissociative effect where people are having a psychological phenomenon from ketamine, that was identical both times and so it kind of, it also challenged this idea that the psychological experience of the psychedelic effect may be all that's necessary to produce an effect and that the pharmacology doesn't matter as long as you can achieve that state and so you know we think we pretty clearly debunked that idea that the underlying pharmacology and the state you know seem to be important. We don't know for sure if you can and a lot of people are working on this if you can take out you know essentially the psychological effect and still have a drug that works to treat the illness that you're trying to target and you know a lot of there was a mal study out this week where they had an LSD analog and they were able to see some animal level data to suggest that could be true but until we figure that out humans it's kind of to be determined but it is curious right being able to kind of use experimental manipulations to try to separate you know some of these phenomenon apart and really understand what's what's doing what. It's so critical and it's so critical to the other conversation that we'll surely get to which is the progression of psychedelics from illicit legal drugs to clinically validated and presumably at some point either decriminalized or legal drugs which has not yet happened at least not in the US but just to make sure that people are getting this and how crucial this is what we're really talking about here is the fact that you know somebody takes a multi-gram dose of psilocybin or somebody takes MDMA or they take ketamine and they experience relief from their trauma their depression their addiction or any number of the other things that indeed those compounds have been shown to be useful for in certain drug use clinically supported etc. There's this gravitational pull to the idea that oh it was the hallucinations it was the dissociative state it was the feeling of connectedness and what we're really saying is that while that certainly could be true it may be the case that a major source of the positive shift that occurs after the effect of the drug is some underlying biology like shifts in the muo opioid receptor a lot of your experiments in the maltrixone or a change in the underlying neuromodulation that had anywhere from nothing to something to do with the real shift. And I know there's a group up at UC Davis that published a paper in nature about a year ago also looking at these are is a chemistry lab essentially modifying psychedelics to remove the hallucinogenic properties the mood altering properties and actually seeing some pretty massive effects in shifts in mood after the drug wears off. And I know this gets people upset when they hear it a lot of people this gets a lot of people upset really because people think oh no it's the it's the intense experience that matters. But in fact that may not be the case at all. In fact it's so powerful for people that sometimes I like in it in my mind to you know take somebody it's like the birth of a new child and it's such an incredible experience and then people feel so much connection and then they sort of connect the experience of the actual birth to the connection when in fact they're that's true it turns out but there are a bunch of other things happening too that are simply that's simply the reflection of the fact that you're holding a child and the pheromonal effects etc. So anyway I think it's very important that these different variables be figured out along those lines I want to make sure that before we dive a bit deeper into ketamine and psilocybin that we do touch on a really important topic that has been in the press a lot lately which is SSRI selective serotonin reuptake inhibitors because we can't really have a discussion about depression without talking about SSRIs and then I want to circle back to ketamine and psilocybin. It seems that there are now data that essentially say state that there's no direct link between serotonin levels and depression although I my understanding is that the SSRIs are powerfully effective for certain forms of obsessive compulsive disorder and they also be effective for treatment of depression but it may again be through some effect unrelated to serotonin itself. Is that right and how should we think about SSRIs or they use full are they not useful what's what's going on with SSRIs your patients and and other people as well. Yeah the the the experiment that I described a bit ago around the naltrexone and ketamine is the first time I'm aware of where we were able to essentially eliminate an antidepressants effect by using a second drug as kind of a blockade and it highlights a bigger issue right the issue that we haven't had a good way of really understanding how these drugs work and so it's the difference I think a lot of the controversy there is that it's been difficult I think for folks to see that something can in one hand work and in the other hand we don't know how it works right and so SSRIs clearly work you know many many meta analyses kind of proving that out right that that in a sub population of individuals they achieve great benefit from depression you know for depression for obsessive compulsive disorder for generalizing anxiety disorder panic you know all these things you can see an improvement in those symptoms with what we call SSRIs or selective serotonin reuptake inhibitors the issue there is that these selective serotonin reuptake inhibitors end up blocking the reuptake of serotonin leaving the serotonin you know in this in this kind of in between between two neurons for a while and allowing for more serotonin to kind of be there the issue is that they don't they don't work immediately right so they don't work like the same day you start taking them and that that suggests that probably it's not exactly the serotonin being in there that's directly driving it that it's much more likely that it may have some say plastic brain plasticity effects right we know that things like brain derived neurotrophic factor get up regulated with chronic oral antidepressant use and and so that's that's kind of the ideas that is that these things work but what's powerful and I think with the authors of this paper is extremely controversial paper were were in part trying to say was that there's not a there's not a deficit of serotonin you're not born with what people call a chemical imbalance in psychiatry is known this this is not actually new information anybody you know it's it's kind of a rehashing of a bunch of information we've known for a while now but in the lay press it's kind of hit in a way that it didn't seem to to grab attention before with previous publications but this idea that this chemical imbalance ideas wrong I really I really think that part's important because I think that you know for a while I think psychiatry you know what I'll call psychiatry 1.0 right this kind of idea of Freud and psychotherapy and its origins it was a lot around you know the your family and those experiences and psychotherapy kind of going and correcting or helping you to figure out or and you know show you being able to see or people hear you so that you can eventually come to the conclusion of certain cognitions that aren't helping you right and there's a huge you know there's a huge importance there but there's a history where you know things like the schizophrenia and the schizophrenic mother and all that you know that was a concept at some point right and so we've transitioned from that to the you know for a long time the chemical imbalance which I'll call psychiatry 2.0 you know this idea that there's something chemically missing and I think that the trouble for a patient who's not a physician who's not someone who's you know who's who's steeped in these sorts of ideas who's you know more of you know kind of kind of a person I kind of average American out there right is that it's telling it's sending a message of there's something missing with me whether it be my experiences I had no control of over when I was a child or a chemical in my brain what I think is really powerful with with TMS you know really powerful TMS and a lovely been powerful the psychedelic story is it saying something different you know TMS works and there's no serotonin coming in or out of the brain right and we're doing a rapid form of TMS that works in one to five days there's no there's it's very unlikely that there's some long term kind of up regulation of serotonin that's driving that so our work actually kind of pushes back on this serotonin hypothesis is being kind of the center of depression because it says look we're not giving anybody any serotonin we're simply turning these brain regions on and we're focused on the circuitry and that's psychiatry 3.0 it's not just like neuromodulation neuromodulations are really nice you know use case for psychiatry 3.0 because it's a way to focal and directly perturb brain regions and whatever modality you're using but you know there are a lot of a lot of groups that are actually doing neuroimaging before and after and they're able to see circuit level changes for something like psilocybin or ketamine long after the drug is gone right suggesting in those same brain regions converge so the subgenual default mode network connection that we see is changing with our our stand Stanford neuromodulation therapy technique at that same set of brain regions that ketamine and psilocybin seem to act on act on these connections between brain networks that seem to shift and so it refocuses the story on something that's highly correctable and it's it's basically electrophysiology and it's basically kind of recalibrating a circuit that is recalibratable instead of I have something missing or have some phenol some set of experiences early in life that are that are going to forever trap me in these these psychiatric diagnoses and so it kind of challenges that idea and I think that's what's so powerful about psychiatry 3.0 this idea of focusing on the circuit because it gets us gets us into thinking about psychiatry and psychiatric illnesses is something that are recoverable people can get better people you know we've seen with our TMS techniques we've seen it was some of the psychedelic work that we've done where people are actually in normal levels of mood for sustained periods of time or within five days within five or less days and in the case of the psychedelics within a few days right so we can get people out of these states they're totally well there's no drug in their system at that point in the case of psychedelics it was never a drug in their system in the case of of TMS and it just tells us that that it's it's fixable it's it's just like the heart it's just like you know it's just like an arrhythmia in the heart it's just like you know these these other illnesses that it's like a broken leg we can go in and do something and we can get somebody better then I think what's what's empowering and what a lot of patients have told me as they say you know I've gotten to you know some people will relapse and need more stimulation or need more psychedelics or whatever it is but they'll tell me I I've relapsed and I'm depressed again but I'll never think about killing myself again because I know that if I go get stimulated again it improves it gets better it it will I will be able to re-achieve it and I can't and I I don't fear that I'm chronically broken I don't fear that the chemical imbalance is still imbalanced I don't fear that these things that I couldn't control in my childhood you know are going to be there and drive this problem forever and I think that's that's what's so powerful about this the sense of control the sense of control the sense of they're not doing the stimulation themselves they're not administering the drug in these trials themselves they probably never will these will probably be medical treatments but they are choosing to do it and in that sense they are in control. Yeah I have a good friend I won't out him for reasons they'll become clear in a moment who was quite obese and lost a lot of weight and was really proud of himself and then I guess we could say he sort of relapsed in the sense not not not all the way but but far along but his tone around it was very different he knew he had accomplished what his goal once before he was disappointed in himself but he knew exactly why he had relapsed it was very clear he had essentially relapsed to the previous set of eating behaviors and lack of exercise behaviors and has now brought himself back again and it it just resonates with your story that you know once somebody understands they can do it because they've been there before this this idea again of of considering new rules that that there's and that brings me to this question about psychedelics and and the frankly the altered thinking and perception that occurs in in high-dose psilocybin clinical sessions it seems that the disorder thinking even though it could be random right hearing hearing colors and and seeing sounds as always the you know kind of cliche statement of the Timothy Leary area also you know right there that's a stupe task of sorts it's a it's a it's a synesthesia it's a combining of perceptions but it's it's sort of stupe task ish in that it's a new set of rules for the same stuff right and people do many people do report improvements in trauma related symptomology and depression as I understand it from my read of the clinical trials after taking psilocybin because during those sessions something comes to mind spontaneously as you and I were talking about earlier they will report for instance a new way of seeing the old problem the problem could be the voice that they're no good they'll never nothing will ever work out or could be even more subtle than that so that raises two questions one is about the basic functioning of the human brain which is why do you think the brain would ever hold on to rules that don't serve us well that's one question and then the same question is what is it about psilocybin and related molecules in terms of their neurochemistry in terms of the ways they disrupt thinking etc during the session that allow this novel rule consideration phenomena yeah so the first question I think it's an it's an evolutionary neurobiology answer right I think that at the individual person level you know it doesn't make a whole lot of sense that when we're really stressed out some of us want to eat more right at the individual person level because like that's not particularly that good for my health in the long term but if you think about it like you know in some 500 years ago a thousand years ago I'm highly stressed out it's most likely that I'm about to not have food at some point and I should eat a bunch of food that is high fat high sugar high carb food to put on weight for that you know next phase where in this stress I may be in battle and I don't have food and I have enough fuel on board right and so we we end up being you know we end up being a result of probably a lot of biology that's not that useful in the modern era and I think in the brain for for say let's say PTSD right a lot of a lot of veterans come back and they experience these PTSD symptoms and they're not it all useful back home right you know they're you know they hear some loud noise and all of a sudden they're behind a car or they're behind a you know I've heard of folks you jump and run behind a trash can or whatever in the middle of San Francisco and they hear a loud noise but if you put them back in the battlefield you're that's highly adaptive right and so I think what what the what's interesting is that we in the absence of using substances like psychedelics end up having these very persistent memories that are attached to negatively balanced emotion predominantly as you were saying earlier the jacket and in elementary school we you know I had various things like that for me too right you you remember these things and and we hold on to those things from I think an evolutionary neuro biology standpoint but what seems to for whatever reason kind of alleviate that are these substances some new like MDMA some that have been around for thousands of years like psilocybin and used in in kind of sacramental and as a sacrament in traditions seem to have a therapeutic effect it seems to be pretty long lasting for these phenomenon and so it's just curious right it's curious that that in the absence of that these things will keep going on and on but in the presence of that exposure then all of a sudden you see a resolution of the problem and we have some work now we're treating folks with Navy Seals and the data still being you know being analyzed but the anecdotes that we're getting right or folks are coming back and they're saying a finally that's finally gone right this kind of these set of PTSD symptoms are finally gone and so this idea that for whatever reason going into what's probably a highly plastic state like we were talking about earlier up regulation of brain derived neurotrophic factor in the case of I began Gleel derived neurotrophic factor this highly plastic state and the ability to re you know kind of re-experience memories and then as you know you know we we we always reconciled it a memory when we bring it back up we always reconciled but we can solidating it in that state for whatever reason may drive drive a therapeutic effect and you know the the the jury is still out there's a I'm a I would say that I'm I'm kind of I'm an agnostic to what tool I'm using kind of guy like I'm my business is to find treatments that help people and so I'm much more like pragmatic about it you know if if this sort of thing which has a lot of cultural baggage but if this sort of thing ultimately ends up being therapeutic if we can design trials that convinced me and others that it is then we should absolutely use it you know and and if it doesn't then then we clearly shouldn't use it right and I think that's a big that's a big question the field is going to have to work out we have a hard time blinding these trials because the placebo condition is not easy to pull off a placebo for a psilocybin journey is hard to imagine we've got you know we've been thinking about this and maybe that ketamine study that I was talking about earlier if we could give people neltrexone and ketamine maybe that's a good you know a good sort of placebo condition right because we know that we can block any of the actual antidepressant effects ketamine they still have an experience you know so that's one way of doing it but thinking about ways to do that really kind of proving this out and that's been yeah I think that's been been kind of central to the way I've been been thinking about this but yeah I think there's the work that's been done so far the first psilocybin trial the first MDMA trial is published in Asia Medicine recently and what are those generally say I mean that that that that they are effective for a number of people after one session two sessions what's the sort of the general contour let's let's start with psilocybin in MDMA yeah so MDMA appears to and you know one to a few MDMA sessions have an anti PTSD effect that seems to be you know outside of the kind of standard assumed levels of PTSD improvement that you can observe in individuals with this level of PTSD right so what we call the effect size which is essentially like a a mesh a coenced effect size a measure that allows for you to compare different treatments to each other for different conditions that are you know agnostic to what the actual illness is you know the effect sizes there you know approach effect sizes the things that are pretty effective like antacids for heartburn right and you see that with with with in the MDMA treatment so does that mean that for people that have trauma who do a and again we're talking about in a clinical setting they they take a one or two doses of of MDMA I think the standard maps dose is 150 to 175 milligrams again doing this with a position et cetera control clinical trial legal yeah exactly they do it once or twice and broadly speaking what percentage of people who had trauma report feeling significant relief from their trauma afterward it's about two thirds of people had had a had a clinically significant change in their PTSD that's impressive which is impressive right and how how long lasting was that I mean that these trials were ended pretty recently so it appears the last for a while in the earlier trials where they followed people out it seemed to last for kind of in the years range for some people and so it's you know it's pretty it's pretty compelling still Simon you know that in contrast that with ketamine which only on average last about a week and a half for a single infusion so it's a much shorter so they have to get repeated infusions of ketamine every ten days or so yeah or ever for some people or they end up getting like like like a bunch of doses for a couple of weeks and then for some people that seems the last a while you know that's where I think I think the the psilocybin story for depression in the in the MDMA story for PTSD seem more interesting to me so for psilocybin what is the rough percentages on and this would be relief not from trauma but from depression yeah yeah exactly so it's you know an open label studies it's closer to like half to two thirds of people end up getting better depending upon their level of treatment resistance in the in the blinded trials it was more like a third or so of people you know experienced relief and this is you know this is a press release of the data you know and so it hasn't to my knowledge it hasn't been published yet and so you know looking forward to seeing the full paper on that one but but it you know separated from from placebo and looks you know looks pretty pretty good as well it looks like it's you know the first of two trials need to be done to get this thing approved for treatment resistant depression and so so that stuff looks looks good in terms of MDMA for many years it was reported in the popular press and there was a paper published in science MDMA was neurotoxic that it would kill serotonin neurons this is what was always said then I saw another paper published in science that wasn't a retraction of the previous paper but rather was a second paper in the same group that essentially admitted that the first time around they had in injected these monkeys because of the with not MDMA but with methamphetamine which is known to be neurotoxic so it was kind of a public admitted in some of the previous or big like really big screw up so oops but never retraction and then never really a publicly acknowledged correction in the popular press so it seems that in the appropriate dosage range and with these one or two sessions my assumption and this again as an assumption tell me if I'm right or wrong here is that MDMA is not neurotoxic for serotonergic neurons that appropriate doses and with appropriate sourcing etc so it was an interesting study that I think guys name is Halpern last name's Halpern it not Casey Halper not Cape different now I think Josh Halpern I'm playing on his first name but but Casey Halpern was a guest on this podcast and as a former colleague of ours at Stanford who unfortunately we lost to University of Pennsylvania and maybe someday we'll we'll bring him back yeah that's right so this this individual you know received some NIH funding to actually NIDA you know National Institute for Drug Abuse funding to to explore individuals of the Mormon faith in Utah who who partake in only MDMA so the way this works is that MDMA happened kind of after a lot of the religious documents were developed and so MDMA isn't on the prohibited drug list the band substance list I have some good friends who are LDS great great people I do as well you know just a kind of set of facts you know and so so these these folks only use MDMA but they don't they're not you know the problem with some people using poly substance users right so you can't you can't say it's the MDMA if they've also taken other psychedelics and they've taken opiates and they've taken cocaine and you have this picture where you can't really tease out that problem but but with this right it was just individuals that were part of the Mormon faith and so they they were kind of purest in the sense they only used MDMA and he confirmed all of that and and it was a brilliant study right because then he was able to go in and look at their cognitive profiles versus individuals of you know of the same geography of the same faith all of that that happened to not take MDMA and found there were no neuro cognitive differences so it does that mean that it it was not damaging it was not damaging it it it's hard to know because to really do this study well you'd have to track these folks down before they ever took MDMA and do a pre post and compare to people that didn't but you know this is about as good of a study as you can do in given the you know given the situation to be able to check this out additionally when I was back in Charleston and working in the medical University of South Carolina I one of my mentors there Dr. Wagner was a neuropsychologist at M. U. S. he was also the neuropsychologist for the early MDMA trials and so he did all the neuro cognitive batteries for individuals pre post and similarly did not see any changes in neuro cognitive profiles in a negative way and so you know there's there's data from experimental patients receiving this there's data from people that are chronic users you know who only take MDMA and that that combination of of data suggests that there's no there's certainly no parent risk in the kind of one to two to three dose range it's probably unlike that at least you know modest dose exposure of real lifetime doesn't appear to have a profound neuro cognitive damaging effect. Interesting. Yeah I know that sourcing is key and we're here we're talking about clinical trials where purity is assured and you know years ago when so called raves were really popular maybe there's still popular never been one so I know if they're happening or not that's how in the know I am but it was clear that you know testing for purity was important because that sometimes the drugs are made such that there are contaminants like methamphetamine which we know is highly neurotoxic. I think that one reason why people think that MDMA might be neurotoxic is the the reported drop in energy or sort of feeling fatigued for a few days afterward I spoke to a physician colleague of ours who said that that very likely has something to do with the surgeon prolactin that arrived subsequent to the big dopamine surge that occurs in in MDMA and I mentioned that because I know a number of people talk about serotonin depletion after taking MDMA. He has it in mind that while that could be true it's likely that anytime somebody takes something or does something where there's a huge lift in dopamine that there's very likely a huge compensatory increase in prolactin that follows and prolactin has a kind of sedative effect numbing effect on mood and libido etc that eventually also wears off. Does that make sense to you as a physician? Yeah it makes sense. I mean you know the difference between say MDMA and and psilocybin is that MDMA is kind of an emphetamine of sorts right so it has it has effects in dopamine and the psilocybin is you know pretty pretty neutral and you know maybe a little bit of dopamine effects but kind of much more of a serotonergic focus drug and so yeah I think you're going to see kind of a different profile after and that makes I haven't heard that story but that makes sense to me too. Since you mentioned psilocybin let's talk a little bit about the neurochemistry of psilocybin as a serotonergic agent my understanding is it operates on these is it the 5HT serotonin 2C receptor? 2A. 2A excuse me 2A and receptors and that I've seen a bunch of different reports in terms of what it's actually doing to the brain while people are under the effects of the drug and this is important for us to segment out because there are the effects that happen while people are under the influence and then the more long lasting effects but some of the effects I've heard about are for instance and tell me again if these are right or wrong that there is increased kind of activation of lateral connection sort of broader areas of the brain being coactive then would normally occur. Maybe that explains some of the synesthesia's you know seeing sounds and hearing colors and as the trivial example but rule breaking within the mind but then I've also heard that perhaps it's lack of gating of sensory input so normally if I'm looking at something I'm not thinking about the sensation in my right toe unless it's irrelevant but if I'm thinking about the sensation in my right toe I'm generally not thinking about the truck around the corner so we have these attentional spotlights but that somehow it creates a more it adds spotlights and it negates the thalamus. It negates the thalamus right through the particular thalamus structure. So what is the evidence that any of that is true and are there other phenomena is there involvement of Dorsalato prefrontal cortex that we are aware of and what I'm really headed here in a few minutes is you know is there a place for combining directed stimulation of the brain with psychedelics so that the effects of serotonin could be primarily within the structures that you know from your work to be relevant to depression. So but to simplify at first what's going on when one takes psilocybin and why is it interesting in light of depression? Yeah definitely so David Nut and Robin Carter Harris's work around neuro imaging psychedelics are kind of the some of the first folks to do that work and you know into their great surprise they thought there was going to be an increase in activity on psychedelics and what they found is the opposite right there's kind of an overall decrease in the level of activity in the brain with psychedelics but they they've also looked at connectivity and there's this kind of small world you know large world connectivity that you think about and so you know small world meaning there's a lot there's kind of a much more kind of focused kind of cortical function or you know sub cortical function or whatever it is and what you see is a difference in that in that level of engagement of brain regions the connectivity kind of global connectivity to your point kind of increases and so you know it's it's interesting you know I think to kind of have a convergent theory on this it's still you know to be determined there's still a lot of work I think that needs to be done but but it's certainly suggestive that there's pretty profound changes in the brain region and so it's probably a lot of work and we've found changes in in brain activity and brain connectivity after and what we've found to be really interesting is the the antidepressants effects of psilocybin have a particular connectivity change that we also see with our TMS approach is right and it's this connectivity between the subgenual anterior single it and the default mode network and so when we do this effective Stanford neuromodulation therapy stimulation we see a down regulation that connectivity between the negatively balanced mood state in the case of depressed individuals in the self representation of the brain and you see that same connectivity change occur post psilocybin suggesting there's a convergent mechanism and it makes sense right you've kind of got an over connected negatively balanced system conflict system that's kind of you know kind of attached on to the self representation and people feel stuck right and then when you when you do whatever you do that's effective it un-unpares those two systems I want to ask you about this phenomenon I've heard about during psilocybin journeys I heard about this from Dr. Matthew Johnson who's running a lot of the clinical trials at John's Hopkins and has been a guest on this podcast he said that there's something seems to be important about the patient who's depressed or who's and is under the influence of psilocybin or the patient who's trying to get a over smoking or needing disorder who's taking psilocybin and is in the clinic that there's something important to this notion of letting go that people will feel as if their thoughts and their feelings and maybe even their body aren't under their control and that the clinician's job under those circumstances is of course to make sure that they're physically safe that they don't jump out a window or try to actually give an example of a patient we thought that I think it was a she could move into the painting in the wall and obviously that wasn't true in the real world although it was true in her mind so they prevented her from doing that but that letting go that somehow untethering from the autonomic arousal that's occurring is important which brings us back to this idea or me back to this idea of a like a seesaw where sort of letting go of the hinge and just sort of letting go of the hinge and just sort of your heart rate's going up like just go with it and trust you know your heart rate's going down just go with it and trust you're thinking about something very powerful and depressing related to your childhood you're just supposed to go there without fear you're thinking about what's possible in terms of what could happen that so anyway you get the picture can we think of that as just the willingness to do a million different variations on the emotional strup task you know you will entertain the full array of rules within your head and consider them where is there something more to it you know it and again we're in the the outer margins of understanding here but what are your thoughts on this notion of letting go at such a key variable for relief from depression during the psychedelic journey yeah so I'll talk a little bit about something called exposure and intervention therapy that's a typical kind of gold standard treatment for OCD and I'll help to you know help this a little bit conceptually and so what that really is it's a letting go therapy and so you know exposure response prevention the idea is that you have to expose the individual to something that you know some something that triggers an obsession that they then want to do whatever the compulsion is and so I'll give you you know my first exposure and response prevention patient when I was a resident he was very concerned about leaving the lights on this car and so what we did is we went out and we turned the lights on in this car and locked his door so his lights were on and he was super worried this is kind of kills battery and we went and we spent an hour talking about things we went back out to his car and his battery was fine and his lights were on and he cranked the car and we did it maybe one other time and then all of a sudden that was gone right and that's the idea is that you know you're essentially exposing and you want to do it at levels that are from an anxiety standpoint tolerable but exposing the person to something and then letting them see that that exposure ends up being fine right and ends up not causing the thing that they end up being worried about and so you know in some sense being in the psychedelic state and we're all we're all taught at a level to retain some level of control you know people have more or less of that but we're all effectively retaining some level of control we all wake up in the morning and put clothes on to go into society we all try to say you know most people try to say the right things they don't try to do things that are outside of cultural norms when they're in conversation and so we're constantly at some level controlling the situation that we're in and so it's you know it's not it makes a lot of sense that in that state part of the therapeutic effect that maybe linked to the neural circuitry is this idea of letting go essentially letting the system you know the network configuration maybe whatever it is assume a state that you've essentially been fighting the whole time the same way that my OCD patient was fighting this need to click the off button on the lights of his car 50 times before he would go and do whatever he needed to do and in some level letting go or letting go meaning letting us just turn the lights on and him not do anything or letting go meaning in the psychedelic state you're just letting go of whatever it is you're holding on to negative really balanced think thoughts about yourself in the setting of having depression or you know re-experience a trauma you know memory and allowing that to just happen and re-seeing it again through a different light and you know and you know and it's the same in the sense that that's allowing for whatever is going on these psychedelic states to do whatever they do fascinating you said exposure response therapies that you're doing exposure response prevention prevention therapy done outside of this psychedelic journey it's done outside the psychedelic journey it's done outside the psychedelic non-anything psychotherapist psychotherapy that we know works really well for OCD and then in that psychedelic state and so people have done studies with psilocybin and now there are some studies with MDMA trying to look at treating OCD with the same sort of idea of letting go and how do you have an OCD patient or you know kind of accepting the idea they're not going to get germs or whatever it is and so it's kind of part of that part and parcel that same sort of thinking when I was in college I developed a compulsive superstition I'm not afraid to admit this I somehow developed a knock on wood superstition and I was actually kind of ashamed of it because it rationally made no sense I don't consider myself a superstitious person I was a kid I'd step on the sidewalk crack, I'd cut I'd walk under ladders even try to walk under a ladder even though I don't suggest it but somehow I picked this thing up and I used to sneak it at times I told my girlfriend at the time that I had it and hopes that that would prevent me from doing it and it's tricky sometimes it actually comes back I think gosh I didn't say it's not crazy but I crazy in the sense that it makes no sense rationally why the events would be linked and yet I think a lot of people out there do have internal superstitions maybe by talking about it now it'll go away I just see clearly I just need to challenge it anyway I mention it because I I consider myself generally rational person but it's interesting how these motor patterns get activated I don't actually know what consequence I fear and the fear as I was hearing the example you gave the fear of the car running battery running down I was about to say well what if the battery actually did run out then the therapy would be under mine and yet that could also be interesting too because it's not that big of a deal you jump the car but in my case I need to think about what the ultimate fear is yeah and I think I think a lot of people it's interesting if you look at say the OCD scale or the depression scale whatever we don't define normal as zero we define normal as some number range above so zero to in the case of the Montgomery Asperg Depression rating scale one of the depression scales we use 10 right that's the normal range and so people could have some sadness and still be considered normal in the case the OCD scale it's about the same 10 where we say it's kind of starts to be you know mildly abnormal or something and I always tell the medical students look my friends that are surf instructors they're more like a zero on the Y-box people that are professionals you know they're non-zero but it's still within the normal range and especially you know in the case that you're talking about it doesn't sound like it got in your way it doesn't sound like you're obviously highly successful 10-year professor at Stanford and do all the great things that you do and so it's very much kind of within the normal range and I think totally totally assumed that a lot of people have these sorts of things and I think something is a psychiatric diagnosis when it severely impairs your ability to function and that's when we kind of cross that threshold but you know I think that I think that a lot of people and it's great that you're bringing this up it's very anti-stigmatizing that you're bringing up right because I think a lot of people are just not going to be able to get this up in and they don't want to talk about it because they're worried that somebody else may think something but the reality is it's a psychiatrist that talks a lot of patients a lot of people that are you know family members you know folks that are just going through it a death in the family whatever it is and what you figure out is like everybody's got a little something here and there everybody has the knock in some way if that makes sense and it's just I think it's important to talk about it because I think that when we start all talking about it then we realize that we're all kind of in this together in a way and then some folks that you know have to knock a hundred times we call that OCD and they have all you know, they're worried about germs and all these other things we call that OCD and then in that circumstance you know they need treatment and they need a lot of people and it's just like blood pressure, it's on a range you know, and it's not just these discrete diagnoses you have them or you don't it's good to know I actually feel some relief just hearing this because I am slightly I wouldn't say ashamed as I've embarrassed by but I offer it as a you know that you know it is what it is as they say and it certainly doesn't seem to we could talk a bit about eye-bagain I don't know much about eye-bagain although anytime I hear the you know, AI&E you know, light-accained eye-bagain I think of an anesthetic and going to the dentist which is an unpleasant experience for me generally what is eye-bagain does this have anything to do with the so-called toad? you know people talk about smoking frog skin and toad skin what is it used for clinically is it legal in the US in terms of a clinical tool who's using it and for what purposes if you could educate me on eye-bagain I truly know nothing about it except I think I know how to spell it yeah that's fair so eye-bagain is one of the alkaloids that you can extract from an iBoga tree root bark that's typically growing in the country of Gabon Africa so Gabon is one of the west African countries can middle of Africa on the west coast and Gabon has a group of folks you know, called the Buiti it's a religious kind of sacramental group that sacramental uses iBoga root bark is part of that's the sacrament and they've been using iBoga root bark for a very long time and it's part of the tradition there's a whole there's a whole set of kind of ceremony around it if you're interested in this there's a book called Breaking Open the Head by Daniel Pinchback that goes through and talks about this this whole process but essentially the Gabonism and using this for a long time and it's a kind of an atypical psychedelic it's not it's not a psychedelic that we normally think about with psilocybin and lst where their visual perceptual changes right so if you have an lst which you experience as you experience this kind of visual perceptual differences in the external world on enough lst or psilocybin an individual can actually perceive something visually in the external world that isn't there as we talked about earlier iBoga doesn't do that it's kind of like if you're seeing a minority report with a movie with Tom Cruise ago or something so it dates us a little bit it was this movie where he would be able to go and see these kind of pre-crimes and he had this big screen where he could look at scenes from time and like kind of go through that scene and see it and so what individuals take iBoga and will say is it open eyes they don't see anything but closed eyes they'll go back through and they'll go back through and see these sort of memories and they will be able to experience it from a place of empathy not only for themselves but from others and kind of detached empathy and being able to see this as almost a third party even though they were there but they're able to see it as a third party so Claudio Naranjo and so you know iBogaine's been around for a long time howard lotsoff american guy that brought it over from from africa was a poly substance user used every drug you know that he had his hands on took iBogaine including a lot of other psychedelics by the way took iBogaine and then never did another drug because he had such a profound iBogaine experience iBogaine is in no way a recreational substance if you want it to be a recreational substance because you're essentially having this what they call life review they also call it 10 years of psychotherapy and a night so these are the terminology that people talk about the issue does it last? it's usually you know we can go depending upon if you get redost or anything going depending upon how fast you metabolize it sometimes 24 sometimes 36 hours of time it's a very long time so it's definitely the longest acting psychedelic substance i know of and so people you will take this and they'll have this re-evaluation of a given memory and then we were talking about really reconsolidate that memory again and then it seems to have you know an effect of that reconsolidation process four or five years ago i was tapped by Robert Malenka one of the you know senior neuroscientists we both know in the university he says well there's a you know there's an unnamed donor that's very interested in funding a group you know a scientific kind of open label study of these Navy SEALs that have been going down to Mexico and taking iBogaine and also on a 5-A-MEO DMT we're going to talk about the treatment of brain injury depression you know that whole constellation of symptoms you know and as it was described to me by various people that had done this by their spouses and what not you know John we'll just say John John couldn't screw a light into a light bulb into a light fixture look at the they're coming back having the traumatic improvements in all aspects of life So we have over the last couple of years been able to do this first in human kind of full neurobiological clinical neuro-cognitive evaluation of what IBogaine is doing in special operations, special forces, individuals, former Navy SEALs, Army Rangers, that kind of crew folks, and look at the preposed changes that we, that their experience to be able to totally quantitate all of that. And so we've been able to capture all the clinical scales, you know, depression scales, PTSD scales, all that standard stuff, neurocognitive batteries. So how does your executive function work specifically? How does your verbal memory all of that? And then neuroimaging and EEG. So this will be the first human study of Ibogaine for those. And the reason why is because Ibogaine's kind of the, both seemingly the most potent and most, and most seemingly to me, at least most powerful psychedelic, but the one that has the most risk too, because it has a cardiac effect. It seems to be that you can screen people out that have risk off of their electrocardiogram and reduce the risk quite a bit. And that's what we all did. But that's why people haven't really studied it as much. And it isn't as, in addition, there's like nobody goes to array of on Ibogaine. There's no recreation at all with it. It's not fun. It's, people say that it's relieving, but it's hard work, right? Because yeah, you're re-examining things. And, you know, and so then, so then we see these folks after and I'll tell you, you know, we haven't fully analyzed the data yet, but I'll tell you that, you know, from what my folks are telling me, it's pretty dramatic. You know, people come back and they're doing a lot better. They're doing a lot better. And nobody, I'm not going to wouldn't nobody's had any sort of cardiac issue at all in the cohort that we've studied. And they look a lot better and they feel a lot better too. And they describe these experiences of being able to go back through and, you know, soldiers experience something called moral injury, right? Where they, maybe they accidentally blew something up and had a kid in it or something like that, you know, if they're an Afghanistan or Iraq, maybe a, you know, child died on accident or maybe a civilian died or whatever it was, right? And they've suffered these moral injuries as part of the job. And it's almost one of the kind of, you know, vocational risks. They come back and say that they've forgiven themselves, you know, which is huge, right? And in part of that is being able to see themselves in a different light and having empathy finally for themselves and being able to kind of have that experience of forgiving. And so, so very cool. The study, you know, what was happening was they were taking, I'm again, and then taking something called five-a-me-o-D-M-T, people call the Toad. It's the Sonoran River Toad. I think it's like you can find these in Mexico, find them in Arizona. And in the back of the Toad, produces something called five-a-me-o-D-M-T, which is a, you know, flavor of DMT that produces a particular psychedelic effect, also used as a sacrament. Is it a dimethyl-triptamine? It is a five-a-me-o-dimethyl-triptamine. So it's a kind of dimethyl-triptamine with a kind of addition to it. The deal there is that it lasts longer than traditional DMT. You know, it's like 20 minutes at five, three or whatever kind of thing. And so then, so these guys were taking, I have again, and then they take the five-a-me-o-D-M-T after we had to kind of divorce those two things, be able to do the study and just understand what I began was doing, and they go back down a month later, and they'll do the five-a-me-o-D-M-T. So two completely separate sessions. Two completely separate sessions. And one quick question about Ivegan before a bit more on five-a-me-o-D-M-T, is the Ivegan journey guided, or the person just closes their eyes, and they just start falling into the back catalog of memories? They have a bunch of preparatory sessions, and then they have a bunch of sessions after that they're able to kind of rehash things. During, there's a sitter that sits there and kind of sits with them and helps them out, but it's pretty, the phenomenon of the drug seems to drive a lot of this, right? And so a lot of it ends up being what we call supportive psychotherapy, just kind of being there, and maybe holding the person's hand, maybe you're just saying, I'm here, maybe whatever it is, but you're making sure they know you're around, but you're not really, there's not really an interaction per se, and then the whole kind of goal there is just to get folks to kind of go back through and re-examine these memories, and ultimately look like they re-consolidate them. And it's very interesting. I mean, there's this kind of, as you said earlier, Timothy Liri, kind of sociocultural construct that ends up being overlaid over psychedelics. And what I think is that if you rid yourself of all of those preconceived notions of what it is and isn't and the counter-culture movement, all that stuff that neither of us, or ever involved in, other of us, or ever partake in, is kind of straight scientists looking at this, right? If you can kind of rid yourself of all those sociocultural constructions and re-examine this, these, if we just discovered these today, we would say that these sorts of drugs are a huge breakthrough in psychiatry because they allow for us to do a lot of the sorts of things we've been thinking about with SSRIs, with psychotherapy, but kind of combined, right? Psychotherapy plus drugs in a substance that kind of allows you to re-examine these things. And so it's interesting, it'll, you know, there's a lot to do to try to figure out if that's true, you know, and I can say that as it stands right now, we don't know if that statement is true, right? There's a lot more work that needs to happen for that statement to be proven to be true, but the hypothesis is if it is true, then it's very likely that this will be seen as a breakthrough because it allows you to do these sorts of things that you can't do with normal waking consciousness, but also why we have to really think about this and, you know, these drugs can't be recreational drugs. They really shouldn't be recreational drugs, right? They're really too powerful to be used in the context of recreation because they can put you into these states. And this generation of psychedelic researchers are really clear about that. You know, I think the 60s folks were not clear about that and they felt like there was a whole kind of cultural thing that was going on there, but I think this cohort of individuals really understands that in order to really make this happen, we have to understand that if you need a prescription for an SSRI, which doesn't change your consciousness a whole lot, and we were very worried about that, and the doctor has to evaluate you for that every week that the idea that some of these substances would go outside of very strict medical supervision is kind of preposterous. Actually, it's kind of a dumb moment, I think for all of medicine to say, look, if we're gonna do this right, we've gotta do it in such a way that's so protected, that's so safe, that we make sure people know these things are not recreational and they're really for the pure purposes of really powerfully changing cognition for a while and letting people have these, what seem to be relatively therapeutic states. I think it's great that you're doing this study and along the lines of the sort of early iterations of psychedelics and the counterculture of the 60s and 70s, some of which took place like one floor of the Kukuznes, I think is actually based on the Menlo Park VA, which is in our neighborhood of Stanford. And things are quite a bit different now. I know you and I have spent some time with the operators and former operators at an event in the last veterans day. In fact, the so-called veteran solutions group that's pioneering a lot of these psychedelic treatments for former special operators and current special operators. And what's interesting to me about that is, in contrast to the counterculture movement of the 60s and 70s, that room was filled with people that are very much of a structure, the military, right? So it's no longer considered left wing, right wing, anti-military, pro-military. Here, this is just about one group of people who's exploring psychedelics as a treatment for trauma and PTSD and other things. And of course, you also have other domains of society looking at this. And in fact, it was really interesting because they were both far left and far right politicians at that event. We're on stage together talking about in kind of lighter terms, heart medicine, but also talking about neurobiology. And it was just fascinating from the perspective of somebody who's trying to learn about this stuff that psychedelic therapies no longer sit within the anti-establishment realm. It's both, it's independent of all that. Certainly when people in the military are adopting as a potential treatment, again, still under exploration, but also under exploration at universities like Stanford and Johns Hopkins and UCSF and of University College London and on and on. Along the lines of tree barks and toad skins, tell me about Iooska and as a plant, it's intriguing. And is it a pro-cerotinergic drug like psilocybin? And is it useful for the same sorts of conditions that we've talked about thus far? And if you could perhaps tell me a little bit also about the Brazilian prisoner study. Yeah, yeah, definitely. Iooska is another psychedelic. It's used as a sacrament in Brazil and Peru and Ecuador and Colombia. So a lot of the South American countries and what they do is they combine two plants together with where one plant of the two plant combination would effectively do nothing. But the two plant combination together is capable of producing this very profound psychedelic effect. And what's really curious is that there, as I understand it, 10 to 20,000 plant species in the Amazon and somehow somebody will try to mull combined these two plants together in certain proportionality and cook this for 5, 10 hours to the point where you cook out the dimethyl triptomine out of one of the plants and cook out the reversible monomine oxidase inhibitor out of the other plant. It's such a way that the reversible monomine oxidase inhibitor prevents the GI breakdown of the dimethyl triptomine in such a way that it's then allowed to cross the blood brain barrier and get into the brain? And if you didn't add the reversible monomine oxidase inhibitor plant derived into this combination, then it would never cross the brain. If you put people on a standard psychiatry prescribed monomine oxidase inhibitor that wasn't reversible, you'd throw them in a serotonin syndrome. So this kind of sweet spot that somehow Iawaska practitioner is a found of being able to get DMT in the brain from an oral source with this combination of a monomine oxidase inhibitor is curious. And so that substance has been explored as an antidepressant agent in some studies have looked at that. It also seems to be very safe. There was a psychiatrist down at UCLA Harbor, who's done a lot of work with this, where he's looked at children, even that have been exposed to small doses of Iawaska as a kind of a sacrament within Amazonian tribes and found no nerve cognitive effects, no nerve cognitive effects and adults. And so it appears to be safe. It's part and brought into various religions, including merged with Catholicism in South America, which is very interesting. And so in some sex of Catholicism in Brazil, it's used as sacrament during religious ceremonies. And so it became interesting to Brazilian researchers as to whether or not they could affect recidivism rates for prisoners in Brazilian prisons. So they gave half of the prisoners some sort of inert substance and half of the prisoners in Iawaska session. And the recidivism rate of the return to prison rate in the Iawaska exposed individuals was statistically significantly lower than the recidivism rate in the control group, suggesting that whatever is going on there seems to have an effect on whatever drives criminal behavior, or whatever criminal behavior that happened to be. And I don't have the details on the exact nature of the crime. I am also in no way saying that we should just be giving psychic elixir to folks. In prison and all of that, I think that that is a very edgy thing to do and probably not something that anybody should try. But it does kind of bring up this curious question of what is it about that that would drive people to change those behaviors? And why do people make those behavioral decisions? And in a lot of times, if you look at prisons in the United States, people say this, what's the biggest mental health facility in the United States? It's a prison. Yeah, there's a lot to unpack there for sure. The homeless issue, the prison issue, it does lead to something that I heard recently, which is related to all this, which is cannabis. We hear a lot nowadays about people will say, well, it's safer than alcohol. And we did an episode on alcohol that, at least by my read of the literature, indeed, alcohol does seem to be quite bad for our health. I think it's pretty clear that not drinking is better for your health than drinking at all. And here, I'm not trying to tell people what to do, but those are what the data say. And forget the studies on red wine. You'd have to drink so much red wine to get enough for a severe trial. It's not even clear with red wine, does anything useful anyway, et cetera, et cetera. Nonetheless, cannabis is now available in a lot of very high potency forms. People are vaping cannabis. People are smoking cannabis. I certainly am not saying that cannabis is bad for people necessarily, although I think children, I would hope that their brain development would be completed first. Get to age 25. I know that sounds late for a lot of people, but the THC obviously taps into some endogenous systems of endocannabinoid systems and is powerful. And I've seen this report that was in Lancet Psychiatry this last year that said that early use of potent cannabis, meaning age 14 to 20 or so, can potentially lead to an exacerbation of psychosis later in life. And I actually put this out on social media, and it sort of exploded. I didn't expect it to. People were saying, well, that's not causal, and obviously it's not causal, because people say, well, maybe people with psychotic tendencies are seeking out cannabis, although that's sort of a weak argument in the sense that there's at least four times 4x increase in these psychotic episodes for people later in life. But what are your thoughts about cannabis? Because I do want to acknowledge that it does have medical benefits for certain things. Pain, chemotherapy, so by no means trying to knock on cannabis and its appropriate medicinal use, but what do we think about cannabis in terms of this finding that can exacerbate a psychosis in certain individuals? Yeah, so I think there's a couple of things, right? So cannabis is multiple cannabinoids, right? T-H-C-C-B-D, CBN, Sativas, and Indica's. Yeah, there's a lot there to unpack. Yeah, there's a lot, but there are two main kind of chemicals you think about and kind of how things are essentially bred, right? And so there's a lot of cannabis that's really bred to be very high, very potent T-H-C, and there's cannabis where the T-H-C-B-D completely out. So there's stories from Colorado, right? This strain of cannabis that's T-H-C-free. There's no T-H-C at all, and it's all CBD, and it's called Charlotte's Web, and a bunch of kids' parents, one kid, and then kind of a string of parents after that moved to Colorado when cannabis was legal, legalized because CBD is anti-epileptic. So CBD is also anti-psychotic, and so there have been a number of studies if you give CBD at high doses, it's anti-psychotic and gets established, gets a frenic patients. The issue is that we've bred CBD out of marijuana selectively over time, we've gotten very good at figuring out how to do that, right? Conversely, T-H-C is pro-psychotic and pro-epileptic, right? And so when you talk about this cannabis cause psychosis or just cannabis treat psychosis, it appears to be more related to the proportions of CBD to T-H-C than it does to the kind of idea of cannabis. So for me, there's a kind of, I have no stock of this or anything like that, but there's a company called GW Pharmaceuticals, and I haven't looked into them in a while, but they have a lot of clinical trials for something called Dravais syndrome, which is a seizure disorder or kids' disease, a whole lot, Linux gasto syndrome, which is a seizure disorder, kids are seizing 300 times a day, both of these are like, kids are seizing so much, they're basically in a seizure or in the post-ictal phase constantly, and they've failed everything, they've failed barbituits, they've failed bromides, which we don't use anymore, except in these cases because of the side effects, and they'll give kids CBD, and I think CBD is a pretty safe drug compared to bromide, right? So this idea that CBD in a kid is actually safe, it's a cannibanoid, but it's CBD and it's safe, right? And so that, to me, is totally fine. Also giving CBD as an adjunctive treatment for schizophrenia, there've been some positive trials and negative trials in that, but there seems to be no negative side effects, it seems to reduce some of the metabolic syndrome issues, and folks with schizophrenia who are having side effects from the primary anti-psychotic, the converse is there's clearly cases where people that are taking very high doses of THC become psychotic, they get put into the psychiatric unit, nothing happens out of me, they kind of get the THC out of their system, and then they resolve their psychosis, right? And so, and, you know, a handful of people have had, you know, seizures related to high doses of THC, and syncopated, all sorts of things, and so this idea that THC, high doses of THC can be pro-psychotic, is also not taking a shot at people that think that cannabis overall is a good thing. It's just, it's just is what it is, and the kind of pure, if you, I think if you zoom back and you say, you're a true naturalist, you're thinking about natural medicines in the world, you should think, well, probably marijuana was balanced THC CBD at some point, and then we just, we humans messed with it, right? And, and that most likely, that was probably okay. At some level, and then we pushed it one way or another, and I mean, what I mean by okay is, in a 45 year old, it's okay, kind of thing. Now, what I think is going on with the kids, with the teenagers, is you've got prefrontal maturation, right? And then you're exposing them to a whole lot of high THC load, and while it's unclear if it's, if it's cause or effect, it's certainly in the picture, and if I were a parent, I wouldn't want my 16 year old smoking marijuana. If I were a parent, in my 30 year old, otherwise healthy, totally fine, you know, whatever, banker, lawyer, kid, decided to try marijuana for the first time, I wouldn't scold them about it, right? So I think it's kind of a different thing, right? I would never want my up to 25 year old, just like you're saying, before prefrontal maturation, I would never want my kid to be exposed at all. But it looks like, except in, you know, susceptible individuals that are susceptible to drug induced psychosis, it looks like, you know, it's a relatively safe thing, past prefrontal maturation. You know, again, I can't, I'm not going to comment on the cause and effect, but I would say that, you know, it doesn't, if you're a parent, it doesn't make much sense, right? You know, you never know what's ultimately going to hurt your kid. I mean, my wife's, we were talking about this earlier, my wife's pregnant now, she kind of avoids everything, right? And rightfully so, right, this idea that we just, we want to be careful when our children's brains are developing, and I think that's really what you were saying, and I think it actually important. The bigger question that you asked, which is relative risks of drugs is an interesting one. So David not published, and I think it was in the Lancet, I'll have to look it up, but I think in the Lancet, an article about relative drug risks for the person and for society, and this was like, he was on the, the UK's like, British drug policy group where essentially what he showed was, if you took, if you look at societal risk, plus personal risk, and you combine those two, you know what, drug is the most dangerous drug in the world. I'm gonna guess it's alcohol. It's alcohol. Right behind heroin and cocaine, and did it, and somewhere in the middle is marijuana, and right on the tail end, on the other, on the exact other end of this, psilocybin. Is caffeine, it usually doesn't act a list. I may have been on the list, it was probably, it was probably pretty close to psilocybin, but somewhere in the middle was ketamine, somewhere in the middle was, was, was, amphetamine, somewhere in the, you know, a little closer to psilocybin, I think it was MDMA, you know, but, but if it's, it's this combined personal, you know, kind of world risk of these things. And so alcohol makes it because there's a huge amount of personal risk, and there's a huge amount of societal risk, right? Drunk drivers kill X amount of, you know, people in the world, fight sexual assault, all that, all that. Yeah, and then all the cancer and all that stuff. And so it beats out cocaine, it beats out heroin, it beats out all of these things. And yet, we don't, we don't as a culture for whatever reason. We don't as a culture, see it as a drug. And that's the part that really baffles me, you know? And I mean, they serve it, I mean, this is no knock on Stanford at all. Of course, I wouldn't do that. This is, every institution I've been to, they serve alcohol at the graduate student events. That's right. You know, they serve alcohol, they do a happy hour. I've never been a drinker, I can take it or leave it. So, and I realize that some people, they really enjoy alcohol, you know, my former partner, I mean, she just was in that, you know, 10% or so, people who have a glass of wine and just feel great. And the second one feel great. I just want to take a nap after I have a bit of alcohol. So it never does much for me. I always feel poisoned. I feel lucky in that sense, but it's unbelievable that it is so prevalent. And it's just, it's baked into the medical, even medical institutions, they'll pop a bottle of champagne to celebrate the opening of a hospital. That's right. That's right. It's pretty crazy. Yeah, no, you're absolutely right. You know, I think what's gonna happen, but this is me, you know, looking at crystal ball a little bit, but I think what's gonna happen is what happened with doctors and smoking. So if you look at the 50s and 60s, right, there are all these pictures of doctors smoking cigarettes. You know, with patients, you know, psychiatrists doing psychotherapy and smoking a cigarette with the patient sitting on a couch, you know, surgeon smoking a cigarette in between cases. There are all these pictures of that, right? And now all of a sudden smoking is totally banned. I think it's totally banned for most of Stanford campus. My suspicion is, as you're suggesting, right? You know, this is everywhere. And it's all kind of ubiquitous. It's some critical point, some tipping point. Everybody's gonna realize that just like with smoking, we've got a red hospital systems and universities of alcohol. And at some point in 50 years, it's my view that we'll look it back at these scenarios that you're talking about and be like, you know what, we were foolish about this. We can't believe that we gave people alcohol on the way, you know, when they graduated from whatever, you know, and I think we'll have a different take on it. But it's gonna take a longer time. I think people did a really good job tying smoking a lung cancer. And it's like very a very simplistic story smoking lung cancer, you know. Now, you know, as you know, alcohol increases the risk of a lot of different cancers. Not so clear which one? I mean, there's like, you know, the kind of oral, like the throat, tongue cancer, that's one. Press cancer. Yeah, press cancer, you know, and so it's kind of, it's a harder story to tell, you know, and I think that's why and everybody, you know, and then there's this whole, it's, you know, my mom says this, it's like, I drink my glass of wine because my doctor told me it was heart healthy and we were talking about this and I try to, no, no, but doctor so and so said it's heart healthy and so it ends up being this thing where like, she's drinking alcohol because she thinks that it's good for her heart. And, you know, and it's hard, I've had those conversations with her, it's hard to untie that. And I think that, yeah, at some point, we're gonna hit some threshold moment and it'll be interesting if we really look at the data and we really look at what's safe and not safe from purely from this analysis, it kind of, it kind of points to the right direction. It's really interesting and also saying nothing of poor judgment under the influence of alcohol. I mean, I would venture that if we were to remove alcohol from university campuses, watch the students are gonna lobby against me if I said this. But if you were to remove alcohol from campuses, I mean, just think about the, what I suspect would be the improvement in good decision making. And that would occur. Or, you know, I've got stories from graduate school and it was very different, you know, 10 years ago. There was a lot more alcohol consumption and that was never my thing. But I know people who make really bad decisions. Yeah. In any case, there's a whole landscape there, immersion, I think you got your finger right on the pulse of it. I want to touch on something slightly different than what we've been talking about, but definitely related to depression. And this again is one of these intriguing but for plexing things, which is that sleep deprivation can improve symptoms of depression. And yet, I'm personally very familiar with the fact that if I don't sleep well for one night or don't sleep at all, in fact, I do have an ability to function pretty well the next day. I'll do this non-sleep deep rest practice that I blabber a lot about on the Puberman Lab podcast, which for me is tremendously restorative. But I like a good night's sleep. I think everybody understands now, thanks to the great work of Matthew Walker and others that have really gotten out into the world saying, look, the foundation of mental health, physical health and high performance, if that's your thing, being a functional human being is to try and get enough quality deep sleep, at least 80% of the nights of your life. If you can, that's something to focus on, just like good nutrition, just like exercise and social connection, et cetera. So sleep deprivation, we know, in particular, I think, rapid eye movement components of sleep deprivation can improve the symptoms of depression. And yet, being sleep deprived can also really dysregulate our control over the autonomic system. I notice on night two or night three, of course, sleep if I'm going through a stressful phase and that's happening. All of a sudden, my heart rate is chronically elevated. My thought patterns become really disrupted. I can't then exercise, my decision making is thrown off, my emotionality is more labeled the hinge as we were referring to it earlier, feels less in control under my control. And maybe I wonder sometimes if I enter that state that you referred to earlier where the door to lateral prefrontal cortex is no longer leading the singular, but the singular is now in charge. The players are in charge of the coach, not a good situation. So I know you've done some work on sleep deprivation and light and effects. Please tell us about that. And please tell us about this triple therapy. Yeah, yeah. So for the mind, Greg Salem, one of the professors at Stanford is very interested in sleep. He did a bunch of training and sleep before he went to medical school and got very interested in this idea that, as you're saying, if you sleep deprived somebody one night in just kind of an isolated single night, at the end of that sleep deprivation, they will have an antidepressant effect. But as soon as they fall asleep, they lose it. So if it's a depressed individual, you can get them to be less depressed acutely. As soon as they fall asleep, they wake up eight hours later, then they come back into the same level of depression. And so the idea is that you needed to do some sort of circadian reset. And part of what depression is, is that it's a dysregulated circadian system. And so mentors of mine say, if you can just get the sleep better, that's half the battle of dealing with depression because so many people have insomnia around depression and have a whole host of types of insomnia, having a hard time falling asleep, waking up in the middle of the night and waking up early are all symptoms of depression. And so what this does is it sleep deprives the individual and then there's a certain calculation of shifting their phase and simultaneously exposing them to bright light. So that's the triple, the phase shift, the sleep deprivation and the bright light, to try to get their circadian rhythm. Essentially, the theory is re-entrained. And so in the trials that we've done, and other trials, prior to ours, and after, it looked like there was a pretty profound anti-depressant effect from this triple therapy that seemed to be durable, meaning durability is this term we use to say that not only can you get kind of point relief, but that the relief ends up, lasting. What's important to know about this is like, you shouldn't do this at home for sure. This is what you would need to do, this is with a professional because it's complicated, it's not just one thing. And in sleep deprivation, while it seems to be antidepressant, it's pro-anxiety. So if you take a highly anxious person, that's not depressed, and you sleep deprived them, it's probably profoundly anxious. And so that's the other thing that you have to really realize is that this is like everything else that I've talked about today, all things that you have to do under medical supervision, but curious, right? And I think the question that always comes up is why isn't this used more? And I think the reason is that there's not really a mechanism for ultimately, and medicine is sad as it is, you have to have a code to do a thing. There has to be a code associated with a treatment, and it's hard to figure out how to make a code for this. And so I think that's part of it. And so if there's a way, and somebody's got to kind of take that baton on that, but if there's a way to make a code for this, I think you could actually turn it into something that was more widely utilized, and you know, we probably dream up ways of how to integrate AI, passive sensing, all that stuff to really make that work. But I think that would be the idea that would be the trajectory I'd see. Yeah, having a billable to insurance code is fundamental. And a lot of listeners of this podcast, I think have a background in engineering science, and we will put a link to that manuscript that talks about the triple therapy, because here we're talking about one night's sleep deprivation, some time to light exposure to the eyes, and then shifting in the circadian clock, and then moving things central to the themes of this podcast that come up often. I think for the typical person, can we say that trying to get a regular light dark cycle at sleep rhythm would be beneficial for overall mood regulation? Yeah, I think for the typical person, really kind of re-regulating your sleep and trying to get a good night's sleep, in which you fall asleep, stay asleep, wake up in a set time every morning is going to be pretty crucial. In mild depression, I think that one has a lot of control over that, as we were talking about earlier, I think when you hit some threshold and depression, where things become kind of semi-volutional, that's harder to kind of will yourself into that. There are therapies like, there's a CBT for insomnia, for instance, where you can do cognitive behavioral therapy to help with insomnia. Sometimes people, and I'm no sleep expert, I kind of pass this to Greg to fully talk about this, but some of what goes on that people with kind of milder insomnia experiences, like blue light out of their computer and things like that, that they, so you can use like blue light blockers to trick your brain, as you know better than me, a trick your brain to think that it's still light outside, and so people will still have insomnia because their brain still thinks that it's light outside, and then people will, you know, the kind of strip CBT for sleep. You know, therapists will say, there are only two things that you should do in your bed, and if you're under a certain age and whatnot, it's really one thing that you should do in your bed, which is to sleep and be with your partner, right? And so those are kind of the two things that you should do in a bedroom, and that's really the only things that you should do in a bedroom if you're having sleep problems, you shouldn't watch TV in a bedroom, shouldn't eat in a bedroom, shouldn't hang out. Keep the phone out of the bedroom. Keep the phone out of the bedroom, yeah. Yeah. We should get Greg Salem on the podcast. We, the, I'll just mention for people that want to regulate their sleep, we have a sleep toolkit that's available as a downloadable PDF at hubermanlab.com, just go to the menu, and a lot of the things in that toolkit are based on work from Stanford sleep laboratories, including Jamie Zyzer's and other lab, not aimed at depression specifically. Listen, Nolan, Dr. Williams, this has been an amazing voyage through the circuitry of autonomic control. This landscape of the prefrontal cortex is a fine, incredibly fascinating. And I just, when I start off by saying, please do come back again, and teach us more about that and your TMS work. I, before we wrap however, I do want to give you the opportunity to talk about the St. Study. Yeah. Is it St. or St. Plural? Yeah, it's St. So, so, St. or what we're calling it, S&T now, St. has, you know, the intent was not to kind of connect it to religion, but we may have accidentally done so. And so we abbreviated it to S&T for the subsequent trials, which was initially Stanford accelerated intelligent neuromodulation therapy, or now what we're calling Stanford Neuromodulation Therapy, but it's the idea there, which is a cool idea, is that TMS is a device that delivers a treatment. And the treatment is the protocol, and the protocol is the stimulation parameter set in a specific brain region for a specific condition. And so what's cool about neuromodulation, whether it be transcranial magnetic stimulation or transcranial direct current stimulation, or deep brain stimulation, like what Casey Halpern talked about, you know, on another podcast, is this idea that in all of those cases, the device itself is a physical layer conduit of a stimulation protocol that's therapeutic for a given condition in a given brain region. And so in the case of depression, which we know the most about with TMS, we've been doing TMS studies for depression for, you know, since 1995, right, in a clearance in 2008, 2009. And in that timeframe, we were able to go from really knowing very little at all about how to do something like this to getting an FDA clearance. And the way that it went down was that there were two groups studying different components that NIH, the first group was studying mood neuroanademy on functional imaging that was kind of the first generation of functional imaging back then. So PET scans, which are kind of metabolic scans and then spect scans. And the idea there was looking at activity and metabolism in prefrontal cortex. And what they found in these kind of more crude scans is a just general hypoeactivity, hypometabolism. The other group, right upstairs, that the National Institute for Neurological Diseases and Stroke in INDS, they were looking at using TMS, which had been around for 10 years and repetitively stimulating in motor cortex. What they found was, gosh, we can get a readout in thumb muscle movement amplitude that's really reproducible across people. It's like, you know, universally reproducible. And if we do certain stimulation approaches, they are biologically active to either increase excitability, i.e. the thumb motion and a set intensity goes up, the amount of amplitude goes up, or inhibitory deep-potentiating, it goes down with other biological stimulation approaches and then a third outcome, which is important, that it's inert, it doesn't do either. So you can have stimulation approaches that do one, you know, increase activity, decrease activity, or you know, or inert. And so what they found was, oh, we can excite certain brain regions, and my mentor, Mark George, said, had this kind of aha moment where he said, wow, there's underactivity in prefrontal cortex and depression, and we can increase activity using this thing that we know, we can increase activity in motor cortex, we just need to put it in the left or a salateral prefrontal cortex, and then they combined the two and started stimulating once a day in this kind of very abbreviated fashion and lo and behold, some of those depression patients resolved their depression and back then, and still today, you can go and as a psychiatric patient stay at the National Institute of Mental Health and go through clinical trials to try to get treated, and there were patients who'd been there for months and they were able to be discharged, because their mood was better. Yeah, and so this is very crude approach where they were using ruler measurements, where a DLPFC was, and they were stimulating with devices that you needed to physically dunk the coil in an ice bath, and with that, they still were able to, the kind of genius of this, Mark and others, there still be able to create a purely engineered stimulation approach. What's cool about that is that they kind of found two things, right? They found this one stimulation protocol, it does have some antidepressant effect, it's limited, it doesn't treat everybody but does have some antidepressant effect, and this bigger concept that a neuromodulation device is kind of like a pharmaceutical company for you, right? That in a given individual, a TMS device or whatever neuromodulation device is able to generate, to create a stimulation approach that is specific to a given condition and specific to an individual. And so the physical layer is just how you exert that, similarly to how we make pharmaceutical drugs in a pharmaceutical company, but the actual therapy itself is what you do where you do it. And so what we learned from another 20, 30 years of this, is that you can modify the stimulation protocol in such a way where you can create a whole new treatment and put it through the same TMS device, or thank God, an evolved version of it where you don't have to dunk it in ice baths, and they can actually really handle much more aggressive stimulation approaches. And so in 2005, a group published a neuron, a paper demonstrating that if you stimulate with the hippocampal rhythms through a TMS coil, you can excite the brain with memory rhythms and it'll last an hour. So you can change cortical excitability in this thumbtwich for an hour, sending three minutes of excitatory or 40 seconds in the case of inhibitory stimulation that mimics the hippocampal rhythms. So much more efficient than the original TMS approaches. And so after that, a group tried to do it in this kind of six week schedule. And after that, and while they were doing that, we decided, gosh, this problem I talked about at the beginning of the show where you have this problem that we don't have a treatment for people who are in these high acuity psychiatric emergency states, this idea that we're going to engineer a treatment where we can reorganize the stimulation approach in time to be much more efficient by utilizing something called space learning theory. And so you probably know about the space learning theory as the idea for the viewers is it's a simple psychological thing, but we've also seen it in hippocampal slice sort of physiology, too, where if I'm cramming for a test, what I do is I write out 60 note cards, and I read each one for a minute until I get to the first note card and again, and that's about an hour later, right? And we just intuitively do this. We all automatically do that. And we intuit that because we know that what doesn't work is writing out one note card and looking at it over and over again. Nobody ever does that, right? We've all been in graduate school, medical school, and we have these big stacks of note cards. That space learning theory, it's this idea that you need to see it about every hour to an hour and a half and that optimizes learning. If you take the same stimulation approach that I'm talking about, this data birth stimulation approach, and you take a hippocampal slice of a mouse, and you stimulate, you enlarge some dendritic spines, and you prime some. And then if you stimulate right after that, you don't get any change, it's called en masse stimulation. But if you wait about an hour to an hour and a half, you get more dendritic spines enlarged and more primed, which by the way, also is what ketamine does. It causes this dendritic spine enlargement. And so what we found was that the old way of doing TMS, this idea of just doing it once a day, every day, five days a week for six weeks, didn't utilize the space learning theory. It's like studying for a month or two, just a little bit once a day. You remember some of that stuff, but it's not as potent as that week where you're cramming. And what we realized is that if we could reorganize the stimulation in times that we took the whole six week course, we actually figured out a way to do it in a day. And then what we also figured out is that people are under-dosing TMS, because if you just keep going after six weeks out to month three, four, five, more and more people got better. So we figured out it's not just one day, we're going to give five times the normal dose, and we have seven and a half months worth in five days, using space learning theory. So every hour? Every hour for 10 hours for five days. For five days. So it's a 50 hour block. It's 90 minutes of actual stimulation, but spread out through the day in the same way of learning, which is perfect for an impatient psychiatric unit, right? Five days is manageable. Yeah, you can get stimulation. Nobody's ever dropped out by the schedule. They're, you know, folks that want to do this, want to do it, so they'll do their nine minutes. They'll go get breakfast, they'll do their nine minutes. They'll go see their therapist or whatever it is. And so what we found with this reorganization and time of the stimulation, dose, and then the third component is we do resting state functional connectivity scans on everybody, and we have ways now in the last five to 10 years of picking out that specific subgenual DLPFC sub-circuit that I was talking about earlier, that's single at DLPFC. We can pick that out in every single one. If you want to come to lab, we can find your DLPFC subgenual. It's even more robust and non-diprotidious. Yeah, we can stimulate too, just while we're in there. Yeah, if you want to, we can move around your hypnotizability. And we can find that spot in each person, instead of finding the same spot on the skull, we find the same spot on the brain, and we can stimulate, we do that every hour on the hour. And what we found is that folks will, will within one to five days, you know, in more cases than not, depending upon if you're looking at the soap and label or in trials, somewhere between 60 and 90% of the time, they will go into full-on remission in this, since they're totally normal from a mood standpoint at the end of this. And like I said, with variable durability, so that's the part we have to figure out now about dosing and how to keep people well. But for some people, you know, we've had four years of remission, you know, a year of remission, and it's really that cramming of the test. It's really that idea that you're laying in that information to the exact right spot, and the signal is a simple signal, but it's a profound one, which is turn on, stay on, remember to stay on. You know, that idea that you're sending this memory signal into the brain, and you're doing it in such a way that you're telling the system, you're kind of taking it out of the hippocampuses, your own hippocampuses hand, and you're sending the same signal the hippocampus normally signals out. Now you're sending that signal into the prefrontal cortex and kind of utilizing the brain's own communication style to get it to get out of the state. And what's very cool about this is that, is that people when they kind of exit out of that, they end up saying they don't have any side effects from it, and they feel back to normal. Like some people, you know, not everybody, but there's a subsection of people with SSRIs, where they'll say, I kind of feel numb, or I have GI side effects, or I can't, I can't, you know, I don't have the sexual interest that I used to have, and that sort of thing. You know, not anything gets SSRIs, as I said earlier, life saving, you know, for a subsection of people, these things really work. But with this, what you see is that people don't talk about any of that stuff. And I think it's likely because you're tapping into that core circuitry and you're reversing it, and you're doing it with a magnet that, because it's a very profound electromagnet, it's the same field strength as an MRI scanner, it's able to induce a current in the brain in this focal targeted way, without getting into the rest of the brain, without getting into the rest of the body at all, and just really kind of acting only on that circuitry that's involved. Incredible. Is the St. Studies still ongoing? And if people are interested in potentially being, um, patients or subjects in the study, can we provide them a portal link? Absolutely, yeah. So we have, now the treatment, some of my students went over to a company called Magnus Medical, and they've been working on this, they've gotten FDA clearance now, and now folks can get it through trials over the next couple of years, because it's gonna take some time for that company to kind of get up and running and get a, you know, get a, get a device and get the whole thing set up nationally, but while that's all going on, there's still about 1,000 patients that need to be recruited across a bunch of different trials all over the country, we'll take people from anywhere in the country, we also have partners in New York and San Diego, and other, and soon to be South Carolina, and other places where we can actually kind of, you know, my lab can help to kind of let people know where to go, where they, you know, based off of where they're at in the US, and get them access to being able to be in a trial, and what we've tried to do is make it so that even if you get the, you know, 50-50 chance you're gonna get the real deal, or you're gonna get the non-real deal, but what we figured out is a way to let everyone have access, if they got the not-real deal version, the kind of sham version of the fake version, for the first part of the trial, there are other trials where they can have access to the real version, so essentially, everybody eventually gets access to having the real version, and so that's been a big thing for me, is I want everybody that comes through one of our trials to be able to have access. I think it's important while, you know, the company's doing what they're doing, and what the lab's doing, and kind of nationally, what, you know, other partner labs are doing. Well, I can assure you're gonna get some interest. I'm happy to have it. Thank you, and listen, thank you so much for taking us on this, incredible voyage through the neurosurcatory underlying certain aspects of depression, the coverage of the different types of depression, the various therapeutic compounds, how they work. We've talked about a lot of things, and you've shared so much knowledge, and even as I say that, I very much wanna have you back to talk about many other things as well that we didn't have time to cover, but I also just really wanna thank you for the work that you do. I know we are colleagues, but you run an enormous lab, you run an enormous laboratory. It's enormous in my, but 40 people is a big group, very big group, plus you're in the clinic, you also have a life of your own outside of work, and to take the time to sit down with us and share all this knowledge that really is in service to mental health and human feeling better, and in fact, avoiding often suicidal depression. It's just incredible work and incredible generosity, and just thank you so much. Well, thank you, man. I mean, I, you know, similarly, I wanna thank you for what you're doing. I mean, I think that what you know, I've got a lot of friends, folks that are not in the medical profession, friends of mine, you know, one of my buddies who's a real estate agent who works with us, who's a big fan of your show, and you know, I told a couple of people like that, I was coming on, and they were like super stoked. They're like, you know, we watch every show, and you know, super excited to watch mine, and they said something very important to me that, you know, you make this complicated neuroscience and kind of brain body science accessible, you know, and a way that you have a gift to do, and I think that that's so important, and this show is doing so much to help with science literacy, and yeah, appreciate you. So. Well, thank you. I'm gratified and honored by your statement, and I look forward to more. Thank you. Absolutely, thank you. Thank you for joining me today for my discussion with Dr. Nolan Williams. I hope you found our discussion about psychedelics and other compounds about transcranial magnetic stimulation and about the treatments for depression in general to be as stimulating as I did. If you'd like to learn more about the work being done in Dr. Williams' laboratory, you can go to the Brain Stimulation Laboratory website, which is BSL.Stanford.edu, and there you have the opportunity to apply to be in one of the clinical trials for depression or other studies, as well, if you like, to support the work being done in Dr. Williams' laboratory for the treatment of depression and other psychiatric disorders. If you're learning from and are enjoying the Hubertman Lab podcast, please subscribe to our YouTube channel. That's a terrific zero-cost way to support us. In addition, please subscribe to the Hubertman Lab podcast on Spotify and Apple, and on both Spotify and Apple, you also have the opportunity to leave us up to a five-star review. If you have questions for us or comments about the information we've covered or suggestions about future guests, please put those in the comment section on YouTube. We do read all the comments. Please also check out the sponsors mentioned at the beginning of today's episode that's the best way to support the Hubertman Lab podcast. Not so much today, but in many previous episodes of the Hubertman Lab podcast, we talk about supplements. While supplements aren't necessary for everybody, many people derive tremendous benefit from them for things like enhancing sleep and focus and hormone optimization. The Hubertman Lab podcast has partnered with momentous supplements. If you'd like to see the supplements of the Hubertman Lab podcast that's partnered with momentous on, you can go to live momentous spelled o-u-s. So live momentous.com slash Hubertman. And there you'll see a number of the supplements that we talk about regularly on the podcast. I should just mention that that catalog of supplements is constantly being updated. As mentioned at the beginning of today's episode, the Hubertman Lab podcast has now launched a premium channel. That premium channel will feature monthly AMAs or ask me anything where I answer your questions in depth, as well as other premium resources. If you'd like to subscribe to the premium channel, you can simply go to HubertmanLab.com slash premium. As you mentioned, that the proceeds from the premium channel go to support the standard Hubertman Lab podcast, which will continue to be released every Monday per usual, as well as supporting various research projects done on humans to create the sorts of tools for mental health, physical health, and performance that you hear about on the Hubertman Lab podcast. Again, it's HubertmanLab.com slash premium to subscribe. It's $10 a month or $100 per year. If you haven't already subscribed to our zero cost newsletter, we have what is called the neural network newsletter. You can subscribe by going to HubertmanLab.com, go to the menu, and click on newsletter. Those newsletters include summaries of podcast episodes, lists of tools from the Hubertman Lab podcast, and if you'd like to see previous newsletters we've released, you can also just go to HubertmanLab.com, click on newsletter in the menu, and you'll see various downloadable PDFs. If you want to sign up for the newsletter, we just ask for your email, we do not share your email with anybody, and again, it's completely zero cost. If you're not already following me on social media, it's HubertmanLab on Twitter, on Facebook, and on Instagram. And at all three of those places, I cover topics and subject matter that are sometimes overlapping with the information covered on the Hubertman Lab podcast, but that's often distinct from information on the Hubertman Lab podcast. Again, it's HubertmanLab on all social media channels. And last but certainly not least, thank you for your interest in science. And thank you for your interest in science.