Dr. Karl Deisseroth: Understanding & Healing the Mind | Huberman Lab Podcast #26

Dr. Karl Deisseroth, MD, PhD, is a Clinical Psychiatrist and scientist who directs a bioengineering research laboratory at Stanford University School of Medicine. His work aims to understand and develop treatments for disorders of the mind such as depression, attention deficit disorders (ADHD & ADD), autism, schizophrenia, anxiety, eating disorders, borderline personality and obsessive-compulsive disorder (OCD). We discuss his experience treating his patients and his laboratory's mission to find and develop cures for mental disease and tools for probing how the brain works.

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[gentle upbeat music] - [Andrew] 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. Karl Deisseroth. Dr. Karl Deisseroth 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. Deisseroth's laboratory has pioneered the development and use of what are called channelopsins, 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 channelopsins 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 channelopsins 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. Deisseroth'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 diseased state, and also reveals the motivation for and discovery of these channelopsins and other technologies by Karl'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 we're understanding how the brain works more generally. We also discuss issues of consciousness, and we even delve into how somebody like Karl who's 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 Karl'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 Karl Deisseroth 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, I'd like to acknowledge the sponsors of today's podcast. Our first sponsor is Roka. Roka makes eyeglasses and sunglasses that in my opinion, are the very highest quality out there. The company was founded by two All-American swimmers from Stanford, and everything about the eyeglasses and sunglasses was developed with performance in mind. One of the things I really love about Roka sunglasses, is that unlike other sunglasses that make it hard to see when there's a lot of cloud cover, or when the shadows change or environmental conditions change, with Roka sunglasses, they clearly understand the signs of the visual system, because when I put them on for the first time, I noticed that as I moved into shadows or the cloud cover changed or the day got brighter or dimmer, everything was still crystal clear. And that's also because the lenses are tremendously high optical clarity, and the glasses are really lightweight. You don't even notice that they're on. The other thing is that the eyeglasses, I wear readers at night, they're incredibly lightweight, and for both the sunglasses and eyeglasses, the aesthetic is terrific. Unlike a lot of performance eyewear, which frankly can look kind of cyborg-like and kind of ridiculous, the aesthetic of the glasses is such that you could really wear them anywhere, indoors or outdoors. If you'd like to try Roka eyeglasses, you can go to Roka, that's R-O-K-A.com, and enter the code "Huberman", to save 20% on your first order. That's Roka, R-O-K-A.com, and enter the code "Huberman", at checkout. Today's podcast is also brought to

us by InsideTracker. InsideTracker is a personalized nutrition platform that analyzes data from your blood and DNA, to help you better understand your body and reach your health goals. I'm a big believer in getting regular blood work done. And now with the advent of good genetic DNA tests, I'm also a believer in analyzing your DNA. The simple reason for this is that many of the factors that impact our immediate and longterm health, can only be measured and evaluated with a quality blood test. And now, the DNA tests further inform our immediate and long-term health. One of the problems with a lot of DNA tests and blood tests out there however, is that you get the information back, and you don't know what to do with that information. With InsideTracker, you get the numbers back of different metabolic factors, hormones, et cetera, but it also provides simple directives, as to how perhaps you might want to change your nutritional intake or your exercise regimen, or other lifestyle factors, to bring those numbers into alignment with where you'd like them to be. InsideTracker also makes this really easy. They have a dashboard that makes organizing that all very simple, and they can even have someone come to your house to take the blood and DNA test. If you'd like to try InsideTracker, you can visit insidetracker.com/huberman, to get 25% off any of InsideTracker's plans. Just use the code "Huberman", at checkout. Today's episode is also brought to us by Athletic Greens. Athletic Greens is an all-in-one vitamin mineral probiotic drink. I started taking Athletic Greens way back in 2012, and I've taken it ever since, so I'm delighted that they're sponsoring the podcast. The reason I started taking Athletic Greens and that I continue to take Athletic Greens, is that it covers all my vitamin and mineral bases, and it covers my probiotic needs. There's now a wealth of data showing that probiotics support a healthy gut microbiome, and that a healthy gut microbiome supports the gut brain access for healthy mood. It also supports metabolism, immune function, endocrine, that means hormone function, and a host of other important biological functions. I drink it once or twice a day. I mix it with water and a little bit of lemon juice or some lime juice, and it's absolutely delicious. If you'd like to try Athletic Greens, you can go to athleticgreens.com/huberman, and if you do that, you can claim a special offer, where they will give you a year's supply of vitamin D3. In addition, they'll give you five free travel packs. Vitamin D3 as we all know, is very important for a huge range of biological functions and health. Again, that's athleticgreens.com/huberman, for your Athletic Greens, the five free travel packs,

00:07:41 Using Language to Understand the Mind

and the year's supply of vitamin D3. And now, my conversation with Dr. Karl Deisseroth. 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. [Karl laughs] 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 and have 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, I'm married to a neurologist and I am a psychiatrist and we make fun of each other all the time. A lot of neuroscientists and a lot of brain clinicians actually think these two should be in 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, and 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 measureables. 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 hyper-verbal, that you have an easier time diagnosing them, as opposed to somebody who's more quiet and reserved? Or it's, I could imagine the opposite might be true as well. - Well, because we only have words, you've 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, reduced speech, but ultimately you do need something. You need some words to help guide you and in fact, there's challenges that I can tell you about where patients with depression were 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, well, 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? - Yeah, 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, they have trouble swallowing, and they can have a truly severe depression. And this is where you might say, "Oh, well, they've got a life-threatening illness", but there are plenty of neurological disorders where depression is not a strongly comorbid symptom, like ALS, Lou Gehrig's disease, for example, depression is not 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,

00:12:19 Blood Tests For Mental Disease

and a neurologist treats the movement associated with the Parkinson's and we work together. - Do you think we 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 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 measureables at some point. Now, is that good or bad? I think that will be good, and 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 quick measurements. Could it be abused or misused?

00:13:38 The Largest Challenges Facing Treatment of Mental Health

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'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... 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, "We don't know how other people feel. Most of the time, we don't even really know how we feel." - [chuckles] Yeah. - [Andrew] Maybe you could elaborate on that a little bit and 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 they're 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. 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. Here there's a tension 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, "I'm depressed", what exactly do they mean by that? And that may be different 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, 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 here now you're getting into actual things you can talk about that are unambiguous. If someone says, "Yeah, I can't even think about tomorrow. I don't see how I'm going to get to tomorrow". That's a nice, precise thing that you know, it's

sad, it's tragic, but also, that means something. And we know what that means. That's the hopelessness symptom of depression. 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, [chuckles] and this shows up across... 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 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, 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 than the average person thinking about what's going on within, but it doesn't mean we have the answers. - So in this area of trying to figure out what's going on under the hood through words, it sounds like certain words would relate to 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? I mean, if I say for instance, and I won't ask you to run a session with me here [chuckles] for free. [Karl laughs] - We'll do that off camera. - [Andrew] Off camera. Right. If I were to say, "I just can't imagine tomorrow. I just can't do it." So that's not an 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's 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 mesh with the words in a way that's going to make your job easier? - I do think that's true. And 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 them of depression, poor sleep, and poor eating. And if you have a baseline for somebody, that's the real challenge there. What's different in that person? Some people with depressed, they sleep more. Some people 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... Here's the challenge is that 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, and how do you collect that baseline information from someone healthy? I don't think that's something we have solved. Of course, with phones and accelerometers and phones, you could in principle, collect a lot of baseline information from people,

00:20:21 Predicting Depression & Suicide

but that would have to be treated very carefully for privacy reasons. - And in terms of measuring one's own behavior, I've heard of work that's going on. Sam Golden up in the University of Washington who works on aggression in 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, 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 back to the statement that I heard you make and it rung in my mind now, I think for more than a decade, which is, "Oftentimes, we don't even know how we feel." - Yeah. You know, 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 ascribe 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, just inexplicably, they're awake at- - This is like 2:00 AM, 3:00 AM awakening? - It could start... Yeah, it could start at 5:00 AM, could go to four, and three- - And are unable to fall back asleep? - Unable to fall back asleep.

Exactly. And they may not know what to do with that. It could just be, [chuckles] from their perspective, it's just something that's happening. But if you put enough of that information together, 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 needing words to self-report or machines to detect how we feel and maybe inform a psychiatrist how a patient feels, touch on some of the technologies

00:22:47 Drugs That Work for Brain Illness

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. And this [chuckles] 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 the mystery we struggled with, many of our treatments are actually... We may be doing better than some other specialties in terms of actually causing therapeutic benefit for patients. We do help patients, 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 potently treat panic disorder that way. - How long does something like that take on average? - For a motivated, insightful patient, you can have a very cookbooky series of sessions, that's six to 12 sessions, or even less for someone who's very insightful and motivated and it can have a very powerful effect that quickly. And that's just with words, there are many psychiatric medications that are very effective for the 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 the paranoia are more effectively treated right now, but they are effectively treated. And then, this is a frustrating, and yet heartening aspect of psychiatry. There are treatments like electroconvulsive therapy, where 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 a 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 cease, 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 [chuckles] as heartening as it is to see patients respond to this 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. In all of these cases though in psychiatry, the frustrating thing is that we don't have the level of understanding that a cardiologist has in 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.

00:27:01 What Would A Cure For the Broken Mind Look Like?

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 'beens 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. 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 something- - Like lithium, is a good example. - Is it true that it was the urine of guinea pigs [Karl laughs] given lithium that was given to manic patients that made them not manic? Is that true? - I don't have firsthand knowledge of that, but I would defer that, but it's true for essentially every treatment, that the antidepressants originally arose as anti-tuberculosis drugs, for example. - I did not know that. - Yeah, and so this is a classic example for illnesses across all of psychiatry, and of course there's the seizures as well. That was noticed that patients who had epilepsy, they had a seizure there and also had depression, that they became much, at least for awhile, they were improved after that seizure. - That's amazing. I don't want to take you off course of the question 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. 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. 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 home. But I have heard that enough that I think there may well be something to that. And anytime 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. And so, it's plausible for sure, that things like that could happen and do happen. And yet, when you think about autism, to take your example, yes, we see changes, but what is the elements of the brain that's analogous to the pumping heart? When we think about the symptoms of depression, we think about motivation and dopamine neurons. When we think about autism, it's a little more challenging. There's a deficit in social interaction and in communication. And so where is that? [chuckles] 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 okay, 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 unifying thing there? It's a lot of information, and that maybe is unmatched in any realm of biology, the amount of

information coming in through a social interaction, particularly with words and language. And so then, that turns our attention as neuroscientists, we think, okay, 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 we know other animals are social in their own way, and we can study those animals. And so 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 atypical. - So that seems like the first to me, the first been 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 end portions of the body and how they connect to one another, and what the patterns of activity are under a normal 'healthy interaction'. - [Karl] Yeah. - If we understand that, then it seems that the next step, which of course could be carried out in parallel, right? Though 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 to speak.

00:32:23 Channelopsins: Tools For Understanding & Treating the Mind

- Right. - You've been very involved in trying to generate those tools. Tell us about channelopsins, why you created them, and where they're at now in the laboratory and perhaps also in the clinic. - Well, first of all, I give nature the credit for creating channelrhodopsins. These are beautiful little proteins that are made by algae, single-celled green algae. And there'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 Andrei Famintsyn 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 he 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 delves into

this a little bit. He identified that with microscopy, 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 the secret that's helped us unlock so many principles of animal behavior. So turns out, these algae achieve this amazing results with a single gene that encodes a single protein. What's a protein? It's just a little bio-molecule 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 pore, a little hole in the membrane and charged particles, ions like sodium rush across the pore. Now, why do they do that? They do that to guide their flagella, that signal coming in, those ions coming in through the pore 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 a neural code in our brains for on or off. Sodium ions rushing into the cells, turns them on. It 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. There are other opsins, we call them, that you can use to turn cells off. It's all fast, real time. You can play in patterns of activity in real time into cells or kinds of cells, just as a conductor elicits the music from the orchestra, the strings and the woodwinds. 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 was quite an honor and a privilege to watch optogenetics move from idea to discovery to the laboratory. I think we were postdocs at the same time, - We were, huh? - which is living proof that people move at different rates, because [laughs] it's a joke at my expense by the way, [Karl laughing] but it's really- - We end up in the same spot. [laughs] - That's right, [laughs] yeah, more or 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 a 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 that channelrhodopsins and their 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. - Yeah. So this whole thing, you know, it's been about, now

going on 17 years that we've been putting channelrhodopsins into neurons. It started just like Andre Famintsyn's work in a dish, that was in 2004. In 2007, we were putting these into behaving mice, and we were able to with a flick of a switch, cause them to move one direction or another, by 2009- - So basically, you're controlling the mouse's 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 channelrhodopsins actually don't move many ions. 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 them to just be in all the cells, 'cause then it becomes just like an electrode. You're just stimulating all the cells that are 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 in safe and 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

00:39:10 Curing Blindness with Channelopsins

the technology to fish, to rats, to mice, to non-human primates like monkeys, and just a couple months ago, my colleague, Botond Rosca in Switzerland, succeeded in putting channelrhodopsins into the eyes of human beings and making a blind person to see. And so that's pretty cool. This was a patient with retinal degeneration, and he provided a channelrhodopsin into the eye of this patient and was able to confer some light sensitivity onto 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. - Well, as you say, it's a very important milestone and the history of that is very deep. Almost 10 years earlier, Botond Rosca and I had published a paper in science in human retina, but X plants taken from cadavers from someone who had died, the living retina taken out, opsins put into this retinal tissue and showing that it worked, recording from the cells showing that in these human retinal neurons, that you could get light responses. But then, from that moment, almost 10 years of how clinical development goes, and this is a gene therapy

and so you've got all the regulations and concerns and all that. It took almost 10 years to get to this point now where a living human being has a new functionality that wasn't there before. Now, that's incredibly inspiring, and it's a beautiful thing. I would say though, that the broader significance of optogenetics 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 a talk therapy or brain stimulation treatment with electrical or magnetic means, if you actually know what matters, [chuckles] that is incredibly powerful. And I think, not intended to disparage the beautiful retinal work and conferring vision on someone who couldn't see, of course that's wonderful, and that's direct what you might call direct optogenetics in patients. Indirect is everything that comes from understanding. Okay, we know these cells matter now, for this symptom. Well, how can we target those cells and help them work better in patients by any means? And I think that's the broader significance of optogenetics, clinically. - I know Botond well, and you and Botond share this incredible big vision, that I think only a clinician can really understand,

00:41:58 Why Karl Became a Scientist

being in close contact within 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 find cures for mental disease? - [chuckles] No, I didn't. It's a really important question to 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 it's okay I think, to embrace [chuckles] 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. We talked about being introspective. I noticed very early on I had a deep love of poetry and stories, and I was a voracious reader, and I was amazed by how words could make me feel in particular ways. Even separate from their, of course, dictionary meanings, the rhythm, and how they work together, even separate from meaning. And I was stunned by poets that could use words in new ways that were even divorced from their meaning at all, and yet could still trigger specific emotions. And this was always fascinating to me. So, I wanted to understand that, and so I was interested and I became interested in the brain and I thought, well, I'm going to to have to study the human brain, because only human

beings can describe what's going on inside enough. So in college, I began to steer myself toward medicine, 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 this summary elective where you can pick what you want to do. I elected to do the neurosurgery first, [chuckles] even before regular surgery. I was that sure I wanted to do it, and I loved it. I had a fantastic time. There was an amazing patient who had a thalamic damage, and there was a 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? - Even though their vision was perfectly fine, exactly. And I loved the operating room, I loved the rhythm of suturing and the precision of it, and I loved being able to help patients immediately, but then a required rotation was in psychiatry, which I was not looking forward to at all. And that completely reset my whole life, that experience in psychiatry. And it was at 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 also it was, I almost feel a little guilty about this. It's so interesting too. 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, 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 can understand that and help these people, that would be just more than anybody could ask for. And so that's how I ended up taking this path, just a required rotation in psychiatry. - It all started with poetry? - And it started with poetry. - Out of respect for poetry, are there any favorites that you spend time with on a regular basis? - I mean, the ones who got me down this path early on, I remember in childhood and 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. - You're bilingual? - I'm not, I wouldn't say. Now I became, at one point I was effectively fluent in Spanish, and I'm pretty good with medical Spanish still because we use Spanish all the time in the clinic here. I wouldn't claim full fluency, but it's something I can definitely use all the time. And that's been very helpful in the clinic. - Yeah, Borges is wonderful. As 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 [Karl laughs] to be an interesting city. - Yes. - So you developed methods to control neurons

00:47:10 Vagus Nerve In Depression

with these algae proteins using light? - Yeah. - In 2015, there was what I thought was a very nice article published in the New Yorker, describing your work and the current state of your work in the laboratory and the clinic, and an interaction with a patient. So this as I recall, a woman who was severely depressed, and you reported in that article some of the discussion with this patient, and then in real time, increased the activation of the so-called vagus nerve, this 10th cranial nerve that extends out of the skull and innervates many of the viscera and body. What is the potential for channelrhodopsins or related types of algae engineering to be used to manipulate the vagus? Because I believe in that instance, it wasn't channelopsin stimulation, it was electrical stimulation, right? Or to manipulate for instance, a very small localized region of the brain? Let me frame it a little bit differently in light of what we were 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, SSRI, serotonergic agents, increased dopamine, increased whatever, that sometimes they experience relief, but they're often serious side effects. Sometimes they don't experience relief, but as I understand it, channelopsins 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 a positive anticipation circuit. Where are we at now in terms of bringing this technology to the nervous system? And let's start with the body, and then move into the skull. - Yup. So starting with the body is a good example because it highlights the opportunity and how far we have to go. So let's take this example of vagus nerve stimulation. So the vagus nerve, it's the 10th cranial nerve. It comes from the brain, it goes down and innervates the heart and innervates the gut. And by innervate, I mean it sends little connections down to help guide what happens in these organs in the abdomen and chest. It also collects information back, and there's information coming back from all those organs that also go through this vagus nerve, the 10th cranial nerve, back to the brain. And so this is somewhat of a super highway to the brain, and it was the idea. And maybe the idea is maybe we could put a little cuff, a little electrical device around the vagus 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 vagus? I mean, it's there and it's accessible- - That's the reason. - [chuckles] That's the reason? - [chuckles] That's the reason, yes. - Really? - Yeah. - You're not kidding? - [Karl] I'm not kidding. - So stimulating the vagus to treat depression, simply because it's accessible. - It started actually as an epilepsy treatment and it can help with epilepsy, but yes, it's simple. - God, you got to love medicine. As a scientist, this is where I get to chuckle and you say, I'm in the field of medicine from that perspective. From the perspective of a scientist and outsider, the field of medicine is a field that goes in and tickles pathways because they're there. I don't know what to say. It's a little shocking. - Yeah. And at least in my laboratory, I always say you never do an experiment because you can, you do an experiment to test a specific hypothesis. - Yeah. Yeah. I mean, there are stories people tell so that the vagus nerve lands on a particular spot on the brain called the solitary tract nucleus, which is just one snaps away from the serotonin and dopamine and the norepinephrine- - So there's a link to chemical systems in the brain- that make an irrational choice? - Yes. It's not irrational, but I can tell you that even if that were not true, the same thing would have been tried. [Andrew laughs] - You guys would have done it anyway. - Because it's accessible. Yeah. - [Andrew] I see. Okay. - And why? Well, it's again, not to disparage what's been happening in this branch of medicine. There's immense suffering, many treatments don't work, and we try things. And this is how so many advances in medicine happen. When think about kidney dialysis which has kept many people alive, that was just started by someone saying, "Hey, let's try this. Maybe there's something building up in the blood and maybe we can dialyze something and help them." Yeah, it worked. And it was just sort of a test pilot mentality. We can access the blood, let's run it across a 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 rigorous, safe, controlled way- - Sure. - which is what we do. And so, anyway, that's how we ended up, but still with the vagus nerve stimulation, okay, so what is it? Does it work? It has, it's FDA approved for depression, this vagus nerve stimulation, but on a population level, if you average across all people, the effect sizes are pretty small. Some patients it has an amazing effect in, 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 that and so 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 vagus nerve stimulator, the patient's voice becomes strangulated and hoarse, they can have trouble swallowing, they can have 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 electrode. And so you can go up just so far with the intensity, and then you have to stop. So, to your initial question, could a more precise stimulation method like optogenetics help in the setting? In principle, it could, because if you would target the light sensitivity to just the right kind of cell, let's say cell X that goes from point A to point B that you know, causes symptom relief of a particular kind, then you're in business. 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 pharynx 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 cells starting at point A going to point B, that relieves this particular symptom.

00:54:12 Challenges To Overcome for Treating Mental Illness with Channelopsins

- We want to fix this key on the piano? - Yeah. - And then I see two other steps that are required. One is to get the channelopsin gene into the cell. In the case of Botond Rosca 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, [Karl laughs] you probably can see signs that maybe I am or maybe I'm not, but let's say we put channelopsin into a specific branch of the vagus 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? 'Cause we're not talking about sunlight or standing in front of a light bulb necessarily, 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 in? How do you get the gene in, in a potent and robust and safe way? And that's now solved, and that's not a challenge. So there are very safe, well-tolerated gene delivery mechanisms that are

called adeno-associated viruses, AAVs, 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 channelrhodopsin 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 nodose 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? - Yep. Yep. - 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 we've worked out. We've worked on making very, very light-sensitive opsins. One challenge, and Botond would be the first to state this in fact, [chuckles] in solving this problem for the patient, he had to build goggles that created much brighter light than the normal ambient light delivery, because as I mentioned earlier, you have to pack a lot of these channelrhodopsins in, they don't have much current. You have to really make sure that you've got a tense enough light to activate enough of them to cause a stimulation- - And it has to be the right wavelength, right? - It has to be the right wavelength- - And going back to your example of the algae moving toward or away the light, it has to be tuned just right. So I'm imagining in my mind as a non-engineer, I know you're [chuckles] also a bioengineer, I'm imagining a little tiny blue light-emitting object, that's a little bigger than a clump of cells, or maybe about the size of a clump of cells. And for those that don't know, your credit card is about 200 microns thick on the side, and a 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 can imagine that being put under my skin, and then I would what, I'd hit an app on my phone, and I'd say, "Dr. Deisseroth, I'm not feeling great today. Can I increase the stimulation?" And you'd say, "Go for it." And then I'd ramp it up. Is that how it would go? - I mean, that's effectively what we already do with the vagus nerve stimulation. The doctor in this case, and I have this

00:58:34 Using the Dialogue with Patients to Guide Treatment

in some of my patients in the clinic, I do vagus nerve stimulation. I talk to them, I say, "How are you?" 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 in real time. - You're holding the remote control essentially to their brain, although it's remote controlled? - Yeah, through a couple of steps, but yeah. And I can turn up the frequency, I can turn up the intensity, all with the radio frequency and control, and then it's reprogrammed or redosed, and then the patient can then leave at this altered dose. - So this is happening now? - This is happening right now, electrically. - You do this routinely? - I do it routinely in my clinic, electrically, yeah. - And you're getting the verbal content, which as you described earlier, is the indication of how well something is working in real time? - Yes. - So this is 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 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 who has been on a particular dose of the stimulation for weeks or longer, and I talk about symptoms, how were things over the past month? How was your hope? How was your energy level? Sleep? What is your mood? And then we talk with the patient and we decide, well, this is not yet where we'd like to be. And so then, I can turn up the intensity of the stimulation in real time in the office. 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. - Yeah. - And so I can get a sense, am I still on a safe side effect regime? And then, I stop at a particular point that looks safe,

01:00:52 How Our Eyes Reveal Our Mental Health

and then the 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, 'cause 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 the context of somebody's inner experience, whether depressed or happy or otherwise. - Yeah. - I want to make sure that we get back to how to maneuver and manipulate the nervous system for the sake of mental health. But, what are you looking for? So as a vision scientist, I think pupils dilating is a sign of arousal, but that could be a positive arousal, positive valence, like excitement, or it could be terror. - Yeah. - You're going to get the same dilation of the pupils. And I'm always reminding people that these two little goodies are two pieces of brain, basically, [Karl chuckles] 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'd like to think they could be used as control knobs too. So, without putting you on the spot, again, to diagnose me, [Karl laughs] that's something I would never ask you to do [Karl laughing] 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 going on there? - Yeah. The eyes are incredibly rich in information. And as you alluded to though, it's not as if any one measurable conveys all the information you need. It's 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 the eye contact question, we all know eye contact is incredibly important. You don't feel you've connected with somebody, unless there's eye contact, but eye contact can go awry too. It 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, almost as if it's a harmful quantity. And so there's an immense amount of information you get from the eyes, but it's the pairing of what's going on in the eyes, with everything else going on, the body language, the verbal content of what's coming out. All that together is the art of psychiatry and social interaction. But 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 in psychiatry, sometimes it's over the phone that you have to make key decisions. And as I recall, 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 their eyes, you

can't see their body or 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. 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 psychiatrists do this, is you develop a way that 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 hone 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 oh, this patient's depression has improved by about half, just by the tone of their voice. And same with eyes, 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 of 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, [Karl laughs] 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 the eyes are a portal to overall arousal state.

01:06:04 Controlling Structures Deep In the Brain

I'm fascinated by the effects of light on circadian biology and just overall desire to be awake or asleep, et cetera. So the eyes are on the outside of the cranial vault. The vagus is outside the cranial vault, obviously. What about the goodies in here? Parkinson's, we know 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 habenula that when active, make animals and presumably people, passive and unwilling, or uninterested in fighting back against pressures of life, whereas another region, the raphe, you stimulate that, and they actively cope. They get their grit going, and they are able to lean into life. So, how does one get to those structures in a focused way? And what does the next two to five, to 10 years look like? - Well, this is the promise on that, and it is on a timescale that I think things may start to play out. The specificity of optogenetics is really only useful if you have some idea of how to use that specificity. And actually, it's a frustrating aspect of

psychiatry that in many cases, the most effective treatments we have, have the least specificity, electroconvulsive therapy being a great example, where you're causing a brainwide- - Which looks barbaric, but as you mentioned is effective. - I mean, it is. These days, it's much more clinically safe- - It doesn't look like one fluid there last seen in the lab [indistinct] - No it doesn't. Now it's a very clinically safe and stable procedure, but I would say yeah, it's got this almost medieval lack of specificity, even if the procedure is well-controlled and clinically safe and stable, and it's not very specific. You're causing a brainwide seizure. How could you be less specific than that? - And we don't know the source of the relief. - [Karl] We don't know- - Presumably it's a dump of neuromodulators like dopamine and serotonin, but we don't really know- - There certainly is a dump of neuromodulators. We don't know that that's the cause for the relief.

01:08:23 The Most Effective Drugs Often Have the Most Side Effects

And likewise with medications, this is an awesome and interesting thing. Some of the most effective antidepressants, some of the most effective anti-psychotics are the ones that have the most side effects and there are many examples of this. For example, the most effective anti-psychotic is something called clozapine, which unquestionably has the most side effects. It has terrible, terrible side effects. - The D4 antagonist? - It has basically every receptor. [laughs] - Does it really? - Yeah. - Interesting. - Yeah, it has prominent serotonin, prominent muscarinic, certainly acts on dopamine receptors, but it causes blood cell counts change- [laughs] - How do people feel? So if I were schizophrenic and I was getting auditory hallucinations, et cetera, and I took clozapine, what could I expect to feel? - Well, so you would notice side effects, and you would notice resolution of symptoms both and- - So the voices would go away? - Yeah. - But in a good situation, the voices would go away? - That's right. - But I would feel not good in my body? - You might have dizziness, you might have drooling, you might have any number of physical sensations that would be due to these off target effects, the medication acting on these other receptors- - I'm certainly not suggesting this, but what if somebody without schizophrenia took clozapine?

01:09:50 Do Psychiatrists Take the Drugs They Prescribe?

- They'd have the same side effects presumably, yeah. And so it would not be something that I would recommend. - Yeah. Do psychiatrists take the drugs that they prescribe? [Karl laughs] I just finished for the third time, Oliver Sacks' autobiography which is marvelous and I highly recommend to people. He certainly took a lot of drugs, not as part of his professional role, but just out of curiosity, what is the interest or kind of role of drugs in the field of psychiatry? Because 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 true. And I will say that probably many or most psychiatrists have sampled the number of these for exactly the reason that you're saying is to understand better and to help treat their patients better. And I've spoken to people who have found this very helpful to know, okay, this sleep disruption caused by this medication or the libido disruption caused by this other medication. Wow, that is a big effect. And it really helps with empathy for the patients to understand. - I'm not suggesting that physicians or anybody experiment with drugs, but I am relieved to hear that, because I think that when you're talking about accessing somebody's mind and their basic physiology, as you've mentioned, relate to appetite, libido and sleep, really, one is acting as a mechanic of the person's whole experience. They walk out of the office and they have a life experience that extends beyond the script. - Yeah. And so 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 clozapine is a great example. That will work in patients where nothing else works. And believe me, we don't take the step of clozapine prescription lightly, because of all these side effects. You have to come in for a weekly blood cell, or every few weeks of 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 clozapine works amazingly well- - That's marvelous. - And so we do it, even though there are the side effects. And so then this comes back to 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'd better be right about where we we're refining to.. - And do you imagine a day where it will be a single, maybe even outpatient neurosurgery, would go in through the skull or the back of the ear, deliver a small viral injection of one of these adenoviruses, a little sticker of light-emitting diode, deep in the brain, is that how you envision this someday? - That certainly

could happen. What I actually prefer as a vision is still medications, because those are minimally invasive. If we knew what we were doing, we could make them more specific, have fewer side effects, but optogenetics, that will arm us with true causal understanding. And so we'll know, and we're already moving rapidly toward this point, we'll know okay, this symptom, loss of pleasure in life that we call anhedonia, or the loss of motivation or energy to overcome challenges, active coping, these are largely subserved, largely controlled by this circuit or that circuit or the cell that inhabits this other circuit. - And we will know that because of the work done with channelopsins? - 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 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'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 and rigorous knowledge, then you can imagine

01:14:15 Moving From Experimental Tools To Novel Treaments

medication development becoming totally different, no longer serendipitous, but truly grounded in causality. - I see. So using channelopsins 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 walking around with wire packs attached to our skull or something like that. - [Karl] Right. Exactly. - That's fantastic. And I realized no one has a crystal ball, but what do you think the arc of that is? Meaning, are we going to see that in a year? In two years? Three years? Let me reframe that. 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 channelopsins? - I think that in some ways it's already happening at the level of individual patients- - Here at Stanford? - Yeah. Yup. And more broadly in terms of new drugs, new multi-centered clinical trials that will play out over 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

01:16:00 Brain-Machine Interfaces & Neuralink

could be relatively swift. - That's very exciting. What are your thoughts about brain machine interface and Neuralink always comes up, although I do want to point out a tremendous respect for the folks at Neuralink including someone who came up through my lab, is now there as a neurosurgeon, but the brain machine interface is something that's been happening for a long time now, some of the best work, among the best work being done here at Stanford and elsewhere too of course, is what you just described compatible with or different than 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 interfaces going forward? - I mean, 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. Yeah. [chuckles] - And even, yes, it is quite even separate from the Neuralink 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 psychiatric disease and neurological disease, and will give us ideas for treatment. It is, of course 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 the 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 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, a particular, almost like the prodrome or the early stage of a seizure, maybe there are events that happened leading up to on some timescale, a psychiatric symptom that we could intervene in a closed loop way to detect what's happening, what's starting to go wrong, feed that back to the brain stimulation electrode, have it be

in that way more efficient and more principled. I think it's great. It's something that of course will be grounded again and causal understanding, we'll 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 optogenetics is helping us. It's helping us know, okay, this pattern of activity in these cells and these circuits, this does mean that there's a particular kind of symptom that's happening. But armed with that knowledge, absolutely, even the simple closed loop device detect and stimulate is going to be part of psychiatry in the future. And then of course, as you get to more cells,

01:19:30 ADHD & Dr. Deissroth's Approach To Focusing His Mind

more connections, the ability that we have to help people will become more powerful. - One of the questions I get asked a lot is about ADHD and attention deficit of various kinds. I have a hunch, that one reason I get asked so often is that people are feeling really distracted and challenged in funneling their attention and their behavior. And there are 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 channelopsins or these downstream technologies that you're developing, what do they offer for people that suffer from ADHD or have a family member that suffers from ADHD? - This is a pretty interesting branch of psychiatry. There's no question that people have been helped by the treatments, there's active debate over what fraction of people who have these symptoms can or should be treated? - This is typically Adderall or stimulants of some kind? - Yeah, for example the stimulants, that's right. So ADHD as its name suggests, it has symptoms of, it can have either a hyperactive state or an 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 what's going on around them- - So the 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 ways. - Probably rarely is somebody hyperactive with their body but their mind is still, [Karl laughs] although I have to say, and this is a benevolent shout out to Botond Rosca, Botond has an incredibly sharp and focused mind. - Yeah. - And his hand movements [Karl laughs] are extremely exact also, so I do sometimes wonder, whether or not our body movements and our head movements, whether or not they're coordinated or not is a readout of how directed our attention is. - I noticed, I have to think complex, abstract thoughts. I noticed 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 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 motionless, [laughs] which is kind of interesting. - How do you go about that? - I sit much like this, I try to have time in each day where I'm literally sitting almost in this position, but without distraction and thinking, and so it's almost meditative in some ways, except it's not true meditation, but I am thinking, well, I'm not moving- - You're trying to structure your thoughts in that time? - Yeah. - Interesting. - Yeah. So, but everybody, as you say is very different. And so with ADHD, the key thing is we want to make sure that this is present across different domains of life, 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 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 a diagnosis looking at particular, externally detectable brainwave rhythm- - So skullcap with some electrodes that don't penetrate the skull? - That's right. - And this can be done in an hour or two-hour session? - Yeah, that's right. - It has to be done in a clinic, right? - Yeah, in the clinic, right, and you have to have the right recording apparatus and so on, but in principle, increase in confidence comes in exactly which measurements one could even imagine moving toward home tests, but we're not there yet. - Amazing. I think one of the reasons 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 a clinical-like ADHD? 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 me more like OCD. And I'll come clean here by saying when I was younger, when I was a kid, I had a grunting tic. I used to hide it. I actually used to hide in the closet, 'cause my dad would make me stop. And I couldn't feel any relief of my mind until I [grunts] would do this. And actually now, if I get very tired, if I've been pushing long hours, it'll come back. - Interesting. - I was not treated for it, but I will confess that I've had the experience of, I always liked sports where I involved a lot of impact, fortunately not football, because I went to a high school where the football team was terrible. Maybe that would have avoided more impact, [Karl laughs] but things like skateboarding, boxing, they bring relief. I feel clarity after a head hit, which I avoid, [Karl laughs] but I used to say that's the only time I feel truly clear for a while. And then eventually it dissipated. By about age 16, 17, it 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, et cetera, 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 it a lot, and you mentioned this tic-like behavior in yourself, it's very common that people who have tics have this building up of something that can only be relieved by executing the tic which can be a motor movement or a vocalization or even a thought. And people do, I think these days, do have this. If they haven't checked their phone in a while, they do have a buildup and buildup and buildup until they can check it and relieve it. And there's some similarities, there is a little reward that comes with the checking. But the key question in all of 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 psychiatric diagnosis requires that it has to be disrupting someone's social or occupational functioning. And these days, checking your phone is pretty adaptive. That pretty much helps your social and occupational functioning. And so we can't make [chuckles] it a psychiatric diagnosis. - Interesting. - At least in the world of today. - Yeah, opting out of communication now, makes you in some ways less adaptive, though I would point to you as an example

01:26:36 How Dr. Deisseroth Balances A Career In Medicine, Science & Family

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 you're a 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? I've received emails 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 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, of course sometimes it's just take it day by day, and so I don't claim- - So you bring the horizon into the unit of the day? - I do, I do. The unit is the day, that's right. And I try to have in each day, as I mentioned earlier, at least an hour of time where I can think, and it can be when kids are napping, actually, because while driving I can do that too, because I'm sitting still, [clears throat] but that's the one thing I try to preserve. When I was writing the book, I adapted that time to be my writing time, but it wasn't enough, so I had to add in a new block of time which was sort of midnight to 2:00 AM, writing time. [chuckles] And carving out these, even small protected times are very important. Of course, obligations will expand to fill the time available and you have to be disciplined. At least I found I had to be disciplined in truly protecting those times where one can think. - So that means no phone? - That means no phone, no checking of the phone. When I was writing the book, there's a focus mode on the MacBook which kind of rules the border, and you just have your documents and it's very pure, and you don't have the 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? - Yes. - So you're actually in conversation with yourself? - Yes. And hearing literally, I mean, not quite literally, I don't actually hear information, but I'm hearing words, and so I discovered this about myself. Other people, I think may operate differently, but I'm extremely verbal in how I think. That's how all my reasoning is done. It's with sentences and [chuckles] construction of almost equations with words. - Complete sentences? - Complete sentences or complete-ish anyway, mostly complete, and when writing the book, everything about the writing, every sentence was always played out in my mind, listening for rhythm and timing, and I would obsess over exact placement of words to get the right rhythm of the spoken sentence in my mind. - 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 friction points? And if so, do you have tools or ways that you quell that anxiety in real time? 'Cause what

we're really talking about here is your mind. But what we're really talking about is this process of converting the activity of neurons, into something physically concrete in the world. And these intermediate steps are so mysterious to everybody. We hear, "Just write the book", "Just do it", whatever that means. In fact, statements like that to me are kind of empty and meaningless, but when you hear your voice and you're trying to find the correct word and you keep hitting, it doesn't sound quite right, what is the experience in your body? - Yeah, when it's not right, it's definitely evasive, it doesn't feel good, but there's also a hope because I know I can solve it too, and it's almost like you're almost there. 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 this propulsive force forward because I know that the solution is there. And that said, there were single words that I would spend days on, 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 quite there. And I was like, no, I can't put that in. - Everything you just said is entirely consistent with my experience of you, [both laughing] 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 each different which is amazing, yet they all, I think do have some appreciation or a lot of appreciation for reading, but some are very musical. Two of the five are extremely musical, very, very talented with guitar and singing and vocal, impressions, it's just astonishing. And some of them are great with drawing and artistry and some are very physical and vigorous and are never happy except when leaping about. And so, it's just amazing how different they are, honestly. But I think there is a shared appreciation for language. - Do you think that one can train their mind in using these practices? I really like your description of the staying physically still and learning to grapple with those challenges. It's something that, especially in laboratory science, we aren't really trained to do. Like many professions we're taught to come in and just get into motion, and I found that very relaxing as someone who probably has an underlying tic [Karl chuckles] 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 some big important part of my life had 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 described? - I remember the rhythms of physical work in the laboratory very well. My

work these days as the laboratory leader, my job has returned mostly to words now, again. And so it's kind of coming full circle. So it's a different mode. I think you just have to embrace the different stages of life, come with the different modes, but you can definitely train yourself for each mode. I loved, as I mentioned, the rhythm of sewing and suturing and surgery, and I worked really hard on that and became good at it. And now, I never do it, but it's what's the next challenge. There's all the various experimental techniques the dissections of the brain,

01:35:41 New Ways of Exploring Brains: CLARITY

I can't tell you how many thousands of brain dissections I've done in my life, and now I don't do them at all. [Karl laughs] - And then you developed a method so that we don't have to dissect brains. - That's right. [chuckles] - As you mentioned there, maybe tell us for a moment about clarity, and for people who will probably never set foot into a laboratory, what an incredible, yet another incredible discovery and development clarity is, and why it helps us understand how the brain is structured. - Yeah. So this is a different technology also developed in my lab here, and it's part of a broader approach that we call hydrogel-tissue chemistry. And what this is, is it's building a gel, like a clear jello-like substance from within all the cells of a tissue or even an animal, all at once. So you're effectively building a gel inside all the cells at once. Now, that's an odd thing to do. Why do we do it? Well, we do it to transform the tissue into a more tractable accessible object. And the reason that works is 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 in to 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 or 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 sub cellular level. And so this is hydrogel-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 and others have developed on this basic concept of building this gel within the tissue and anchoring molecules into place. - Literally glass-clear brains. I've done this, I've taken a brain cleared with this method, and looked at somebody through it, [Karl laughing] and although you don't want to get it too close to your eye, you don't want to touch it to your own eye, and you can see direct all the way through it. - [Karl] Yeah. - That's incredible for it raises an important question, which is again, about the human brain, and as somebody who essentially started out in neuroanatomy and then got into other things, I always am bothered by the fact that we actually know very little about the microstructure of the human brain, compared to the brains of other organisms. - Yeah. - And in thinking about understanding the circuitry

01:38:49 What Is Special About the Human Brain?

and the piano, so to speak and how to manipulate it in order to relieve suffering, one wonders, are the 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 animals report in to each other there. Maybe they have little psychiatric sessions with one another. - You know, 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 we do. That said, we do have amazing, wonderful brains and many structures that are very highly developed in our brains that are not nearly so developed in mice and fish for example. Now, that said, when I look at the big picture, what is the mammalian brain really doing? There are things that you would never have thought we could study in animals and laboratory mammals like mice, that it turns out you can, actually, 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 statement like that. And a good example of that is we've been able to study just in the past year, come to an understanding of dissociation, and 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. Now, 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 experience 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. So you can have someone who, it's not as if you're numb, you're not anesthetized. You can still know that something's happening to the body, but you just don't care, because you don't ascribe it to yourself, which is very interesting, right? How interesting is that? - The cells report narrative. - Yeah. Yeah. - In your book, you touch on this. And I will say is the most precise, and meaningful and eloquent description of what might be consciousness, this narrative toward the self or of the self, and where it might reside. So in dissociative conditions, people are feeling as kind of an absence of a merge between mind and body. - Right. - Is that one way to describe it? - That's right. - 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 other psychiatric conditions can cause it. But we were able to manifest this in mice, administering these dissociative agents in mice. We could make them still able to detect stimulus, but not care that it was happening. All the while we were recording the activity of individual cells in the brain to see what was going on, what was happening along with this dissociation, and then use optogenetics to see that it mattered to actually provide that pattern of activity and see, oh, that actually causes the dissociation. So we could do all that in mice, which who would've thought that you could study something like this in mice? And we were able to go back and forth with human work because here in our Stanford Comprehensive Epilepsy Center, there's 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 has 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, who 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 the mouse and human because in the human we could cause it to happen. - I just 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 same structure or group of structures and see the emergences. So essentially, these days you hear a lot about gain of function research in the context of viral manipulation, but 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 exactly. And so with optogenetics, we were able to provide in animals without being on any ketamine or any drug and we could cause the dissociative state by playing in a precise pattern of activity. And who would have thought you could do that? But that 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. - So these animals are not viewing anything? - Not viewing 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, behaviorally, 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 too. It looked like the brain was seeing something visual. So that's gain of function too, you know, playing in, providing a complex sensation or percept that wasn't there before. And we can do that across species. So, and of course mice are social, and they do amazing acts of information processing and 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 various sensitivities about animal research, but the work that's been carried out

01:46:03 Psychedelics

in mice has been absolutely vital and instructional for treatment of human disease. - That's right. - 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, 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 who 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 overuse of psychedelics. I'll 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 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, but 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. You know we have [chuckles] big... We have safes with many interesting psychedelics that are all very carefully regulated. We get inspections from the DEA and so on. - If anyone's hoping to find these labs, [Karl laughing] they exist in outer space, so you need to be on board one of the SpaceX missions in order to access them. So don't try and come find them. - No, that's exactly true. Yes. 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 be creating 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 in 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 carefully and rigorously, of course there's risk, but there's risk with many other kinds of treatments. 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, let's say that indeed their main effect is to create more connectivity, at least in the moment between brain areas. So the

way I think about the two extremes of my experience anyways, a high degree of stress and focus for whatever reason, is going to create changes in my visual field and changes in the way that I perceive times, so that I'm on a micro-sliced time, I might be in a very contracted view of whatever my experience is, whereas on the opposite extreme 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, or it might not be. Psychedelics seemed to be a trajectory. I'm not 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. You hear these reports, anyway. Why would having that dream-like experience somehow relieve depression, long-term? Do we have any idea why that might be? - Yeah. We have some ideas, and no deep understanding. One way I think about the psychedelics is they increase our willingness to... They increase the willingness of our brain to accept unlikely ways of constructing the world, unlikely hypothesis, as it were, as to what's going on. The brain, in particular our 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, hypothesis 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 book quite a bit, is many of these are filtered out before they get to our conscious mind, and that's good. Think how distracted we'd be if we were constantly having to evaluate all these 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 concepts that might be noise but are just wrong, and so are never allowed to get into our conscious mind. Now, that's pretty interesting, and it goes wrong in psychiatric disorders. I think in schizophrenia there's some of the times 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've gotten out there. Now, how could something like this in the right way, help with something like depression? Patients with depression often are stuck. They can't look into the future world of possibilities as effectively. Everything seems hopeless. And what does that really mean? 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 escape of some tendrils of process of forward progression through the world. That's a concept, that's how I think about it. There are ways we can make that rigorous. 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, all right, is this really the case?

01:54:12 MDMA

Are these opening up new paths 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 realized that the neuromodulators like dopamine and serotonin often work in concert, not alone, the way they're commonly described in 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, and in some cases can be useful for the treatment of trauma, PTSD and similar things. Why would that work? And a larger question, perhaps the more important question is, psychedelics, MDMA, LSD, all those compounds, 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 and serotonin released, having this highly abnormal experience in order to be normal again? - Yeah. I think the brain learns from those experiences. That's the way I see it, and so for example, people who have taken MDMA, as you say, there will be the acute phase of being on the drug and experiencing this extreme connectedness with other people for example, and then the drug wears off, but the brain learned from that experience. And so what people will report is, yeah, I'm not in that state, but I saw what was possible. I saw it. Yeah. There 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 that is helpful. And so I think it's the learning that happens in

that state, that actually matters. - And as you described 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. - Exactly right. Yeah. - And that probably, I'm assuming is still the goal of really good psychiatry also. - As a part of- - Intimacy, really. - It should be. When we have time, I think all good psychiatrists try to achieve that level of connection and learning,

01:57:15 Dr. Deisseroth's New Book "Projections: A Story of Emotions"

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, amidst this very tragic cases and sadness, and a lot of the weight that that puts on the clinician, on you also, that there's a central cord of optimism, that where we're headed is not just possible but very likely, and better. - Yeah. - And, are you an optimist? - [chuckles] I am. And 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, literally everybody in the world who wants to read it. And yet at the same time, I wanted to stay absolutely rigorously close to the science, what was actually known, when I was speaking about science. When I was speaking about the neurobiology of the brain or psychiatry, I wanted 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 on 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 were, 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 [chuckles] 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 it came through in the book - It certainly did, and at least from this colleague, you did achieve both. And it's a wonderful, it's a masterful book, really, and one that as a scientist and somebody who is a fellow brain explorer, hits all the marks of rigor and is incredibly interesting and there's a ton of storytelling.

01:59:42 Connecting with Dr. Deisseroth on Twitter

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 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 Karl Deisseroth, as I 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 [chuckles] went into the book, I can't even imagine, [Karl laughs] for the laboratory work and the development of channelopsins, clarity, and all the related technologies and for the clinical work you're doing and for sharing with us. - Well, thank you for all you're doing in 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. Deisseroth 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 comment 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/andrewhuberman. There you can support us at any level that you'd 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.