The Science & Treatment of Obsessive Compulsive Disorder (OCD) | Huberman Lab Podcast #78

In this episode, I explain the biology and psychology of obsessive-compulsive disorder (OCD)—a prevalent and debilitating condition. I also discuss the efficacy and mechanisms behind OCD treatments—both behavioral and pharmacologic as well as holistic and combination treatments and new emerging treatments, including directed brain stimulation. I explain the neural circuitry underlying repetitive “thought-action loops” and why in OCD, the compulsive actions merely make the obsessions even stronger. I review cognitive-behavioral therapies like exposure therapy and SSRIs, holistic approaches, and nutraceuticals, detailing the efficacy of each approach and what science says about how to combine and sequence treatments. I describe an often effective approach for treating OCD where clinicians use cognitive behavioral therapy (CBT) to deliberately bring patients into states of high anxiety while encouraging them to suppress compulsive actions in order to help them learn to overcome repetitious thought/action cycles. This episode should interest anyone with OCD, anyone who knows someone with OCD or OCPD, and more generally, those interested in how the brain works to control thoughts and actions, whether those thoughts are intrusive or not.

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- Welcome to The Huberman Lab Podcast where we discuss science and science-based tools for everyday life. [upbeat guitar music] I'm Andrew Huberman and I'm a professor of neurobiology and ophthalmology at Stanford School of Medicine. Today, we are talking about obsessive-compulsive disorder or OCD. We are also going to talk about obsessive-compulsive personality disorder which, as you will soon learn, is distinct from obsessive-compulsive disorder. In fact, many people that refer to themselves or others as obsessive or compulsive or quote-unquote, having OCD or OCD about this or OCD about that do not have clinically diagnosable OCD, rather, many people have obsessive-compulsive personality disorder. However, there are many people in the world that have actual OCD, and for those people, there's a tremendous amount of suffering. In fact, OCD turns out to be number seven on the list of most debilitating illnesses, not just psychiatric illnesses, but of all illnesses which is remarkable and somewhat frightening. The good news is thanks to the fields of psychiatry, psychology, and science in general, there are now excellent treatments for OCD. We're going to talk about those treatments today. Those treatments range from behavioral therapies, to drug therapies, and brain stimulation, and even some of the more holistic or natural therapies. As you'll soon learn, for certain people, they may want to focus more on the behavioral therapies, whereas for

others, more on the drug-based therapies and so on and so forth. One extremely interesting and important thing I learned from this episode is that the particular sequence that behavioral and/or drug and/or holistic therapies are applied is extremely important. In fact, the outcomes of studies often depend on whether not people start on drug treatment and then follow with cognitive behavioral treatment or vice versa. We're going to go into all those details and how they relate to different types of OCD, because it turns out there are indeed different types of obsessions and compulsions, and the age of onset for OCD, and so on and so forth. What I can assure you is by the end of this episode, you'll have a much greater understanding of what OCD is and what it isn't and what obsessive-compulsive personality disorder is and what it is not. And you'll have a rich array of different therapy options to explore in yourself or in others that are suffering from OCD. And if neither you or others that you know suffer from OCD or obsessive-compulsive personality disorder, the information covered in today's episode will also provide insight into how the brain and nervous system translate thought into action generally. And also, you're going to learn a lot about goal-directed behavior generally. My hope is that by the end of the episode you'll both understand a lot about this disease state that we call OCD, you will have access to information that will allow you to direct treatments to yourself or others in better ways,

00:03:01 Momentous Supplements, AG1 (Athletic Greens), Thesis, Eight Sleep

and that you will gain greater insight into how you function and how human beings function in general. The Huberman Lab Podcast is proud to announce that we've partnered with Momentous Supplements. We've done that for several reasons. First of all, the quality of their supplements is exceedingly high. Second of all, we wanted to have a location where you could find all of the supplements discussed on The Huberman Lab Podcast in one easy-defined place. You can now find that place at livemomentous.com/huberman. In addition, Momentous Supplements ship internationally, something that a lot of other supplement companies simply do not do. So that's terrific whether or not you live in the US or you live abroad. Right now, not all of the supplements that we'd discuss on The Huberman Lab Podcast are listed, but that catalog of supplements is being expanded very rapidly and a good number of them that we've talked about, some of the more prominent ones for sleep and focus and other aspects of mental and physical health are already there. Again, you can find them at

livemomentous.com/huberman. Before we begin, I'd like to emphasize that this podcast is separate from my teaching and research roles at Stanford. It is, however, part of my desire and effort to bring zero cost to consumer information about science and science-related tools to the general public. In keeping with that theme, I'd like to thank the sponsors of today's podcast. Our first sponsor is Athletic Greens. Athletic Greens is an all-in-one vitamin-mineral probiotic drink that also has adaptogens and digestive enzymes. I started taking Athletic Greens way back in 2012 and I've taken it every day since so I'm delighted that they're sponsoring the podcast. The reason I started taking Athletic Greens and the reason I still take Athletic Greens once or twice a day is that it covers all of my foundational nutritional needs. In fact, when people ask me, "what's the one supplement I should take?" I always say Athletic Greens because by taking Athletic Greens, you give support to your immune system, to your endocrine system, to your nervous system and to the so-called gut-brain axis and the gut microbiome. As many of you've probably heard, our gut, meaning everywhere from our mouth down all the way through our intestine, is populated by trillions of little microbacteria that support the different systems of our body. Athletic Greens has the probiotics that support the microbiome, and in turn, support things like mood, endocrine function, immune system, and so on. If you'd like to try Athletic Greens, you can go to athleticgreens.com/huberman and claim their special offer. They'll give you five free travel packs plus a year supply of vitamin D3 K2. Many people are deficient in vitamin D3 and in general, vitamin D3 and K2 support a huge number of factors in your brain and body that support your immediate and long-term health. Again, that's athleticgreens.com/huberman to claim their special offer. Today's episode is also brought to us by Thesis. Thesis makes custom nootropics, and frankly, I'm not a big fan of the word nootropics. I've said that on various podcasts and on social media posts and the reason I'm not a fan of the word nootropics is it means smart drugs. But as a neuroscientist, I know that we don't have circuits in the brain or chemicals in the brain for being smart, we have circuits in the brain for focus and for task switching and for creativity, and oftentimes those circuits differ from one another although they collaborate to create things that we think of as intelligence or focus or creativity, et cetera. Thesis understands this and for that reason, has developed custom nootropics that match your particular goals and to your particular biology. They give you the opportunity to try several different blends over the course of a month and discover which ones work best for you and which ones don't. In addition to that personalization, they take it a step

further by offering free consultations with a coach to help you optimize your experience and dial in your perfect formulas. I've been using Thesis for about eight months now and I can confidently say that their nootropics are the best that I've ever used. My go-to formula is the Clarity Formula or the Motivation Formula when I'm going to work or work out, meaning when I'm going to do focus cognitive work, or I'm going to exercise. I also like their Energy Formula prior to exercise. To get your own personalized nootropics starter kit, go online to takethesis.com/huberman. You can take a three minute quiz that will help match you to the best custom nootropics to start with. And Thesis will send you four different formulas to try in that first month. Again, that's takethesis.com/huberman and use the code Huberman at checkout to get 10% off your first order. Today's episode is also brought to us by Eight Sleep. Eight Sleep makes smart mattress covers that have cooling, heating, and sleep tracking capacity. I've talked many times on this podcast and another podcast and on social media about the critical relationship between temperature and sleep. Generally speaking, your body temperature has to drop by about one to three degrees in order to get into and to stay in deep sleep. And waking up has a lot to do with an increase in body temperature of about one to three degrees. So for many people like myself who run warm during the night, I find myself waking up in the middle of the night. However, recently I started using an Eight Sleep mattress cover and by programming in the specific temperatures that work for me across the night, I'm staying asleep through the whole night and as a consequence, I'm feeling far better during the day, much more focus, alertness, et cetera, all the great things that come from getting excellent sleep consistently. The Pro Pod Cover by Eight Sleep is their most advanced solution on the market for thermal regulation during sleep, that's the one I use. It pairs dynamic cooling and heating with biometric tracking. It also has this really nice feature where your mattress basically vibrates a little bit right upon waking, I like that as well. You can cover any mattress with it. You can start sleeping as cool as 55 degrees Fahrenheit, or as warm as 110 degrees Fahrenheit, And that range is available to you simply because Eight Sleep understands that people have a tremendous range in natural body temperatures and sleeping environments. If you want to try Eight Sleep, you can go to eightsleep.com/huberman and check out their Pro Pod Cover and save $150 at checkout. Eight Sleep currently ships within the USA, Canada,

00:08:28 What is OCD and Obsessive-Compulsive Personality Disorder?

and in the United Kingdom. Again, that's eightsleep.com/huberman to save $150 at checkout. Let's talk about OCD or obsessive-compulsive disorder. First of all, as the name suggests, OCD includes thoughts or obsessions and compulsions which are actions. The obsessions and the compulsions are often linked. In fact, most of the time, the obsessions and the compulsions are linked such that the compulsion, the behavior, is designed to relieve the obsession. However, one of the hallmark themes of obsessive-compulsive disorder is that the obsessions are intrusive. People don't want to have them. They don't enjoy having them. They just seem to pop into people's minds and they seem to pop into their mind recurrently. And the compulsions, unlike other sorts of behaviors, provide brief relief to the obsession, but then very quickly reinforce or strengthen the obsession. This is a very key theme to realize about obsessive-compulsive disorder so I'm just going to repeat it again. These two features, first, the fact that the obsessions are intrusive and recurrent, as well as the fact that the compulsions, the behaviors, provide, if anything, only brief relief for the obsessions, but in most cases simply serve to make the obsessions stronger are the hallmark features of obsessive-compulsive disorder. And it turns out to be very important to keep these in mind as we go forward, not just because they define obsessive-compulsive disorder, but they also define the sorts of treatments that will and will not work for obsessive-compulsive disorder. And then once you understand a little bit about the neural circuitry underlying obsessive-compulsive disorder, which we'll talk about in a few moments, then you will clearly understand why being a quote-unquote, obsessive person or having obsessive-compulsive personality is not the same as OCD. In fact, we can leap ahead a little bit and compare and contrast OCD with obsessive-compulsive personality disorder along one very particular set of features. Again, I'll go into this in more detail later, but it's fair to say that OCD is characterized by these recurrent and intrusive obsessions. And as I mentioned before, the fact that those obsessions get stronger as a function of people performing certain behaviors. So unlike an itch that you feel, and then you scratch it and it feels better, OCD is more like an itch that you feel, you scratch it, and the itch intensifies. That contour or that pattern of behaviors and thoughts interacting is very different than obsessive-compulsive personality disorder, which mainly involves a sense of delayed gratification that people want and somewhat enjoy because it allows them to function better or more in line with how they would like to show up in the world. So again, OCD has mainly to do with obsessions that are intrusive and recurrent, whereas obsessive-compulsive personality disorder does not have that intrusive feature to it.

People do not mind, or in fact,

00:11:18 OCD: Major Incidence & Severity

often invite or like the particular patterns of thought that lead them to be compulsive along certain dimensions. So leaving aside obsessive-compulsive personality disorder for the moment, let's focus a bit more on OCD and define how it tends to show up in the world. First of all, OCD is extremely common. In fact, current estimates are that anywhere from 2.5% to as high as 3 or even 4% of people suffer from true OCD, that is an astonishingly high number. Now, the reason the range is so big, 2.5% all the way up to 3, or maybe even 4%, is that a lot of the features of OCD go unnoticed both in the clinician's office and simply because people don't report it and don't talk about it. In fact, it is possible to have recurrent and intrusive obsessions and not engage in the sorts of behaviors that would ever allow people to notice that somebody has OCD. That can be because some of the intrusive thoughts don't actually lead to overt behaviors like hand washing or checking that other people would notice. It can also be because people learn to disguise or hide their obsessions and their compulsions out of shame or fear of looking strange or whatever it might be such that they have these obsessive and intrusive thoughts, and they do little micro-behaviors like they might tap their fingers on their thigh as a way to avoid, at least in their own mind, something catastrophic happening. That might seem crazy to you, it might seem bizarre, but this is the sort of thing that operates in a lot of people. And I really want to emphasize this because the clinical literature that are out there really point to the fact that many people have OCD, full blown OCD, and never report it because of the kind of shame and hiding associated with it. Another thing to point out is that OCD is extremely debilitating. I mentioned this a few minutes ago, but OCD is currently listed as number seven in terms of the most debilitating illnesses, not just mental illnesses or disorders, but all types of illnesses including things like asthma and cancer, et cetera. So you can imagine with that standing at number seven, that it is both extremely common and extremely debilitating. And as a consequence, it's now realized that many hours, days, weeks, months, or even years of work performance or showing up at work of relational interactions really suffer as a consequence of people having OCD. So this is a vital problem that the scientific and psychiatric and psychological communities understand. And it's one of the reasons that I'm doing this podcast. And of course, I received a ton of interest in OCD because of

this incredibly high incidence of OCD and how debilitating it is. We could go really deep into why it's so debilitating. I don't want to spend too much time on that because I think most of that is pretty obvious, but some of it is not. For instance, one of the things that makes OCD so debilitating is, of course, the shame that we talked about before. But it's also the fact that when people are focusing on their obsessions and their compulsions, they're not able to focus on other things. That's simply the way that the brain works. We're not able to focus on too many things at once. The other thing is that OCD takes a lot of time out of people's lives. With recurrent intrusive thoughts happening at very high frequency, or even at moderate frequency, people are spending a lot of time thinking about this stuff and they're thinking about the behaviors they need to engage in, and then engaging in the behaviors, which as I mentioned before, just serve to strengthen the compulsions and so they're not actually doing the other things that make us functional human beings like commuting to work or doing homework or doing work or listening when people are talking or interacting or sports or working out, all the things that make for a rich quality life are taken over by OCD in many cases. So while that might be obvious to some, I'm not sure that it's obvious to everybody just how much time OCD can occupy. Another thing you'll soon learn is that sadly,

00:15:10 Categories of OCD

a lot of the obsessions and compulsions in OCD often relate to taboo topics. And that's because the general categories of OCD fall into three different bins, checking obsessions and compulsions, repetition obsessions and compulsions, and order obsessions and compulsions. The checking ones are somewhat obvious, checking the stove or checking the locks, which I think we all tend to do. I'm somebody typically I'll head off to the car to commute to work and I'll think, did I lock the front door, and I'll go back once, but I won't go back twice or 50 times. People with OCD will often go back 20 or 30 times before they'll actually allow themselves to drive off. And then it's a real challenge for them to continue to drive off and discard with the idea that they didn't check the stove or they didn't check the locks or they didn't check something else critical. Repetition obsessions and compulsions, obviously can dovetail with the the checking ones, but those tend to be things like counting off of a certain number of numbers, like one, two, three, four, five, six, seven, seven, six, five, four, three, two, one. People perform that repeatedly, repeatedly, repeatedly, or feel that they have to. I

remember years ago watching a documentary about the band, The Ramones, right? Most people heard of The Ramones, right? Jeans, T-shirts, aviator glasses, everyone had to change their last name to Ramone. They weren't actually all related to one another, by the way. You had to change your last name to Ramone. The Ramones had one band member who was admittedly and known to others as having OCD. And during that documentary, which I forget the name, I think it was called, can't remember, anyway, can't remember, hippocampal lapse there, but in this documentary, the band members describe Joey Ramone as leaving hotels, walking down the stairs to the parking lot, but then having to walk up and down them seven or eight times, and sometimes getting out of the van again and walking up and down them seven or eight times and it always had to be a certain number of times, given a certain number of stairs. This appears, quote-unquote, crazy, but of course, we don't want to think of this as crazy. This is somebody who very likely had full blown OCD. Now that particular example, believe it or not, is not all that uncommon. It just so happens that that example entailed certain compulsions and behaviors that were overt and that other people could see. And you can imagine how that would prevent somebody from moving about their daily life easily. A lot of people, as I mentioned before, have obsessions and compulsions that they hide and they do these little micro behaviors, or they'll just count off in their head as opposed to generating some sort of walking up and downstairs or tapping or things of that sort. So we have checking, we have repetition, and then there's order. Order oftentimes is thought of as putting cleanliness or making sure everything is aligned and perfect and orderly. And oftentimes that is the case, but there are other forms of order that people with OCD can focus on in a obsessive and compulsive way. Things like incompleteness, the idea that one can't walk away from something or stop doing something because something's not right or complete in that picture. It could be the way the table is set. It could be the way that something's written on a page. It could be an email. Again, now we're still talking about OCD, the disorder. We're not talking about obsessive-compulsive personality disorder. I'm aware of, well, I'll just be direct, several colleagues of mine and it's just remarkable, the order in their emails. Every email is perfect, punctuated, perfect, grammar, perfect, everything's spaced perfect. Do they have OCD? Well, they might, they might not. How would I know unless they disclose that to me. But they might have obsessive-compulsive personality disorder, or they just might be able to generate a lot of order and they have a lot of discipline around the way they write, and the way they present any communication with anybody at all. So if somebody

has a OCD that's in the domain of order, it could be incompleteness and the constant feeling of something not being completed and a need to complete it. It can also be in terms of symmetry, that everything be aligned in symmetric in some way. This could be seen perhaps in young kids. This is one example that I read in the literature of children that need to arrange their stuffed animals in exact same order every day and in a particular order to the point where if you were to move the little stuffed frog over next to the stuffed rabbit, that the child would have an anxiety reaction to that and feel literally compelled, driven to fix that maybe even multiple times over and over again. We'll talk about OCD in children versus adults in a little bit. And then the other aspect of order, which is a little bit less than intuitive, is this notion of disgust, this idea that something is contaminated. So we often think about OCD and hand washing behavior in response to people feeling that something is contaminated, a space, a towel, et cetera, or even simply somebody else's hand and so they're unwilling to shake somebody's hand. You can imagine how these different bins of obsessions and compulsions, checking repetition and order be extremely debilitating depending on how severe they are and how many different domains of life they show up in. Because oftentimes in movies and even the way I'm describing it now it sounds as if, okay, well somebody has to check the locks but they don't have to also check the stove, or somebody has the need to count to seven back and forth up to seven and down to seven seven times seven times a day or something of that sort where they need symmetry in very specific domains of life. But it turns out that this recurrent and intrusive aspect of obsessions leads people with OCD to have checking repetition and/or order compulsions everywhere. So whether or not somebody is at work or in school or trying to engage in sport or trying to engage in relationship or just something simple like walking down the street, the obsessions are so intrusive that they show up and they compel people to do things in that domain independent of whether or not they happen to be in one location or another. In other words, the thought patterns and the behaviors take over the environment as opposed to the environment driving the thought patterns and behaviors. So it therefore becomes impossible to ever find a room that's clean enough, to find a bed that's made well enough, to find anything that's done well enough to remove the obsession. And I know I've said it multiple times now, but I'm going to say it many times throughout this episode in a somewhat obsessive, but I believe justified way that every time that one engages in the compulsion related to the obsession, the obsession simply becomes stronger.

00:21:33 Anxiety: Linking Obsessions & Compulsions

So you can imagine what a powerful and debilitating loop that really is. So let's drill a little bit deeper into how the obsessions and compulsions relate to one another. If we were to draw a line between the obsessions and the compulsions, that line could be described as anxiety. Now, we need to define what anxiety is and to be quite honest, most of psychology and science can't agree on exactly what anxiety is. Typically the way we think about fear is that it's a heightened state of autonomic arousal, so increased heart rate, increased breathing, sweating, et cetera, in response to an immediate and present threat or perceived threat. Whereas anxiety, generally speaking in the scientific literature, relates to the same sorts of thought patterns and somatic bodily responses, heart rate, breathing, et cetera, but without a clear and present danger being in the environment or right there. So that's the way that we're going to talk about anxiety now. And anxiety is really what binds the obsessions and compulsions such that someone will have an intrusive thought. So for instance, someone will have the thought that if they turn left on any street, that something bad will happen. Okay, that's an obsession. It's actually not all that uncommon. Now, how bad and what the specificity of that bad thing really is will vary. Some people will think, if I turn left, something generally bad will happen, it just makes me feel anxious, So they always insist on going right. Whereas other people will think if I turn left, so and so will die, or I will die, or something terrible will happen, I'll get a disease or someone else will get a disease or I'll be cursing myself or somebody else in some very specific way. This is unfortunately quite common in people with OCD. So they have this feeling and the feeling can be generally or specifically related to a particular outcome. But beneath that is a feeling of anxiety, a quickening of the heartbeat, a quickening of breathing, a narrowing of one's visual focus. I've talked about this before in another podcast, the Master Stress, another podcast but if you haven't heard those, let me just briefly describe that when we are in a state of increased so-called autonomic arousal, alertness, stress, et cetera, our visual field literally narrows, the aperture of our visual field gets smaller and that's because of the relationship between the autonomic nervous system and your visual system, so you start seeing the world through sort of soda straw view or through binocular-like view, as opposed to seeing the big picture. Why is that important? Well, it literally sharpens and narrows your focus toward the very thing that the obsessions and the compulsions are focused on. So the person walking down the street who sees the opportunity to go left or

right will only see the bad decision, their visual field narrows very tightly along that possibility of taking a left turn. And I know as I describe this seems totally irrational, but I want to emphasize that the person with OCD knows it's irrational. They might feel crazy because they're having these thoughts, but they know it makes no sense whatsoever that left somehow would be different than right in terms of outcomes in this particular case, and yet it feels as if it would. In fact, in some cases it feels as if they went left, they would have a full blown panic attack. So the idea here is that the obsessions and compulsions are bound by anxiety, but then by taking a right-hand turn, again, in this one particular example, by taking a right-hand turn, there's a very brief, I should mention, very brief relief of that anxiety at the time of the decision to go right, not left and there's an additional drop in anxiety while one takes the right-hand turn as opposed to the left-hand turn. And then as I alluded to before, there's a reinforcement of the compulsion. In other words, by going right, it doesn't create a situation in the brain and psychology of the person that, oh, you know what, I'm not anxious anymore, left would've probably been okay. It reinforces the idea that right made me feel better, or turning right made me feel better, and going left would've been that much worse. Again, it reinforces the obsession even further. And again, we could swap out right turns and left turns with something like hand washing, the feeling that something is contaminated and the need to wash one's hands even though one already washed their hands 20, 30, 50 times prior. And we're actually going to go back to that example a little bit later when we talk about one particular category of therapies that are very effective in many people for OCD which are the cognitive behavioral and exposure therapies. I think some of you have heard of cognitive behavioral and exposure therapies, but the way they're used to treat OCD is very much different than the way they're used to treat other sorts of anxiety disorders and other sorts of disorders generally. So it's fair to say that up to 70% of people with OCD have some sort of anxiety or elevated anxiety, either directly related to the OCD or indirectly related to the OCD and it's really hard to tease those apart because OCD can create its own anxiety, as I mentioned before, it can even increase its own anxiety. And there's also an issue of depression. Having OCD can be very depressing, especially if some of these OCD thoughts and behaviors start to really impede people's ability to function in life. At work, and school, and relationship, they can start feeling less optimistic about life. And in fact, some people can become suicidally depressed. That's how bad OCD can be for us. So we have to be careful when saying that 70% of people with OCD also have anxiety or X number of people with OCD are

also depressed because we don't know whether or not the depression led the OCD or the other way around or whether or not they're operating, as we say in science, in parallel. Some of the drug treatments for OCD and depression and anxiety can tease some of that apart and we'll talk about that, but I think it's fair to say that what binds the obsessions and compulsions is anxiety, that there's a feeling of, or I should say an urgent feeling of a need to get rid of the obsession. And the person feels as if the only way

00:27:33 OCD & Familial Heredity

they can do that is to engage in a particular compulsive behavior. Some people are probably wondering if there's a genetic component to OCD and indeed there is, although the nature of it isn't exactly clear. And oftentimes when people hear that something has a genetic component, they think it's always directly inherited from a parent, and that's not always the case. There can be genes that surface in siblings or genes that surface in children that are not readily apparent in terms of what we call a phenotype. So you have a genotype, the gene, and then you have a phenotype, the way it shows up as a body form or like eye color or how it shows up in terms of a behavior or behavioral pattern. Based on twin studies where researchers have examined identical twins, fraternal twins, even identical twins that share the same sack in utero, the what we call monochorionic, so sitting in the same little bag during pregnancy or in different little bags, you can see different levels of what's called genetic concordance. But if we were to just sort of cut a broad swath through all of the genetic data, it's fair to say that about 40 to 50% of OCD cases have some genetic component, some mutation or some inherited aspect that's genetic and that one could point to if they got their genome mapped. Now, while that's interesting, I don't think it's terribly useful for most people. First of all, you can't really control your genes, at least at this point in history, even though there are things like epigenetic control and people are very excited about technologies like CRISPR for modifying the genome in humans at some point, most people can't control their genetics, right? You can't pick who your parents were as they say.

00:29:10 Biological Mechanisms of OCD, Cortico-Striatal-Thalamic Loops

So just know that there is a genetic component in about half of people with OCD, but not

always. Now as is typical for this podcast, I want to focus on some of the neural mechanisms and chemical systems in the brain and body that generate obsessive-compulsive disorder. In fact, if you've watched this podcast before, listen to this podcast before, this is always how I structure things. First, we introduce a topic and we explore that topic in detail and really define what it is and what it isn't. And then it's very important that we focus on what is known and what is not known about the biological mechanisms that generate whatever that thing happens to be, in this case, OCD and obsessive-compulsive personality disorder. Now I want to emphasize that even if you don't have a background in biology, I will make this information accessible to you. And I also want to emphasize that for those of you that are interested in treatments and are anxiously awaiting the description of things that can help with OCD, I encourage you, if you will, to please try and digest some of the material about the underlying mechanisms because understanding even just a little bit of those biological mechanisms can really help shed light on why particular drug and behavioral treatments and other sorts of treatments work and don't work. This is especially important in the case of OCD where it turns out that the order and type of treatment can really vary according to individual, and that's something really special and important about OCD that we really can't say for a number of the other sorts of disorders that we've described on previous podcasts. So let's take a step back and look at the neural circuitry. What's going on in the brain and body of people with OCD? Why the intrusive recurrent thoughts? Why the compulsions? Why is that whole system bound by anxiety? And in some ways in thinking about that, I want you to keep in mind that the brain has two main functions. The brain's main functions are to take care of all the housekeeping stuff, make sure digestion works, make sure the heart beats, make sure you keep breathing no matter what, make sure that you can see, you can hear, you can smell, et cetera, the basic stuff, and then there's an enormous amount of brain real estate that's designed to allow you to predict what's going to happen next, either in the immediate future or in the long-term future. And largely that's done based on your knowledge of the past. So you also have memory systems. And of course you have systems in the brain and body that are designed to bind what's happening at the housekeeping level, like your heart rate, to your anticipation of what's going to happen next. So if you're thinking about something very fearful, your body will have one type of reaction. If you're thinking about something very pleasant and relaxing, your body will have another type of reaction. So whenever I hear about the brain-body distinction, I have to just remind everybody that there really is no

distinction between brain and body when you think about it through the nervous system. The nervous system is the brain, the eyes, the spinal cord, but of course all their connections with all the organs of the body and the connections of all the organs of the body with the brain, the spinal cord, et cetera. So as I describe these neural circuits, I don't want you to think of them as just things happening in the head, they are certainly happening in the head, in fact, the circuits all described most in detail do exist within the confines of your cranial vault, that's nerd speak for skull, but those circuits are driving particular predictions and therefore particular biases towards particular actions in your body. They're creating a state of readiness or a state of desire to check or desire to count or desire to avoid et cetera, et cetera. So what are these circuits? Well, there's been a lot of wonderful research exploring the neural circuit's underlying obsessive-compulsive disorder and that's mainly been accomplished through a couple of methods. Most of those methods when applied in humans involve getting some look into which brain areas are active when people are having obsessions and when people are engaging in compulsions. Now that might seem simple to do, but of course your brain is housed inside the cranial vault. And in order to look inside it, you have to use things like magnetic resonance imaging, which is just fancy technology for looking at blood flow, which relates to activation of neurons, nerve cells, or things lik PET, P-E-T, imaging, which has nothing to do with the verb pet and has nothing to do with your house pet, has everything to do with positron emission tomography, which is just another way of seeing which brain areas are active and then you can also use PET to figure out what sorts of neurochemicals are active, like dopamine, et cetera. Many studies, we can fairly say dozens if not hundreds of studies, have now identified a particular circuit or loop of brain areas that are interconnected and very active in obsessive-compulsive disorder. That loop includes the cortex, which is kind of the outer shell of the human brain. The lumpy stuff, as it's sometimes appears, if the skull is removed. And it involves an area called the striatum which is involved in action selection and holding back action. The striatum is involved in what's commonly called go and no-go types of behaviors. So every type of behavior like picking up a pen or a mug of coffee involves a go type function. It involves generating an action. But every time I resist an action, my nervous system is also doing that using this brain structure, the striatum, which includes, among other things, the basal ganglia. We've talked about that before. I'm not trying to overload you with terminology here, but I know some people are interested in terminology. So you have go behaviors and you have no-go, resisting of behaviors, not going toward behavior. The

cortex and the striatum are in this intricate back and forth talk. It's really loops of connections. The cortex doesn't tell the striatum what to do, the striatum doesn't tell the cortex what to do. They're in a crosstalk. Like any good relationship, there's a lot of back and forth communication. There's a third element in this cortico-striatal loop as it's called, and that's the thalamus. Now, the thalamus is not a structure I've talked a lot about before on this podcast, but it's one of my favorite structures to think about and teach about in neuroanatomy, which I teach back at Stanford and I've taught for many years elsewhere because the thalamus is this incredible egg-like structure in the center of your brain that has different channels through it. Channels for relaying visual information or auditory information or touch information from your environment up into your cortex, and as a consequence, making certain things that are happening to you and around you apparent to you, making you aware of them, making you perceive them and suppressing others. So for instance, right now, if you're hearing me say this, your thalamus has what are called auditory nuclei, there's collections of neurons that respond to sound waves that are of course coming in through your ears, and your thalamus is active in a way that those particular regions of your thalamus are allowed, literally permitted to pass the information coming from your ears through some other steps but then to your thalamus, your auditory thalamus, then up to your cortex and you can hear what I'm saying right now. At the same time, your thalamus is surrounded by a kind of a shell, something called the thalamic reticular nucleus. Again, you don't have to remember the names, but this thalamic reticular nucleus, also sometimes called the reticular thalamic nucleus, this is, believe it or not, a subject of debate in science. There are people that literally hated each other, probably still hate each other, even though one of them is dead for decades, because they would argue it was thalamic reticular nucleus, the other was reticular thalamic nucleus. Anyway, these are scientists, they're people, they tend to debate. but the thalamic reticular nucleus, as I'm going to call it, serves as a sort of gate as to which information is allowed to pass through up to your conscious experience, and which is not. And that gating mechanism is strongly regulated by the chemical GABA. GABA is a neurotransmitter that is inhibitory, as we say, it serves to shut down or suppress the activity of other neurons. So the thalamic reticular nucleus is really saying, no, touch information cannot come in right now. You should not be thinking about the contact of the back of your legs with the chair that you're sitting on, Andrew, you should be thinking about what you're trying to say and what you're hearing and how your voice sounds and what you see in front of you, et cetera. Whereas if I'm about to get an injection from a

doctor or I'm in pain, or I'm in pleasure, I'm going to think about my somatic sensation at the level of touch and I'm probably going to think less about smells in the room, although I might also think about smells in the room or what I'm seeing and what I'm hearing. We can combine all these different sensory modalities, but the thalamic reticular nucleus really allows us to funnel, to direct particular categories of sensory experience into our conscious awareness and suppress other categories of sensory experience. In addition, the thalamic reticular nucleus plays a critical role in which thoughts are allowed to pass up to our conscious perception and which ones are not, so much so that some neuroscientists and indeed some neurophilosophers, if you want call them that, have theorized or philosophized that the thalamic reticular nucleus is actually involved in our consciousness. Now, consciousness isn't a topic that I really want to talk about this episode and it's a very kind of mushy-murky, as we say in science, it's a shmooey term because it doesn't really have clear definitions so arguments about it often get lost in the fact that people are arguing about different things. But when I say consciousness, what I mean is conscious awareness. So let's zoom out and take a look at the circuit that we've got and that we now know based on neuroimaging studies is intimately involved in generating obsessions and compulsions in OCD. We have a cortex or neocortex, which is involved in perception and understanding of what's happening. We have the striatum and basal ganglia, which are involved in generating behaviors, go, and suppressing behaviors, no-go. And we have the thalamus which collects all of our sensory experience in parallel, hearing, touch, smell, et cetera, not so much smell through the thalamus, I should mention, but the other senses that is. And then that thalamus is encased by the thalamic reticular nucleus, which serves as a kind of a guard saying you can pass through and you can pass through, but you, you, you can't pass through up to conscious understanding and perception. So that loop, this cortico-striatal-thalamic loop, cortico-striatal-thalamic loop is the circuit thought to underlie OCD, and dysfunction in that circuit is what's thought to underlie OCD. Now, again, this circuit exists in all of us and it can operate in healthy ways,

00:39:36 Cortico-Striatal-Thalamic Loop & OCD

or it can operate in ways that make us feel unhealthy or even suffer from full blown OCD. How do we know that this circuit is involved in OCD? Well there, we can look to some really interesting studies that involve bringing human subjects into the laboratory and

generating their obsessions and compulsions and then imaging their brain using any variety of techniques that we talked about before. What would such an experiment look like? Well, in order to do that sort of experiment, first of all, you need people who have OCD and of course you need control subjects that don't, and you need to be able to reliably evoke the obsessions and the compulsions. Now, it turns out this is most easily, or I should say most simply done, 'cause it can't be easy for the people with OCD, but this is most straightforward, that's the word I was looking for, most straightforward when looking at the category of obsessions and compulsions that relate to order and cleanliness. So what they do typically is bring subjects into the laboratory who have a obsession about germs and contamination and a compulsion to hand wash, and they give these people, believe it or not, a sweaty towel that contains the sweat and the odor and the liquid, basically, from somebody else's hands. In fact, they'll sometimes have someone wipe their own sweat off the back of their neck and put it on the towel and then they'll put it in front of the person, which as you can imagine for someone with OCD is incredibly anxiety-provoking and almost always evokes these obsessions about, ugh, this is really, this is really bad. This is really bad, I need to clean, I need to clean. I need to clean. Now they're doing all this while someone is in a brain scanner or while they're being imaged for positron emission tomography. And then they can also look at the patterns of activation in the brain while the person is doing hand washing. Although sometimes the apparati associated with these imaging studies make it hard to do a lot of movement, they can do these sorts of studies. They have done these sorts of studies in many subjects using different variations of what I just described. And low and behold what lights up? And when I say lights up, what sorts of brain regions are more metabolically active, more blood flow, more neural activity? Well, it's this particular cortico-striatal-thalamic loop. In addition to that, some of the drug treatments that are effective in some, and I want to emphasize some individuals, at suppressing obsessions and or compulsions such as the selective serotonin reuptake inhibitors or SSRIs, which we'll talk about in a little bit, when people take those drugs, they see not just a suppression of the obsession and compulsion, but also a suppression of these particular neural circuits. They become less active. Now I want to emphasize and telegraph a little bit of what's coming later, these drugs like SSRIs do not work for everybody with OCD. And as many of you know, they carry other certain problems and side effects for many but not all individuals. But nonetheless, what we have now is an observation that this circuit, the cortico-striatal-thalamic loop, is active in OCD. We have a manipulation that

when people take a drug that at least in those individuals is effective in suppressing or eliminating the obsessions and compulsions, there's less activity in this loop. And thanks to some very good animal model studies, that at least at this point in time, you really couldn't do in humans, although soon that may change, we now know in a causal way that the equivalent circuitry exists in other animals, such as mice, such as cats, such as monkeys, and that activation of those particular cortico-striatal-thalamic circuits in animal models can indeed evoke OCD in an individual that prior to that did not have OCD. So I'm just going to briefly describe one study. This is a now classic study published in the journal Science, one of the three apex journals in 2013. The first author on this paper is Susanne Ahmari, A-H-M-A-R-I. I will provide a link to this in the show notes. It's a truly landmark paper done in Rene Hen's lab at Columbia University. And the title of the paper is repeated cortico-striatal stimulation generates, that's the key word here, generates persistent OCD-like behavior. What they did is they took mice, mice do mouse things. They move around, they play with toys, they eat, they pee, they mate, they do various things in their cage, but they also groom. Humans groom, animals with fur groom, Well, you hope most people groom, some people over-groom, some people under-groom, but most people groom. They'll comb their hair, they'll clean, et cetera. Those are normal behaviors that humans engage in. I'm not aware that mice comb their hair, but mice adjust their hair. So they'll kind of pet their hair and they'll do this. They'll sometimes even do it to each other. We used to have mice in the lab, now we only do human studies, but the mice will groom themselves, and typical, what we call wild type mice, not because they're wild, but because they're typical, will groom themselves at a particular frequency, but not to the point where their hair is falling out. Not constantly, they are grooming some of the time and they're doing other mouse things other mouse times. So in this particular study, what they did is they used some technology, which it actually was discussed on a previous episode of The Huberman Lab Podcast, this is technology that was developed by a psychiatrist and bioengineer by the name of Karl Deisseroth, one of my colleagues at Stanford School of Medicine. This is technology that allows researchers to use the presentation of light to control neural activity in particular brain areas in a very high fidelity way. You control the activity in the cortex of the striatum or the thalamus when you want and how you want. It's really a beautiful technology. In any event, what they did in this study is, or I should say what Susan Ahmari and colleagues did in this study was to stimulate the cortico-striatal circuitry in animals that did not have any OCD-like behavior. And when they did that, those animals

started grooming incessantly to the point where their hair was falling out or they even, they didn't take the experiments this far, fortunately, but the animals would have a tendency to almost rub themselves raw in the same way that somebody who has a compulsion to hand wash would, sadly, people will hand wash to the point where their hands are actually bleeding and raw. It's really that bad. I know that's tough imagery to imagine, and you can't even imagine why someone would self harm in that way, but again, that's that incredible anxiety relationship between the compulsion, excuse me, the obsession and the compulsion, and the fact that engaging in the compulsion simply strengthens the obsession and therefore the anxiety. So that collection of studies, of data, FMRI, PET scanning in humans, the treatment with SSRIs, and these experiments where researchers have actively triggered these particular circuits in animal models that previously did not have too much activity in these circuits and then they observe OCD emerging really points squarely to the fact that the cortico-striatal-thalamic loop is likely to be the basis of OCD. Now, of course, other circuits could also be involved,

00:46:39 Clinical OCD Diagnosis, Y-BOCS Index

but the cortico-striatal-thalamic circuit seems to be the main circuit generating OCD-like behavior. That's a lot of mechanism. Hopefully it was described in a way that you can digest and understand. And some of you might be thinking, well, so what? Why does that help me? I mean, I can't reach into my brain and turn off my cortex. I can't reach into my brain and turn off my thalamus. And indeed, on the one hand, that's true. But as you'll next learn when thinking about the various behavioral treatments and drug treatments and holistic treatments for OCD, what you'll notice is that each one taps into a different component of this cortico-striatal-thalamic loop. And by understanding that, you can start to see why certain treatments might work at one stage of the illness versus others. You will also start to understand why obsessive-compulsive personality disorder does not have the same sorts of engagements of these neural loops, and yet relies on other aspects of brain and body and therefore responds best to other sorts of treatments. Or in some cases, people with obsessive-compulsive personality disorder are not even seeking treatment as I alluded to before. The point here is that by understanding the underlying mechanism why certain drugs and behavioral treatments work and don't work will become immediately apparent and in thinking about that, in knowing that, you'll be able to make excellent choices, I believe, in terms of what sorts of

treatments you pursue, what sorts of treatments you abandon, and most importantly, the order, the sequence that you pursue and apply those treatments. Before we go any further, I'd like to give people a little bit of a window into what a diagnosis for OCD would look like. Give you a sense of the sorts of questions that a clinician would ask to determine whether or not somebody has OCD or not. Now, I want to be clear, I'm not going to do this in an exhaustive way. I wouldn't want anyone to self-diagnose. Although I'm hoping that by sharing some of this, that some of you might get insight into whether or not you do have obsessions and compulsions that might qualify for OCD, and perhaps even to seek out help. The most commonly used test of OCD, or for OCD, I should say, is called the Yale-Brown Obsessive Compulsive Scale. And this is, scientists love acronyms as do the military, and it's the Y-BOCS, the Y-B-O-C-S, the Y-BOCS. So typically someone will go into the clinic either because a family member encouraged them to or because they feel that they're suffering from obsessions and compulsions, and before the clinician would proceed with any kind of direct questions, they would very clearly define what obsessions and compulsions are. And here I'm actually reading from the Y-BOCS. So quote, "obsessions are unwelcome and distressing ideas, thoughts, images or impulses that repeatedly enter your mind. They may seem to occur against your will. They may be repugnant to you, you may recognize them as senseless and they may not fit your personality." Then there are compulsions. Quote, "Compulsions, on the other hand, are behaviors or acts that you feel driven to perform although you may recognize them as senseless or excessive. At times, you may try to resist doing them but this may prove difficult. You may experience anxiety that does not diminish until the behavior is completed." And as I mentioned before in many cases, immediately after the behavior has completed, the anxiety doesn't just return, it indeed can strengthen. Now, there are a tremendous number of questions on the Y-BOCS. So I'm just going to highlight a few of the general categories. Typically, the person will fill out a checklist, so they will designate whether or not currently or in the past they have, for instance, aggressive obsessions, fear that one might harm themselves, fear that one might harm others, fear that they'll steal things, fear that they will act on unwanted impulses, currently or in the past or both, that's one category. The other one are contamination obsessions. So concern with dirt or germs, bothered by sticky substances or residues, et cetera, et cetera. So there are a bunch of different categories that include, for instance, sexual obsessions, what are called saving obsessions, even moral obsessions, excess concern with right or wrong or morality, concerned with sacrilege and blasphemy,

obsession with need for symmetry and exactness. Again, all of these questions being answered as either present in the past or not present in the past, present currently or not present currently. And then the test generally transitions over to questions about target symptoms. They really try and get people to identify if they have obsessions, what are their exact obsessions? Now, this turns out to be really important because as we talk about some of the therapies that really work, I'll just give away a little bit of why they work best in certain cases and why they don't work as well in other cases, it turns out that it becomes very important for the clinician and the patient to not just identify the obsessions and the compulsions generally in a kind of a generic or top contour way, but to really encourage or even force the patient to define very precisely what the biggest, most catastrophic fear is, what the obsession really relates to. That turns out to be very important in disrupting this cortico-striatal-thalamic loop

00:51:38 OCD & Fear, Cognitive Behavioral Therapy (CBT) & Exposure Therapy

and getting relief from symptoms one way or the other. So the Yale-Brown Obsessive Compulsive Scale, this Y-BOCS, again, is very extensive, it goes on for dozens of pages actually, and has all these different categories, not so much designed to just pinpoint what people obsess about or what they feel compelled to do, but to also try and identify what is the fear that's driving all this. In the way that we've set this up thus far, we've been talking about obsessions and compulsions is kind of existing in a vacuum. You're obsessed about germs and you're compelled to wash your hands, obsessed about germs, compelled to wash your hands. Or obsessed about symmetry, compelled to put right angles on everything. Or obsessed about counting and therefore counting, et cetera. But beneath that is a cognitive component that is not at all apparent from someone describing their obsession and from someone describing or displaying their compulsion. The deeper layer to all that is what is the fear, exactly, if one were to not perform the compulsion, meaning what is the fear that's driving the obsession? So that brings us to a very powerful category of treatments that I should say does not work in everybody with OCD but works in many people with OCD and really speaks to the underlying neural circuitry that generates OCD and how to interrupt it. And that is the treatment of cognitive behavioral therapy and in particular, exposure-based cognitive behavioral therapy. So we're going to talk about cognitive behavioral therapy and exposure therapy now, but right at the outset, I want to distinguish the kinds of cognitive

behavioral therapy and exposure therapies that are done for obsessive-compulsive disorder, for the sorts of cognitive behavioral therapies that are done for other types of mental challenges and disorders because cognitive behavioral therapy for OCD really has everything to do with identifying the utmost fear. In some sense, we can think of fears as kind of along a hierarchy. An the example earlier of somebody being afraid to turn left and therefore feeling compelled to turn right, you would want to take that person and really understand what do they fear most about turning left? Now they might not be aware of it. They might not be conscious to what that really is, but if you were to probe them in a clinical setting, you would eventually get to an answer. That answer could be at first, I don't know, just, it's just bad. I don't know why it's bad, it makes no sense, but it's just bad. I do not want to go left. I don't know why, I don't know why. But if you were to push that person a little bit in a respectful and kind and caring way aimed at their treatment, if you were to push 'em and say, well, what do you mean by bad? If you turn left, you think the world would end? They might say, no, the world's not going to end, but you know, someone is going to die suddenly. I know that sounds crazy, but somebody's going to die suddenly. This almost sounds like superstition, we'll talk about superstitions later, but indeed it is somewhat superstitious. So for instance, you would say, who's going to die? And they'd say, I don't know. And you'd say, no, really who's going to die? If you think about this, are you going to die? Is so and so going to die? And very often, very often what you find is that people will start to reveal the underlying obsession at a level of detail that both to the clinician and to them can be somewhat astonishing even though they've been living with that detail in their mind for a very long time. Now, how could somebody start to reveal detail about something that's existed in their mind for a very long time, but not known about it, right? Not been aware of it. Now, some of you might think, oh, it's repressed or something. That's not at all what's happening. If you think about the architecture of OCD, typically, people will have an obsession and then they'll engage in the compulsion as quickly as they can to relieve that obsession. So in many ways, the disease itself prevents people from ever getting to the bottom of that trough, ever getting to the point where they really clearly articulate to themselves exactly what it is that they fear. But it becomes so essential to articulate exactly what it is that they fear for a somewhat counterintuitive reason. You might think, oh, the moment they realize exactly what they fear, everything lifts, the circuit turns off and they just feel better because they realized it. I wish I could tell you that's the case, but it turns out it's the opposite. What the clinician is actually trying to do is get people to feel more anxiety, not

less. What they're trying to get them to do is to short circuit, no pun intended, to intervene in their own neural circuit, I should say, with that relief of anxiety, however brief, brought on by engaging in the compulsion related to the obsession. So, whereas typically someone would feel the obsession with, ugh, I don't want to turn left 'cause something bad's going to happen, someone's going to die, and then they turn right, they never get the option or the opportunity to really explore what would happen were they to turn left or to not be able to turn right. By forcing them down the path of inquiry, that leads them to the place where they very clearly identify the fear, the anxiety, it raises the anxiety in them, and that's actually what the clinician is after. Cognitive behavioral therapy and exposure therapy in the context of OCD, most often involves trying to get people to tolerate, not relieve their anxiety. This is extremely important. And I realize there's variation to this depending on the style of cognitive behavioral therapy, the style of exposure therapy, but almost across the board, The goal, again, is to get people to feel the anxiety that normally they are able to at least partially relieve, however briefly, by engaging in the compulsion. So if we think back to that circuit of cortico-striatal-thalamic, what's going on here? Where is CBT intervening? What part of the circuit is getting interrupted? Well, as you recall, the cortex is involved in conscious perception. The thalamus and that thalamic reticular nucleus are involved in the passage of certain types of experience up to our conscious perception, not others. And the striatum is involved in this go, no-go type behavior. When OCD is really expressing itself in its fullness, people feel an anxiety around a particular thought and they either have a go, for instance, wash hands, or a no-go, do not turn left type reaction. By having people progressively, in a kind of hierarchical way, reveal their precise source of anxiety, their utmost fear in this context, what happens is they feel enormous amounts of autonomic arousal. Now in the context of anxiety treatment or other types of treatments, the goal would be to teach people to dampen, to lessen their anxiety through breathing techniques or through visualization techniques or through self-talk or through social support, any of the number of things that are well-known to help people self regulate their own anxiety. Here, it's the opposite. What they're trying to get the patient to do is to really feel the anxiety at its maximum, but then do the exact opposite of whatever the normal compulsion is. So if normally the compulsion is to wash one's hands, then the idea is to suppress hand washing while being in the experience of the utmost anxiety. Or in the case of not turning left, the person is expected to or would hopefully be able to actually turn left, and as you can imagine, that would evoke tremendous anxiety and yet to tolerate that anxiety. Now I

want to be very clear, this is not the sort of thing you want to do on your own. This is not the sort of thing you want to do for a friend. This is done by trained licensed psychologists and psychiatrists. But nonetheless, it really points to the fact that as a anxiety-related disorder, OCD is distinct from other types of anxiety and anxiety-related disorders, things like PTSD and panic disorder, et cetera, because the goal again is to bring the person right up close to the thing that they fear the most and then to interrupt the circuit. And now you should be able to know, just intuitively, 'cause you understand the mechanisms, that the circuit you're trying to disrupt is the pattern of information flow from the thinking part of the brain, the perception part of the brain, which is the cortex, to the striatum. The striatum has these neurons which are active that essentially are, I know it sounds a little bit like a discussion about free will, but they're trying to get some, the person to generate a certain behavior, suppress a certain behavior. And as anxiety ramps up, it's sort of a hydraulic pressure to do that very thing that they've done for so long and they suffer from so much. We talked about hydraulic pressure in the context of aggression in the aggression episode, this is very similar. There's a kind of a, now when I say hydraulic pressure, it's not actual hydraulic pressure, it's the confluence of a lot of different systems. It's neurochemicals, we'll soon learn, it's hormonal, it's electrical, it's a lot of different things operating in parallel so we can't point to one chemical or transmitter. What's happening is the person is feeling compelled to act, act, act to relieve the anxiety and through a progressive type of exposure, you don't throw people in the deep end in this kind of therapy right off the bat, you gradually ratchet them toward or move them toward the discussion of exactly what they fear the most and then eventually move them toward the interruption of the compulsion as they're feeling this extremely elevated anxiety, of course, within the context of a supportive clinical setting. But in doing that, what you are teaching people is that the anxiety can exist without the need to engage in the compulsion. Now some of this might sound to people like, oh, this is a lot of kind of fancy psychological neuroscience speak around something that's kind of intuitive. But I think for most people, this is not intuitive. And for people with OCD, there's no really other way to put it, the impulse, the compulsion to avoid anxiety is such a powerful driving force that it should now make sense to you as to why being able to tolerate anxiety and really sit with it and do the exact opposite of what you're normally compelled to do is going to be the path to treatment. And indeed CBT has been shown to be enormously effective, again for a large number of people with OCD, but not all of them. And oftentimes it requires that it also be

01:01:56 Unique Characteristics of CBT/Exposure Therapy in OCD Treatment

used in concert with certain drug treatments, which we're going to talk about in a moment. Next, let's talk about some of the really unique features of cognitive behavioral therapy and exposure therapy in the context of OCD that you often don't see in the use of CBT, that is cognitive behavioral therapy, for other types of psychiatric challenges and disorders. The first element is one of stair casing. And I already mentioned this before, but this gradual and progressive increase in the anxiety that you're trying to evoke from the patient, from the person suffering from OCD. That's done in the context of the office or the laboratory, again, by a trained and licensed clinician. But then the person leaves, right? They leave the office, they leave the laboratory. And a very vital component of CBT and exposure therapy for people with OCD is that they have and perform what's called homework, is literally what they call. This might be seen in other sorts of treatments but for OCD, homework is extremely important, because within the context of a laboratory experiment or the clinic, patients often feel so much support that they can tolerate those heightened levels of anxiety and interrupt their compulsions. Whereas when they get home, oftentimes the familiarity of the environment brings 'em to a place where all of a sudden those obsessions and compulsions start interacting the same way and they have a very hard time suppressing the behaviors. Why would that be? Well in neuroscience, we have a phrase, it's called conditioned place preference and conditioned place avoidance. There's some other phrases too but basically it all has to do with a simple thing which is, when you feel something repeatedly in a given environment, or sometimes even once within a given environment, you tend to feel that same thing again when you return to that or similar environments. Okay, So conditioned place blank, or conditioned place that is simply fancy nerd speak for the fact that when you're in a place and something good happens, you tend to feel good if you return to that place or a place like it, or if something bad happens in a given place, you tend to feel bad when you return to that place or a place like it. I think that most salient example that leaps to mind is in, unfortunately, the category of bad, but I had some friends years ago visit San Francisco. There's been a ongoing, it seems like it's been happening forever, but this is really in the last decade of daytime break-ins and nighttime break-ins into cars to steal anything from computers to what seems to be like a box of tissues. And there are numerous reasons for this, I don't want to get into, it's not the topic of today's

podcast, but I will use this as an opportunity to say if you're visiting anywhere in the Bay Area, do not leave anything in your car because the window will get broken into, sometimes in broad daylight. Some good friends of mine were visiting the Bay Area and I texted them and said, hey, by the way, when you're headed to dinner, guys, make sure you bring in all your luggage and computers however inconvenient that might be. They wrote back, too late, everything got stolen. So some years ago now, I think five, six years ago this happened, sadly, everything got stolen. Most of it could be replaced, but some of it was very sentimental to them. Every time we talk, every time we consider having a meeting in a particular city, this comes up as I don't want to be there, I don't like that city anymore, et cetera. And of course, San Francisco has some wonderful redeeming features, but it only takes one bad incident in one location to kind of color the whole picture dark, so to speak. The brain works that way. The brain generalizes, it's not a very specific organ, again, it's a prediction machine in addition to other things. So in the case of CBT therapy, the reason there's homework is that when people go home, oftentimes that's when they relapse, if you want to call it that, back into their obsessions and compulsions. And that location, that conditioned place is where it becomes most important to challenge the anxiety and to deal with the anxiety, to not try and suppress the anxiety through compulsions or other means. And when I say other means, I want to highlight something, it will come up again a little bit later in the podcast, that substance abuse is very common in people with OCD because of the anxiety component and also because of people's feelings that they just can't escape from the thoughts or behavioral patterns that are so characteristic of OCD. So alcohol abuse or cannabis abuse, or other forms of narcotics abuse are very common in OCD. Later, we'll talk about whether or not cannabis can or cannot help with OCD. But needless to say, suppressing anxiety is exactly the wrong direction that one should take if the goal is to ultimately relieve or eliminate the OCD. So we now have two characteristics of CBT exposure therapy that are extremely important for OCD and somewhat unique to the treatment of OCD and that's the staircasing up towards the really bad fear, the really severe and specific articulation and understanding and feeling of how bad things really would be if someone engaged in a particular behavior or avoided a particular behavior. Then there's the component of homework given by the clinician for the person to be able to create a broader set of context in which they can deal with the anxiety, not engage in the compulsions. And then a very unique feature of treatment of OCD that you don't see in many other psychiatric disorders are home visits. And I find this fascinating. I think that

the field of psychiatry and psychology traditionally doesn't allow for or invite home visits, but this component of context, location and context being so vital to the treatment and relief of OCD has inspired many psychiatrists and psychologists to get permission to do home visits where they actually go visit their patients in their native setting, in their home cages, right? They're not mice, but in their home-home cages, I'm being facetious here, but people, mice live in cages, at least in the laboratory, and humans generally live in houses or elsewhere, so they visit them in their home in order to see how they're interacting and the particular locations that evoke the most anxiety and the least anxiety. Some of the, I don't want to call them crutches, but some of the tools that people are using to confront and deal with the obsessions and compulsions and in particular to try and identify some of the tools and tricks that people are using to try and avoid that heightened anxiety, because, once again, and I know I'm repeating myself, but I think this is just so vital and so unique about OCD and the treatment of OCD, the critical need for the patient to be able to tolerate extremely elevated levels of anxiety is so crucial. So if people are avoiding certain rooms in the house, or if people are avoiding certain foods or certain locations in the kitchen, the clinician can start to identify that by mere observation. And I should mention here that patients are not always aware of how they're interacting with their home environment. Some of these patterns are so deeply ingrained in people that they don't even realize that they're constantly turning to the left, or they don't even realize that they're only washing their hands on one side of the sink. And so the clinician, by visiting the home, can start to interrogate a bit in a polite way, in a friendly, in a supportive way as to, do you ever think about why you always flip the faucet to the left or flip the faucet to the right, et cetera. Now, we all do a lot of things that are habitual. We all do things that are somewhat regular from day to day. In fact, I would invite you to ask yourself, do you always put your toothbrush in the same location? Do you always cap the toothbrush before or after you use it? What sorts of things do you- You wipe the little threading on the toothpaste or not? I'm somebody, I confess that I have, well, I have about 3,500 pet peeves, but one of my pet peeves is toothpaste kind of on the thread of the toothpaste. It really bothers me, I don't know why, almost as much as trying to wipe it off bothers me, which creates a certain challenge. And if I talk about this any further, then I think I would qualify for obsessive-compulsive personality disorder. But I have to say, I don't experience a ton of anxiety about it. It doesn't govern my life. In fact, I realize that right now there are tubes of toothpaste that have toothpaste along the thread everywhere in the world and it doesn't really bother me. I can still sit

here and provide some information about OCD to you. It's not intrusive, at least not to my awareness. So by the home visit, the therapist can really start to explore through direct questioning and can allow the patient to explore through direct questioning of themselves the things that they might be conscious of

01:10:18 CBT/Exposure Therapy & Selective Serotonin Reuptake Inhibitors (SSRIs)

and the things that they might not be conscious of that would qualify for OCD. So I'd like to just briefly summarize the key elements of cognitive behavioral therapy and exposure therapy and how they can be combined with drug treatments that are very effective. Much of what I'm going to talk about next relates to the data and indeed the practice of an incredible research scientist and clinician. So this is Helen Blair Simpson, or I should say Dr. Helen Blair Simpson, because she is indeed an MD medical doctor and a PhD research scientist at Columbia University School of Medicine. And one of the world's foremost experts, if not the expert, I would put her in a category of maybe just one to three people who is most knowledgeable about the mechanisms of OCD, is actively researching OCD in humans, trying to find new treatments, trying to unveil new mechanisms and expand on our current understanding and who also treats OCD quite actively in her own clinic. Dr. Simpson gave a beautiful presentation which she summarized some of the core elements of CBT and exposure therapy for the treatment of obsessive-compulsive disorders. She describes that the key procedures are exposures, of course, done in person and with the actual thing that evokes the obsessions and compulsions. So this could be the sweaty towel as described earlier, or could be any number of different triggers done with the patient in real time, so in vivo, as we say. And it could also be things that are imaginal, sitting somebody down in a chair, in an office and saying, okay, I want you to imagine the thing that triggers the intrusive thought, or let's just focus on the intrusive thought as it arises, and then to explore and expose the patient to their obsessions and compulsions that way. So it can be real, or it can be imaginal. And the goal, of course, then is to gradually and progressively increase the level of anxiety, but then to intervene in so-called ritual prevention to prevent the person from engaging in the compulsion. The goals, again I'm paraphrasing here, are to, as she states, disconfirm fears and challenge the beliefs about the obsessions and compulsions, to intervene in the thoughts and the behaviors, and to break the habit of ritualizing and avoiding. Now, how is this typically done? What are the nuts and bolts of

this procedure? Typically, this is done through two planning sessions with the patient. So describing to the patient what will happen and when it will happen and how long it will happen so that they're not just thrown into this out of the blue. And then 15 exposure sessions done twice a week or more. So the one thing to really understand about cognitive behavioral therapy is that it can take some period of time, several or more weeks, as many as 10 or 12 weeks. However, as you'll soon learn, many of the drug treatments that are effective in treating OCD either alone or in combination with behavioral therapies also can take 8, 10, 12 weeks or longer, and many of those never work at all. So even though 10 to 12 weeks seems like a long period of time, it's actually a pretty standard. If you'd like to see more complete description of the protocols for cognitive behavioral therapy and exposure therapy for OCD, I'll provide links to two papers, Kozak and Foa, F-O-A, which is published in 1997, which might seem like a long time ago, but nonetheless, that the protocols are still very useful. And then the second paper is by that last author, FOA et al in 2012 and we'll provide links to both of those. In addition, Dr. Blair Simpson and others have explored what are the best treatments for patients with OCD by comparing cognitive behavioral therapy alone, placebo, so essentially no intervention or something that takes an equivalent amount of time but is not thought to be effective in treatment. As well as selective serotonin reuptake inhibitors. So what is an SSRI? An SSRI is a drug that prevents the re-uptake of serotonin at the synapse. What are synapses? They're the little spaces between neurons where neurons communicate with one another by vomiting little bits of chemical into the space, the synapse, and then those chemicals either evoke or suppress the electrical activity of the next neuron across the synapse. And in this case, the neurotransmitter, the chemical that we're referring to is serotonin. SSRI, selective serotonin reuptake inhibitors prevent the reuptake of the chemical that's left, in this case, the serotonin that's left in the synapse. After that, I call it vomiting to be dramatic, but it's not actually vomiting, the extrusion of the chemical into the synapse. And as a consequence, there's more serotonin around to have more of an effect over time, the net effect being more serotonergic transmission, more serotonin overall. So not more serotonin being made, more serotonin being available for use, that's what an SSRI does. So they compared cognitive behavioral therapy, SSRIs, they also had the placebo group and they had cognitive behavioral therapy plus the selective serotonin reuptake inhibitor. This was a 12-week study done as described before, two times a week over the course of 12 weeks. First of all, the most important thing, of course, placebo did nothing. It did not

relieve the OCD to any significant degree. How did they know that? They gave them the Y-BOCS test that we talked about before, the Yale-Brown test with all those questions of which I read a few. So the OCD severity that one has to have on the Y-BOCS is measured in terms of an index that goes from here from 8 all the way up to 28, that shouldn't mean anything. So that number eight is kind of meaningless here. It's in terms of an index that's only meaningful for the Y-BOCS, but if somebody has a threshold of 16 or higher, it means that they're still having somewhat debilitating symptoms or very debilitating symptoms. Placebo did not reduce the obsessions or compulsions to any significant degree. However, and I think quite excitingly, cognitive behavioral therapy had a dramatic effect in reducing the obsessions and compulsions such that by four weeks, that score that, in this case, ranged from 8 to 28, dropped all the way from 25 down to about 11. So it's a huge drop in the severity of the symptoms. Now, what's really interesting is that when you look at the effects of SSRIs in the treatment of OCD symptoms, they had a significant effect in reducing the symptoms of OCD that showed up first at four weeks, and then continued to eight weeks. In fact, there was a progressive and further reduction in OCD symptoms from the four to eight week period. Again, these are the people just taking the SSRI, and then it sort of flattened out a little bit, such that by 12 weeks, there was still a significant reduction in OCD symptoms for people taking SSRIs as compared to placebo. But the severity of their symptoms was still much greater than those receiving cognitive behavioral therapy alone. So at least in this study, and I should tell you which study it is, this is Foa, Liebowitz et al 2005 in the American Journal of Psychiatry, we'll also provide a link to this so you can peruse the data if you like. But at least in this study, cognitive behavioral therapy was the most effective, selective serotonin reuptake inhibitors, less effective. So what happens when you combine them? Well, they explored that as well, and the combination of cognitive behavioral therapy and the SSRIs together did not lead to any further decrease in OCD symptoms. This points to the idea that cognitive behavioral therapy is the most effective treatment. And again, when I say cognitive behavioral therapy, now I'm still referring to cognitive behavioral, slash, exposure therapy done in the way that I detailed before, twice a week for 12 weeks or more. So all of the data, at least in this study, point to the fact that cognitive behavioral therapy is really effective and the most effective. Does it alleviate OCD symptoms for everybody? No. Is it very time consuming? Yes. Twice a week for two sessions or more of 15 minutes, sometimes in the office, plus there's homework, plus, in an ideal case, there's also home visits from the psychiatrist or

psychologist, that's a lot of investment, a lot of time investment, to say nothing of the potential financial investment. Now, Dr. Blair Simpson has given some beautiful talks where she describes these data and also emphasizes the fact that despite the demonstrated power of cognitive behavioral therapy for the treatment of OCD, most people are given drug treatments simply because of the availability of those drug treatments. Now, when I say most people, I want to emphasize that I'm referring to most people who actually go seek treatment because a really important thing to realize is that most people with OCD do not actually go seek evidence-based treatment. I want to repeat that, most people with OCD do not seek evidence-based treatment, which is a tragic thing. One of the motivations for doing this podcast episode is to try and encourage people who think they may have persistent obsessions and compulsions to seek treatment, but most people don't for a variety of reasons we spelled out earlier, shame, et cetera. Of those that do, the first line of attack is typically a prescription, most often an SSRI, although not always just SSRIs because soon we'll talk about the somewhat common use of also prescribing a low dose of a neuroleptic or an antipsychotic, not always but often. So the important thing to understand here is that excellent researchers like Dr. Simpson understand that while there are treatments that we could say are best or are ideal based on the data, that doesn't necessarily mean that's what's being deployed most often in the general public. As a consequence, Dr. Simpson and others have explored in a very practical way whether or not it matters if somebody is getting SSRI treatment and is experiencing that reduction in OCD symptoms that as you may recall, is more than what they would experience with placebo alone, but not as dramatic a reduction in OCD symptoms as they would get with cognitive behavioral therapy. And as I mentioned before, there was this exploration of combining drug treatment with cognitive behavioral therapy from the outset, but they also quite impressively explored what happens when people who are already taking SSRIs initiate cognitive behavioral therapy. This is a really wonderful thing that they've done this because in doing that, first of all, they're acknowledging that there are many people out there who have sought treatment and are getting some relief from those SSRIs, but it perhaps is not as much relief as they could get. And they are actively acknowledging that many people are getting these drug treatments first. In fact, most often people are getting these drug treatments first. So what happens when you add in cognitive behavioral therapy? Well, the good news is when you add cognitive behavioral therapy to someone who's already taking SSRIs, that further improves their symptoms.

Now that's different than the results that I described before from the same laboratory in fact, that if you combine cognitive behavioral therapy with SSRIs from the outset, there's no additional benefit of SSRI. However, as I just described, if someone is already taking an SSRI and they're experiencing a reduction in their OCD symptoms, by adding in cognitive behavioral therapy, there is a further reduction in the symptoms of OCD. This is very important. So for those of you that have sought treatment and you're taking a SSRI, or if you're thinking about treatment and you're prescribed an SSRI, the ideal scenario really would be to combine the drug treatment with cognitive behavioral therapy, or in some cases, maybe cognitive behavioral therapy alone, although that's a decision that you really have to make with the close advice and oversight of a licensed physician, because, of course, these are prescription drugs. And anytime you're going to add or remove a prescription drug or change dosage, you really want to do that in close discussion with and on the advice of your physician. I don't just say that to protect me, I say that to protect you 'cause it's just the right thing to do. So again, cognitive behavioral therapy is extremely powerful. Drug treatments seem less powerful though.

01:22:30 Considerations with SSRIs & Prescription Drug Treatments

If you're already on a drug treatment, adding cognitive behavioral therapy can really help. So I've been talking about SSRIs and described a little bit about how they work at a kind of superficial level of keeping more serotonin in the synapse so that more serotonin can be in action as opposed to gobbled back up by those neurons. I should just mention what some of the selective serotonin reuptake inhibitors are. So things like clomipramine, which is not entirely selective, I should say that that one generally falls into a category of less selective. So it can impair or can enhance some of the other neurotransmitter or neuromodulator systems like epinephrine, et cetera. The selective serotonin reuptake inhibitors are, at least the classic ones are, fluoxetine, Prozac, fluvoxamine, Luvox, paroxetine, sertraline, citalopram, et cetera, et cetera. There are about six or classic SSRIs, some of them like citalopram are used in children and are available in pediatric doses. Some like Prozac may or may not be used in children. The details of which SSRIs, et cetera, is a very extensive literature and discussion. And I think it's safe to say that which drugs to use and which dosage and whether or not to continue, excuse me, the same dosage over time depends a lot on the individual variation that people express and the responses that they have. All of these drugs, in

fact, I think we can say all drugs have side effects. The question is how detrimental those side effects are to daily life. The SSRIs are well known to have effects on appetite. In some cases, they abolish appetite. In some cases, they just reduce it a little bit. In some cases, they increase appetite. Really is highly individual. They can have effects on libido. For instance, they can reduce sex drive, sometimes in a dose dependent way, sometimes in a way that's more like a step function where people are fine at say 5 or 10 milligrams, but then they get to 15 milligrams and there's a cliff for their libido. That can happen, it really depends. Please don't take those dosages as exact values 'cause this is going to depend on what they're being used for, depression or anxiety or OCD, and it's also going to depend on the drug, et cetera. I just threw out those numbers as a way to illustrate what a kind of a step function would look like. It's not gradual, it's immediate at a given dose is what that means. The other thing is that some of these drugs will have transient effects. So side effects that show up and then disappear or sadly people will sometimes take these drugs for a while and then side effects will surface later that weren't there previously depending on life factors, nutrition factors. So it's a very complicated landscape overall. And that's why it's really important to explore any kind of drug treatment, SSRI or otherwise, really in close communication with a psychiatrist who really understands the pharmacokinetics

01:25:17 Serotonin & Cognitive Flexibility, Psilocybin Studies

and has a lot of patient history and experience with them. So what I'm about to tell you next is most certainly going to come as a big surprise, which is that despite the fact that the selective serotonin reuptake inhibitors can be effective in reducing the symptoms of OCD, at least somewhat, and certainly more than placebo, there is very little, if any evidence, that the serotonin system is disrupted in OCD. And I have to point out that this is a somewhat consistent theme in the field of psychiatry, that is a given drug can be very effective or even partially effective in reducing symptoms or in changing the overall landscape of a psychiatric disorder or illness, and yet there is very little, if any evidence, that that particular system is what's causal for OCD, or anxiety, or depression, et cetera. This is just the landscape that we're living in in terms of our understanding of the brain and psychiatry and the ways of treating brain disorders. So as a consequence, there are a huge number of academic reviews that clinicians and research scientists have generated and read and share. One of the more, I think, thorough ones in recent years

was published in 2021. I'll provide a link to this. This is by an excellent, truly excellent researcher from Yale university School of Medicine, I should say not just a researcher but a clinician scientist, again, an MD-PhD. This is Christopher Pittenger And the title of the review is Pharmacotherapeutic Strategies and New Targets in OCD. And again, we'll provide a link to it. This is a just gorgeous review describing, as I just told you, that the serotonin system isn't really disrupted in OCD and yet SSRIs can be very effective. The review goes on to explore even what sorts of receptors for serotonin might be involved. If it's in fact the case that serotonin is a culprit in the creation of OCD symptoms. Talk about the serotonin 2A receptor and the serotonin 1A receptor. Why am I mentioning all that detail? If in fact it's not clear, serotonin is involved because I'll just tell you right now, there is currently a lot of interest in whether or not some of the psychedelics, in particular psilocybin, can be effective in the treatment of OCD. Psilocybin has been shown in various clinical trials in particular the clinical trials done at Johns Hopkins School of Medicine by Matthew Johnson and others. Matthew was on The Huberman Lab Podcast. He's been on the Tim Ferris podcast. He's been on the Lex Fridman podcast. He's a world class researcher on the use of psychedelics for depression and other psychiatric challenges. And their psilocybin treatment has been seen, at least in those trials, to be very effective in the treatment of certain kinds of major depression. Currently the exploration of psilocybin for the treatment of OCD has not yielded similar results, although the studies are ongoing. Again, has not yielded similar effectiveness, but the studies are ongoing And the serotonin 2A receptor and the serotonin 1A receptors are primary targets for the drug psilocybin. So I figured there were going to be some questions about whether or not psychedelics help with OCD, thus far it's inconclusive. If any of you have been part of clinical trials or have knowledge or intuition about this relationship or potential relationship, I should say, between psilocybin and other psychedelics in OCD, please put them in the comment section. We'd love to love to hear from you. One thing I should point out is that even though serotonin has not been directly implicated in OCD, serotonin and the general systems of serotonin, the circuits in the brain that carry serotonin and depend on it have been shown to impact cognitive flexibility and inflexibility, which are kind of hallmark themes of OCD. So in animals that have their serotonin depleted or in humans that have very low levels of serotonin, you can see evidence of cognitive inflexibility, challenges in tasks, switching challenges and switching the rules by which one performs a game, challenges in any kind of cognitive domain switching. And so that does indirectly implicate serotonin in some of the aspects

of OCD. Again, when one starts to explore the different transmitter systems that have been explored in animal models and in humans, it's a vast, vast landscape, but serotonergic drugs do seem to be the most effective drugs in treating OCD despite the fact, again, despite the fact that there's no direct evidence that serotonin systems are the problem in OCD. If you recall the cortico-striatal-thalamic loop that is so central to the etiology, the presence and the patterns of symptoms in OCD, of course, serotonin is impacting that system. Serotonin is impacting just about every system in the brain, but there's no evidence that tinkering with serotonin levels, specifically in that network, is what's leading to the improvements in OCD. However, if people go into a FMRI scanner and those people have OCD and they evoke the obsessions and compulsions, you see activity in that cortico-striatal-thalamic loop. Treatments like SSRIs that reduce the symptoms of OCD equate to a situation where there is less activity in that loop. And I should point out cognitive behavioral therapy, which we have no reason to believe only taps into the serotonin system, I think it would be extreme stretch, it would be false actually to say that that cognitive behavioral therapy taps only into the serotonin system, clearly it's going to affect a huge number of circuits in neurochemical systems. Well, people who do cognitive behavioral therapy and find some relief for OCD, they also show reductions in those cortico-striatal-thalamic loops. So basically we have a situation where we have a behavioral therapy that works, in many people, not all, and we have a pretty good understanding of about why it works. It increases anxiety tolerance, and interference with pattern execution, getting people to not engage in the same sorts of behaviors that are detrimental to them. And we have drug treatments that work at least to some degree, but we don't know how they work or where they work in the brain. One of the things that really unifies the behavioral treatments and the drug treatments is that they take some period of time. Some relief from symptoms seems to show up around four weeks and certainly by eight weeks for both cognitive behavioral therapy and the SSRIs, but it's really at the 10 to 12 week stage when someone's been doing these twice a week, cognitive behavioral sessions, where they've been taking a SSRI for 10 to 12 weeks,

01:31:50 Neuroleptics & Neuromodulators

that the really significant reduction in OCD symptoms starts to really show up. Now, up until now, I've been talking about the fact that people are getting relief from these

treatments, but sadly, in the case of OCD, there is a significant population that simply does not respond to CBT or to SSRIs, or to their combination, which is why psychiatrists also explore the combination of SSRIs and neuroleptics or drugs that tap into the so-called dopamine system or the glutamate system. These are other neurotransmitters and neuromodulators that impact different circuits in the brain. And just to really remind you what neurotransmitters and neuromodulators do, because this is important to contextualize all this, neurotransmitters are typically involved in the rapid communication between neurons. And the two most common neurotransmitters for that are the neurotransmitter glutamate, which we say is excitatory, meaning when it's released into the synapse, it causes the next neuron to be more active, or active, and GABA which is a neurotransmitter that is inhibitory, meaning when it's released into the synapse, typically, not always, but typically, that GABA is going to encourage the next neuron to be less electrically active or even silence its activity. The neuromodulators, by contrast, So not neurotransmitters, but neuromodulators like dopamine, serotonin, epinephrine, and acetylcholine and others operate a little bit differently. They tend to act a little bit more broadly. They can act within the synapse, but they can also change the general patterns of activity in the brain, making certain circuits more likely to be active and other circuits less likely to be active. So when we say dopamine does X or dopamine does Y, or serotonin does X or serotonin does Y, they don't really do one thing, they change the sort of overall tonality. They make it more likely or less likely that certain circuits will be active. You can think of them as kind of activating playlists or genres of activity in the brain, rather than being involved in the specific communication or specific songs, if you will, in this analogy, or discussions between particular neurons. So when we hear that SSRIs increase serotonin and reduce the symptoms of OCD, or a neuroleptic reduces the amount of dopamine and makes people feel calmer for instance, or can remove some stereotype, repetitive motor behavior, which they can either generate or reduce motor behavior it turns out. So when I say that, what I'm referring to is the fact that these neuromodulators are kind of turning up the volume on certain circuits and turning down the volume on other circuits. I say that because if you are going to explore drug treatments again with a licensed physician, if you're going to explore drug treatments for OCD, and in particular, if you are not getting results from SSRIs, or you're not getting results from cognitive behavioral therapy or the side effect profiles of the drugs that you're taking for OCD are causing problems that you don't want to take them, well, then it's important to understand that anytime you take one of these drugs, they're not acting

specifically on the cortico-striatal-thalamic circuit. That would be wonderful. That's the future of psychiatry, but as now, when you take a drug, it acts systemically. So it's impacting serotonin in your gut. It's also impacting serotonin in other areas of the brain, hence the effects on things like digestion or libido or any number of different things that serotonin is involved in. Likewise, if you take a neuroleptic like haloperidol or something that reduces dopamine transmission, well, then it's going to have some motor effects 'cause dopamine is involved in the generation of motor sequences and smooth limb movement. That's why people with Parkinson's who don't have much dopamine will get a resting tremor, have a hard time generating smooth movement. And so the side effects start to make sense, given the huge number of different neural circuits that these different neuromodulators are involved in. I don't say that to be discouraging, I say that to encourage patients and careful systematic exploration of different drug treatments for OCD always again with the careful and close guidance and oversight of a psychiatrist because psychiatrists really understand which side effect profiles make it likely that you can or cannot or will never, or maybe someday will be able to take a given drug at a given dose. They're the ones that really have that knowledge.

01:36:09 OCD & Cannabis, THC & CBD

This is not the sort of thing that you want to cowboy and go try and figure out yourself. Now, I also want to acknowledge that there are other forms of drug treatments. We touched on psilocybin briefly, but there are other forms of drug treatments that have been explored for OCD. Earlier, we talked a little bit about cannabis. Why would cannabis be a place of exploration at all? Well, first of all, a number of people try and self medicate for OCD. There is some clinical evidence, I'm not talking about recreational use, I'm talking about clinical evidence that cannabis can reduce anxiety. Now earlier we were talking about not reducing anxiety, but learning anxiety tolerance in order to deal with and treat OCD in the context of cognitive behavioral therapies. That doesn't necessarily rule out cannabis as a candidate for the treatment of OCD. And in fact, this has been explored. A study from Dr. Blair Simpson herself looked at this. This was a fairly small scale study. So first of all, I'll give you the title. And again, we'll provide a link. This is entitled, Acute effects of cannabinoids on symptoms of obsessive-compulsive disorder: A human laboratory study. very briefly, this was 14 adults with OCD. They had prior experience with cannabis. This was randomized, placebo-controlled. The cannabis

was smoked, they had different varietals, as they're called. They had a placebo. So this is basically a condition in which certain subjects consumed a cigarette that had 0% THC, others had 7% THC, other groups that is, or some had 0.4% CBD and THC. So they looked at CBD. I know a lot of people out there are interested in CBD. This is one of the few studies I could find where they explored different percentages of THC and CBD in these cannabis or marijuana cigarettes basically. The total amount that they consumed, I believe, was 800 milligrams. These, again, are not suggestions. These are just simply reporting what's in this study. You can, again, I'll provide a link. They looked at OCD symptoms, ratings. They looked at cardiovascular effects. They had a large number of different things that they explored. And I should say this study was done in 2020, and it was the first placebo-controlled investigation of cannabis in adults with obsessive-compulsive disorder. Pretty interesting. And I'm just reading from their conclusions here. The data suggests that smoked cannabis, whether containing primarily THC or CBD, remember they looked at different concentrations of those, has little acute impact, meaning immediate impact on OCD symptoms and yield smaller reductions in anxiety compared to placebo. So they did not see a, when I say a positive effect, I mean a ameliorative effect, an effect in reducing symptoms of OCD from cannabis or CBD, which, it's unfortunate. I think it's unfortunate anytime a treatment doesn't work. But nonetheless, those are the data, I'm sure there are going to be other studies. I'm sure there are also going to be people in the YouTube comments section saying that cannabis and CBD helps their OCD symptoms, at least I anticipate there probably will. Almost everything I say here, somebody will contradict it with something from their experience, which I encourage, by the way. I want to hear about your experience with certain things even if it's not from randomized placebo-controlled studies, I still find it very interesting to know what people are doing and what they're experiencing. I think that's one of the better uses of social media comment sections, is to be able to share some of that, not in an advice-giving way or prescriptive way,

01:39:29 Ketamine Treatment

but simply as a way to share and encourage different types of exploration. There are other sorts of drug treatments that are gaining popularity for OCD, at least in the research realm. One treatment that is a legal, L-E-G-A-L. Sometimes when I say legal, sometimes people think I say illegal, but that is legal, at least by prescription in the

United States, is ketamine. The actions of ketamine are somewhat complex although we know, for instance, that ketamine acts on the glutamate system, it tends to disrupt the transmission or the relationship, I should say, between glutamate, not glutamine, not the amino acid, but glutamate, the neurotransmitter, and the so-called NMDA, the N-methyl-D-aspartate receptor, which is a receptor that's very special in the nervous system because when glutamate binds to the NMDA receptor, it tends to offer the opportunity for that particular synapse to get stronger, so-called neuroplasticity and ketamine is a, essentially, an antagonist, although it works through a complicated mechanism, it tends to block that binding of glutamate to the NMDA receptor or the effectiveness of that. Ketamine therapy is now being used quite extensively for the treatment of trauma and for depression. It leads to a dissociative state. It's a so-called dissociative analgesic in the variety of ways in which that happens. We did an episode on depression. We're going to do another entire episode all about ketamine describing the networks that ketamine impacts, et cetera. Ketamine therapies are being explored for OCD. As of now, the data look somewhat promising, but there's still a lot more work that needs to be done. My read of the data are that the more extensive clinical trials have not happened yet. The smaller studies that have happened revealed that some patients do get some relief from ketamine therapy for OCD, but there was nothing overwhelmingly pointing to the fact that ketamine is a magic bullet for OCD treatment. So cannabis, CBD, at least now, even though it's one smaller study, there's no real evidence that it can alleviate OCD symptoms. If there are new studies published soon, I'll be sure to update you. And if you see those studies, please send them to me. Ketamine therapy, the jury is still out,

01:41:43 Transcranial Magnetic Stimulation (TMS)

psilocybin, The jury is still out. These are early days. Another treatment that's becoming somewhat common, or at least people are commonly excited about is transcranial magnetic stimulation. So this is the use of a magnetic coil. This is completely noninvasive, placed on one portion of the skull, and one can direct magnetic energy toward particular areas of the brain to either suppress, or nowadays, you can also activate particular brain regions. There are some interesting data showing that if TMS is applied to areas of the brain involved in the generation of motor action, so the so-called motor areas, or supplementary motor areas as they're called, while people think about or have intrusive thoughts, we know that the TMS coil can interrupt the motor behaviors,

the compulsive behaviors, and at least in a small cohort of studies and a small number of patients within those studies, this has been shown to be effective, not just while the coil is on the head, of course, but after the study has been performed or the treatment's been performed in reducing OCD symptoms by disrupting the tendency for the compulsive behavior to be so automatic. One of the key features of obsessive-compulsive disorder is that, especially if it's been around for a while, the person's been dealing with it for a while, there isn't a pattern in which the person thinks, oh, I have this contamination fear, or I need symmetry, or I'm kind of obsessed to count to the number seven. And then they pause and they go, ooh, and then they do it. No, typically there's a very close pairing of the obsession and the compulsion in time so that somebody's walking down the street, thinking one, two, three, four, five, six, seven, one, two, three, four, five, six seven, seven... and then they're doing this in such rapid succession because the obsessions are coming up so quickly. Thoughts can be generated very quickly. And then they're generating the compulsions as a way to beat down or to try and suppress that anxiety and then it comes right back up again at even stronger as I described earlier. So transcranial magnetic stimulation seems to intervene in these various fast processes. Right now, I don't think it's fair to say that TMS is a magic bullet either. I think there's a lot of excitement about TMS and in particular, I really want to nail this point home, in particular, there's excitement about the combination of TMS with drug treatments, or the combination of TMS with cognitive behavioral therapy. And this is a really important point, not just for sake of discussion about obsessive-compulsive disorder, but also depression, ADHD, schizophrenia, any number of different psychiatric challenges and disorders in most cases are going to respond best to a combination of behavioral treatment that's ongoing that occurs in the laboratory and clinical setting, but also in the home setting where there's homework, maybe even home visits. Drug treatments, often, not always, are a terrific augment to those cognitive behavioral therapies or other behavioral therapies. And then now we are living in the age of brain-machine interface. You have companies like Neuralink that I think it's fair to say are going to enter the brain machine-interface world first through the treatment of certain syndromes, movement syndromes or psychiatric syndromes probably before they start putting electrodes into the brain to stimulate enhanced memory or enhanced cognition, who knows, I don't know exactly what they're doing behind the walls of Neuralink. But I have to imagine, in fact, I would wager maybe not both arms, but I'll wager my left arm that the first set of FDA approved technologies to come out of companies like Neuralink

are going to be those for the treatment of things like Parkinson's and movement disorders and cognitive disorders, rather than, shall we say, kind of recreational cognitive enhancement or things of that sort. So transcranial magnetic stimulation is noninvasive. It doesn't involve going down below the skull, can have some effect, but most laboratories that I'm aware of at Stanford and elsewhere that are exploring TMS for things like OCD and other types of psychiatric challenges are using TMS in combination with drug therapies, are using, in some cases, for instance, a laboratory at Stanford, hope to get 'em on the podcast, a psychiatrist, Nolan Williams, is exploring TMS in combination with psychedelic therapies, not necessarily at the same time, but nonetheless combining them or exploring how they impact brain circuitry. So if you have OCD, should you run out and get TMS, or should you try ketamine therapy, of course, with a licensed physician? I think it's too early to say yes. I think the answer is we need to wait and see. I think cognitive behavioral therapy, the SSRIs, and some other drug treatments like neuroleptics

01:46:22 Cannabis CBD & Focus

combined with SSRIs and cognitive behavioral therapy are where the real bulk of the data are. I want to make one additional point about cannabis CBD as it relates to obsessive-compulsive disorder. To me, it's not at all surprising that cannabis CBD did not improve symptoms of OCD. Because in my discussion with Dr. Paul Conti a few weeks ago, and I should mention, Dr. Conti is indeed a medical doctor, a psychiatrist, we were talking about cannabis and its various uses, because it does have some clinical applications. And he mentioned that one of the main effects of cannabis is to tighten focus and to enhance concentration on and thoughts about one particular thing. And in some cases that can be clinically beneficial, and in other cases that can be clinically detrimental. If you accept the idea that cannabis increases focus, and you think about OCD and the networks involved, and you think about the anxiety and the relationship between the obsession and compulsion, well, then it shouldn't come as any surprise that cannabis did not improve the symptoms of OCD because if anything, it would increase focus on the obsessions and the compulsions. Now that's not what they observed. They did not see an exacerbation or a worsening of the symptoms of OCD with cannabis, at least that's not my read of the data, but they did not see an improvement in OCD symptoms with cannabis or CBD.

01:47:50 Thoughts Are Not Actions

And to me, that's not surprising given that cannabis CBD seems to increase focus. Next, I'd like to talk about some of the research on and the roles of hormones in OCD, because it turns out to be a very interesting relationship there. But before I do, I want to point out something that I realize I probably should have said earlier, which is one of the key things for someone with OCD to come to understand if they're going to experience any relief of their symptoms, whether or not they're doing drug treatments or behavioral treatments or otherwise, is that thoughts are not as bad as actions. Thoughts are not as bad as actions. One of the kind of rules that people with OCD seem to adopt for themselves is that thoughts are really, truly the equivalent of actions. So they'll have an intrusive thought and, we haven't spent too much time on this today, but earlier I touched on the fact that some of the intrusive thoughts that people have in OCD are really disturbing. They can be really gross, or at least gross to that person. They can evoke imagery that is toxic or infectious, or is highly sexualized in a way that is disturbing to them, it can be very taboo. This is not uncommon when you start talking to people with OCD and you start pulling on the thread. Again, this would be a psychiatrist who was trained to ask the right questions and gain the comfort and trust of a patient. And they start to reveal that these thoughts are really intrusive and kind of disturbing, which is why they feel so compelled to try and suppress them with behaviors. One of the powerful elements of treatment for OCD is to really support the patient and make them realize that thoughts are just thoughts and that everyone has disturbing thoughts. And that oftentimes those disturbing thoughts arise at the most inconvenient, and sometimes, what seems like the most inappropriate circumstances. And this relates to a whole larger discussion that we could have about what are thoughts and why do they surface, and how come when you stand at the edge of a bridge, even if you do not want to jump off, you think about jumping off. And this has to do with the fact that your nervous system, as a prediction machine, is oftentimes testing possibilities. And sometimes that testing goes way off into the Netherlands of the thought patterns and emotional patterns that we all have inside of us. The big difference between a thought and an action is that, of course, the nervous system is, in one case, not translating those patterns of thinking into motor sequences. That nerdy way of saying thoughts aren't actions, believe it or not, can be helpful for people if they really think about that and use it as an opportunity to realize

that, first of all, they're not crazy. They're not thinking and feeling this stuff because they're bad or evil. And of course, sometimes this can cross over with other elements of life where we place moral judgment on people for certain behaviors. I think that's part of a healthy society, of course, that's why we have laws and punishments and rewards for that matter for certain types of behaviors. But this idea that thoughts are not as bad as actions and that thoughts can be tolerated and the anxiety around thoughts can be tolerated and over time can diminish, that's a very powerful hallmark theme of the treatment of OCD so I'd be remiss if I didn't mention it. Thoughts are not actions. Actions can harm us, they can harm other people, they can soak up enormous amounts of time. Thoughts can soak up enormous amounts of time. They can be very troubling. They can be very detrimental. We of course want to be sensitive to that, but when it really comes down to it, the first step in treatment for OCD is this realization

01:51:27 Hormones, Cortisol, DHEA, Testosterone & GABA

where the approach to the realization that thoughts are not as bad as actions. So what about hormones in OCD? Well, this has been explored, albeit not as extensively as I would've liked to find, but when I went into the literature, I found one particularly interesting study, entitled, Neurosteroid Levels in Patients with Obsessive-Compulsive Disorder. First author, Erbay And as always, we'll provide a link to the study. The objective of this study was to explore serum within blood, neurosteroid levels in people with OCD. Why? Well, because of the relationship between OCD and anxiety and the fact that in stress-related disorders such as anxiety and depression, the hormones have been extensively explored, but not so much in OCD, at least until this study. So they compared serum levels of a number of different hormones, progesterone, pregnenolone, DHEA, cortisol, and testosterone. This was done in 30 patients with OCD and 30 healthy controls. So it's not a huge study, but it's enough to draw some pretty nice conclusions. These subjects were 18 to 49 years old, and the controls were age and sex matched healthy volunteers. Again, no OCD. What was the basic takeaway from the study? The basic takeaway from the study was that in females with OCD, there was evidence for significantly elevated cortisol and DHEA. Now that's interesting because cortisol is well known to be associated with the stress system. Although every day, should mention, we all, male or female, everybody experiences an increase in cortisol shortly after awakening. That's a healthy increase in cortisol. Late shift, I mean, late in the day peaks

in cortisol where a shift in that cortisol peak to later in the day is a known correlate of depression and anxiety disorders. So the fact that cortisol is elevated and DHEA are elevated in female patients with OCD suggests that cortisol is either reflective of or causal for the increase in anxiety. We don't know the direction of that effect. Now in male patients with OCD, there was evidence for increased cortisol. Again, not surprising given the role of anxiety in cortisol, or I should say, given the role of cortisol in anxiety and the increasing anxiety seen in OCD, but there are also significant reductions in testosterone, which should also not surprise us because cortisol and testosterone more or less compete in some fashion for their own production, both are derived from the molecule cholesterol. And there are certain biochemical pathways that can either direct that cholesterol molecule toward cortisol synthesis or testosterone synthesis, but not both. So they compete. So when cortisol goes up in general, not always, but in general, testosterone goes down and vice versa. If you want to learn more about the relationship between cortisol and testosterone, and there are even some tools to try and optimize those ratios in both males and females, you can find that in our episode on optimizing testosterone and estrogen, that's at hubermanlab.com. Now, I would say the most interesting aspect of this study is not that DHEA and cortisol are elevated in females with OCD or that cortisol and testosterone have this opposite effect, cortisol up and testosterone down in males with OCD, but rather the relationship between all of those, DHEA, cortisol, and testosterone. In terms of GABA, GABA again being this inhibitory neurotransmitter that tends to quiet certain neuronal pathways, it does different things at different synapses, but in general, the more GABA that's present, the more inhibition that's present, and therefore the more suppression of neural activity. And DHEA is known to be a potent antagonist of the GABA system. So here we have elevated DHEA in females. And I should also mention that testosterone is also known to tap into the GABA system. Typically, when testosterone is elevated, GABA transmission, at least is slightly elevated. So here we have a situation in which the pattern of hormones in females and males with OCD are different from those in people without OCD such that GABA transmission is altered and the net effect would be an overall reduction in GABA. Now GABA, as an inhibitory neurotransmitter, and broadly speaking is associated with lower levels of anxiety, and it tends to create balance within various neural circuits. Now, that's a very broad statement, but we know for instance, in epilepsy, that GABA levels are reduced and therefore you get runaway excitation of certain circuits in the brain, and therefore seizures, either petite mal, mini seizures, or grand mal, massive seizures, or

even drop seizures where people completely collapse to the floor in seizure. You may have seen this before. I certainly have, it's very dramatic and it actually is quite debilitating for people because obviously they don't know when these seizures are coming on most often, and then they can fall into a stove or while driving, et cetera. So the situation with OCD is one in which, for whatever reason, we don't know the direction of effect. Certain hormones are elevated in females and certain hormones are elevated in males and those hormones differ between males and females, and yet they both funnel into a system where GABAergic or GABA transmission in the brain is reduced because of this ability for those particular hormones to be antagonists to GABA, and as a consequence, there's likely to be overall levels of increased excitation in certain networks in the brain and that brings us back to this cortico-striatal-thalamic loop, this repetitive loop that seems to reinforce, we can say reinforces obsession, leads to anxiety, leads to compulsion, leads to transient relief of anxiety, but then increase in anxiety, increased obsession, anxiety, compulsion, anxiety, compulsion, anxiety, compulsion, and so on and so forth. So I have not found studies that have explored adjusting testosterone levels through exogenous administration, cream or injection or otherwise, or that have focused on reducing DHEA in females. If anyone is aware of such studies, please put them in the comment section on YouTube or send them to us. We have a contact site on the website at hubermanlab.com, but the comment section on YouTube would be best. But because we know that hormones impact neuromodulators and neurotransmitters, as I just described, and that those neuromodulators and neurotransmitters play an intimate role in the generation and the treatment of things like OCD, it stands to reason that manipulations of those hormone systems, however subtle or dramatic might, I want to highlight, might prove useful in adjusting the symptoms of OCD and I hope that this is an area that researchers are going to pursue in the very near future because many of the treatments for reducing DHEA or increasing testosterone or reducing cortisol have already made it through FDA approval. They're out there, they're readily prescribed. Many of them are already in generic form which means that the patents have already lapsed on the first versions of those drugs. So when they're available as generic drugs, very often, they're available at significantly lower cost. There's a whole discussion we had there about patent laws and prescription drugs. But because these drugs are largely available in prescription yet generic form, I think there's a great opportunity to explore how hormones, not just cortisol, testosterone, and DHA, but the huge category of hormones might impact the symptoms of OCD, especially since

many of the symptoms of OCD show up right around the time of puberty. We haven't talked a lot about childhood OCD, 'cause we're going to do an entire series on childhood psychiatric disorders and challenges but many children develop OCD early as young as three or four, believe it or not, or even 6 or 7 and 10 and in adolescence, and certainly around puberty. and in young adulthood. It is rare, although it does happen, that people will develop OCD very late in life around 40 or older, just kind of spontaneously. Most often when you look at their clinical history, you find that either they were hiding it or is being suppressed in some way, or if it does spontaneously show up late in life like mid-thirties or in one's forties, typically there's a traumatic brain injury, could be due to stroke or physical injury to the head or something of that sort. Nonetheless, there is a interesting correlation between the onset of puberty in certain forms of OCD. There's certain forms of, or I should say, there's certain aspects of menopause that can relate to OCD. You can find all these things in the literature. All this to say that hormones impact neurotransmitters and neuromodulators, which clearly impact the kinds of circuits that are involved in OCD and it makes sense that, and I would hope that there would be an exploration of how these hormones impact OCD in the not too distant future. Now there is an extensive literature exploring how testosterone therapy, both in males and females, can be effective in some cases in the treatment of anxiety-related disorders, but not, at least to my knowledge, in OCD in particular. So this whole area of the use of testosterone and estrogen therapies, DHEA, cortisol suppression, or maybe even enhancement for the treatment of OCD

02:00:55 Holistic Treatments: Mindfulness Meditation & OCD

is essentially a big black box that very soon, I believe, will be lit. I realize that a number of listeners of this podcast are probably interested in the non-typical or holistic treatments for OCD. Dr. Blair Simpson's lab has at least one study exploring the role of mindfulness meditation for the treatment of OCD. There, the data are a little bit complicated and I should mention that good things are happening, at least in the United States, probably elsewhere as well, but good things are happening in terms of the exploration of things like meditation and other, let's call them non-traditional or holistic forms of treatment for psychiatric disorders because of the division of complimentary health that's now been launched by the National Institutes of Health. So, whereas before people would think about meditation or yoga nidra, or even CBD supplementation for

that matter, as kind of fringe maybe, or kind of woo or non-traditional at the very least, the National Institutes of Health in the United States has now devoted an entire division, an entire Institute, purely for the exploration of things like breathing practices, meditation, et cetera. So there's a cancer institute, there's a hearing and deafness institute, there's a vision institute, and now there's this complimentary health Institute, which I think is a wonderful addition to the more traditional aspects of medicine. I think no possible useful treatment should be overlooked or unresearched in my opinion, provided that can be done safely. And as I mentioned, Dr. Blair Simpson's lab has looked at the role of mindfulness meditation and the treatment of OCD. Now we should all keep in mind, no pun intended, that most of the data on mindfulness meditation shows that it increases the ability to focus. Now, this brings us back to a kind of repeating theme today, which is that increased focus may not be the best thing for somebody with OCD because it might increase focus on the obsession and/or compulsion. Turns out that mindfulness meditation can be useful in the treatment of OCD, but mainly by way of how it impacts the focus on and the ability to engage in cognitive behavioral therapies. So it's very unlikely, at least by my read of the data, to be a direct effect of meditation on relieving the symptoms, rather it seems that meditation is increasing focus on things like cognitive behavioral therapy homework

02:03:28 Nutraceuticals & Supplements: Myo-Inositol, Glycine

and to not focus on other things and therefore indirectly improving the symptoms of OCD. Now somewhat surprisingly, at least to me, there have also been a fairly large number of studies exploring how nutraceuticals, as they're sometimes called, supplements that are available over the counter can impact the treatment of obsessive-compulsive disorder. Now there's such an extensive number of different compounds and supplements that fall under the category of nutraceuticals and that have been explored in the treatment of OCD that I'd like to point you to a review that is entitled, Nutraceuticals in the treatment of obsessive-compulsive disorder: a review, excuse me, of mechanistic and clinical evidence. So it's published in 2011, so it's over 10-years-old. And so by now, I have to imagine that there are an enormous number of additional substances that could be explored, but there are just one or two here that I want to focus on. Here in this review, they describe effects of 5-HTP and tryptophan, so things that are in the serotonin pathway, which would make sense given what we know about the

SSRIs that people would explore how different supplements that increase serotonergic transmission might impact OCD. What you find is that they do have significant effects in improving or reducing the symptoms of OCD in somewhat similar way to some of the SSRIs. But you of course have to be careful. Anything that's going to tap into a given neurochemical system to the same degree may very likely have the same sorts of side effects that a prescription drug would. One compound that I like to focus on in a little more depth, however, because it's exciting and interesting to me is inositol. Inositol is a compound that we are going to talk about in several future podcasts, because, well, first of all, it seems that it can have impressive effects on reducing anxiety. It also can have pretty impressive effects in improving fertility and particular in women with polycystic ovarian syndrome. And here I'm referring specifically to myo-inositol because it comes in several forms. And it does appear that 900 milligrams of inositol can improve sleep and can reduce anxiety perhaps when taken at that dosage or higher dosages. I will just confess, first of all, I don't have OCD, although I will also confess that when I was a child, I had a transient tick. I've talked about this on podcast before. It was a grunting tick. So when I was about six or seven, I recall a trip to Washington DC with my family, where I was feeling a strong desire or need even as I recall, to grunt in order to clear something in my throat, but I didn't have anything in my throat. I didn't have a cold or any postnasal drip, it was really just the feeling that I needed to do that, to release some sort of tension. And I remember my dad at the time telling me don't do that. Don't do that, it's not good to grunt or something like that. I think he saw that it was a kind of compulsive behavior. And so I would actually hide in the back seat of the rental car and do it, or I'd hide in my room. Fortunately for me, it was transient, I think about six months or a year later, it disappeared. Although I did notice, actually an ex-girlfriend of mine point out that when I get very tired and I've been working very long hours, sometimes that grunting tick will reappear. What does that mean? Do I have Tourette's? I don't know, maybe. I was never diagnosed with Tourette's. Do I have OCD? Maybe. I certainly could be accused of having obsessive-compulsive personality disorder, which we'll talk about still in a few minutes. But the point here is that many children transiently express ticks or low level Tourette's or OCD, and again, transiently and it disappears over time. So inositol has been explored in a bunch of different contexts, including for ticks in OCD, et cetera. Going back to inositol and its current use, or I should say my current use, I've been taking 900 milligrams of inositol as in addition to my existing toolkit for sleep, which I've talked about many times on this podcast and other podcasts, consists of magnesium

threonate, apigenin, and theanine. If you want to know more about that kit, you can go to our newsletter, Neural Network Newsletter at hubermanlab.com. The toolkit for sleep is there. You don't even have to sign up for the newsletter but it'll give you a flavor of the sorts of things that are in the newsletter. In any case, I've been experimenting a bit with taking 900 milligrams of myo-inositol either alone or combination with that sleep kit. And I must say the sleep I've been getting on inositol is extremely deep and does seem to lead to enhanced levels of focus and alertness during the day. And perhaps you're noticing that 'cause I'm talking more quickly on this podcast than in previous podcast. No, I'm just kidding. I don't think the two things relate in any kind of causal way. The point here is that inositol is known to be pretty effective in reducing anxiety, but when taken at very high dosages. Can it do the same at low dosages? We don't know. I would consider 900 milligrams a low dose. Most of this, given the fact that most of the studies of inositol have explored very high dosages, like even 10 or 12 grams per day, which I must say seems exceedingly high and they do report that some of the subjects in those experiments actually stop taking the inositol because of gastric discomfort or gastric distress as it's called. So I've reported my results with sleep in a kind of anecdotal way. They certainly aren't peer-reviewed studies that I described about my own experience in an anecdotal way. But nonetheless, it's been explored that things like glycine, which is another, which is an amino acid, which also acts as an inhibitory neurotransmitter in the brain, taken at very high dosages, 60 grams per day, that is a absolutely astonishingly high amount of glycine. I would not recommend taking that much glycine unless you're part of a study where they tell you to and you know it's safe. 18 grams, excuse me, of an inositol, these are very, very high dosages used in these studies. Nonetheless, there's some interesting data about inositol leading to some alleviation of OCD symptoms or partial alleviation of OCD symptoms in as little as two weeks after initiating the supplement protocol. So I think there's a great future for these nutraceuticals, meaning I think more systematic exploration in particular of lower dosages in the context of OCD treatment. And as we saw before for the SSRIs and other prescription drug treatments, I think there really needs to be an exploration of these nutraceuticals in combination with behavioral therapies.

02:09:45 OCD vs. Obsessive Compulsive Personality Disorder

And who knows, maybe with brain machine interface like cranial magnetic stimulation as

well. Now way back at the beginning of the episode, I alluded to the fact that OCD is one thing, obsessive-compulsive disorder, and it's truly a disorder and it's truly debilitating and it's extremely common, and then there's this other thing called obsessive-compulsive personality disorder, which is distinct from that does not have the intrusive component so people don't feel overwhelmed or overtaken by these thoughts, rather, they find that the obsessions can sometimes serve them or they even welcome them. And I think many of us know people like this, I perhaps even could be accused or who knows, maybe have been accused of having an obsessive-compulsive personality at times. Why do I draw this distinction? Well, first of all, we've come to a point in human history, I think in large part because of social media but also in large part because there are a number of discussions being held about mental health that have brought terms like trauma, depression, OCD, et cetera, into the common vernacular so that people will say, ah, you're so OCD, or someone will say I was traumatized by that, or I was traumatized by this. We should be very careful, right? I'm certainly not the word police, but we should be very careful in the use of certain types of language, especially language that has real psychiatric and psychological definitions because it can really draw us off course in providing relief for some of these syndromes. For instance, the word trauma is thrown around left and right nowadays. I was traumatized by this, or that caused trauma, you're giving me trauma. Listen, I realize that many people are traumatized by certain events including things that are said to them, I absolutely acknowledge that, hence our episodes on trauma and trauma treatment, several of them, in fact. Dr. Conti, Dr. David Spiegel, and then dedicated solo episodes with just me blabbing about trauma and trauma treatment. But as Dr. Conti so appropriately pointed out, trauma is really something that changes our neural circuitry and therefore our thoughts and our behaviors in a very persistent way that is detrimental to us. Not every bad event is traumatizing, not everything that we dislike or even that we hate or that feels terrible to us is traumatizing. For something to reach the level of trauma, it really needs to change our neural circuitry and therefore our thoughts and our behaviors in a persistent way that is maladaptive for us. Similarly, just calling someone obsessive is one thing, saying that someone has OCD or assuming one has OCD simply because they have a personality or a phenotype, as we say, where they need things in perfect order, like I find myself correcting these pens making sure that the caps are facing in the same direction for instance right now, that is not the same as OCD. If, for instance, I can tolerate these pens being at different orientation or even throw the cap on the floor or something, it doesn't create a lot of

anxiety for me. I confess, I agree it's a little bit in the moment, but then I can forget about it and move on. That's one of the key distinctions between obsessive-compulsive personality disorder and obsessive-compulsive disorder in its strictest form. Now, once one hears that OCD is different than obsessive-compulsive personality disorder because of this difference in how intrusive the thoughts are or not, then that's useful, but it really doesn't tell us anything about what is happening mechanistically in one situation or another. Fortunately, there are beautiful data again from Dr. Blair Simpson's lab. And you can tell based on the number of studies that I've referred to from her laboratory, she's truly one of the luminaries in this field, that there really are some fundamental wiring differences and behavioral differences and psychological differences between people who have obsessive-compulsive disorder and those who have obsessive-compulsive personality disorder. So this is a study, first author, Pinto, P-I-N-T-O entitled, Capacity to delay reward differentiates obsessive-compulsive disorder and obsessive-compulsive personality disorder. And the methods in this study were to take 25 people with OCD and 25 people with obsessive-compulsive personality disorder and 25 people who have both, because it is possible to have both and that's important to point out, and 25 so-called healthy controls, people that don't have obsessive-compulsive personality disorder or obsessive-compulsive disorder. They take clinical assessments and then they took a number of tests that probed their ability to defer gratification, something called, in the laboratory, we call it delayed discounting. So their ability to defer gratification through a task where they can either accept reward right away or accept reward later. Some of you may have heard of the two marshmallow task. This is based on a study that was performed years ago on young children at Stanford and elsewhere where they take young children into a room, they offer them a marshmallow, kids like marshmallows generally, and you say, you can eat the marshmallow right now or you can wait some period of time, and if you are able to wait and not eat the marshmallow, you can have two marshmallows. And in general, children want two marshmallows more than they want one marshmallow. So really what you're probing is their ability to access delayed gratification. And they're very entertaining, even truly amusing videos of this on the internet. So if you just do two marshmallow task video and you go into YouTube, what you'll find is that the children will use all sorts of strategies to delay gratification. Some of the kids will cover the marshmallow. Others will talk to the marshmallow and say, I know you're not that delicious. You look delicious, but no, you're not delicious. They'll engage with the marshmallow in all sorts of cute ways. They'll turn around and try

to, you know, avoidance, which actually speaks to a whole category of behaviors that people with OCD also use. I'm not saying these kids had OCD, but avoidance behaviors are very much a component of OCD. People really trying to avoid the thing that evokes the obsession. Well some kids are able to delay gratification, some aren't and it's debatable as to whether or not the kids that are able to delay gratification go on to have more successful lives or not. Initially, that was the conclusion of those studies. There's still a lot of debate about it, we'll bring an expert on to give us the final conclusion on this 'cause there is one and it's very interesting and not intuitive. Nonetheless, adults are also faced with decisions every day, all day as to whether or not they can delay gratification. And this study used a, not a two marshmallow task, but a game that involved rewards where people could delay in order to get greater rewards later. What is the conclusion? Well, first of all, obsessive-compulsive and obsessive-compulsive personality disorder subjects both showed impairments in their psychosocial functioning and quality of life. They had compulsive behavior. So these are people that are suffering in their life because their compulsions are really strong. So it's not just being really nit-picky or really orderly in one case and having full blown OCD in the other, both sets of subjects are challenged in life because they're having relationship issues or job-related issues, et cetera, because they are that compulsive. However, the individuals with obsessive-compulsive personality disorder, they discounted the value of delayed gratification significantly less than those with obsessive-compulsive disorder. What do I mean? They are both impairing disorders that are marked by compulsive behaviors, here I'm paraphrasing, but they can be differentiated by the presence of obsessions in OCD. So obsessions in OCD. People with OCD are absolutely fixated on certain ideas and those ideas are intrusive. Again, that's the hallmark theme. And by an excessive capacity to delay reward in obsessive-compulsive personality disorder. That is people who have obsessive-compulsive personality disorder are really good at delaying gratification. So they are able to concentrate very intensely and perform very intensely in ways that allow them to instill order such that they can delay reward. Now you can see why this contour of symptoms, meaning that the people with OCD are experiencing intrusive thoughts, whereas the people with obsessive-compulsive personality disorder show an enhanced ability to defer gratification. You could see how that would lead to very different outcomes. People with obsessive-compulsive personality disorder can actually leverage that personality disorder to perform better in certain domains of life, not all domains of life, because remember, again, these people are in this study and they're

showing up as experiencing challenges in life because of their obsessive-compulsive personality disorder. Nonetheless, people with obsessive-compulsive personality disorder, you could imagine, would be very good at say architecture or anything that involves instilling a ton of order. Maybe sushi chef, for instance, maybe a chef in general. I know chefs that just kind of throw things around like the chef on the Muppets and just like throw things everywhere and still produce amazing food. And then there's some people there incredibly exacting, they're just incredibly precise. I think that movie, what is it? Jiro Dreams of Sushi? That movie is incredible. Certainly not saying he has obsessive-compulsive personality disorder, but I think it's fair to say that he is obsessive or extremely meticulous and orderly about everything from start to finish. You can imagine a huge array of different occupations and life endeavors where this would be beneficial, science being one of them where data collection and analysis is exceedingly important that one be precise, or mathematics or physics or engineering, anything where precision has a payoff and gaining precision takes time and delay of immediate gratification, you can imagine that obsessive-compulsive personality disorder would synergize well with those sorts of activities and professions. Whereas obsessive-compulsive disorder is really intrusive. It's preventing functionality in many different domains of life. So the key takeaway here is that when we use the words obsessive-compulsive, or we call someone obsessive-compulsive, or we are trying to evaluate whether or not we are obsessive compulsive, it's very important that we highlight that obsessive compulsive disorder is very intrusive. It involves intrusive thoughts and it interrupts with normal functioning in life. Whereas obsessive-compulsive personality disorder, while it can interrupt normal functioning in life, it also can be productive. It can enhance functioning in life, not just in work, but perhaps at home as well. If you are somebody and you have family members that really place enormous value on having a beautiful and highly organized home, well, then it could lend itself well to that. it's going to be a matter of degrees, of course. None of these things is an absolute, it's going to be on a continuum, but I think it is fair to say that obsessive-compulsive disorder, whether or not in mild, moderate, or severe form is impairing normal functioning, whereas obsessive-compulsive personality disorder, there's a range of expressions of that, some of which can be adaptive,

02:20:53 Superstitions, Compulsions & Obsessions

some of which can be maladaptive, and again, it's all going to depend on context. Before we conclude, I do want to touch on something that I think a lot of people experience and that's superstitions. Superstitions are fascinating, and there's some fascinating research on superstitions. One particular study that I'm a big fan of is the work of Bence Olveczky at Harvard. He studies motor sequences and motor learning, and he has beautiful data on how people learn, for instance, a tennis swing and the patterns that they engage in early on and then the patterns of swinging that they, swinging the racket that is, that they engage in later as they acquire more skill. And basically the takeaway is that the amount of error or variation from swing to swing is dramatically reduced as they acquire skill. That's all fine and good, and there's some beautiful mechanistic data that he and others have discovered to support how that comes to be, but they also explore animal models, in particular, rats pressing sequences of buttons and levers to obtain a reward. Believe it or not, rats are pretty smart. I've seen this with my own eyes. You can teach a rat to press a lever for a pellet of food. Rats can also learn to press levers in a particular sequence in order to gain a piece of food. And they can actually learn to press an enormous number of levers in very particular sequences in order to obtain pellets of food. You can also give them little buttons to press or even a paddle to, or I should say a pedal, excuse me, to stomp on with their foot in order to obtain a pellet of food. Basically rats can learn exactly what they need to do in order to obtain a piece of food, especially if they're made a little bit hungry first. Bence's lab has published beautiful data showing that as animals and humans come to learn a particular motor sequence, very often they will introduce motor patterns in that sequence that are irrelevant to the outcome and yet that persist. If you've ever watched a game of baseball, you've seen this before. Oftentimes the pitcher up on the mound will bring the ball to their chin. They'll look over their shoulder, they'll look back over the other shoulder, and then they will, of course, reel back and pitch the ball. But if you watch closely, oftentimes there are components in the motor sequence, which are completely unrelated to the pitch. They're not looking necessarily to see if someone's stealing a base. They're not necessarily looking down at home plate where the batter is. They're also doing things like touching the back of their ear before they bring the ball to their chin or adjusting their hat. And if you watch individual pictures, what you'll find is that they'll do the same sequence of completely irrelevant motor patterns before each and every single pitch. Similarly, rats that have been trained to, for instance, hit two levers and step on a pedal with their left hind foot, and then tap a button up above that is the red button, will do that to gain a piece of food.

But sometimes they'll also introduce a pattern into that motor sequence where they will shake their tail a little bit, or they'll turn their head a little bit, or they'll move their ears a little bit, et cetera. Motor patterns that have nothing to do with obtaining the particular outcome in mind. In other words, you could eliminate certain components of the motor sequence and it would not matter, the rat would still get the pellet, the pitcher would still be able to pitch, and yet that get introduced because somehow because they were performed again and again prior to successful trials, the rat or the human baseball pitcher comes to believe in some way that it was involved in generating the outcome, hence superstition, right? I confess I have a few superstitions. I occasionally will knock on wood. I'll say something that I want to happen, and I'll say, oh, knock on wood, and I'll just do it. And occasionally I'll challenge myself and think, ah, I don't want to knock, don't knock on wood, Andrew, don't do that. I don't think anyone wants to be superstitious, I certainly don't. And so every once in a while, I'll just challenge it, and I won't actually knock on wood. I'm admitting this to you to kind of I guess normalize some of this. Some people have superstitions that border on or even become compulsions. They really come to believe that if they don't knock on wood, that something terrible is going to happen, maybe something in particular. Or in the case of the baseball pitcher, they come to believe that if they don't touch their right ear before they reel back on the pitch, that the pitch won't be any good or that they're going to lose the game. Well, I don't know what their thought process is. Now, I also don't know what the rat is thinking, but the rat is clearly doing something or thinking something is related to the final outcome. I don't know of any studies where they've intervened with the particular superstition-like behaviors of the rat to see whether or not the rat somehow doesn't continue to do the motor sequence to get the pellet. We don't know the rats, they're rats. I don't speak rat, most people don't, or if you speak to a rat, if it speaks back, it's not in English. Anyway, the point is that superstitions are beliefs that we, on an individual scale, come to believe are linked to the probability of an outcome when in fact we know, we actually know in our rational minds, they have no real relationship to the outcome. Superstitions can become full-blown compulsions and obsessions when we repeat them often enough that they become automatic. And I think this is what we observe most of the time when we see a pitcher touching their ear, or for instance, in tennis, you see this a lot, you'll see someone they'll slap their shoes. Often, I see this, they'll like slap the undersides of their soles. They may tell themselves that this is, I don't know, maybe moving out some of the dust or something in the bottoms of their soles, that gives them more traction and they

want that to be ready for the serve or something like that. And maybe there's some truth to that, but here, what we're referring to are behaviors that really have no rational relationship to the outcome, and yet we perform in a compulsive way. People with OCD, yes, tend to have more superstitions. People with more superstitions, yes, tend to have a tendency towards OCD and I should mention, obsessive-compulsive personality disorder. If you think way back to the first part of this episode, when I was just describing what the brain does, right? What does your brain do? Housekeeping functions to keep you alive and it's a prediction machine. Your neural circuits, you, have an enormous amount of biological investment of real estate, literally, cells and chemicals that are there to try and make your world predictable and to try and give you control, or at least the sense of control over that world and that's a normal process. Low-level superstitions, moderate superstitions represent a kind of a healthy range, I would say, of behaviors that are aimed at generating predictability that don't disrupt normal function. Obsessive-compulsive personality disorder, provided is not too severe, would I think represent the next level along that continuum. And then obsessive-compulsive disorder, as I pointed out earlier, is really a case of highly debilitating, highly intrusive, really overtake of neural circuitry over our thoughts and behaviors that requires very dedicated, very persistent, and very effective treatments in order to stop those obsessions and compulsions and the anxiety that links them somewhat counterintuitively by teaching people to tolerate that level of increased anxiety and interrupt those patterns. And fortunately, as we described earlier, such treatments exist, cognitive behavioral therapy, drug treatments like SSRIs, also drug treatments that tap into the glutamate system and into perhaps also the dopamine system, the so-called neuroleptics. And then, as we described, there's now an extensive exploration of things like ketamine, psilocybin, cannabis, the initial studies don't seem to hold much promise for cannabis and CBD and the treatment of OCD, but who knows, maybe more studies will come along that will change that story. And then of course, brain machine interface like transcranial magnetic stimulation. And then just to remind you what I already told you before combinations of behavioral and drug treatments and brain machine interface, I think, is really where the future lies. Fortunately, good treatments exist. We cannot say that any one individual treatment works for everybody. There are fairly large percentages of people that won't respond to one set of treatments or another, and therefore one has to try different ones. And then there are the so-called supplementation-based or more holistic therapies. Today, I've tried to cover each and all of these in a fairly substantial amount of detail. I realize this is

a fairly long episode, that is intentional. Much like our episode on ADHD, on attention deficit hyperactivity disorder, I received an enormous number of requests to talk about OCD, and my decision to make this a very long and detailed episode about OCD really doesn't stem from any desire to subject you to too much information or to avoid the opportunity to just list things off, but what I've tried to provide is an opportunity to really drill deep into the neural circuitry and an understanding of where OCD comes from, how OCD is different from things like the personality disorders that I described. And also to give you a sense of how the individual behavioral and drug treatments work and perhaps don't work so that you can really make the best informed choices, again, highlighting the fact that OCD is an extremely common, extremely common, and yet extremely debilitating condition and one that I hope that if any of you have, or that you know people that have it that you'll both gain sympathy and understanding for what they're dealing with, perhaps as a consequence of some of the information presented today, and maybe help them direct their treatment,

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