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 I have the pleasure of introducing the first guest of the Huberman Lab Podcast. My guest is Dr. Carl Diceroth. Dr. Carl Diceroth is a medical doctor, he's a psychiatrist, and a research scientist at Stanford School of Medicine. In his clinical practice, he sees patients dealing with a range of nervous system disorders, including obsessive compulsive disorder, autism, attention deficit disorders, schizophrenia, mania, anxiety disorders, and eating disorders. His laboratory develops and explores tools with which to understand how the nervous system works in the healthy situation, as well as in disorders of the mind. Dr. Diceroth's laboratory has pioneered the development and use of what are called channel options, proteins that come from algae, which can now be introduced to the nervous systems of animals and humans in order to precisely control the activity of neurons in the brain and body with the use of light. This is a absolutely transformative technology, because whereas certain drug treatments can often relieve certain symptoms of disorders, they often carry various side effects. And in some individuals, often many individuals, these drug treatments simply do not work. The channel options and their related technologies stand to transform the way that we treat psychiatric illness and various disorders of movement and perception. In fact, just recently, the channel options were applied in a human patient to allow an adult, fully blind human being to see light for the very first time. We also discuss Dr. Diceroth's newly released book, which is entitled, Projections, a Story of Human Emotions. This is an absolutely remarkable book that uses stories about his interactions with his patients to teach you how the brain works in the healthy and disease state, and also reveals the motivation for and discovery of these channel options and other technologies by Carl's laboratory that are being used now to treat various disorders of the nervous system, and that it is a very important tool for the brain to treat the brain. And so it is a very important tool for the brain to treat other people, and that it is a very important tool for the brain to treat their patients and other technologies by Carl's laboratory that are being used now to treat various disorders of the nervous system, and that in the future are certain to transform the fields of psychiatry, mental health, and health in general. I found our conversation to be an absolutely fascinating one about how the brain functions in the healthy state and why and how it breaks down in disorders of the mind. We also discuss the current status and future of psychedelic treatments for psychiatric illness, as well as for understanding how the brain works more generally. We also discuss issues of consciousness, and we even delve into how somebody like Carl who is managing a full-time clinical practice and a 40-plus person laboratory and a family of five children and is happily married, how he organizes his internal landscape, his own thinking in order to manage that immense workload and to progress forward for the sake of medicine and his pursuits in science. I found this to be an incredible conversation I learned so much. I also learned through the course of reading Carl's book, Projections, that not only is he an accomplished psychiatrist and obviously an accomplished research scientist and a family man, but he's also a phenomenal writer. Projections is absolutely masterfully written. It's just beautiful, and it's accessible to anybody, even if you don't have a science background. So I hope that you'll enjoy my conversation with Carl Dyseroth as much as I did, and thank you for tuning in. Before we begin, I want to point out that this podcast is separate from my teaching and research roles at Stanford. In my desire and effort to bring zero cost to consumer information about science and science-related tools to the general public. And now, my conversation with Dr. Carl Diceroff. Well, thanks for being here. Thanks for having me. It's been a long time coming for me because you may not know this, but one of the reasons I started this podcast was actually so I could have this conversation. It's, it's but one. There are other reasons, but one of the goals is to be able to hold conversations with colleagues of mine that are doing incredible work in the realm of science. And then here we also have this really special opportunity because you're also a clinician. You see patients in a half for a long time. So for people that might not be so familiar with the fields of neuroscience, et cetera, what is the difference between neurology and psychiatry? Well, you know, I'm married to a neurologist and I am a psychiatrist and we make fun of each other all the time. So this is a lot of neuroscientists and a lot of brain clinicians actually think these two should be the same field at some point in the future. They were in the past. They started together. Psychiatry though focuses on disorders where we can't see something that's physically wrong where we don't have a measurable where there's no blood test that makes the diagnosis. There's no brain scan that tells us this is schizophrenia. This is depression for an individual patient. And so psychiatry is much more mysterious and the only tools we have are words. Neurologists are fantastic physicians. They see the stroke on brain scans. They see the seizure and the pre seizure activity with an EEG. And they can measure and treat based on those measurables in psychiatry. We have a harder job, I think. We use words. We have rating scales for symptoms. We can measure depression and autism with rating scales. But those are words still. And ultimately that's what psychiatry is built around. It's an odd situation because we've got the most complex, beautiful, mysterious, incredibly engineered object in the universe. And yet all we have are words to find our way in. So do you find that if a patient is very verbal or hyperverbal, that you have an easier time diagnosing them as opposed to somebody who's more quiet and reserved or I could imagine the opposite might be true as well. Well, because we only have words, you put your finger on a key point. If they don't speak that much in principle, it's harder. The lack of speech can be a symptom. We can see that in depression. We can see that in the negative symptoms of schizophrenia. We can see that in autism sometimes by itself. That is a symptom of reduced speech. But ultimately you do need something. You need some words to help guide you. And that in fact, there's challenges that I can tell you about where patients with depression who are so depressed, they can't speak. That makes it a bit of a challenge to distinguish depression from some of the other reasons they might not be speaking. And this is sort of the art and the science of psychiatry. Do you find that there are patients that have, let's call them comorbidities or conditions where they would land in both psychiatry and neurology, meaning there's damage to a particular area of the brain and therefore they're depressed. And how do you tease that out as a psychiatrist? This happens all the time. Parkinson's disease is a great example. It can be debilitating in so many ways. People have trouble moving, they have trouble walking, trouble swallowing. And they can have a truly severe depression. And this is, you might say, oh well, they've got a life threatening illness. But there are plenty of neurological disorders where depression is not a strong. A strongly comorbid symptom like ALS, Lou Gehrig's disease, for example, and depression is not a strong, strongly comorbid in that disease. But in Parkinson's it is extremely common. And as you know, in Parkinson's disease, we have loss of the dopamine neurons in the midbrain. And this is a very specific population of cells that's dying. And probably that leads to both the movement disorder. And the depression. There are many examples of that where these two fields come together. And you really need to work as a team. I've had patients in my clinic that I treat the depression associated with their Parkinson's and a neurologist treats the movement associated with the Parkinson's and we work together. Do you think will you will ever have a blood test for depression or schizophrenia or autism? And would that be a good or a bad thing? I think ultimately there will be quantitative tests already efforts are being made to look at certain rhythms in the brain using external EEGs to look at brain waves effectively, look at the ratios of certain frequencies to other frequencies. And there's some progress being made on that front. It's not as good as it could be. It doesn't really give you the confidence for the individual patient that you would you would like. But ultimately what's going on in the brain in psychiatric disease is physical and it's due to the circuits and the connections and the projections in the brain that are not working as they would in a typical situation. And I do think we'll have those measurements at some point now is that good or bad. I think that will be good. One of the challenges we have with psychiatry is it is an art as well as a science to elicit these symptoms in a precise way. It does take some time. And it would be great if we could just do a quick measurement. Could it be abused or misused? Certainly, but that's I think true for all of medicine. I want to know and I'm sure there are several, but what do you see as the biggest challenge facing psychiatry and the treatment of mental illness today? I think we have we're making progress on what the biggest challenge is, which I think there's still such a strong stigma for psychiatric disease that patients often don't come to us. And they feel that they should be able to handle this on their own. And that can slow treatment. It can lead to worsening symptoms. We know for example, patients who have untreated anxiety issues. If you go for a year or more with a serious untreated anxiety issue that can convert to depression, you can add another problem on top of the anxiety. And so it would be, you know, why do people not come for treatment? They feel like this is something they should be able to master on their own, which can be true. But usually some help is a good thing. That raises a question related to something I heard you say many years ago at a lecture, which was that this was a scientific lecture and you said, you know, we don't know how other people feel. Most of the time, we don't even really know how we feel. You could elaborate on that a little bit. And the the dearth of ways that we have to talk about feelings. I mean, there's so many words. I don't know how many, but I'm guessing there are more than a dozen words to describe the state that I call sadness. But as far as I understand, we don't have any way of comparing that in a real objective sense. So how, as a psychiatrist, when your job is to use words to diagnose words of the patient to diagnose, do you maneuver around that? And what is this landscape that we call feelings or emotions? This is really interesting. People here, we have a there's attention between the words that we've built up in the clinic that mean something to the physicians. And then there's the colloquial use of words that may not be the same. And so that's the first level we have to sort out when someone says, you know, I'm depressed. What exactly do they mean by that? That may be different from from what we're talking about in terms of depression. So part of psychiatry is to get beyond that word and to get into how they're actually feeling, get rid of the jargon and get to real world examples of how they're feeling. So, you know, how do you, what, how much do you look forward into the future? How much hope do you have? How much planning are you doing for the future? So these here, now you're getting into actual things you can talk about that are unambiguous. If someone says, yeah, I can't even, I can't even think about tomorrow. I don't see how I'm going to get to tomorrow. That, that's a nice precise thing that, you know, it's sad. It's tragic. But, but it's also that means something and we know what that means. That's the hopelessness symptom of depression. And, and that is what I try to do when I do a psychiatric interview. I try to get past the jargon and get to what's actually happening in a patient's life and in their mind. But as you say, ultimately, you know, this shows up across, I, I address this issue every day in my life, whether it's in the lab where we're looking at animals, whether fish or mice or rats and studying their behavior or when I'm in a conversation with just a friend or a colleague or when I'm talking to a patient, I never really know what's going on inside the mind of the other person. I get, I get some feedback, I get words, I get behaviors, I get actions, but I never really know. And as you said at the very beginning of the question, you know, often we don't even have the words and the insight to even understand what's going on in our own mind. I think a lot of psychiatrists are pretty introspective. That's part of the reason they end up in that specialty. And so maybe we spend a little more time in the average person thinking about what's going on within, but it doesn't mean we have answers. So in this area of trying to figure out what's going on under the hood through words, sounds like certain words would relate to this, this idea of anticipation and hope. Is it fair to say that that somehow relates to the dopamine system in the sense that dopamine is involved in motivated behaviors? If I say, for instance, and I won't ask you to run a session with me here for free, we'll do that off camera. Okay, right. If I were to say, you know, I just can't imagine the tomorrow, I just can't do it. So that's, that's not action based. That's purely based on my internal narrative. But I could imagine things like, you know, I have a terrible time sleeping. I'm not hungry. I'm not eating. So statements about physical actions I'm guessing also have validity. Absolutely. And there are now ways to measure the accuracy of those statements. Like, for instance, if I gave you permission, you could know if I slept last night or whether or not I was just saying I had a poor night sleep. Yes. That's right. So in moving forward through 2021 and into the next 10 and 100 years of psychiatry, do you think that the body reporting some of the actions of a human are going to become useful and and mesh with the words in a way that's going to make your job easier? I do think that's true. And these the two things you've mentioned eating and sleeping, those are additional criteria that we use to diagnose depression. These are the vegetative signs we call the depression, poor sleep and poor eating. And if you have a baseline for somebody, that's the real challenge. So what's different in that person? Some people would depressed, they sleep more. Some people would, who are depressed, they sleep less. Some people who are depressed, they're more physically agitated and they move around more. Some people who are depressed, they move less even while they're awake. And so you need that here's the challenge is you can't just look at how they are now. You have to get a baseline and then see how it's changed. And that can be a challenge that raises ethical issues. How do you collect that baseline information from someone healthy? I don't think that's something we have solved. Of course, you know, with phones and accelerometers and phones, you could in principle collect a lot of baseline information from people. But that would have to be treated very carefully for privacy reasons. And in terms of measuring one's own behavior, you know, I've heard of work that's going on Sam Golden up in the University of Washington, who works on aggression and animal models was telling me that there's some efforts that he's making and perhaps you're involved in this work as well. I don't know of devices that would allow people to detect, for instance, when they're veering towards a depressive episode for themselves, that they may choose or not choose to report that to their clinician. Maybe they don't even have a clinician. Maybe this person that you referred to at the beginning, this person who doesn't feel comfortable coming to talk to you, they maybe something is measuring changes in the inflection of their voice or the speed at which they get up from a chair. Do you think that those kind of metrics will eventually inform somebody, hey, you know, you're in trouble. This is getting to this question of back to the statement that I heard you make and rung in my mind now, I think for more than a decade, which is oftentimes we don't even know how we feel. That I do like because that gives the patient the agency to detect what's going on. And even separate from modern technology, this has been part of the art of psychiatry is to help patients realize that sometimes other people observing them can give them the earliest warning signs of depression. We see this very often in family, they'll notice when the patient is changing before the patient does. And then there are things the patient may notice, but not correctly. I scurried to the onset of depression and a classic example of that is what we call early morning awakening. And this is something that can happen very early as people start to slide into depression. They start to wake up earlier and earlier, you know, just inexplicably their wake. This is like 2 a.m. 3 a.m. waking. It could start. Yeah, it could start at 5 a.m. could go to 4 a.m. and unable to fall back asleep. And they will fall back asleep exactly. So that's and that they may not know what to do with that. It could just be from their perspective. It's just something that's happening. But if you put enough of that information together, that that could be a useful warning sign for the patient and it could help them seek treatment. And I think that is something that could be really valuable. Interesting. So in this framework of, you know, needing words to self-report or machines to detect how we feel or maybe inform of a psychiatrist. How a patient feels. Want to touch on some of the technologies that you've been involved in building. But as a way to march into that. Are there any very good treatments for psychiatric disease, meaning are there currently any pills, potions, forms of communication that reliably work every time or work in most patients? And could you give a couple examples of great successes of psychiatry if they exist? Yes. Yeah, we are fortunate in this coming back to my, you know, the joking between my wife and myself in terms of neurology and psychiatry. We actually in psychiatry, despite the depths of our, the mystery we struggle with. Many of our treatments are actually, you know, we're, we may be doing better than some other specialties in terms of actually causing, you know, therapeutic benefit for patients. We do help patients, you know, the patients who suffer from, by the way, both medications and talk therapy have been shown to be extremely effective in many cases. For example, people with panic disorder, cognitive behavioral therapy, just working with words, helping people identify the early signs of when they're starting to move toward a panic attack. What are the cognitions that are happening? You can train people to derail that and you can very politely treat panic disorder that way. How long does something like that take for on average? For a motivated, insightful patient, you can have a very, you know, cookbook-y series of sessions, you know, six to 12 sessions or even less for someone who's very insightful and motivated and can have a very powerful effect that quickly. And that's just with words, there are many psychiatric medications that are very effective for conditions that they're treating anti-psychotic medications. They have side effects, but boy, do they work? They really can clear up, particularly the positive symptoms of schizophrenia, for example, the auditory hallucinations, the paranoia. People's lives can be turned around by these. We should clarify positive symptoms. You mean not positive in the qualitative sense? You mean positive meaning that the appearance of something abnormal? Exactly. Yeah, thank you for that clarification. When we say positive symptoms, we do mean the addition of something that wasn't there before, like a hallucination or a paranoia. And that stands in contrast to the negative symptoms where something is taken away. And these are patients who are withdrawn. They have what we call thought blocking. They can't even progress forward in a sequence of thoughts. Both of those can be part of schizophrenia. The hallucinations and a paranoia are more effectively treated right now, but they are effectively treated. And then, you know, this is a frustrating and yet heartening aspect of psychiatry. There are treatments like electroconvulsive therapy, which is where, you know, it's extremely effective for depression. We have patients who nothing else works for them, where they can't tolerate medications. And you can administer under very safe controlled condition where the patient's body is not moving. They're put into a very safe situation where the body doesn't move or sees. It's just an internal process that's triggered in the brain. This is an extraordinarily effective treatment for treatment resistant depression. At the same time, I find it as heartening as it is to see patients respond to this with who have severe depression. I'm also frustrated by it. Why can't we do something more precise than this for these very severe cases? And people have sought for decades to understand how is it that a seizure is leading to the relief of depression? And we don't know the answer yet. We would love to do that. People are working hard on that. But that is a treatment that does work too. All in all these cases, though, in psychiatry, the frustrating thing is that we don't have the level of understanding that a cardiologist has and thinking about the heart. You know, the heart is, we now know it's a pump. It's pumping blood. And so you can look at everything about how it's working or not working in terms of that frame. It's clearly a pump. We don't really have that level of what is the circuit really there for in psychiatry. And that's what is missing. That's what we need to find so we can design truly effective and specific treatments. So what are the pieces that are going to be required to cure autism, cure Parkinson's, cure schizophrenia? I would imagine there are several elements and bins here. Understanding the natural biology, understanding what the activity patterns are, how to modify those. Maybe you could just tell us what you think. What is the bento box of the perfect cure? I think the first thing we need is understanding. We need almost every psychiatric treatment has been serendipitously identified, just noting by chance that something that was done for some person also had a side effect. Like lithium or psych. Lithium is a good example. Is it true that it was the urine of guinea pigs given lithium that was given to manic patients that made them not manic? Is that true? I don't have a firsthand knowledge of that, but I would defer that. But it's true for essentially every treatment. You know, the antidepressants originally, you know, aroses, antide tuberculosis drugs, for example. And so this is a classic example for. And this is across all of psychiatry. And of course, the seizures as well. That was noticed that patients who had epilepsy, they or had a seizure. They're also had depression that they became much at least for a while. They were improved after the seizure. That's amazing. I don't want to give off course of the question that answering the question I asked, but I've heard before that if autistic children get a fever that their symptoms improve, is that true? I've done a fair bit of work with autism. I'm in my clinical practice. I work with adult autism. And I have heard statements like that and descriptions like that from patients and their families. It's that is very hard to study quantitatively because often with the children, you have this not as quantitative as you'd like collection of symptom information from from from home. But I have heard that enough that I think there may well be something to that. And you know, what is any time you have a fever, what's going on? Well, we know all the cells in the brain, and I know this as an electrophysiologist. If you just change the temperature by a few degrees, everything changes about how neurons work. And that's even just a single neuron. It's even more likely to be complex and different with a circuit of neurons that are all affecting each other. Just elevate the temperature a little bit. Everything's different. So it's plausible for sure that things like that could happen and do happen. Now, but and yet when you think about autism to take your example, yes, we see changes. But what is the element in the brain that's analogous to the pumping heart when we think about the symptoms of depression, that's maybe, you know, we think about motivation and dopamine neurons. When we think about autism, it's a little more challenging. You had there's a deficit in social interaction and in communication. And so where is that? Where is this? Where is that situated? What is the key principle governing the social interaction? This is where we need the basic science to bring us a step forward. So we can say, OK, this is the process that's going on. This is what's needed for the incredibly complex task of social interaction. Where you've got incredibly rich data streams of sound and meaning eye contact body movement. And that's just for one person. What if there's a group of people? This is overwhelming for people with autism. What's the what's the unifying thing there? It's a lot of information. And and that maybe is unmatched in any realm of biology, the amount of information coming in through social interaction, particularly with words and language. And so then that turns our attention as neuroscientists, we think, OK, let's think about the parts of the brain that are involved in dealing with merging complex data streams that are very high in bit rate that need to be fused together into a unitary concept. And that starts to guide us and maybe we can and we know what other animals are social in their own way and we can study those animals. And so that there's that's how I think about it. There's hope for the future thinking about the symptoms as an engineer might. And trying to identify the circuits that are likely working to make this typical behavior happen and that will help us understand how it becomes a typical. So that seems like the first to me, the first bin of this, what I call the bento box for lack of a better analogy that we need to know the circuits. We need to know the cells in the various brain regions and portions of the body and how they connect to one another. And what the patterns of activity are under a normal quote unquote healthy interaction. If we understand that, then it seems that the next step, which of course could be carried out in parallel, right, that that work can be done alongside work where various elements within those circuits are tweaked just right, like the tuning of a piano in the subtle way or maybe even like the replacement of a whole set of keys if the piano is lacking keys. So you've been very involved in trying to generate those tools. So tell us about channel options. Why you created them and where they're at now in the laboratory and perhaps also in the clinic. Well, this is a first of all, I give nature the credit for creating channel revapsons. These are beautiful little proteins that are made by algae single cell green algae. And it's a great story in basic science that our understanding of animal behavior, sensation, cognition and action in our brains all the way back to a botanist in the 1850s and 1860s in Russia is where the story begins. So this was a botanist named Andre Fomensen who worked at St. Petersburg and he had noticed in the river near his laboratory that there were algae that he could look at in a dish in a saucer. He could put them there and we had light shining from the side. The green tinge in the saucer of water would move to a particular distance from the light that he was shining from the side, which was an amazing thing. If he made the light brighter, the green tinge would back off a little bit to a more optimal location. So just the right light level. So this was plant behavior. It was light driven plant behavior and he delved into this a little bit. He identified that he would might my cross could be he could see that there were little single cell algae with flagella that were swimming to the right light level. So behaving plants and this has been a secret that's that's helped us unlock so many principles of animal behavior. So turns out you know these algae achieve this amazing result with a single gene that encodes a single protein. What's a protein? It's just a little biomotryl that does a job in a cell. And these are proteins that sit in the surface of cells in their surface membrane. And when a photon a light particle hits them, they open a little poor a little hole in the membrane and charge particles ions like sodium rush across the poor. Now why do they do that? They do that to guide their flagella that signal coming in those ions coming in through the poor in response to light guide their flagella motor that guides them to a particular spot in the saucer. Now that's plant behavior, but it turns out as you know this movement of ions across the membrane this happens to also be neural code in our brains for on or off. So do my own rushing into cells turns them on makes them fire away fire action potentials communicate to the next cell down the chain. And this is an amazing opportunity because we can borrow these proteins. In fact we can take the gene that directs the creation of the protein and we can use genetic tricks modern genetic tricks to put that gene into neurons in the brains of mammals. And then use light to turn those cells the specific cells that we put this gene into turn them on their other options we call them that you can use to turn cells off. It's all fast real time you can play in patterns of activity and real time into cells or kinds of cells just as a conductor it lists it's the music from the orchestra the strings and the woodwinds and. And you can see what matters what matters for sensation what matters for cognition what matters for action and we call this optogenetics beautiful and I must say it's quite an honor to privilege to watch optogenetics move from idea to discovery to the laboratory. And I think we were postdocs at the same time which is living proof that people move at different rates because that's a joke at my expense by the way. But it's we are in the same spot. And we're less physically if not professionally but nonetheless it's been a marvelous story thus far and I'd like to maybe you could give us I'd like to just touch on couple examples of where the technology resides in laboratories now so maybe the range of animals that it's being used in and some of the phenomenon net channel up chill word options and and they're related genes and proteins are starting to elicit what you've seen. And then I'd like to talk about their applicability to the clinic which is I think the bigger mission if you will. So this is you know this this whole thing you know it's been about now going on 17 years that we've been putting channel word options into neurons it started just like Andre Feminzen's work in a dish by 2000 that was in 2004 and 2007 we were putting these into behaving mice and we were able to. To with the give a switch cause them to move one direction or another by 2009 so basically you're controlling the mouse is behavior yeah exactly in real time so we could make a mouse that was just sitting there doing nothing to then turn left very consistently in fact go around in a circle and as soon as we turn off the light it would stop that was an eye opening moment. It took really a few years to make optogenetics work there was a lot of putting all the there are a lot of problems that had to be solved these these channel word options actually don't move many ions that they have a small current small conductance as we say and so we had to figure out ways to pack a lot of them into cells without damaging cells. And still make them targetable so we don't want to just be in all the cells because then it becomes just like an electrode you're just in lighting all the cells there nearby we had to keep that specificity make them. Targetable to just one kind of cell or another while still packing in large numbers of them into those cells and we had to get in the light and safe in specific ways and so it took probably about four or five years to really create optogenetics between 2004 and 2009. By the end of that time though we had all the basic light delivery gene delivery principles worked out and people started to apply the technology to fish to rats to mice to non human primates like monkeys and just a couple months ago my colleague boat on Rosca in Switzerland succeeded in putting a channel of options into the eyes of human beings and making a blind person to see and so that's pretty cool. This was a patient patient with retinal degeneration and he provided a channel of the eye of this patient was able to confer some light sensitivity on to this patient that wasn't there before. An amazing paper and discovery I realize it was one patient but it's such an important milestone and well it's a it's a very important milestone and and the history of that is is very deep almost 10 years earlier. Botan Roscan I had published a paper in science in human retina but ex planted taken from cadavers from someone who had died living retina taken out. Options put into this retinal tissue and showing that it that it worked recording from the cells showing that in these human neurons retinal neurons that you could get light responses. But then from that moment you know almost 10 years of you know how clinical development goes and this is a gene therapy so you've got all the regulations and concerns and all that it took almost 10 years to get to to this point now where a living human being has a new functionality that wasn't there before. Now that's incredibly inspiring you know and it's a it's a beautiful thing I would say though that the broader significance of optogenics is really still understanding because once you understand how the circuitry works and which cells actually matter then any kind of treatment becomes more grounded and logical and specific and principled. And whether it's a medication or talk therapy or brain stimulation treatment with electrical or magnetic means if you actually know what matters that is incredibly powerful and I think no no you know not intended to disparage this beautiful you know retinal work and and conferring you know vision on someone who couldn't see of course that's wonderful. But and that's direct what you might call direct optogenetics and patients indirect is everything that comes from understanding you know okay we know these cells matter now for the symptom well how can we target those those cells and help them work better in patients by any means and I think that's the broader significance of optogenetics clinically. You and I know both on well and you both on share this incredible big vision that I think only a clinician can really understand you know being in close contact with and the suffering of patients as a ultimate motivator of developing technologies which makes me have to ask did you decide to become a scientist to cure fine cures for mental disease. No I didn't it's a it's a really important questions actually look back and see the steps that brought you to a particular place and that was not what brought me initially to science and and it's okay to I think to embrace the twists and turns that life brings to you but I was always interested in the brain and so that was something that for me started from a very early age I was you know we talked about being introspective I'm not going to be a doctor. I was being introspective I noticed very early on I had a deep love of of poetry and stories and I was a voracious reader and I was amazed by how words could could make me feel in particular ways just the even even separate from their you know of course dictionary meanings that the rhythm and how they work together even separate from meaning stunned by poets that could use words and new ways that were even divorced from their meaning at all and yet could still trigger specific emotions and I was that this was always fascinating to me. So you know I I wanted to understand that and so I was interested in and I became interested in the brain and I thought well I'm going to have to study the human brain because only human beings can describe what's going on inside and off. So in college I began to steer myself toward medicine and with the idea of becoming a neurosurgeon and so I came here to medical school and did an MD PhD program planning neurosurgery all the way through the first rotation I did at the end of medical school as you know you do rotations you go through different specialties and some of these are required rotations everybody has to do some are elected where you can you can pick what you want to do. I elected to do neurosurgery first even before regular surgery I was that sure I wanted to do it and I loved it had a fantastic time there was an amazing patient you had a lot of athletic damage and there was neglect syndrome where the patient was not able to be aware of something that was right in front of him even though their vision was perfectly fine exactly. And so I was and I loved the operating room I loved the rhythm of suturing and precision of it and I love being able to help patients immediately. And so I was required rotation was in psychiatry which I was not looking forward to at all and that completely reset my whole life that that experience in psychiatry and it was that that that moment that I saw this is first of all the greatest need the depth of suffering and the depth of the mystery together and it was I also feel a little guilty about this it's so interesting to you know yes yes there's yes we can help yes there's need but as a scientist this is amazing that someone's reality can be different from my own you know with everything physically as far as we can tell the same with the measures we have. And yet we've got a different reality that is an amazing thing and if we couldn't understand that and help these people that would be just more than anybody could ask for and so that's that's how I ended up taking this path just. A required rotation psychiatry it all started with poetry and started with poetry at it out of respect for poetry are there any favorites that you spend time with on a regular basis. I mean the ones who who got me down this path early on I remember in childhood in high school. Borges had an immense influence on me I studied Spanish all the way through and reading his work he was a great writer he wrote both in English and in Spanish and being able to appreciate his poetry both in English and in Spanish was a pretty amazing thing not many poets can do that. I'm not I wouldn't say now I became at one point I was effectively fluent in Spanish and I have I'm pretty good with medical Spanish still because you know we use Spanish all the time and in the clinic here. I wouldn't claim full fluency but it's something I can I definitely use all the time and it's been very helpful in the clinic. Yeah, Borges is wonderful is the son of an Argentine I grew up hearing about it and I learned that Borges favorite city was Geneva so I spent time in Geneva only for that reason. It's also turns out to be an interesting city. So you developed methods to control neurons with these algae proteins using light. In 2015 there was this what I thought was a very nice article published in the New Yorker describing your work and the current state of your work in in the laboratory in the clinic and an interaction with a patient. So as I recall woman who was severely depressed and you reported in that article some of the discussion with this patient and then in real time increase the activation of the so called Vegas nerve this 10th cranial nerve that extends out of skull and it's many of the viscera and body. What is the potential for channel red options or related types of algae engineering to be used to manipulate the Vegas because I believe in that instance it wasn't channel options to be like show electrical stimulation right or to manipulate for instance a very small localized region of the brain let me frame a little bit differently. And light of what we're talking about a couple minutes ago my understanding is that if somebody has severe depression and they take any number of the available pharmaceutical agents that are out there SS rise or a ton of chicken agents increased dopamine increase whatever that sometimes they experience relief but they're often serious side effects sometimes they don't experience relief but as I understand it channel options and their related technology in principle. Would allow you to turn on or off the specific regions of the brain that lead to the depressive symptoms or maybe you turn up a happiness circuit or an or a positive anticipation circuit where we at now in terms of bringing this technology to the nervous system and let's start with body and then move into the skull. So starting with the bodies a good example because it it highlights the opportunity and how far we have to go so let's take this example of Vegas nerve stimulation so the Vegas nerve it's the 10th cranial nerve it comes from the brain it goes down it innervates the heart it's the gut by innervade I means it sends little connections down to help guide what happens in these these organs in the in the abdomen and chest. It also collects information back and and there's information coming back from all those organs that go also go through this Vegas nerve the 10th cranial nerve back to the brain and so this is somewhat of a of a super highway to the brain then it was the idea and maybe the idea is maybe we could put a little cuff a little electrical device around the Vegas nerve itself and maybe have just like a pacemaker battery have a little power source here under the clavicle everything under the skin. And have a little cuff and drive signals and maybe they'll get back to the brain so a way of getting into the brain without. Putting something physical into the brain and why the Vegas I mean it's there but and it's accessible that's the reason that's the reason yes really you're not kidding I'm not kidding so stimulating the Vegas to treat depression simply because it's accessible it started as actually as an epilepsy treatment and it can help with epilepsy but yes it's a lot of medicine as a scientist I got this is where I get to chuckle and you say I mean the field of medicine it from that perspective from from the perspective of a scientist and outsider the field of medicine as a field that goes in and tickles pathways because they're there it's I don't know what to say it's a little shocking yeah and we all at least in my laboratory I always say you never do an experiment because you can you you do an experiment to test a specific hypothesis yeah yeah I mean we there are stories people tell so the the the Vegas nerve lands on a particular spot on the brain called the solitary track nucleus which is just one snaps away from the serotonin and dopamine in the north from the link to chemical systems of the brain that make it a rational choice it's not it's not irrational but I can tell you that even if that we're not true the same thing would have been tried you know you got you would have done it because it's accessible yeah see okay and and but and and why well it's it's not again not to disparage what what's been happening in this branch of medicine there's immense suffering treatments many treatments don't work and and we try things and and this is how so many advances in medicine happen you think about kidney dialysis which is kept many people live that that was just started by someone saying hey let's let's try this maybe there's something building up in the blood maybe we can dialize something and help them yeah it worked and and it was just sort of a test pilot mentality we can we can access the blood let's run it across the dialysis membrane put it back in the body oh my god that actually works and sometimes you do need that test pilot mentality of course to do it in a in a rigorous safe control way which is what we do and so anyway that's how we we ended up with but still with the Vegas nurse stimulation okay so what does it does it work it has its FDA approved for depression this Vegas nurse stimulation but on the population level if you average across all people the effect sizes are pretty small some patients it has an amazing effect and how but some patients it doesn't work at all and average across everybody the effect size is pretty small how do you think it's working when it does work is it triggering the activation of neurons that release more serotonin or dopamine it could be but I would say we don't have evidence for for that and so I I just don't know but what is clear is that it's dose limited in how high and strongly we can stimulate and why it's because it's an electrode and it's stimulating everything nearby and when you turn on the Vegas nurse stimulator the voice patients voice becomes strangulated and horse they can have trouble swallowing they can trouble speaking for sure even some trouble breathing because everything in the neck every electrically responsive cell and projection in the neck is being affected by this and so you can go up just so far with the intensity and then you have to stop so you know to your initial question could a more precise stimulation method like optogenetics help in the setting in principle it could because that would if you would target the light sensitivity to just the right kind of cell let's say cell acts that goes from point A to point B that you know causes symptom relief of a particular kind then you can have that be the only cell that's light sensitive you're not going to affect any of the other cells the larynx and the fairings and the projections passing through so that's the hope that's the opportunity the problem is that we don't yet have that level of specific knowledge we don't know okay it's the cell starting point A going to point B that release this particular sense we want to fix this key on the piano and then I see two other steps they're required one is to get the channel ops engine into the cell in the case of but on roska and colleagues rescuing vision in this patient they did that by an injection of a virus that doesn't damage the neurons the virus itself is fairly innocuous but carries a cargo and it's a one time injection the cells express and then they used light to stimulate so let's say I'm depressed which I don't think I am although now sitting in front of a psychiatrist you probably can see signs that maybe I am or maybe I'm not but let's say we put channel ops and into my specific branch of the Vegas that we understand is responsible for mood how are we going to get it in there and then how are we going to deliver the light because we're not talking about sunlight or standing in front of a light bulb necessarily but what are what are the mechanisms for the body yeah so we had to solve exactly these questions you're saying how do you get the light and how do you get the gene in in a potent and robust and safe way and it's that's no solved and that's not a challenge so there are very safe well-tolerated gene delivery mechanisms that are called adno associated viruses a a these and these are things that are associated with the common cold they themselves don't cause any symptoms they've been engineered and there's been a broad community of viral engineering that's been going on for decades making these safer well-tolerated and so on we can put the channel redops and gene into these viral vectors that deliver the gene and we can have little bits of additional DNA that govern expression only in one kind of cell but not another these are called promoters and enhancers all genetic tricks built up by a very broad community of great scientists over the decades we can put these different bits of DNA package them into this AAV this little virus and that can be then injected into a particular part of the body and sticking with this vagus nerve example we know that there are particular clumps of neurons there's one called the no dos ganglion that has a clump of cells related to the vagus nerve and you could for example target a little injection into that ganglion would that be an outpatient procedure yeah yeah so you come in in the morning get your injection maybe walk out a few hours later yeah that's right and so that's the gene then the light delivery this is also something that that we worked out we worked on making very very light sensitive options one challenge and and Botan would be the first to state this in fact and solving this problem for the patient he had to build goggles that created much brighter light than normal ambient light delivery because as I mentioned earlier you have to pack a lot of these channel redops and they don't have much current you have to really make sure that you've got it tense enough light to activate enough of them to cause a stimulation and it has to be the right wavelength going back to your example of the algae moving toward or away the light it has to be tuned just right so could you are could I'm imagining in my mind as a non-engineer I know you're also a bioengineer the I'm imagining a little tiny blue light emitting thing object that's a little bigger than a clump of cells or maybe about the size of a clump of cells and for those who don't know you know your credit card is about 200 microns thick on the side and micron is a thousandths of a millimeter and so we're talking about a little tiny stamp that's basically half a millimeter in size all around each edge half a millimeter in size I could imagine that being put under my skin and then I would what I'd hit an apple my phone and I'd say I'd say doctor Diceroth I'm not feeling great today can I increase the stimulation and you say go for it and then I ramp it up is that how it would go I mean that's effectively what we already do with the vagus nerve stimulation the the doctor in this case and I I have this in some of my patients in the clinic I do vagus nerve stimulation I talk to them I say how I go through the symptoms I use the psychiatric interview to elicit their internal states and then I have a radio frequency controller that I can dial in right there in real time right there and you're holding the remote control to essentially to their brain although it's remote remote control through a couple steps yeah yeah yeah and I can I can turn up I can turn up the frequency I can turn up the intensity all with the radio frequency and control and then it's it's reprogrammed or a redost and then the patient can can then leave at this altered dose so this is happening now this is having right now electrically you do this routinely I do it routinely in my clinic electrically and you're getting the verbal content which as you described earlier is the indication of how well something is working in real time so this what maybe you could just describe a little bit of the interaction with that particular patient or another patient what's a typical arc of narrative as you go from no stimulation to increased stimulation in most in most patients the actual therapeutic effects the benefits actually take many days to weeks and so what I'm mostly focusing on in the office in real time is making sure I'm in a safe low side effect regime and so first I talk to the patient you know how who who has been on a particular dose of the stimulation for weeks or or longer and I I talked about symptoms how were things over the past month how has your hope how is your energy level sleep you know how what is your mood and and then we talk with the patient we decide oh this is this is not yet where we'd like to be and so then I can turn up the intensity of the stimulation real time in the office I don't in most patients I don't expect an immediate mood change what I do is I increase the dose until a next level up while asking the patient for side effects can you still breathe okay can you still swallow okay and I can hear their voice as well and I can get a sense and you're looking at their face and I'm looking at their face and so I can get a sense is there a am I in a still in a safe side effect regime and I and and and then you know I stop at a particular point that looks safe and then patient goes home comes back a month later and I get the report on how things were over that month I asked if you're looking at their face because in your book you describe the incredible complexity of social interactions and at one point you describe the incredible amount of information that the eyes inform about the brain and and the context of somebody's inner experience whether depressed or happier otherwise I want to make sure that we get back to how to maneuver them and manipulate the nervous system for sake of mental health but what are you looking for so as a vision scientist I think you know pupils dilating as a sign of arousal but that could be a positive arousal positive valence like excitement or it could be terror you're going to get the same dilation of the pupils and I'm always reminding people of these two little goodies are two pieces of brain basically they're just outside the cranial vault so they're not unlike the vagus in that sense but they're more of a report than a control knob although I like to think they could be used as control knobs too so without putting you on the spot again to diagnose me not something I would never ask you to do with the cameras rolling but what are you looking for that the patient might not be aware of? in other words can you see depression in somebody's eyes and if you know a patient or if you don't can you see it in their body posture when they walk in realizing of course that a trained psychiatrist like yourself develops an intuitive sense that's aggregating lots of different features of a patient but what about the eyes what's what's going on there? the eyes are incredibly rich in information and as you as you alluded though it's not as if any one measurable conveys all the information you need it's what we you know what an engineer would say joint statistics it's many things all at once whether they're in synchrony or out of synchrony that actually turns out to matter and you know the eye contact question we all know eye contact is incredibly important you don't feel you've connected with somebody unless you must there's eye contact but eye contact can go awry too it can be you can be too intense or it can be mistimed or if there's someone with autism it can be barely there at all and this is one of the most striking symptoms of autism is the avoidance of eye contact as if it's almost as if it's a harmful quantity and so there's an immense amount of information you can't you get from the eyes but it's it's the pairing of what's going on in the eyes with everything else going on in the body language the what's the verbal content of what's what's coming out all that together is is is is the art of psychiatry and and social interaction but you know sometimes you don't have the eye contact and this is an amazing thing and I do talk about this in the book as well in many cases you know in psychiatry sometimes it's over the phone that you have to make key decisions and as a recall you know vividly being as a resident very often you have to take these phone calls from people who are not in the hospital people you can't see you can't see there I can't see their body anything about them just the sound of their voice and you can ask them questions and you have to make in some cases life or death decisions you know is this person truly suicidal something like that as it comes up all the time and so I developed over the course of training and I think all all psychiatrists do this is you develop a way to whatever data stream you have whether it's the eyes or whether it's just the sound of a voice coming over the phone you learn to home in on that data stream you have and focus on it and identify changes and it's quite amazing I found that you can actually if you know a patient you can detect very precise changes in mood just from the sound of the voice and you can have a realization that all of this patient's depression has improved you know by by about half just by the tone of their voice and same with eyes you can with enough practice you can get enough information from a single data stream to give you some information but when you do have the whole picture that of course is best so so many theories out there about excessive blinking and lying lack of blinking and sociopathy I like to remind people that people have varying degrees of lubrication of the eyes which also influence the frequency of blinking and presumably have nothing to do with whether or not what they're saying is true or not but incredible nonetheless that it's that the eyes are a portal to overall a rousal state I'm fascinated by the effects of light on circadian biology just overall desire to be awake or asleep et cetera so the eyes are on the outside of the cranial vault the Vegas is outside the cranial vault obviously what about the goodies in here Parkinson's we know the at least one of the major sites of degeneration and failure that lead to those symptoms I can name off any number of other things in your book you talk about the beautiful work done with optogenetics of active versus passive coping that there are areas of the brain like the venue that make a when active make animals and presumably people passive and unwilling or uninterested in fighting back against pressures of life whereas another region with the Raffa used to me like that and and they actively cope they they get their grit going and they and they are able to lean into life so how do how does one get to those structures in it in a focused way and what what is the next two to five to 10 years look like yeah well this is the this is the promise on that and it is on that time scale that I think things may start to play out you know that the specificity of optogenetics is really only useful if you have some idea of how to use that specificity and it's in actually it's a frustrating aspect of psychiatry that in many cases the most effective treatments we have have the least specificity and electroconvulsive therapy being a great example where you're causing a brain wide which looks barbaric but as you mentioned is effective I mean it is it it these days it's it's much more clinically you know it doesn't look like one flu it they're last seen in one flu or the cookies now it's a very clinically safe and stable procedure but I what where I I would say yeah it is it is it's got this almost medieval lack of of specificity even if the procedures well control and clinically safe and stable and it has a it's not very specific you're causing a brain wide procedure how how could you be less specific than that and we don't know that the the source of the relief we don't usually it's a dump of neuromodulators like dopamine and serotonin but we don't there certainly is a dump of neuromodulators we don't know that that's the the cause for the relief and likewise with medications this is also an interesting thing some some of the most effective antidepressants some of the most effective antistyconics are the ones that are have the most side effects and many examples of this for example the most effective antistycotic is something called clasopein which has some question has the most side effects terrible terrible size the D4 antagonist has basically every receptor does it really it acts it's interesting it has prominent serotonin prominent muscarinic certainly acts on dopamine receptors but it had causes you know blood blood cell counts how do people feel so if if if I were schizophrenic and I was getting auditory hallucinations et cetera and I took clasopein what could I expect to feel well so you would notice side effects and you would notice resolution of of symptoms both and so the voices would go away if in a good situation or the voices would go away but I would feel not good in my body you would have you might have dizziness you might have a drooling you might have any number of physical sensations that that would be due to these off target effects the medication acting on these other receptors and I'm certainly not suggesting this but what if somebody without schizophrenia took clasopein they had the same side effects presumably yeah and so it would not be something that that would recommend to psychiatrist take the drugs that they prescribe I just finished for the third time all of her sacks is yeah autobiography which is marvelous and and I highly recommend to people he certainly took a lot of drugs he hit not as part of his professional role yeah but what just out of curiosity what is the interest or kind of role of of drugs in the field of psychiatry because for I would imagine for a group of very curious introspective people who are making recommendations about what to take there could actually be some benefit for understanding what the experience of those drugs was like for their patients I think that's that's true and I I will say that probably many or most psychiatrist have you know sample the number of these for exactly the reason that you're trying to understand better and to help treat their patients better and I've I've spoken to people who have you know really been found this very helpful to know OK this this sleep disruption caused by this medication or the libido disruption caused by this other medication wow that is that is a big effect and it really helps with empathy for the patients to understand I'm not I'm not suggesting that physicians or anybody experiment with drugs but I I'm relieved to hear that because I think that when you're talking about act accessing somebody's mind and their basic physiology as you mentioned related to appetite libido and sleep you really you really want is acting as a mechanic of their the person's whole experience they walk out of the office and they have a life experience that extends beyond the script yeah yeah and so and yeah and so that so with at the same time though you can't let that completely guide your clinical decisions because as I mentioned some of these medications that have the most side effects they are also the most effective and clasping is a great example that will work in patients where nothing else works and believe me we don't take the step of of clasping prescription lightly because of all these side effects you have to come in for a weekly blood cell or every few weeks a blood cell check to make sure that the blood counts are not off for example but there are patients where no other medication works for the schizophrenia and clasping works it's more well and and so we do it even though there are the side effects and so then this comes back to your your question what if we had better and better specificity well only if we know exactly what we're doing is the point and so because as we become more refined we better be right about where we're finding to and you imagine a day where it will be a single maybe even outpatient neurosurgery would go in through the scholar the back of the year deliver a small viral injection of one of these identifiers is a little sticker of light emitting diode is that deep in the brain is that how you envision this that certainly could happen what I would I actually prefer as a vision is is still medications because those are you know minimally invasive if we knew what we were doing we could make them more specific have fewer side effects but optogenetics that'll arm us with true cause of understanding and so we'll know and we're already moving rapidly toward this point we'll know okay this symptom the loss of pleasure in life that we call anandonia or the loss of of motivation or or energy to overcome challenges active coping these are largely subserved largely controlled by this circuit or that circuit or the cell that's inhabits this other circuit and we will know that because of the work done with channel ups exactly yeah I agree in ways that we never could have the confidence otherwise and so we'll know that this is the circuit that that underlies the symptom or its resolution and then we'll get to understand these cells very deeply okay these cells that are causal that do matter who are they what are they what's their wiring what are the proteins that they make what are the little things that are on the surface of the cell that could be receptors for specific medications or combinations of receptors that would give us the specificity we need and then armed with that causal and precise rigorous knowledge then you can imagine medication development becoming totally different no longer serendipitous but truly grounded in causality I see so using channel ups since as a way to probe the circuitry and figure out the sites that are disrupted what patterns of activity are required and then by understanding the constituents of those cells like what they express and what they make then developing drugs that could target those cells not necessarily putting light inducing diodes into the brain or right walking around with wire packs attached our skull or something that that's fantastic and you it I realize no one has a crystal ball but what do you think the arc of of that is meaning are we going to see that in a year in two years three years in let me reframe that if how soon will a pill-based treatment for a psychiatric disease be available that targets a specific set of cells that we know are important because of the work done with channel ups since I think that is in some ways it's already happening at the level of individual patients and here it's Stanford yeah yep and and more broadly in terms of new new drugs new multi-center you know clinical trials that'll play out of the next few years and these could be drugs that are already safe and approved for other purposes but we might say okay now we know that this medication based on what we know from causal optogenetics this could be useful for this other purpose this psychiatric symptom and so the path to helping patients is could be relatively swift. That's very exciting. What are your thoughts about brain machine interface and neural link always comes up although I do want to point out at tremendous respect for the folks at neural link including someone who came up through my lab is now there is a neurosurgeon but brain machine interface is something that's been happening for a long time now some of the some of the best work among the best work being done here at Stanford and elsewhere to of course always what you just described compatible with or different in brain machine interface meaning devices little probes are going to stimulate different patterns of activity and ensembles of neurons and what are your general thoughts about brain machine interface as going forward. I mean this is first of all it's an amazing scientific discovery approach as you mentioned we and others here at Stanford are using electrodes collecting information from tens of thousands of neurons in humans I should add. And even yes there's quite even separate from the neural link work as you point out many people have been doing this in humans as well as in non human primates. And this is pretty powerful it's important this will let us understand what's going on in the brain in in psychiatric disease in neurological disease and will give us ideas for treatment. It is of course it's still invasive you still are talking about putting a device into the brain and that has to be treated as a situation that has some risks and a step that has to be taken carefully. I see that as something that will be part of psychiatry in long run already with deep brain stimulation approaches we can help people with psychiatric disorders and that's putting just a single electrode not even a complex you know closed loop system where you're both playing in and getting information back even just a single stimulation electrode in the brain can help people with OCD for example quite powerfully. And that will become much more powerful when we get to a true brain machine interface collecting information back stimulating only when you need to if we could identify a pathological activity pattern particular almost like the the pro drone or the early stage of a seizure maybe their events that happen leading up to on some timescale. Psychiatric symptom we could intervene in a closed loop way detect what's happening what's starting to go wrong feed that back to the brain stimulation electrode have it be you know in that way more efficient and more principled. This is is I think that's great it's it's something that of course will be grounded again and causal understanding will need to know what is that pathological pattern that we're detecting and we need to know that it matters and so again that's where optogenics is helping us helping us know okay this this pattern of activity in these cells in these circuits this does mean that there's a particular kind of symptom that's happening. But armed with that knowledge absolutely even the even the simple closed loop device detect and stimulate is going to be part of psychiatry in the future and then and then of course as you get to more cells more connections the ability that we have to help people become more powerful. One of the questions I get asked a lot is about ADHD and attention deficit of various kinds I have the hunch that one reason I get asked so often is that people are feeling really distracted and and challenged in funneling their attention and their behavior but. And there are a number of reasons for that of course but what is true ADHD and what does it look like what can be done for it and what if any role for Channel options or these downstream technologies that you're developing what are they what are they offer for people that suffer from ADHD or have a family member that suffers from ADHD yeah. This is a pretty interesting branch of of psychiatry there's no question that people have been helped by the treatments there's you active you know debate over you know what fraction of people who have these symptoms can or should be treated this is typically at or all stimulants of some kind for example stimulants that's right so ADHD it's as its name suggests it has symptoms of it can have either a hyperactive state or. Inattentive state and those can be completely separate from each other you could have a patient who effectively is not hyperactive at all but can remain focused on the what's going on around them so their body can be still but their mind is darting around that's right or they can be very hyperactive with their body yeah it happens both probably rarely somebody hyperactive with their body but their mind is still although I have to say and this is a benevolent shout out to botan raska. Botan is an incredibly sharp and focused mind and his hand movements are extremely exact also so I do sometimes wonder whether or not our body movements and our head movements are whether or not their coordinator or not is a is a readout of how directed our attention is I notice I have to think complex abstract thoughts I know I have to be very still so my body has to be almost completely on moving for me to think very abstractly and deeply other people are not going to be able to do that. And deeply other people are different some people when they're running they get their best thoughts I can't even imagine that my brain does not work that way at all I have to be totally emotional. Which is kind of interesting how do you go about that I I sit much like this you know I try to have time in each day where I am I'm literally sitting almost in this in this position but but without distraction and thinking and and so it's kind of a it's almost meditative in some ways except it's not. True meditation but I am thinking while not moving in your structure you're trying to structure your thoughts yeah that's interesting so but everybody as you say is is is very different and so with with ADHD you have the key thing is we want to make sure that this is present across different domains of wife school and home to show that it really is a pervasive pattern and not something specific to the teacher or the home situation or something. And then you can help patients it's interesting that that ADHD is one of those disorders where people are trying to work on quantitative EEG based diagnoses and so there's some progress toward making up a diagnosis with looking at particular externally detectable brain wave rhythm so skull cap some electrodes that don't penetrate the skull and this can be done in an hour to our session has to be done in clinic right in the clinic right you have to have the right recording apparatus. So that's in principle as you increasing confidence comes in exactly which measurements one could even imagine moving toward you know home tests but we're not there yet. Amazing I think one of the reason I get asked about it so much is a lot of people wonder if they have ADHD do you think that some of the lifestyle factors that inhabit us all these days could induce a subclinical or clinical like ADHD meaning if I look at people's phone use including my own and I don't think of it like addiction it looks to me and feels to be more like OCD and I'll come clean here by saying when I was younger when I was a kid I had a grunting tick. I used to hide it actually used to hide in the closet because my dad would make me stop and I used to I couldn't feel any relief of my mind until I do this and actually now if I get very tired if I've been pushing long hours it'll come back I was not treated for it but I will confess that I've had the experience of I always liked sports where I involve a lot of impact football because I went to high school where the football team was terrible maybe that would have avoided more impact but things like skateboarding boxing they bring relief I feel clarity after a head hit which I avoid but I used to say that's the only time I feel truly clear for a lot and then eventually it dissipated by about age 16 7 he had just disappeared. So I have great empathy for those that feel like there's something contained in them that won't allow them to focus on what they want to focus on and these days with the phone and all these email etc I wonder and I empathize a bit when I hear people saying like I think I might have ADHD or ADD do you think it's possible that our behaviors and our interaction with the sensory world which is really what phones and email really are. Could induce ADD or reactivate it. This is a great question I think about a lot and you mentioned this tick-like behavior in yourself it's very common that people who have ticks have this building up of something that can only be relieved by executing the tick which can be a motor movement or a localization or even a thought. People do I think these days do have this if they haven't checked their phone and while they do have a build up build up a build up until they can check it and really it. And there's some similarities you know there is a little reward that comes with the checking. But the key question in all the psychiatry what we do is we don't diagnose something unless it's disrupting what we call social or occupational functioning like you could have. Any number of symptoms but literally every every psychiatric diagnosis requires that it has to be disrupting someone's social or occupational functioning and these days you know checking your phone is pretty adaptive that pretty much helps your social and occupational functioning and so we can't. We can't make and we can't make it a psychiatric diagnosis interesting at least in the world of today yeah opting out of communication now makes it. It's always less adaptive though I would point to you as an example of somebody who is quite good at managing his interactions at least from the outsider perspective I do want to ask you a little bit about you and first of all and I realize this is only a partial list but your clinician you see patients you run a big laboratory how many people are in your laboratory now. That's a huge laboratory from experience I can say that's an enormous laboratory. You have a family of five children and you're happily married to a wonderful colleague of ours as well who does incredible work. How do you organize at a kind of conceptual level the day and the week and I should say what stress mitigation practices if any do you incorporate ever see females from you at three in the morning I sometimes send emails at three in the morning but that's when I wake up maybe I'm depressed but I go back to sleep so maybe just describe the arc of the blocks of the day not hour by hour necessarily the details of what are in those blocks but. How do you conceptualize the day how do you conceptualize the week and how do you feel about how that's lined up with your larger goals of making sure these five young people you know flourish which I hear they are but how do you go about this what for most people would just be an overwhelming set of items well it's of course it's sometimes it's just take it day by day and and so I don't you bring the horizon into the unit of the day I do I do it's the unit is the day that's right and what I I try to have in each day as I mentioned earlier some at least an hour of time where I can think and that can be it can be when kids are napping it can be you know actually because like while driving I can do that too because I'm sitting still but that that's the one thing I try to preserve when I was writing the book I adapted that time to be my my writing time but it wasn't enough it's you know so I had to add in a new block of time which was sort of midnight to 2 a.m. writing time and and so that carving out these even small protected times are very important there's of course you know obligations will will expand the fill the time available and you have to be disciplined in my at least I found I had to be disciplined in in truly protecting those times where where one can think so that means no phone that means no phone no checking of the phone I would you know when I was writing the book I would I would have a focus mode on the the Mac book which kind of rules the border and you just have your your your documents and it's it's very pure and you don't have a temptation of distraction I'm a big believer in because the vision and the eyes play such a prominent role in directing our cognition something you talk about in the book really beautifully and with a lot of depth and rigor using visual tools to harness one's complete mental attention when you do this practice of sitting and just thinking sitting still and thinking you said your eyes are open are you hearing your own verbal voice although in your head so you're actually in conversation with yourself yes and hearing literally I mean not quite whether I don't actually hear a phonation but I I'm hearing words and so it's I'm I discovered this about myself other people I think you know they operate differently but I'm extremely verbal and how I think that's how all my reasoning is done it's with sentences and construction of of you know almost equations with words complete sentences complete or complete ish anyway mostly complete and then and when writing the book everything about the writing I would always every sentence was always played out in my mind listening for rhythm and timing and and and I would obsess over exact placement of words to get the right rhythm of the spoken sentence in my mind could I I don't mean to interrupt your flow but when you do that and having experienced this process a bit although differently do you experience any kind of welling up of anxiety when you're hitting the the friction points and if so do you have tools or ways that you are well that anxiety in real time because what we're really talking about here is your mind but what we're really talking about is this process of of converting the activity of neurons into something physically concrete in the world and these intermediate steps are so mysterious to everybody we hear you you know just write the book just do it whatever that means in fact the statements like that to me are kind of empty meaningless but when you hear your voice and you're trying to find the correct word and you keep hitting the it doesn't sound quite right what is the experience in your body yeah I when it's not right it's definitely it's it's a verse of it doesn't feel good but it's not but I but there's also a hope because I know I can solve it too and and so there's there's this it's almost like you're you're almost there you know you've there's a path that you know is there you don't quite see it but it's there and I keep that in mind and so there's there's there's this propulsive force forward because I know that the solution is there and and that said I you know there were there were single words that would occupy you know I would spend days on you know because I was just not happy until I got it right and there were some things that I never quite got perfect and so I left out of the book entirely because it was so close but not not quite there and so I and I was like no I can't put that in everything you just said is entirely consistent with my experience of you and the way you go about everything I have to ask are your kids writers do they like books and words and poetry I know one of your children is going on to a career in medicine and science yeah they're they're each different which is amazing yet they all I think do have some appreciation or a lot of appreciation for for reading but some are very musical two of the five are extremely musical very very talented with guitar and singing and vocal you know impressions is just astonishing and some of them are great withdrawing and and artistry and and some are very physical and vigorous and and are never happy except when you know leaping about and so it's just amazing how different they are honestly but there is a shared appreciation for for language do you think the that one can train their mind in using these practices I I really like your description of the sitting staying physically still and and learning to grapple with those those challenges that something that especially in laboratory science we aren't really trained to do like many professions were taught to come in and just get into and I found that very relaxing and someone who probably has an underlying tick or something like that it felt great to be in motion one of the hardest things about becoming a university professor and running a lab was that I no longer working with my hands and it felt like I was I it felt like some big important part of my life have been amputated but what sorts of practices do you incorporate there and do you think people can learn to get better at focusing through a dedicated practice of the sort that you describe I think you know that I also you know I remember the rhythms of of physical work in the laboratory very well I my work you know these days as as the laboratory leader my job is return mostly to words now again and so it's kind of coming full circle I was it's a different mode I think you just have to embrace the different stages of life come with different modes but you can definitely train yourself for each mode I was not you know I I I I loved you know the as I mentioned the the rhythm of of sewing and and and suturing and and surgery and I worked really hard on that and became you know good at it and now I never do it but it's what's the next challenge you know there's all the various experimental techniques the sections of the brain you know I can't tell you how many thousands of brain to sections I've done in my life and now I don't do them at all and then you develop the methods so that we don't have to the second brain to mention maybe tell us for a moment about clarity and for that for people who will probably never set foot into a laboratory what an incredible yet another incredible discovery and discovery discovery and development clarity is and why it helps us understand how the brain is structured yeah so this is this is a different technology also developed in in my lab here and it's a part of a broader approach that we call hydrogel tissue chemistry and what this is is it's building a gel like a clear gel like substance from within all the cells of a tissue or even an animal all at once so you're building it effectively building a gel inside all the cells at once now that's a odd thing to do well how do we do it well we do it to transform the tissue into a more tractable accessible object and the reason that works is we having built this gel this new infrastructure inside the tissue we can then use chemical tricks and we can link the molecules we care about like proteins or RNAs which are the things as you know right before they become proteins we can link them physically anchor them to this gel which is a scaffold basically it's an interlocking network of polymers we can link all these interesting molecules in place lock them in where they were initially in the tissue in the cell in all the cells and then we can remove very vigorously everything we don't care about that's blocking our light that's blocking our molecules coming into exchange information with the tissue we can get rid of everything else like the lipids the fats we can effectively use detergents to get them all out and then we can see in all the things that were absorbing our scattering light are gone you can have a brain that's completely transparent and yet all the interesting molecules are still locked into place there at the cellular and subcellular level and so this is hydrogeo tissue chemistry the first form we described was called clarity we use that quite a bit still but there are many variants now that we another set developed on this basic concept of building this gel than the tissue and anchoring molecules into place literally glass clear brains I've done this I think in a brain cleared with this method and looked at somebody through it and although you don't want to get it too close to your I don't touch it to your own eye but and you can see direct all the way through it yeah that's incredible for the raises an important question which is again about the human brain and somebody who essentially started out in neuro anatomy and then got into other things I I always think about the other things that are being done and then bothered by the fact that we actually know very little about the microstructure of the human brain compared to the brains of other organisms and in thinking about understanding the circuitry and the piano so to speak that and how to manipulate it in order to relief suffering structures in these animal brains and how they behave and active coping passive coping ADD et cetera those models how well they translate to the human condition do you think it's fair to say that there are entire regions of the human brain that aren't just bigger but that exist only in the brains of humans especially given that we have this speech although I do wonder sometimes if you know animals reporting to each other there maybe they have little psychiatric sessions with one another you know I I'm always careful to not assume we do things better we certainly understand what we're doing better than we understand what animals are doing and they certainly do things better than than we do that said we do have amazing wonderful brains and many structures that are very highly developed in our brains that are are not nearly so developed in mice and and fish for example now that said when I look at the big picture you know what what is the mammalian brain really doing there are things that you would never have thought we could study in animals and in laboratory mammals like mice that it turns out you can actually and and so I would never draw the line and say here's something you can't study in mice or here's something that has no parallel in mice I would be very careful before making any any statement like that a good example of that as we've been able to study just in the past year come to an understanding of dissociation and both we had a paper that came out in late 2020 both mouse and human work in which we got to the sort of the circuit basis for dissociation what is dissociation a lot of people might not have experienced it but it's actually very common more than 70% of people who've been through trauma experienced dissociation it shows up in borderline personality it shows up in PTSD what it is is a separation of the sense of self from the body and so you can have someone who it's not as if you're numb you're not anesthetized you can still you know that something's happening to the body but you just don't care because you don't describe it to yourself which is very interesting right that is how interesting is that the source of the important narrative yeah almost in your book you touch on this and I I will say is the most precise and meaningful and eloquent description of what might be consciousness this this narrative toward the self or of the self and where it might reside so in dissociative conditions people are are feeling as kind of an absence of a merge between mind and body is that one way to describe it and as I recall this paper involved an exploration of ketamine ketamine was a big part of it yeah that's right and so ketamine is another one of those cases where people can experience dissociation ketamine or PCP we call these the dissociative drugs they cause it just like these these other psychiatric conditions can cause it and so we were but we were able to manifest this in in mice administering these dissociative agents in mice we could make them still able to detect stimulus but not care that it was was happening all the while we were recording in the activity of individual cells in the brain to see what was going on what what was happening along with this dissociation and then use optogenetics to see that it mattered to actually provide that pattern of activity and CO that actually causes the dissociation so we could do all that in mice which which was you know just a who would have thought that you could study something like this in mice and we were able to go back and forth with a human worked because here in our Stanford comprehensive epilepsy center there are a lot of what we call stereo EEG recording patients who come in and in the course of normal clinical care they have electrodes recording in their brain to identify where the seizure is so they can be candidates for removing a little patch of the brain that's causing the seizure this is done for patients who medications are not helping their seizure disorder and there was a patient who had a dissociative state before every seizure so this was a human being who was really dissociating he could tell us literally as it was happening and we could see this pattern the same pattern that was happening in the mice in the same patch of the brain we could see that happening in the human being at exactly the right time in the same patch of the brain that's homologous across these immense evolutionary distances and we knew that it mattered to both in mouse and human because in the human we could cause it to happen and I just want to underscore the power of not just that I want to underscore the power of optogenetics and the ability to not just remove a particular experience or behavior by lesioning or destroying but then to go back and actually activate the same structure or group of structures and see the emergence so it's essentially these days you hear a lot about gain of function research in the context of viral manipulation and the moment of manipulation of gain of function is something that we do in the laboratory and you do in patients to both take away something and put it back which gives you causality that's right yeah and so and exactly and so without the genetics we were able to provide in animals without being on any ketamine or any drug and we could cause the dissociative state by playing an exercise pattern of activity and that who would have thought you could do that but there was a combined mouse and human paper likewise we've been able to play in visual sensations into the brains of mice and by observing which cells in the visual part of the brain visual cortex are naturally responsive to for example vertical bars instead of horizontal bars in the visual world we could see which cells were normally reporting on vertical bars and then we could use optogenetics to come and play in activity just to those cells to these animals are not viewing anything not doing anything at all and we could activate just the vertical bar cells and not only did the animal act as if it was seeing a vertical bar behaviorly it was trained to do a particular thing if it saw a vertical bar and it did that just as if it was seeing something visually but everything in the brain that we were recording to the internal representation of this external world was naturalistic to it looked like the brain was seeing something visual so that's gain a function too you know playing in providing a complex sensation or percept that wasn't there before and we can do that and you know across species so I we haven't you know and of course mice are social and they do they do amazing acts of information processing and so I don't I try not to disparage our cousins too much they certainly have helped the field of neuroscience and medicine I should mention and I know that people have very sensitivities about animal research but the work that's been carried out in mice has been absolutely vital and instructional for treatment of human disease since we talked about dissociation and dissociative states rather and ketamine I'd love your thoughts on psychedelic medicine you know I sort of half joke having grown up in this area in Northern California when it was much more counter culture than it is now but that many of the things that we're hearing about now at least from my read of the history books happened before there was a movement aimed at taking the very same compounds essentially putting them into patients or people were obviously using them recreationally but putting them into patients and seeing tremendous positive effects but also tremendous examples of induced psychiatric illness in other words many people lost their minds as a consequence of over use of psychedelics I probably lose a few people out there but I do want to talk about what is the state of these compounds and I realize it's a huge category of compounds but LSD and psilocybin as I understand trigger activation of particular serotonin receptor mechanisms may or may not lead to more widespread activation of the brain or that one wouldn't see otherwise but when you look at the clinical and experimental literature what is your sort of top contour sense of how effective these tools are going to be for treating depression and then if we have the time we could talk about trauma and MDMA and some of that work well you're right to highlight both the opportunity and the parallel that is there and of course we want to help patients and of course we want to explore anything that might be helpful and what we want to do it in a safe and rigorous way but I do think we should explore these avenues these are agents that alter reality and alter the experience of reality I should say in relatively precise ways they do have problems they can be addictive they can cause lasting change that is not desirable but we have to see these as opportunities we have to first of all study in the laboratory and I'm doing this here we have big we have safes with many interesting psychedelics that all very carefully regulated we get inspections from the DEA and so on they find these labs exist in outer space so you need to be on board one of the space ex missions in order to access them so don't try and combine them no that's exactly true and we're doing exactly this we're saying this is an incredible opportunity if we could understand how the perception of reality is altered we could create new kinds of intervention that don't have the risks and the problems of causing lasting change or addiction now that said even as these medications exist now as you know there's an impulse to use them and very small doses and to use them as adjunctive treatments for the therapy of various kinds and I'm also supportive of that if done you know carefully and rigorously of course there's risk but there's risk with many other kinds of treatment and I'm not sure that the risks for these medications vastly outweigh the risks that we normally tolerate in other branches of medicine why would they work I mean the you know let's say that indeed their main effect is to create more more connectivity at least in the in the moment between brain areas so the way I think about a very I think about the two extremes of my experience anyways a high degree of stress and focus for whatever reason is going to make create changes in my visual field changes in the way that I perceive time so that I'm in a micro slice time I might I'm a very contracted view of whatever my experiences whereas on the opposite extreme in a in a dream or in sleep space and time are very fluid and I'm essentially relaxed although it might be a very interesting dream it might not be psychedelic seem to be a trajectory I'm not all too far off from the dream state where space and time are essentially not as rigid and there is this element of synesthesia blending of the senses you know feeling colors and hearing light and things of that sort it you hear these reports anyway why would having that dream like experience somehow relieved depression long term is do we have any idea why that might be I we have some ideas and no no deep understanding one way I think about the psychedelics is they increase our willingness to are they increase the willingness of our brain to accept unlikely ways of constructing the world unlikely hypotheses as it were as to what's going on the brain in particular cortex I think is a hypothesis generation and testing machine it's coming up with models about everything it's got a lot of bits of data coming in and it's making models and updating the models and changing them theories hypotheses for what's going on and some of those never reach our conscious mind and this is something I talk about in projections in the in the book quite a bit is many of these are filtered out before they get to our conscious mind and that's good we think how distracted we'd be if we were constantly having to evaluate all these you know hypotheses about what kinds of shapes or objects or processes were out there and so a lot of this is handled before it gets to consciousness what the psychedelics seem to do is they change the threshold for us to become aware of these incomplete hypotheses or wrong hypotheses or or concepts that might be noise but are just wrong and so are never allowed to get into our conscious mind now you know that that's pretty interesting and it goes wrong in psychiatric disorders I think in schizophrenia that sometimes the paranoid delusions that people have are examples of these poor models that escape into the conscious mind and become accepted as reality and they never should have gotten out there now how could something like this in the right way help with something like depression patients with depression often are our stock they can't look into the future world of possibilities as effectively there's everything seems hopeless and what does that really mean they they discount the value of their own action they discount the value of the world at giving rise to a future that matters everything seems to run out like a river just running out into a desert and drying up and what these agents may do that increase the flow through circuitry if you will the percolation of activity through circuitry may end up doing for depression is increasing the the escape of some some tendrils of of of process of of forward progression through through the world that's a concept that's how I think about it there are ways we can make that rigorous we we can indeed identify in the brain by recording we can see cells that represent steps along a path and look into the future and we can rigorously define these cells and we can see if these are altered on psychedelics and so that's one of the reasons that we're working with these agents in the laboratory to say art is this really the case or these opening up new paths or or representations of paths into the future MDMA ecstasy is a unique compound in that it leads to big increases in brain levels of dopamine and serotonin simultaneously and I realize that the neuromodulators like dopamine serotonin often work in concert not alone the way they're commonly described in the you know the more general popular discussions however it is a unique compound and it's different than the serotonergic compounds like LSD and psilocybin and there are now data still emerging that it might be in and in some cases can be useful for the treatment of trauma PTSD and similar things why why would that work and do you and a larger question perhaps the more important question is psychedelics MDMA LSD all those compounds there to in my mind there are two components there's the experience you have while you're on them and then there's the effect they have after people are generating variations of these compounds that are non hallucinatory variations but how crucial do you think it is to have let's stay with MDMA the experience of huge levels of dopamine huge levels of serotonin atypical levels of dopamine serotonin released having this highly abnormal experience in order to be normal again I think the brain learns from those experiences that's that's the way I see it and and so for example people on who have taken MDMA they will as you say they'll have the BD acute phase of being you know on the the drug and experiencing the extreme connectedness with other people for example and then the drug wears off and but the brain learned from that experience and so what what people will report is yeah I'm not I'm not in that state but I saw what was possible you know I saw yeah you can but they don't need to be barriers or at least not as many barriers as I thought I can connect with more people in a way that is helpful and so I think it's the learning that happens in that state that actually matters and this as you describe that that sounds a lot like what I understand to be the hallmark feature of really good psychoanalysis that the relationship between patient and therapist hopefully evolves to the point where these kinds of tests can be run within the context of that relationship and then exported to other relations that exactly right and that probably I'm assuming is still the goal of really good psychiatry also it's a part of it intimacy really it should be when we have time I think all good psychiatrist try to achieve that level of of connection and learning try to help patients create a new model that is stable that is learned and that can help instruct future behavior one of the things that I took from reading your book in addition to learning so much science and the future of psychiatry and brain science was you know amidst these very many in many cases very tragic cases and sadness and a lot of the the weight that that puts on the clinician on you also that there's a that there's a central chord of optimism that where we're headed is not just possible but very likely and better and you know it are you an optimist I am and this this is by the way this was a really interesting experience in writing projections because I had a dual goal I wanted it to be for everybody and everybody in the world who wants to to to to breed it and yet at the same time I wanted to stay absolutely rigorously close to the the science what was actually known when I was speaking about science when speaking about the the neuro biology of the brain or or psychiatrist I wanted to to not have any of my scientific colleagues think, oh, he's going too far, he's saying too much. And so I had these two goals, which I kept in my mind the entire time. And a lot of this trying to find exactly the right word we talked about was on this path of staying excruciatingly rigorous in the science. And yet, letting people see the hope, where things have everybody see that we've come a long way, we have a long way to go. But the trajectory and the path is beautiful. And so that was the goal. I think, of course, that sounds almost impossible to jointly satisfy those two goals. But I kept that in my mind the whole way through. And yes, I am optimistic. And I hope that came through in the book. It certainly did. And at least from this colleague, you did achieve both. And it's a masterful book, really, and one that, as a scientist, and somebody who's a fellow brain explorer, hits all the marks of rigor and is incredibly interesting. And there's a ton of storytelling. I don't want to give away too much about it. But people should definitely check out the book. Are you active on social media? If people want to follow you and connect with what you're doing now and going forward? Yeah, I have a Twitter. That's where I mainly do exchange, tell people about things that are happening. We'll provide a link to it. But that's Carl Diceroth, is that a recall with a K? That's right. Yeah. That's right. And so you're on Twitter. And people will hear this. Definitely check out the book. There are other people in our community that, of course, are going to be reaching out on your behalf. But it's incredible that you juggle this enormous number of things, perhaps even more important. However, is that it's all in service to this larger thing of relieving suffering. So thank you so much for your time today for the book and the work that went into the book. I can't even imagine for the laboratory work and the development of channel options, clarity and all the related technologies. And for the clinical work you're doing it. And for sharing with us. Well, thank you for all you're doing and reaching out. I'm very impressed by it. It's important. And it's so valuable and thank you for taking the time. And for all your gracious words about the book. Thank you. I hope you enjoyed today's discussion with Dr. Diceroth as much as I did. Be sure to check out his new book, Projections, A Story of Human Emotions. It's available on Amazon, Audible, and all the other standard places where books are found. If you'd like to support this podcast, please subscribe to us on YouTube. As well, you can subscribe to us on Apple or Spotify. At Apple, you also have the opportunity to leave us a five-star review and to give us feedback. Please put any questions you have in the comments section below the YouTube video. If you'd like us to address certain things in future episodes or if you have questions about this particular episode. In addition, please check out our sponsors. That's a terrific way to support us. We also have a Patreon. It's patreon.com slash Andrew Huberman. There you can support us at any level that you like. Last but not least, if you're interested in understanding more about how the brain works and how it functions and how it breaks down in various conditions, check out the first episode of the Huberman Lab podcast. The title of that episode is How Your Nervous System Works and Changes. If you're watching this right now on YouTube, you can simply click on the title card for that episode. And last but not least, thank you for your interest in science.