

The Science & Treatment of Bipolar Disorder | Huberman Lab Podcast #82

In this episode, I explain the biology, symptoms, causes and types of bipolar disorder (sometimes called bipolar depression). I discuss neuroplasticity and how the brain normally regulates mood, energy, and perceptions; then, I contrast that with the biology of bipolar disorder, which is characterized by extremes of energy and mood, e.g., mania and depression. I outline the mechanisms through which bipolar disorder manifests in the brain, including deficits of interoception and reduced connections between the parietal and limbic systems. I also outline how treatment options (such as lithium) work in part through homeostatic plasticity. I discuss not only lithium but also the treatment of bipolar with ketamine, different talk therapies, electroconvulsive therapy, transcranial magnetic stimulation, and nutraceuticals, including Omega-3 and Inositol supplementation. This episode should interest anyone who has or knows someone with bipolar disorder and, more broadly, those interested in how the brain works to create a balance between thoughts, energy levels, focus, and mood.

#HubermanLab #Bipolar #BipolarDisorder

Thank you to our sponsors

InsideTracker: <https://insidetracker.com/huberman>

ROKA: <https://www.roka.com/huberman>

Blinkist: <https://www.blinkist.com/huberman>

Supplements from Momentous

<https://www.livemomentous.com/huberman>

Social & Website

Instagram - <https://www.instagram.com/hubermanlab>

Twitter - <https://twitter.com/hubermanlab>

Facebook - <https://www.facebook.com/hubermanlab>

TikTok - <https://www.tiktok.com/@hubermanlab>

Website - <https://hubermanlab.com>

Newsletter - <https://hubermanlab.com/neural-network>

Subscribe to the Huberman Lab Podcast

Apple Podcasts: <https://apple.co/3thCToZ>

Spotify: <https://spoti.fi/3PYzuFs>

Google Podcasts: <https://bit.ly/3aml809>

Other platforms: <https://hubermanlab.com/follow>

Full show notes & links to peer-reviewed articles: <https://hubermanlab.com/the-science-and-treatment-of-bipolar-disorder>

Timestamps

00:00:00 Bipolar Disorder

00:02:23 Momentous Supplements

00:03:42 Tool: Appetite Suppression & GLP-1, Parallel Pathways, Yerba Mate

00:10:23 InsideTracker, ROKA, Blinkist

00:14:24 Prevalence & Severity of Bipolar Disorder

00:16:30 Bipolar Disorder I, Diagnostic Criteria of Mania

00:28:58 Bipolar Disorder II, Individual Variability

00:33:07 Bipolar I vs. Bipolar II: Manic, Depressive & Symptom-Free States

00:38:20 Consequences of Bipolar Disorder, Heritability

00:46:53 Bipolar Disorder vs. Borderline Personality Disorder

00:51:51 Mania & Depression, Negative Impacts

00:53:06 History of Lithium Treatment

01:02:44 Lithium Treatment & Side-Effects

01:05:05 Effects of Lithium: BDNF, Anti-inflammatory & Neuroprotection

01:10:10 Neural Circuits of Bipolar Disorder, Interoception, Hyper- vs. Hypoactivity

01:17:11 Neural States & Mania, Parietal Lobe & Limbic System

01:22:58 Homeostatic Plasticity, Synaptic Scaling, Lithium & Ketamine

01:36:00 Talk Therapies: Cognitive Behavioral Therapy, Family-Focused Therapy, Interpersonal & Social Rhythm Therapy

01:43:18 Electroconvulsive Therapy (ECT), Transcranial Magnetic Stimulation (rTMS)

01:48:01 Psilocibin, Cannabis

01:51:50 Lifestyle Support, Supplements: Inositol & Omega-3 Fatty Acids

02:03:31 Omega-3s, Membrane Fluidity & Neuroplasticity

02:06:44 Mania, Creativity & Occupations

02:15:33 Bipolar Disorder: Diagnosis, Neural Circuits & Treatment

02:17:45 Zero-Cost Support, YouTube Feedback, Spotify & Apple Reviews, Sponsors, Momentous Supplements, Instagram, Twitter, Neural Network Newsletter

The Huberman Lab Podcast is for general informational purposes only and does not constitute the practice of medicine, nursing or other professional health care services, including the giving of medical advice, and no doctor/patient relationship is formed. The use of information on this podcast or materials linked from this podcast is at the user's own risk. The content of this podcast is not intended to be a substitute for professional medical advice, diagnosis, or treatment. Users should not disregard or delay in obtaining medical advice for any medical condition they may have and should seek the assistance of their health care professionals for any such conditions.

Title Card Photo Credit: Mike Blabac - <https://www.blabacphoto.com>

- Welcome to the Huberman Lab Podcast, where we discuss science and science-based tools for everyday life. [upbeat rock music] I'm Andrew Huberman, and I'm a professor of neurobiology and ophthalmology at Stanford School of Medicine. Today we are going to be discussing bipolar disorder, often called bipolar depression. Bipolar depression is a condition in which people undergo massive shifts in their energy, their perception, and their mood. However, it is very important to note that these shifts in mood, energy, and perception are all maladaptive. They can often cause tremendous damage to the person suffering from bipolar disorder and tremendous damage to the people in their lives. Today we are going to parse the biology that leads to these shifts in mood, energy, and perception. And we are going to talk about the various treatments that exist. Some of those treatments have been around for a very long time, and indeed one of those treatments, lithium, has an incredible backstory about its discovery and in understanding how lithium works and some of the ways in which it does not work well, it reveals a tremendous amount about how the brain works normally in all individuals. So that's a miraculous story that I look forward to sharing with you. As we go forward in this discussion about bipolar disorder, I want everyone to keep in mind that it is a very severe condition. In fact, people suffering from bipolar disorder are at 20 to 30 times greater risk of suicide. So today is a serious discussion and it's certainly one in which people who are suffering from manic bipolar disorder or who know people that are

suffering from manic bipolar disorder can benefit from. However, for those of you that might know people or who themselves suffer from major depression, we will also be talking about important treatment developments for major depression. Major depression is a very common thing for many people. In fact, most people will suffer from depression of some sort at some point in their life, although not necessarily a major depressive episode, and yet major depression is very common. So you'll soon learn up to 20% of people will suffer from major depression. So today's discussion will encompass all of that. And it will also encompass basic brain mechanisms of neuroplasticity, the brain's ability to change in response to experience both for good and for worse.

00:02:23 Momentous Supplements

And you'll learn a lot about the basic biology of how the brain regulates mood, energy, and perception. I'm pleased to announce that the Huberman Lab Podcast is now partnered with Momentous Supplements. We often talk about supplements on the Huberman Lab Podcast and while supplements aren't necessary for everybody, many people derive tremendous benefit from them for things like enhancing the quality and speed with which you get into sleep, or for enhancing focus or for hormone support. The reason we partnered with Momentous Supplements is several fold. First of all, their supplements are of the absolute highest quality. Second of all, they ship internationally which is important because many of our podcast listeners reside outside the US. Third, many of the supplements that Momentous makes and most all of the supplements that we partnered with them directly on are single ingredient formulations. This is important for a number of reasons. First of all, if you're going to create a supplement protocol that's customized for your needs, you want to be able to figure out which supplement ingredients are most essential and only use those and supplements that combine lots of ingredients simply won't allow you to do that. If you'd like to see the supplements that we partnered with Momentous on, you can go to livemomentous.com/huberman, and there you'll see many of the supplements that we've talked repeatedly about on the Huberman Lab Podcast episodes. I should mention that the catalog of supplements that are available at livemomentous.com/Huberman is constantly being expanded So you can check back there, livemomentous.com/huberman to see what's currently available.

00:03:42 Tool: Appetite Suppression & GLP-1, Parallel Pathways, Yerba Mate

And from time to time, you'll notice new supplements being added to the inventory. Before we dive into the discussion about manic bipolar disorder, I want to highlight some recent findings in an area totally separate from mental health that I think are really important for everyone to know about. This is a paper published in the journal Cell, which is a Cell Press Journal, an excellent journal. In fact, one of the three apex journals. So for those of you that are curious, papers published in the journal Nature, Science and Cell are considered the sort of Super Bowl, Stanley Cup, and NBA championships of publishing. And this paper entitled, an inter-organ neural circuit for appetite suppression illustrates a very important principle that I think everyone should know about, and that's the principle of so-called parallel pathways. Parallel pathways, as the name suggests, are pathways, they could be neural pathways or hormonal pathways or otherwise that operate independently of one another to accomplish a common goal. And what this paper really shows is that there's a set of peptides in the body and the peptide that I'm referring to today is called GLP-1, Glucagon-like peptide-1, and some related peptides. I've talked about these on the podcast before for two reasons. First of all, I'm a big proponent and consumer of yerba mate. Yerba mate is a tea that can promote the release of glucagon-like peptide-1. And there are also new prescription drugs that are now hitting the market. And for which there are really impressive clinical trials for diabetes and obesity that are essentially glucagon-like peptide-1 stimulator, so they stimulate the release of that, or they are in fact, a synthetic version of glucagon-like peptide-1. What is glucagon-like peptide-1? It is a peptide, which is a small little protein, that can dramatically suppress appetite. So that's why these drugs are being explored and are showing quite impressive results for things like treatment of type 2 diabetes and other forms of diabetes, as well as obesity. So they lead to weight loss. Now in terms of the yerba mate stimulation of glucagon-like peptide-1, that's going to be a much lower amount of glucagon-like peptide-1 that's released from drinking yerba mate as opposed to say, taking a drug that stimulates GLP-1 or taking a drug that is GLP-1. Nonetheless, should also point out that yerba mate comes in a bunch of different forms. There is some concern about certain smokey-flavored forms of yerba mate being carcinogenic, so that's why I avoid those forms of yerba mate. But for me, yerba mate is one of the preferred sources of caffeine. For me, I like the way it tastes. It does provide that sort of caffeine kick that I like to have early in the day for focus and for work and for exercise. And yet I actively avoid the smoked varieties of yerba mate because of the potential carcinogenic

effects of the smoked varieties. Glucagon-like peptide-1, as I mentioned earlier, can suppress appetite. But what this paper shows is it does that by at least two mechanisms through parallel pathways. What this paper shows is that glucagon-like peptide-1 axon receptors in the body in a portion of the nervous system called the enteric nervous system, E-N-T-E-R-I-C, enteric nervous system. This is a component of your nervous system that you don't really have control over, it's autonomic or automatic. GLP-1 binds to what are called intestinofugal enteric neurons, you don't need to know the name, but those neurons do two things. First of all, they cause some gut distension, so they actually make you feel full. This is incredible, right? A peptide, not actual physical food, but a peptide that stimulates neurons that cause changes in the so-called mechanoreceptors of the gut, of the enteric nervous system and make people feel full. So it can lead to actually mild, or I suppose if levels of GLP-1 are very high, to major gut distension. I think that the levels of GLP-1 that would come from drinking yerba mate and hopefully from appropriate dosaging of the synthetic forms of GLP-1 or drugs that stimulate GLP-1 would cause mild, not major, gut distension, 'cause major gut distension would be uncomfortable. So GLP-1 is acting at the level of gut to increase gut distension, and by way of a pathway that goes from the gut up to the hypothalamus, this little cluster of neurons about the size of a marble that sits above the roof of your mouth, is also suppressing appetite through brain mechanisms. So this is really beautiful, right? You have a peptide, a small little protein that's released in the gut and that release within the gut causes gut distension, which makes you feel full. And by way of neural stimulation of the hypothalamus also activates neural pathways within the brain that trigger satiety, the feeling of having had enough food. So to me, GLP-1 is both impressive and important. Why? Because this recent category of drugs that's now hitting the market seems to adjust obesity or can help people with weight loss in order to help their health. And it's doing so by at least two mechanisms. One is within the brain, and the other is within the gut and communication through the so-called gut brain access. Because again, these enteric neurons are communicating to the brain, the hypothalamus, by way of this, what's called the sympatho-gastro-spinal-reticular-hypothalamic pathway, you absolutely do not need to know all of that. That's a mouthful, that's enough to make your mouth feel distended. But at the same time, things like yerba mate, and I'm sure there are other compounds out there as well, but certainly yerba mate can stimulate the release of GLP-1. So for those of you that are looking for some mild appetite suppression and want to accomplish that while also ingesting caffeine,

yerba mate might be a good option for that. And just know that it's operating through two mechanisms, on the body through mild gut distension to make you feel full, and on the brain to increase satiety and make you feel less hungry. And then for everybody, not just those that are interested in appetite suppression, I think it's important to understand that these parallel pathways are fundamental to how we are organized. Another good example of this would be when we are excited by something positive or negative, so it could be stressful or we are positively aroused, there is a parallel activation of epinephrine, adrenaline, both from your adrenals and from an area in the brain called the locus coeruleus. So again and again, we see this in biology and in neuroscience that your brain and your body are acting in concert. They're acting together through mechanisms that either are independent, so separately in the brain and separately in the body, but directed towards a common goal, or through communication between brain and body, and almost always that communication is going to be bidirectional, body to brain and brain to body. So I think these results are really interesting and really important for sake of weight loss, for sake of appetite suppression, and just generally for the way that they illustrate this very important theme

00:10:23 InsideTracker, ROKA, Blinkist

of the way that we are constructed at a biological level which is parallel pathways. 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 InsideTracker. InsideTracker is a personalized nutrition platform that analyzes data from your blood and DNA to help you better understand your body and help you reach your health goals. I've long been a believer in getting regular blood work done for the simple reason that many of the factors that impact your immediate and long-term health can only be assessed with a quality blood test. And nowadays, with the advent of modern DNA tests, you can also get insight into, for instance, what your biological age is and compare that to your chronological age. And of course your biological age is the one that's important for your longevity and your understanding of your current health needs. One major problem with most blood tests and DNA tests out there however, is that you get information back about levels of metabolic factors, levels

of hormones and lipids and so forth, but you don't know exactly what to do with that information. InsideTracker solves that problem through their personalized platform which can tell you, for instance, lifestyle factors like fitness or nutrition or supplementation that you can use to bring the numbers into the ranges that are ideal for your health needs. If you'd like to try InsideTracker, you can visit insidetracker.com/huberman to get 20% off any of InsideTracker's plans. That's insidetracker.com/huberman to get 20% off. Today's episode is also brought to us by ROKA. ROKA makes eyeglasses and sunglasses that are of the absolute highest quality. The company was founded by two all-American swimmers from Stanford and everything about ROKA eyeglasses and sunglasses were designed with performance in mind. I've spent a lifetime working on the biology of the visual system and I can tell you that your visual system has to contend with a number of very important challenges in order for you to see clearly. The designers of ROKA eyeglasses and sunglasses understand this and for that reason, ROKA eyeglasses and sunglasses allow you, for instance, to move from a shady area to a bright area or from a bright area to a shady area and still see everything with crystal clarity. Originally, their glasses and sunglasses were designed for performance, that is for running and cycling, and as a consequence, the eyeglasses and sunglasses stay on your face even if you get sweaty and they're extremely lightweight. In fact, most of the time, I don't even realize that they're on my face. I wear ROKA eyeglasses for reading and for driving at night and I wear their sunglasses when I'm out during the day and it's really bright and I need to use sunglasses in order to be able to navigate in that bright sunlight. If you'd like to try ROKA glasses, you can go to roka.com, that's R-O-K-A.com, and enter the code Huberman to save 20% off your first order. Again, that's ROKA, R-O-K-A.com and enter the code Huberman at checkout. Today's episode is also brought to us by Blinkist. Blinkist is an app that has thousands of nonfiction books condensed down to just 15 minutes each of key takeaways that you can read or listen to. I'm a big believer in reading physical books, I actually own a lot of hard cover books and paperback books and I like holding them in my hand and flipping through the pages. I also like listening to audiobooks. But the reality is I don't have a ton of time to read books and I don't have a lot of time to listen to entire audiobooks. There are also a lot of books that I've really enjoyed in the past that I have read in their entirety but then I like to update myself on the information on every once in a while. Blinkist has terrific books available. For instance, I'm a big fan of Tim Ferris's 4-Hour Body, gleaned so much knowledge from that book. Also from Nassim Taleb's book, The Black Swan and the great Matt Walker's

book, *Why We Sleep*, which is a book that I've read several times and I actually listen to the synopsis of on Blinkist over and over because there's so many key takeaways. With Blinkist you get unlimited access to read or listen to a massive library of condensed non-fiction books, essentially all of the books that you ever wanted to listen to, and now you have time because they're condensed down to just 15 minutes each. Right now, Blinkist has a special offer just for Huberman Lab Podcast listeners. If you go to blinkist.com/huberman, you can get a free seven-day trial and you can get 20% off a Blinkist premium membership. That's Blinkist spelled B-L-I-N-K-I-S-T,

00:14:24 Prevalence & Severity of Bipolar Disorder

blinkist.com/huberman to get 25% off and a seven-day free trial. Let's talk about bipolar disorder. And today I'm going to refer to bipolar disorder interchangeably with bipolar depression, although as you will soon learn, not everyone with bipolar disorder necessarily goes through highs and lows. There is a subset of people who suffer from bipolar disorder who experience the manic phases, the highly elevated mood and energy, and then drop down to so-called baseline, so they don't necessarily go down into a depressive state. They often will return to a somewhat normal state. In fact, we will talk about the percentage of time that people with bipolar disorder tend to be symptom-free manic or depressed in the context of the different categories of bipolar disorder. But as we wade into this topic that is bipolar disorder, I just want to give you a little bit of the background statistics to anchor us in just how serious and prevalent bipolar disorder is. So bipolar disorder impacts about 1% of people, that might seem like a small percentage, but if you think about a room of a hundred people, that means that at least one of them is very likely to have bipolar disorder. And as I mentioned earlier in the introduction, bipolar disorder is very serious. It has a 20 to 30% greater incidence of suicide than the general population, which is, first of all, extremely tragic and extremely concerning. So anyone that thinks they might have bipolar disorder or who knows someone with bipolar disorder should be especially vigilant about this. And we'll talk about some of the, or signs and risk factors, age of onset, et cetera, as we move forward. So 1% of people have bipolar disorder. The typical age of onset is anywhere from 20 to 25 years old, although it can be much earlier. And the earlier the onset of a bipolar episode, which we will define in a few minutes, the earlier the onset of that episode, the higher likelihood that the bipolar disorder is going to be a stable feature of

that person's psychology going forward. And yet, I also want to point out that there are some very good treatments

00:16:30 Bipolar Disorder I, Diagnostic Criteria of Mania

for bipolar disorder that those people could still benefit from. There are basically two kinds of bipolar disorder referred to as bipolar 1 and bipolar 2. So let's just talk about bipolar 1 first. Bipolar 1 is characterized by a fairly extended period of mania. What is mania? Mania is a period of very elevated mood, energy, distractibility, impulsivity, and some other symptomology that we'll talk about going forward. But this manic episode is extreme. This is a condition in which the energy lift, the mood lift, and the sort of impulsivity and actions and words of the person suffering from manic bipolar disorder are very noticeable and very extreme. Now a key thing, however, is that it's not always noticeable to the person suffering from it that they are in this mode. Sometimes they recognize that, sometimes they don't, but it's always highly recognizable to other people that the person suffering from manic bipolar disorder is not like other people. So let's talk about bipolar 1 in a little bit more depth. One of the key clinical criteria or diagnostic criteria for bipolar 1 is that a person suffer from these manic episodes or display these manic episodes for seven days or more. That turns out to be very key. The stability of that manic episode for seven days or more turns out to be very important. And for those seven days, the person is in an elevated mood, expansive thought all day, every day for those seven days. Now there are a lot of reasons why somebody could be in a manic mode. It doesn't necessarily mean that somebody has bipolar disorder. In fact, someone could be in a manic mode for seven days or more and still not be diagnosed with bipolar disorder. Why? Well, there are other things that can create manic episodes, things like traumatic brain injury, things like seizure, things like various prescription drugs or illicit drugs, things like amphetamine and cocaine, that is not the same as bipolar disorder even though from a symptomology perspective, they might look even identical. So let's think about these symptoms and the diagnostic criteria that a psychiatrist would use in order to ask whether or not someone is manic because they have manic by bipolar disorder or whether or not that person is manic for some other reason, such as traumatic brain injury, illicit drugs, et cetera. So typically a person would be brought into a clinic or a person would bring themselves to a clinic or meet with a psychiatrist, it seems more likely that they would be directed toward a psychiatrist because oftentimes people who

are in a manic episode just simply won't have the perspective or the foresight to bring themselves into the clinic. And the psychiatrist is going to start to evaluate for a couple of different things. But first of all, what they're going to try and figure out is whether or not the person has at least three of the following symptoms. The first symptom is distractibility. Is the person distractable? Are they going from one thing to the next. People who are in a manic episode will be talking about a pen and then they'll be talking about something they saw the other day and then something they want to purchase and then a place they're going to travel to, et cetera, but they are also very prone to any stimulus within the room. Meaning a bell could go off or there could be a sound out in the hallway and they'll orient to that. And then they'll orient to the clinician and then they'll orient to something in their pocket, so they're all over the place. You could think of this a little bit like ADHD or attention-deficit disorder, but it's very extreme. So highly distractable, highly impulsive, impulsivity relates to actions. So the person might be fidgeting with something and then they might try and leave the room or the person might, if they were out in the real world, somebody might notice that the person is going and purchasing multiples of something that would be unusual for someone to purchase. So for instance, I happen to know someone whose ex-spouse had bipolar disorder and their ex-spouse went out and bought 10 plus air fryers. I mean, I think unless you're a restaurant that's using a lot of air fryers, the idea that you would need more than one or two air fryers might just seem a little bit out of the norm. And so that impulsivity can be purchasing, it can be other things as well. It can be booking 12 international trips in one afternoon or going and buying three cars, et cetera. So impulsivity. the other is grandiosity. People who have manic bipolar disorder who are in a manic episode will often display words of or actions of grandiosity. And keep in mind, these are not lies in the sense that the person isn't lying in order to try and pull one over on anybody, these are actual beliefs that the person comes to have about their grandiose position in the world or grandiose opportunities or potential in the world. Typical forms of grandiosity and manic episodes would be that the person suddenly decides that they are going to win a Pulitzer Prize. They are the person selected to win a Pulitzer Prize. They're going to write a novel that afternoon, and they're going to win a Pulitzer Prize that year, which is more or less a delusion of grandeur. The idea that someone could do that in one afternoon, I suppose it is possible in the realm of all possibilities, but it's extremely unlikely. Other forms of grandiosity that often present themselves in people suffering from a manic episode will be that they're going to run for president or that they are the

person that they believe is selected by the citizens of a given country or by the universe to be the president of that country or to be present of the universe. It sounds ridiculous, but those sorts of delusions of grandiosity are one condition that often presents itself, or one set of symptoms that presents itself. Flight of ideas are also typical of manic episodes. So this is a little bit like distractibility, but this would be people talking extensively about one thing and then switching and talking extensively about something else. It would be as if I was doing this podcast talking about manic bipolar disorder and then suddenly switching to OCD and then to deliberate cold exposure and then to the role of sugar and its impact on the brain, et cetera. So essentially a random selection of the different topics that exist in science, all of which I happen to be very interested in and curious about, but just as we have episodes of the podcast that are about one or two topics, and we focus on those in a fairly narrow trench of discussion, somebody who has a flight of ideas would be jumping between categories and topics in a kind of pseudo random way. So they might take off down a path of one thing and then switch to another without any transition or with transitions that that don't have any logical structure to them. The other aspect of manic bipolar disorder that often presents itself in the manic episodes are agitation. People feeling extremely physically agitated, so a lot of shaking and moving about. This can venture into the realm of paranoia, but a lot of agitation, a difficulty sitting down and being still, a difficulty in just looking, feeling and acting calm. And then another condition is no sleep. And when I say no sleep, I mean no sleep or very minimal sleep. As incredible as it sounds, people who are in a manic episode can often go seven days or more with zero sleep. And a key feature of this zero sleep is that they're not troubled by it. They're not thinking, oh, I'm suffering from insomnia and I really, really want to sleep. Sometimes that's the case, but more often than not, they are simply not sleeping. They're staying up 24 hours then another 24 hours, it just continues for an entire week. Again, inconceivable to those of us that don't suffer from manic episodes. I can only imagine how pulled apart most of us would feel under those conditions, and yet they are just going and going and going with no sleep, up all hours, shopping, talking, running, doing all sorts of different things in the categories of other symptoms that we talked about before. And it doesn't bother them that they're not sleeping. And then the last sort of category of symptoms that the psychiatrist is evaluating for and seeing if they present is rapid pressured speech. The rapid pressured speech is something that when you hear it, you recognize it. This is somebody that almost seems to be hitting you with speech like machine gun fire, it's coming at you,

coming at you, coming at you and there's really no room for conversation. They're not offering any opportunity for a back and forth, or if there is a back and forth, they might ask you how you feel about something and then you started, well, I, [speaking gibberish] then they're going to hit you with another barrage or a paragraph of information or of just speech, that pseudo random. So we've got distractibility, impulsivity, grandiosity, flight of ideas, agitation, no sleep, and rapid pressured speech. For someone to be diagnosed as in a manic episode, they do not have to be engaging in or displaying all of those symptoms. They do however need to present at least three of those symptoms, and then in order to meet the condition of bipolar 1, they have to be presenting those three symptoms for at least seven days. It could be longer, but at least seven days. Now, this seems pretty straightforward, right? At one level, the way that I describe this and the way that it exists in the clinical literature, you could think, well, this should be pretty easy to diagnose. And yet there's a complication there or a challenge there because the psychiatrist, again, has to determine that these manic episodes are not due to something other than bipolar disorder. For instance, again, it could be TBI, traumatic brain injury, it could be seizures, or meds or other sorts of drugs. Corticosteroids, which are often prescribed for a number of immune conditions or for wound healing can also cause manic episodes. So they have to determine that everything that's happening meets the criteria I described before, three out of seven of these symptom categories for seven days or more and that it can't be better explained by something else going on in that person's life or immediate medical history. That's very important. Now, the other challenge, and this is something that's going to come up again and again today, not just in the description of the biology of bipolar disorder, but also the description of different treatments and treatment approaches, is that typically, when somebody is sitting in front of a psychiatrist, in particular for the first time those two people are interacting, the psychiatrist is just getting one snapshot of the person at that moment. So the person could be on day one of a manic episode, the person might be on day six of a manic episode, the person could be transitioning out of a manic episode, or the person could be suffering from a combination of manic episode where, because of the impulsivity of bipolar disorder, they went out and used illicit drugs. They also used cocaine. So the psychiatrist has a serious challenge. The psychiatrist has to determine based on a conversation, this isn't a blood test, this isn't a measurement that you can take on a scale or with a biomarker, they have to use language, a conversation with somebody who, by all accounts, is pretty impaired at conversation to determine whether or not

they're suffering from a manic episode that is the consequence of bipolar disorder. You can imagine this in the real world, as somebody says, well, how long has it been since you slept? And the person starts to answer, oh, well, the other day I went down to the basement. I was going to get something out of the refrigerator and I thought I might take a nap. And then all of a sudden they're talking about something completely different. So they might not even have an answer. So the psychiatrist has to be a really good detective, a benevolent detective, but a detective nonetheless in determining whether or not these symptoms have existed for seven days or more, and whether or not they meet the, at least three, it could be more, but at least three of the criteria of symptom categories I talked about before. Now, assuming that they do, assuming that the patient meets those criteria, they are likely to be diagnosed with bipolar 1. Now bipolar 1 disorder means they're having these extended manic episodes, seven days or more, but it does not necessarily mean that they are dropping into a depressive episode as well. This is a common misconception about bipolar disorder because as it's often called, bipolar disorder is referred to as bipolar depression, and yet many people with bipolar disorder don't necessarily experience the deep depressive episodes. Many of them do, but many of them do not. So somebody can truly be diagnosed accurately with bipolar one, even though they're only experiencing manic episodes and then dropping down to baseline.

00:28:58 Bipolar Disorder II, Individual Variability

Manic episode, then dropping down to baseline. That's very important to understand. Now, the second category of bipolar disorder is bipolar 2. So BP-II or bipolar disorder 2 is somewhat different than bipolar disorder 1. First of all, it's characterized most often by the presence of both manic episodes, mania, and depressive episodes, or what's referred to as hypomania. Now, anytime in biology or in medicine you hear hypo, it's the opposite of hyper. So we've got normal hyper and hypo. Hypomania is a somewhat suppressed level of mania. So this is not going to be as extreme as the mania that we typically think of. And yet the hypo can be due to the duration, not the intensity of mania. That's right. Hypomania can mean a lessened intensity of mania, but it can also be used to refer to a shorter duration of mania. And in fact, that's one of the key criteria for bipolar 2. Bipolar 2 is often diagnosed on the basis of the presence of manic episodes that are lasting four days or even less. So someone with BP-II might have four days of this

increased energy, goal-directed activity, they're irritable, they're euphoric, they're not sleeping, et cetera, but it's only lasting for about four days. Or they could be having longer extended periods of mania, but they are hypomanic episodes. They're not quite as intense so the pressured speech isn't quite as pressured. The impulsivity isn't quite as severe, et cetera, et cetera. The other aspect of bipolar 2 is one that I had mentioned briefly a moment ago, which is that it's often associated with the drops into the depressive episode. So people are going from manic episodes for four days or less, then they're dropping into a depression, going back to normal, manic again. I do want to point out however that people who have bipolar 1 can indeed go from manic episodes to severe, what we call major depression, so they can oscillate like a sine wave, really high highs, really low lows. And very important to understand in terms of understanding both bipolar 1 and bipolar 2 is that it's not always a sine wave. This is really important and it's something that frankly I did not know until I started researching this episode and talking to some psychiatrists. I should mention, I've talked to several board certified psychiatrists in preparation for this episode, I'll give some references to them. And in fact, some of them are going to be coming on the podcast as guests in the future for more in-depth discussion about bipolar and other psychiatric disorders. But all the psychiatrists I spoke to confirmed what the other was saying, which was that the way that bipolar disorder can present can vary tremendously between individuals. One person might go from very high highs that last seven days or more, to very low lows. Bouts of depression, major depression that can last two weeks or more. Other people are rapid cycling by way of three days manic, three days normal, three days manic, and then dropping into three days depression. So you want to erase that picture in your mind that manic bipolar disorder is this sine wave, this cycling up and down between mania and depression. It can take a lot of different forms. And again, this is a serious challenge for the psychiatrist to diagnose people because of that fact that they're only getting a snapshot of the person unless they've known them for some time and are working with them for some time. But this is also especially important for those of you that either have bipolar depression or suspect that you might, or that know someone with bipolar depression or suspect somebody might have bipolar depression, AKA bipolar disorder. Because if you're noticing that somebody is very manic and then normal, well, that's a very different picture than somebody who's going from very manic to very deep bouts of depression. The very manic to deep bouts of depression is easier to recognize because of the extremes of those highs and lows. Now, this might seem somewhat obvious to all of you

as I describe it, and yet it's very important as a, frankly, a citizen of the planet who knows other human beings to keep an eye out for these manic episodes, because again, whether or not it's four days or less, or whether or not it's seven days or more,

00:33:07 Bipolar I vs. Bipolar II: Manic, Depressive & Symptom-Free States

these manic episodes really are the defining criteria of bipolar disorder, AKA bipolar depression. There are a couple other key features about bipolar 1 and bipolar 2 that can allow us to get better insight into whether or not somebody has bipolar 1 or bipolar 2, and that's the percentage of time that people with bipolar 1 versus bipolar 2 spend in a manic state, a depressed state, or a symptom-free state. And this is also important to discuss because it turns out that people with genuine diagnosed bipolar 1 or bipolar 2 are often symptom-free, which again can make it difficult for us as people that know them or for people that are treating people with bipolar disorder to identify whether or not somebody is in a manic episode or a depressive episode, or whether or not they are headed into a manic or depressive episode. So the numbers on this have been studied. This from a paper, actually two papers, first author, Judd, J-U-D-D et al. published some years ago, 20 years ago, but the data hold up really nicely over time. These were both published in Journal American Medical Association Psychiatry. So JAMA Psychiatry is a superb journal. And basically people who have bipolar 1 on average spend about 50%, it's actually 53% was the number that was eventually converged upon, but about 50% of their time symptom-free. That's interesting, right? Somebody who has genuine bipolar 1 disorder can spend as much as half of their life symptom-free, sleeping normally, speaking normally, et cetera. About 32% of the time depressed, And when we say depressed, we mean major depression. So severe challenges with waking up at two or three in the morning, and having trouble falling back asleep. That's one of the defining characteristics of depression, or sleeping far too much, having a hard time getting out of bed in the morning, suppressed appetite, suppressed libido, suppressed motivation, all the general symptoms of major depression which we'll talk about a little bit more later and in an upcoming episode about major depression in particular. And then about 15% of their time in this kind of manic state or mixed manic state, where they are showing long, again, seven days or more bouts of sleeplessness, irritability, pressured speech, grandiosity, et cetera. Contrast that with people who have bipolar 2 disorder who are spending about half of their time in a depressed state. So that's interesting, people with

bipolar 2 disorder, while not always displaying depressed states or oscillations between mania or hypomania and depressed states, they tend to be in the depressed state more often. And again, this is major depression. This isn't just a little bit of a low, this is a serious depression of their nervous system, their mood, and as we say, their affect, their outlook on life, and that's one of the key distinguishing features of major depression is that people's outlook on life becomes very diminished in the sense that they don't see a future. You ask them about, how's work going? How're your relationships? And it's not just that they feel that that's going poorly, they really feel as if there's no opportunity for those things to improve. Those people with bipolar 2 tend to be symptom-free about 45% of the time. Again, these are averages, so about 45% of the time, that's a considerable amount of the time. And they tend to be in these hypomanic states only about 4 or 5% of the time. Again, the criteria for BP-II, bipolar 2 is these four days or less of mania or hypomania, but only 4% of the time or 5% of the time is a small enough sliver of the pie that is these people's existence that you could imagine why it would be easy for them or other people to overlook the fact that they have bipolar disorder and not major depression. Think about it. This is a person who, or I should say a collection of people who are spending about half of their time depressed, close to half, 45% of their time symptom-free, and then about 5% of their time in a hypomanic state. So either shorten bouts of high intensity mania or hypomania that is of reduced intensity. One of the reasons that I mentioned these percentages of time spent in a symptom-free, depressed manic or hypomanic state is because one of my major goals for today's episode is that it will increase awareness of whether or not you or somebody you know, could be a coworker, could be family member, et cetera, might be suffering from bipolar 1 or bipolar 2. I think it's fair to say that if somebody is suffering from bipolar 1, that is likely to be revealed or to reveal itself before too long, because of the fact that people have these extended periods of mania and mania is such an extreme state, not just for the person who's experiencing it, but the way that it presents is just so extreme and out of the ordinary. But bipolar 2, you can imagine could really duck under the radar of our awareness. And you could imagine that we might just think somebody is low or depressed, especially if that person tends to self-medicate with alcohol or other substances. We might think, oh, they're drinking more than often more than usual, excuse me, or they're spending more time alone and isolating. But then when they're in their hypomanic state, that might actually present as normal to us because they were in such a depressed state before. So it's very important that we dial up our awareness, that

we have tune our antennae to the possibility that people out there who might appear depressed

00:38:20 Consequences of Bipolar Disorder, Heritability

or that we haven't heard from in a while might actually be suffering from bipolar 2 disorder. Before we move into a in-depth discussion about the different kinds of treatments for bipolar disorder, I'd like to touch on just a few additional aspects of what bipolar disorder can do in terms of its negative consequences. And also talk about some of the inherited risk that is the genetic factors and the environmental factors that can contribute to bipolar disorder. In terms of the burden, the very real, emotional, and occupational and educational burden that can occur for somebody with bipolar disorder, that's actually been studied. There's a measure of this, it's called global burden which is defined as the years lost in engaging a normal life due to some disability. So that disability could be cancer or that disability, in this case, is bipolar disorder. And basically the way this sort of study is done is that through questionnaires, I should say quite in-depth questionnaires, there's a probing for whether or not somebody has lost two consecutive weeks or more of interest in normal activities. Now, for people who have depression, that's a kind of straightforward thing to address, right? You ask somebody, when was the last time you ate, or when was the last time that you went a few days without food or lost interest in relationships or work or sex or things of that sort and they answer and you can figure out the amount of time that you've essentially been withdrawn from normal levels of activity for them. With bipolar disorder, What it turns out is that the global burden of having bipolar 1 and even bipolar 2 is massive. In fact, having bipolar disorder sits as one of the highest risk factors for being in the top 10 of all categories of disabilities leading to global burden. Put in plain English, what that means is having bipolar 1 or bipolar 2 disorder is extremely debilitating. It really slows down one's life trajectory unless it's treated properly. Now, the other aspect of bipolar disorder is its heritability. And this gets into a little bit of some tricky science related to inheritability versus the genetic contribution of a given disease. So that might sound like the same thing, you think, okay, genes relate to heritability, heritability relates to genes, but of course, everything about the way that our nervous system works and functions and expresses itself, healthy or otherwise, is an interaction between our genes and our environment. And so typically the way these studies are done is you address what is the

risk of somebody having a given condition in the general population? We talked about that before, bipolar disorder is a 1% of the world's population. Compare that to people who have only major depression. So this would be repeated bouts of two weeks or more of serious depression, not just low mood or something due to a life loss, but major depression, which is 10 to 17% of people have major depression. They suffer from major depressive disorder, compared to bipolar disorder which, again, is 1%. Now, you can address how much of the 1% of bipolar disorder that exists is due to genes versus environment in a somewhat exact way. This is never an exact science. And the way that this is typically done is to look at concordance, that is the likelihood that two identical twins will both have a given condition as opposed to two fraternal twins, which have more different genes than identical twins, of course. And then two siblings who have similar genes, of course, but less similar than identical or fraternal twins and so on and so forth. So what you basically do is you evaluate the probability that two people in the general population who are completely unrelated will have the same condition, versus two people in the general population who are very related, identical twins. And what you find is that in identical twins, if one identical twin has true major depression or major depressive disorder, there's a 20 to 45% chance that their identical twin will also have major depressive disorder. Now that tells you right there that it can't all be genes, that is not a gene for major depression per se, or if it is a gene or a collection of genes, that those genes are also subject to environmental influences, either prenatal, within the womb or after children are born. Now the large range there of 20 to 45% could be due to any number of things. It could be experimental, meaning the techniques that were used in experiments, it could be due to regional differences, one part of the world versus another. There are a lot of different factors. Right now, we probably shouldn't delve into all that. At some point, we'll probably do an episode all about the genetics of nervous system heritability and heritability of features and mental health, et cetera. But we can compare major depression and the heritability or the genetic concordance between identical twins in major depression and bipolar disorder and ask, if one twin of an identical twin pair has bipolar depression, what is the likelihood that the other twin will have it? And it turns out that number is much higher. It's 40 to 70% likelihood or probability that if one twin has bipolar disorder, that their identical twin will also have bipolar disorder. So again, the total incidence of bipolar disorder in the general population is much lower than it is for major depressions, 1% for bipolar versus 10 to 17% for major depression. But the genetic component is much higher, 40 to 70% for

bipolar disorder versus 20 to 45% for major depression. I know I'm throwing a lot of numbers out there, but basically what this means is that researchers have been able to take those numbers and filter them through a number of different risk factors that are related to early development, ask questions like if two twins were raised separately or together, or in one part of the world versus another, or had a two parent household versus one parent household, evaluate a lot of different variables, what they were able to discover, and this has been shown again and again, is that the genetic contribution to bipolar disorder is very, very high. That is the heritability of bipolar disorder is 85%. So again, I want to be really clear what this means, the total occurrence in the general population, fairly low, still serious, 1%, but fairly low compared to other things like major depression. However, if someone has bipolar disorder, it's very likely that they inherited some gene or sets of genes, or more accurately, a susceptibility within their genes to environmental influences that can trigger bipolar disorder. There are a lot of different ways to discuss and to conceptualize heritability so I want to be very careful with the way that I'm wording this. What this means is that people with bipolar disorder very likely have a gene, or more typically it's going to be a set of genes that creates a susceptibility for bipolar disorder to present itself. Now, what environmental factors trigger or increase that susceptibility is not entirely clear. This always seems to center back onto the same sets of things like early life stress, trauma, et cetera, certainly those are going to exacerbate the likelihood that someone who has a genetic propensity for bipolar disorder will express that bipolar disorder and its full array of symptomology, but 85%, while very, very high, is not 100%. Again, 85%, while a very high number for heritability is not 100%. What that means is that there is no single gene or identified gene cluster for bipolar disorder. The reason I keep drilling into this over and over is that I think we can confidently say that if someone has bipolar disorder, that there was something in their genetic lineage that led to that, or that very likely led to that, and yet it's not like eye color or some other physical feature, which we can actually do the direct, so it's called Mendelian genetics, and figure out whether or not somebody directly inherited that gene from one parent or the other parent. So the takeaway here is that if you have certainly an identical twin, or a fraternal twin, or a sibling or a parent, or even a cousin or an uncle that has bipolar disorder, in particular bipolar 1, well, then you need to be on the lookout

00:46:53 Bipolar Disorder vs. Borderline Personality Disorder

for bipolar disorder, perhaps in yourself and for the family members of that person. My goal within this episode up until now has been to provide a clear and detailed picture of bipolar disorder and its various forms. Before we start to talk about treatments for bipolar disorder and some of the neural circuit basis for bipolar disorder, I want to make sure that I distinguish bipolar disorder from borderline personality disorder. We will do an entire episode or maybe even several episodes about borderline personality disorder. Borderline personality disorder can indeed present itself in ways that resemble bipolar disorder and vice versa, but there's some key distinctions that need to be made because it turns out that bipolar disorder and borderline personality disorder are quite distinct in terms of their defining criteria. The key distinction between somebody with borderline personality disorder and bipolar disorder is that in borderline personality disorder, there can be episodes that can resemble mania or hypomania. So periods of flights of ideas, or where people are spending money excessively or sexually promiscuous in ways that seem manic or could even be a little bit manic or a lot manic, and yet more often than not, there is an environmental trigger for those manic episodes. That is distinctly different from bipolar disorder where the person will have manic episodes without any need for a trigger. There doesn't need to be a call from someone saying, hey, let's go on a vacation together, or there's something coming up this Friday that's really exciting, or let's enter a relationship together of one form or another. The person with bipolar disorder will have episodes of mania or episodes of major depression without any need for an external stimulus or environmental trigger. But the person with borderline personality disorder, almost always, again, there's never an always in biology and psychiatry, but almost always is going to exhibit flights of mania or depressive episodes or other types of mood shifts that are dramatic and maladaptive in response to things that are coming in through the external environment or relationships of some kind. In fact, one of the defining characteristics of borderline personality disorder is this thing that's referred to as splitting. A good example of splitting in a person with borderline personality disorder is that they will feel that they absolutely adore you and want to spend all their time with you and just think the world of you. You can do no wrong. And in fact, they genuinely can feel that way and can genuinely think that way about you. And then for whatever reason, it could be a perception of something that you did or something that you said or suspicion that you're thinking something about them, they can suddenly shift or split their emotions in what's called move you from a good object or a can do no wrong object to a bad object. They'll suddenly decide that you are cheating on them or that you are being

mean to them or that you're insulting them or that something that you're doing is in violation to their self worth, their wellbeing, et cetera and that can send them down a pathway of being very angry, very depressed, et cetera. As I describe the contour of a person with borderline personality disorder as somebody who splits very suddenly in response to some environmental trigger, real or perceived, there's the risk, of course, that it makes the person with borderline personality disorder sound like a bad person, that they're very volatile. And while they can be volatile, I want to be very careful to point out that the person with borderline personality disorder is also suffering in this context. So while those sorts of relationships with people with borderline personality disorder, whether or not they're romantic relationships or familial or coworkers, et cetera, can be very challenged, can be very high friction because of the good object, bad object shifts, et cetera, it's bidirectional, meaning the person with borderline personality disorder, as you can imagine, is also going through a lot of suffering. At one moment, they feel as if someone is wonderful and can do no wrong to them and they want to be so strongly affiliated with them, and then in the next moment, they feel as if that person is attacking them through their actions or even through their non actions. So again, we will return to borderline personality disorder in a separate episode, it's a serious disorder, both for the person that has it and for people around them. Fortunately, there are some emerging treatments that are showing promise and it's a fairly common disorder, but it's important that we distinguish borderline personality disorder from bipolar disorder, mostly on the basis of this need for a trigger. Again, in bipolar disorder, there is no need for a trigger to create a manic episode or a major depressive episode, they just happen or they can just happen. Whereas in borderline personality disorder, almost always there's an external trigger or a perception that something happened in the environment or that somebody is behaving a certain way that dramatically shifts

00:51:51 Mania & Depression, Negative Impacts

the person with borderline personality disorder from one mode to the next. As we move into our discussion about the treatments for and neural circuits underlying bipolar disorder, I want to just nail down one more key point. This is a very brief point but it's perhaps the most important point, which is the highs and lows, or we should say the highs, these manic episodes, and sometimes lows, 'cause again, not everybody with bipolar disorder 1 or 2 suffers from depressive episodes, sometimes yes, sometimes no,

in particular in bipolar 2, yes, but people with bipolar 1 can have extreme manic episodes and then just return to normal as you recall. Well, those extreme lows and or extreme highs of people with bipolar disorder impact their lives in very negative ways. This is essential and it's something that we're going to return to a little bit later when we talk about the relationship between bipolar disorder and creativity, because it turns out that there's a quite strong association there, one that would almost lead you to believe that being bipolar can be beneficial in certain contexts, and yet, on whole, having bipolar disorder is extremely detrimental and challenging to the person suffering from it. And it's something that we want to keep in mind

00:53:06 History of Lithium Treatment

as we think about treatments and the underlying biology. Now I'd like to talk about some of the treatments for bipolar disorder. And in the discussion of those treatments, there's an absolutely incredible history of the discovery of one particular treatment that still shows great success in many patients, although some people can't take it for reasons that we'll talk about. And in the description of the discovery of this treatment for bipolar disorder, it also reveals to us that sometimes treatments come to the profession of medicine and through science in ways that precede the discovery of the underlying biology. That's right, every once in a while, someone will discover a treatment for a disease without any understanding about the underlying biological basis of that disease. And in fact, that is the case for bipolar disorder and the treatment that we are referring to is lithium. Lithium, as some of you know, is on the periodic table of elements. It is indeed a naturally occurring substance. It actually arrived on earth by way of star dust. Yes, we are talking about star dust on this podcast, but if you'd like to learn more about the origins of lithium and how lithium arrived here on earth for its discovery and applications in psychiatry, there's a beautiful talk that exists on YouTube and we'll provide a link to this in the show note captions that describes the history of lithium in terms of its interplanetary travels and arrival on earth. This is a talk delivered by a physicist who is expert in quantum mechanics and is expert in lithium. And it's a just wonderful talk that I can refer you to, less on the biology in that talk, but certainly a lot about lithium as an element. So for those of you nerds like me, that love to know how things came to be here on the planet in one form or another, I'll encourage you to take a brief listen to that talk. We are going to discuss lithium in the context of its applications for treatment of

bipolar disorder. And the discovery of lithium as a treatment for bipolar disorder is truly a miraculous story that I think everyone should know. The key player in this story is a physician by the last name Cade, he was an Australian physician. And Cade has a very interesting story in his own right. Cade was an Australian psychiatrist or Australian psychiatrist who also was a soldier. And during World War II, after the fall of Singapore to Japan, he became a prisoner of war and he was a prisoner of war from 1942 until 1945. So he had some time for observation and during his imprisonment, he observed some of his fellow inmates is going through pretty wild vacillations in mood and energy, essentially going from manic episodes to depressed episodes, or from manic to normal episodes. And for one reason or another, we don't know why because I couldn't find any report as to why he hypothesized this, but he hypothesized that there was some buildup of some chemical in these people's brains that then they would urinate out. And that urinating out of whatever chemical was in there would allow them to be more relaxed and not manic. In other words, Cade hypothesized that there's a buildup of a chemical in certain people's brains that makes them manic and they urinate that chemical out. So eventually he got out of this prison, as we mentioned in 1945, and he started doing experiments in addition to seeing patients in his clinic. And what he did is he started to take urine from people who exhibited mania and urine from people who were not manic, and he took that urine and he would inject it into guinea pigs as an experimental model. And his general observation was that there was something in the urine that was indeed making the guinea pigs more manic if they were injected with urine from a manic patient. The exact measures that he was taking in these guinea pigs wasn't exactly clear. This is at a time or an era in science when you could just sort of report things a little bit more subjectively, although there were still numbers and statistics, it was a little bit more of like case studies and descriptions, but it turns out that even though that all seems a little bit loose, it led to some incredible and still important discoveries for psychiatric health. So what he figured out was that the urine from manic patients seemed to be more toxic for these guinea pigs. And he also knew that there are two toxic substances in urine, urea and uric acid. So he was able to separate the urea and uric acid from people with mania and patients that did not have mania. And he figured out that the urea was the same in both these mentally ill, manic patients and the non manic patients. So it did not seem that urea was the compound that was creating these manic episodes or related to manic episodes or held the toxicity so instead he focused on the uric acid. Now in order to put the uric acid into solution so that he could inject it into these guinea pigs, he had to

try a number of different compounds in order to dilute it. It just so happens that, and you chemists will be familiar with this, but there's certain things that just don't go into solution easily. You put the powder in a vial, you add some water or a saline or another solution, you mix it up and the powder stays suspended in there, it doesn't actually ever become a clear liquid that you can inject. So in order to try injecting different strengths of uric acid, he ended up using lithium to assist in the dilution, and lithium worked. So what he basically was doing, again for you chemists, is he was taking uric acid, he was adding lithium, and making a solution of lithium urate. This is a lot of details, but this is important because what he eventually found is that when he diluted the uric acid with lithium and created lithium urate, lithium urate could actually calm down these guinea pigs that were injected with the toxic urea. He also found that lithium urate had a generally calming effect on these guinea pigs. So now we're really off in crazy territory, we're talking about urine from patients that's separating out urea and uric acid, we're adding lithium to the uric acid, we're injecting this into guinea pigs, this is getting pretty wild and pretty weird, but this is medicine, and from time to time, this is medicine and science. Cade was a good scientist in addition to being a good physician, and by good scientists, I mean that he did control experiments. Here he was injecting lithium urate into animals and seeing an effect, but he knew that that solution of lithium urate contained not just the uric acid, but it also contained lithium. And so he quite appropriately asked, maybe the lithium alone is having this calming effect on these guinea pigs. And indeed, that was the case. When he did the proper control experiment and injected only lithium solution into these guinea pigs, they calmed down. From there, he in sort of 1940 style medicine, this would not happen now, he very quickly moved from that animal model into human patients and started injecting human patients with lithium or providing lithium orally to those patients. And lo and behold, found an absolutely profound and positive effect of lithium in reducing symptoms of mania. And as all good physician scientists do, he wrote up his results. And he wrote it up in a paper entitled, Lithium Salts in the Treatment of Psychotic Excitement. Okay, back then they didn't call it mania, they called it psychotic excitement. This is a paper that was published September 3rd, 1949 in the Medical Journal of Australia. We will provide a link to this study, is now a classic study in the field of psychiatry. It's a really wonderful paper to read. And actually I encourage people, even if you're not a scientist or a clinician to just take a quick look at the second page in this paper that we've made available to you where he describes each of the various case studies or the individuals that he looked at. I'm not going to read these in detail now,

'cause it would take a lot of unnecessary time, but things like case seven, MC, aged 40-years-old, suffering from manic recurrent mania. In this episode, he'd been excited, restless, and violent for over two months and was interfering so often that had to be confined to a single room during the day. So this is very debilitating, what we now know to be bipolar depression. He commenced taking lithium citrate, 20 grains, that's a measure of the amount of lithium, three times a day. In four days, he was distinctly quieter and by February 13th, 1949, appeared practically normal. He continued well and on February 20th, 1949, the dose of citrate was reduced to 10 grains, et cetera, et cetera. He left the hospital. There are numerous descriptions of this sort within this paper, including some descriptions of patients that did not see such success, and including some descriptions of patients that suffered from some negative side effects. So that's important to point out as well, but it's an absolutely wonderful paper and it's an absolutely wonderful voyage into the history of psychiatry right down to the discussion where in just three short paragraphs, Cade really lays out the case for why lithium is such a important discovery in the treatment of what, at that time,

01:02:44 Lithium Treatment & Side-Effects

they were calling psychotic excitement and what we now know to be manic bipolar depression. Lithium, I should mention, has a number of important features, but it also a number of important side effects that need to be considered. First of all, it does have a certain toxicity and so levels of lithium in the blood need to be monitored extremely carefully. So it's not the sort of thing that people can just take at a given dose and every patient responds the same, there's a lot of oversight and a lot of blood tests that have to be done, especially in the first three months of lithium treatment. I should mention that lithium treatment is still used to some great degree of success in many, not all people suffering from bipolar depression, or bipolar disorder rather, but there are a number of important things that happened between 1949 and present day that prevented lithium from reaching patients that really needed it. And that all can be summarized in two or three short sentences. Basically, by virtue of the fact that lithium is a naturally occurring element, it could not be patented. And as a consequence of that, there wasn't a lot of potential profit for drug companies to produce lithium. In fact, still to this day, it's very low cost, and still to this day, no one really owns the patent for lithium in its purest form. So that made it unattractive. It turns out that the FDA in the United States didn't allow lithium

to be used as a treatment for manic bipolar disorder until 1970. So we're talking about a full 21 years from the publication of this paper by Cade in the Medical Journal of Australia showing quite beautifully the great potential in use of lithium for quelling the symptoms of bipolar disorder until the first patients in the United States were starting to access lithium regularly. And nowadays, of course, lithium is available, but still not able to be patented 'cause it's element number three on the periodic table, it's naturally occurring. It's not literally falling down from the stars as stardust and going into pill form, but rather it can be synthesized in laboratories, but it is available. It does show not only great potential in many patients but great application in many patients despite its side effects. So lithium really stands as this kind of golden example of a treatment that works, at least in many individuals,

01:05:05 Effects of Lithium: BDNF, Anti-inflammatory & Neuroprotection

prior to an understanding of the biological basis of the disease for which that treatment is needed. Now with that said, scientists and clinicians have been quite rigorous in trying to understand why and how lithium works in order to understand the why and how of bipolar disorder. This is the way that proper medicine and science is done. Even if there's an excellent treatment for something, it's important to understand why that treatment works because, first of all, not everyone responds to that treatment. Second of all, scientists and physicians understand that just because we have one treatment that works, if it has any side effects at all, there is the possibility for better treatments. So it's not just about trying to bypass a drug that doesn't make much money for drug companies, I know a lot of people think in those terms, they think, oh, well, there's this continued search for better treatments for bipolar disorder even though lithium works because lithium doesn't allow drug companies to make much money. That's not really the case. The fact of the matter is is that the toxicity, some of the other issues that are created with lithium, the fact that people need the ongoing blood testing, et cetera, really stimulates the need, really an urgent need for new and better treatments for bipolar disorder. And only by understanding how lithium works at the cellular level, at the neural circuit level, et cetera, do we really stand to find those new discoveries. If you were to do a literature search on the actions and mechanisms of lithium in terms of how it can calm people down and reduce their manic episodes, you would find an enormous array of papers, literally thousands of scientific studies in animals and in humans, which, for

instance will tell you that lithium treatment will increase so-called BDNF, brain-derived neurotrophic factor. BDNF is often talked about in the context of neuroplasticity, the brain and nervous system's ability to change in response to experience. And indeed it does seem that ingesting lithium increases BDNF. BDNF is what we call permissive for neuroplasticity. It doesn't create specific changes in the brain, meaning it's not going to make your memory better or your coordination better, or your emotional state better per se, what BDNF does is it permits the neurons, the nerve cells and their connections in the brain to be more likely to change if the proper environmental conditions are met. That is BDNF creates a kind of buoyancy to neuroplasticity. It opens the gates to neuroplasticity. So lithium does increase BDNF, we'll talk about why that's important in the context of the neural circuits involved with bipolar disorder in a few minutes. It also seems to be a potent anti-inflammatory. Now, inflammation is one of those words that's thrown around extensively nowadays, especially on social media and especially as it relates to any health condition, it's like inflammation, inflammation, inflammation, always seems to be discussed in the context of inflammation being bad. But I do want to point out that inflammation is a natural adaptive response to physical injury to a cell or organ or tissue of any kind. Inflammation is the basis by which adaptations occur to exercise. So if, for instance, you were to weight train and use a heavier than normal weight kind, do a set to failure or create some little micro tears in the muscle that are healthy in the sense that they would create adaptations and make that muscle stronger, maybe even grow that muscle, there's an inflammatory response associated with that that is critical to the positive adaptation. So inflammation isn't always bad, although excessive, or as we say, runaway inflammation is bad. Lithium seems to be able to suppress inflammation and, importantly, it can suppress inflammation in neural tissues and within the brain in particular. That is important. And we return to that and why it's important in a little bit. The other thing about lithium is that lithium is neuroprotective, that is it can prevent neurons from dying under certain conditions. Why would neurons die? Well, there are a lot of reasons why neurons can die. There can be a physical insult to the neurons. You can get hit really hard in the head, a bullet, God forbid, can enter the skull and kill neurons, there are a lot of reasons why neurons can die. Neuroprotection is a situation in which a neuron is given some sort of chemical or physical resiliency that allows it to suffer an insult and yet bounce back. So it's very similar to the way that we think about psychological resiliency, neuroprotection is an ability for neurons to be better able to handle stress of different kinds, in particular, excitotoxicity. There's a phenomenon in

bipolar disorder and a lot of other psychiatric conditions in which hyperactivity of certain brain areas actually starts to kill off neurons. Hyperactivity doesn't always do this, but it turns out that if certain brain circuits are too active for too long, some of the chemicals associated with neuroactivity, things like calcium and neurotransmitters like glutamate can actually kill the very neurons that are active. So it seems that lithium can prevent some of that neurotoxicity. Now, this turns out to be particularly important for this discussion about bipolar disorder

01:10:10 Neural Circuits of Bipolar Disorder, Interoception, Hyper- vs. Hypoactivity

and the neural circuit basis of bipolar disorder because if we are just take a step back and ask, what's different in the brains of people with bipolar disorder? There are some very interesting answers that start to emerge. There are basically two main neural circuits that are present in normal individuals, I say normal, I say that respectfully to the people with bipolar disorder by referring to people who do not suffer from manic episodes or from manic depression. There are circuits that are present in people with bipolar disorder and in people that do not suffer from bipolar disorder, both of those circuits do the same thing in both sets of individuals, and yet in people with bipolar disorder, there seems to be an atrophy or a removal of certain neural connections over time that leads to a situation in which people with bipolar disorder become very poor at registering their own internal state, in particular, their emotional states and their somatic states. What we're referring to here is something called interoception. I've talked about this a little bit on the Huberman Lab Podcast before, but there are two modes of perception. Perception, of course, is a attention to something that's happening in our environment or to us on or within our body. Exteroception is literally an attention to things that are happening beyond the confines of our skin. So seeing that person's face over there, or seeing that color of leaf over there, or hearing a sound over to my left, that is exteroception, perception of things beyond the confines of one's skin. Then there's interoception which is perception of things that are happening internally like, how full does my gut feel? How fast is my heart beating? Some people can measure that quite accurately just by thinking about it, other people can't. How happy am I, how sad am I, how energetic am I, how lethargic am I, et cetera, et cetera. So we are always existing in a balance between exteroception and interoception, but as it turns out, people with bipolar disorder over time, and especially into the second and third decade of having

bipolar disorder seem to have progressively diminished levels of interoception. And that very likely is important in their inability to register, for instance, that, wow, they are talking at an excessive rate or they haven't slept in 5 or even 10 days, or they haven't eaten in a long period of time. This atrophy of neural circuits for interoception is starting to emerge as one of the defining neural circuit characteristics or underpinnings of bipolar. Now I bridge to this conversation about neural circuits from the statement that lithium can protect against some of the neurotoxic effects of neural circuits being very active. Now this can get a little bit complicated, but I promise I'm going to make it clear for any of you that are watching and or listening. The reality is that people with bipolar depression very likely have a hyperactivity, that is an increased level of activity in certain circuits within the brain early in the expression of their disease. And that typically, as I mentioned earlier, sets in around the early 20s, although sometimes that can be even earlier, in the teens and so forth. But that hyperactivity, we think, leads to a toxicity and excitotoxicity of certain elements of the neural circuits that are responsible for interoception. In other words, the overuse of certain circuits can lead to a diminishing, an atrophy, or even a death of certain elements within those circuits and it appears that lithium, through its anti-inflammatory and neuroprotective effects and through its ability to increase BDNF, very likely protects us against some of that atrophy of those circuits for interoception. So this isn't a case in which people with bipolar have a neural circuit or lack a neural circuit and people without bipolar are the opposite. This is a case in which everyone more or less starts out the same, but it seems that there's a hyperactivity of certain neural circuits in people with bipolar disorder that over time actually causes those circuits to diminish. Now, this is very important because some of the more recent longitudinal studies doing brain imaging on people with bipolar disorder and those without, and doing that over time in patients starting as early as their teens, but into their 20s and 30s reveals just that, that there can be hyperactivity of circuits early on, but then hypo, reduced activity of those very same circuits at a time 5 or 10 years later. Again, this speaks to the complicated nature of bipolar disorder and the complicated nature of psychiatry and linking specific psychiatric disorders to neural circuits in general. Because if you have a situation in which in one disease, let's just, hypothesize here for a second that for instance, in certain forms of schizophrenia, there's elevated dopamine and where we to just reduce the amount of dopamine, that they would receive relief from those schizophrenic symptoms, well, that's all pretty straightforward on the face of it, but in this situation with bipolar disorder, what we're talking about is hyperactivity, too much activity

leading to hypoactivity through death of those very circuits. And so now you can especially appreciate why when the patient shows up to the psychiatrist or when the psychiatrist shows up to the patient in the total course of their disease is going to be very important. And then layer on top of that the complexity of the fact that the very defining characteristic of bipolar disorder is that there are oscillations in mood. So now we need to think about treatments, not just for the manic episodes, but also treatments for the depressive episodes. And that's, in fact, what psychiatrists do. Turns out that they apply different treatments or combinations of treatments for patients that are in manic episodes versus depressive episodes and they have to infer all that from discussions, again, just exchange of words depending on when that person walked into their office, where they are in terms of manic episodes, no symptomology or depressive symptomology, and whether or not they've had that symptomology for an extended period of time. And then just to make the situation even more complicated, the very circuits that atrophy that start to wane and disappear in people with bipolar disorder are the circuits for interoception, for understanding of what's going on in one's own body. So you can imagine if you sit down and ask somebody, well, how long have, has it been since you've slept, that person may genuinely not know. Or if you ask the very depressed person, how depressed are you? That person may not be able to articulate that. So fortunately there are solutions to this and the solution is that more often than not, the accurate understanding of whether or not someone has bipolar depression or not, and what stage of the illness they might be in or not is going to depend on the reports of people around them and not the patient themselves, hence the importance of having a rather detailed and admittedly a rather intense discussion about the symptomology of bipolar disorder, so that you can have an understanding of the people around you and have an eye and an ear

01:17:11 Neural States & Mania, Parietal Lobe & Limbic System

to whether or not those people might be suffering from bipolar, and if so, at what stage of the disease they might happen to be at. Now I'd like to talk a little bit more about what is known about the neural circuits that lead to the manic states, as well as the depressive states, but mainly the manic states of bipolar disorder. We already discussed the fact that interoception, registering of one's own internal emotions and bodily states is diminished in people with bipolar disorder. But we haven't really talked about the neural

circuits that are responsible for that lack of recognition. For that reason, I'd like to point out a paper. This is a fairly recent paper, just came out this year, but it's an excellent one, Looking at the changes over time in neural circuitry in people with high genetic risk for bipolar disorder, and in particular in young people. And studies of this sort are rare, but are exceedingly important because of the fact that they track individuals over time. The title of this paper is, Longitudinal Changes in Structural Connectivity in Young People at High Genetic Risk for Bipolar Disorder. We will provide a link to this study in the show note captions. There are a lot of data in this paper, in particular, neuroimaging data, and it's quite extensive in terms of analyzing the so-called connectomics. You've probably heard of genomics, which is the analysis of genes and their display in different individuals or different animals, et cetera. You have proteomics, which is the display of, or the existence of different proteins. So omics is a big thing now in science, you kind of throw omics behind anything and it becomes its own Wikipedia page, which means it becomes its own thing, so to speak, I say that only partially in jest. Nonetheless, connectomics is the analysis of connections between different neurons and neural circuit elements. And what this paper really showed by analyzing the connectomics of neural circuits in the brains of many different people with different categories of, and onset of, and severity of bipolar disorder, as well as controls in different age groups, et cetera, is that people who are of particularly high risk for having bipolar disorder or that have full blown bipolar disorder, have deficits and actually reductions in the amount of connectivity between what are called the parietal brain regions and the limbic system. Now, the limbic system I've talked about before in this podcast, if you're not familiar with it, I'll explain what it is in a moment, it's simply a collection of brain structures, not one brain structure, but a collection of brain structures that generally are responsible for shifting the overall state that we're in from states of more relaxed and calm to states of more alert and focused. The limbic system is intimately related to the so-called autonomic nervous system, which regulates our sleep wake cycles and a number of other things like our digestion, et cetera, our level of hunger and on and on. So the limbic system is really kind of like a volume control or as nerd scientists like to say, a kind of gain control on the overall level or amplitude of alertness or calmness. In fact, if we're very, very calm, we are asleep or even more calm, we can be in a coma. If we are very alert, we can be wide awake and ready to work and run, et cetera. Or if we are very, very, very alert by way of limbic autonomic interactions, well, then we can be in anxiety. We can be in full blown panic attack, or we can be in mania. We can have so much

energy that we feel like we don't need to sleep. And in fact, disruptions in the circuitry really seems to be what's going on in people who have bipolar disorder. Now, if disruptions in the circuitry are present in the limbic system, that doesn't necessarily mean that the limbic system is at fault because the way that neural circuits work is that different brain areas are talking to one another through electrical-chemical signaling, and they're regulating one another. And what this paper really tells us is that there are elements within the parietal lobe, which is a kind of a section of the brain that sits off to the side, it's not really off to the side, but in neuroanatomical nomenclature, the parietal lobe is connected in two ways, bidirectionally. So parietal lobe is connecting to limbic system and limbic system is connecting to parietal lobe. And in people with bipolar disorder, it seems that the parietal lobe is able to exert less top down control, that is less suppression of certain elements of the limbic system, which, at least right now, is leading researchers to hypothesize that the limbic system is sort of revving at higher levels. It's kind of like RPM in your cars or kind of redlining at times and for durations that are inappropriate or at least abnormal. So we have two major sets of neural circuit deficits or changes in people with bipolar. Their lack of internal awareness is reduced, and that turns out to be, by way of neural structures, like the insula which is a brain region that is connected in a very direct way to our somatosensory cortex, so the part of our cortex that registers how we feel, literally, sense of touch and internal state. So those circuits, excuse me, for those of you listening I just bumped the microphone, excuse me. Those circuits are disrupted in people with bipolar and the top down control, that kind of accelerator and break on our overall levels of energy are also disrupted. Now that's all fine and good because, well, it's true, at least according to what the data at this point in time tell us, there may be new discoveries to come, but that all seems to be the case, but it doesn't tell us how to modulate or change that circuitry. It also doesn't tell us how something like lithium can actually benefit a large number of patients or how a good number of the other treatments

01:22:58 Homeostatic Plasticity, Synaptic Scaling, Lithium & Ketamine

for bipolar disorder, which we'll talk about going forward can benefit patients with bipolar. So it appears that lithium is exerting its positive effects on bipolar depression treatment, at least in part by preventing the loss of certain neural circuits, namely the neural circuits for interoception and the top down control over the limbic system. Now it turns out to be

examining lithium's effects at an even more reductionist level, we can gain really important insight into what's going on in bipolar depression and some of the other treatments for bipolar depression, including behavioral treatments, things like transcranial magnetic stimulation, and even some of the more natural or so-called nutraceutical treatments including things like high dose omega-3 supplementation, which we're going to talk about extensively. Now, in order to understand what we're going to talk about next, it's important that everybody understand a key concept of neuroplasticity. And this is a key concept regardless of whether or not one is talking about bipolar depression. In fact, it's something I think everybody, every citizen of earth should know about, and that's called homeostatic plasticity. Homeostatic plasticity is a particular form of neuroplasticity in which if a neural circuit is overactive for a period of time, there are changes that occur at the cellular level that lead to a balance or a homeostatic regulation of that circuit so that it's no longer overactive. Conversely, if a neural circuit is underactive for a period of time, certain changes happen within the cells of that circuit to ramp up their activity or make them more likely to be active. And whether or not a neural circuit and the neurons within it become more active or less active in the context of homeostatic plasticity largely depends on one mechanism, and it's a beautiful mechanism that I'll make very clear to you right now, even if you don't have a background in biology. Neurons communicate with one another by releasing so-called neurotransmitters, which are just chemicals. Those neurotransmitters are vomited out, they're not actually vomited, but they're spit out into the so-called synaptic cleft, often called the synapse. The synapse is just a little gap between neurons. And when they are released into the synapse, they don't just stay there, they actually park or bind to receptors on what's called the postsynaptic neuron. And depending on how many receptors they bind to and how many receptors are available, et cetera, they can have a greater or lesser effect on the postsynaptic neuron. This scenario of neurotransmitters being released into synapses then binding to receptors on postsynaptic neurons and influencing the electrical excitability of those postsynaptic neurons sits central to not just the treatment of bipolar disorder, but to all treatments of all psychiatric conditions and indeed to things like neuropathic pain as well. For example, the so-called SSRIs, Prozac, Zoloft and others, et cetera, stands for selective serotonin re-uptake inhibitor. What does that mean? Well, serotonin is a neurotransmitter. It's actually a neuromodulator that's released into the synapse, and then the SSRI, the selective serotonin re-uptake inhibitor allows more of that serotonin to sit within the synapse for longer, it's a re-uptake

inhibitor, it prevents re-uptake by the presynaptic neuron. and that serotonin therefore can park in or dock in the receptors, as it's called, of the postsynaptic neuron in greater numbers, and have a greater impact on that postsynaptic neuron. So the drugs that are used to treat depression or other things of that sort, things like SSRIs, work by changing the availability of neurotransmitter in the synapse. Other things like MAO inhibitors, Monoamine oxidase inhibitors, work a different way. They inhibit the enzyme. Anytime you hear an enzyme in biology, it's very likely an enzyme which breaks things down. so MAO inhibitors prevent the breakdown, not the re-uptake, but the breakdown of neurotransmitter and therefore allow more neurotransmitter to be available in the synapse and influence the postsynaptic cell. Homeostatic plasticity is a form of neuroplasticity in which overall circuits can become much more excitable or much less excitable by the addition of more receptors in the postsynaptic neuron or by the removal of more receptors from the postsynaptic neuron. And the way this happens is just beautiful. It was first discovered in the visual system and the person primarily responsible for the discovery of homeostatic plasticity, although there are several, is a woman by the name of Gina Turrigiano, she's a professor at Brandeis University. And what the Turrigiano Laboratory showed was that for instance, if we are in the dark for a long period of time, literally, and we're not seeing much for a long period of time, there's an increase in the number of receptors in the postsynaptic neurons so that a smaller amount of light and excitability within the visual system can lead to greater amounts of activity in the visual system. Conversely, if there's an overactivity or an increase in that activity in the visual system for some period of time, then a number of receptors in the postsynaptic neuron are removed from that postsynaptic neuron surface, making any neurotransmitter that's available only able to bind the receptors that are left and have less of an influence on those cells. In other words, keeping a circuit in so-called homeostatic balance in a particular range of excitability. Now, while that's a mouthful and an earful and a concept-full, I don't know if a concept-full is a word, but in any case, that's a lot to think about, but all you need to know is that if a neural circuit is very active for a period of time, in normal individuals, there will be a reduction in the amount of activity by way of removing receptors that bind neurotransmitter. Whereas, if a neural circuit is very quiet, it's not activated for a period of time, maybe your leg is in a cast for instance, and you're not activating your quadriceps and calves very much, well when that cast comes off, sure, the muscle might be atrophied but the nerves that connect to that muscle are actually in a position to influence that muscle even more once you start using

that muscle or those muscles, because whatever neurotransmitter is released now has the opportunity to bind to more receptors, in that case in muscle, or in the case of brain circuits, in postsynaptic neurons. So homeostatic plasticity is this beautiful, balancing mechanism that makes sure that neural circuits are never too active nor too quiet for too long. And in a beautiful display of how treatments can lead to a better understanding of biology, which can lead to the discovery of even better treatments, lithium and another compound, which we'll talk about, ketamine seem to exert their actions largely through effects on homeostatic neuroplasticity. There's a wonderful paper that describes all the nitty-gritty of this. Certainly most people listening, I'm guessing, are not going to be interested in all this detail, but for those of you that you are and you want to delve deep into this, this paper was published in Neuron Cell Press journal, excellent journal, it's titled, Targeting Homeostatic Plasticity for the Treatment of Mood Disorders. And there's one particular figure in this paper that I'll just describe to you in which measurements were made from neurons and the number of receptors in those neurons, it's done somewhat indirectly through a method that's detailed and neuroscientists are familiar with. Basically what it measures is how excited a given neuron is, electrically excited a given neuron is to a given amount of neurotransmitter. So that the amount of neurotransmitter that's vomited onto a neuron is essentially kept constant, and then the response of the postsynaptic neuron is measured. So it can be of one level or higher or lower depending on homeostatic plasticity. And what this paper shows and what's been shown over and over again, is that when neurons are exposed to lithium for a period of time, there is a reduction in the excitability of the postsynaptic neuron, that is neurons within the brain become less excitable over time if lithium is present, whereas ketamine, which is now a common FDA-approved, at least in the US, it's approved for the treatment of major depression, ketamine does the opposite. Ketamine seems to increase the number of receptors in the postsynaptic neuron and lead to greater levels of excitability and electrical activity within neural circuits to a given fixed amount of neurotransmitter. So this is super interesting because what it means is that lithium is causing circuits to be less active, ketamine is causing circuits to be more active. And we know from excellent clinical data now that ketamine seems to be a very effective treatment for major depression, and for the major depressive episodes of people that suffer from bipolar depression, that includes these major depressive episodes of two weeks or longer of suppressed mood, appetite, sleep issues, et cetera. Now, the key thing about ketamine that's often not discussed is that while its effects are very potent,

they are transient. So one major drawback to ketamine therapy for depression is that it has to be done repeatedly, and how repeatedly, or how often, rather, depends, of course, on a discussion between the psychiatrist and the patient. This is not something to cowboy on your own. I know that, and many of you are probably familiar with the fact that ketamine also is abused recreationally. It is a so-called NMDA, N-methyl-D-aspartate receptor antagonist, so it blocks the very receptor that's responsible for neuroplasticity for changes in neural circuits. It also changes excitability in neurons as I just described. So ketamine is a very potent chemical that has been shown over and over again and is now FDA approved for the treatment of major depression, but its effects seem to be transient. Lithium, as I described earlier, seems to reduce the manic episodes or the intensity of manic episodes in symptomology, in people with bipolar disorder, it's doing that through neuroprotection. So protecting neural circuits from dying away that initially are overactive and that overactivity causing excitotoxicity, blocks that excitotoxicity, we believe. And it seems to do that in part by diminishing the amount of activity in those circuits. So this is a beautiful mechanistic story, and it's the sort of story that you'd love to have for a great number of psychiatric illnesses. And fortunately we have for bipolar disorder. Overactivity of a given circuit eventually leads to neurotoxicity, excuse me, lithium is preventing that neurotoxicity by reducing the number of receptors in certain elements within those circuits, so called homeostatic scaling, it's downregulating the number of receptors leading to less excitability and preventing, we think, excitotoxicity. And in that sense, you can see exactly why it's important to get lithium treatment in there early for people with bipolar disorder. Ketamine as a treatment for major depression seems to be effective but transient. And you can also see why it would be important, not just to reduce the manic episodes for people with bipolar disorder, but to also treat the depressive episodes. So this is a key feature of the treatment for bipolar depression and for bipolar disorder. there needs to be treatment both of the mania and of the depressive episodes if they're present. And fortunately, there are excellent drugs to do that. And I should mention that ketamine and lithium are just two of the drugs within the kit that psychiatrists have access to. There are many things, olanzapines and a number of different, including Clozapine. Clozapine is an antipsychotic which is commonly prescribed to as a sedative in some cases that allows people in manic episodes to sleep. It's classically described as so called dopamine receptor 4 antagonist, although it does other things as well. Clozapine has a number of side effect features related to white blood cell and things of that sort that require careful

monitoring. So there are an enormous number now, literally dozens and dozens of different drugs, each designed to target either the manic phase, the depressive phase, or some what we call acute sort of early phases versus ongoing treatments. This is a vast galaxy of drug treatments that really should be navigated, I should say, absolutely should be navigated by a board certified psychiatrist. And of course in close discussion with both the person suffering from bipolar disorder, but also ideally the family members of the person suffering from bipolar disorder. But I think, at least up until now, we've focused on the two major pathways for treatment, lithium and ketamine. And we've talked about why lithium and ketamine work, that they're working on opposite ends of this homeostatic scaling. We talked a bit about the circuits that are involved in generating what we think are the manic symptomology and the lack of interception. Why people can just persist in staying awake, awake, awake, not eating, et cetera. Now you have in mind how all that is put together. And I think you have in mind, some of the well-demonstrated treatments for the different component parts of bipolar disorder, which now I'm hoping you're also well versed in

01:36:00 Talk Therapies: Cognitive Behavioral Therapy, Family-Focused Therapy, Interpersonal & Social Rhythm Therapy

based on our early, early discussion of what constitutes bipolar 1 and bipolar 2. Now I would like to also talk about some of the not so typical therapeutics for bipolar disorder and also point to the things that have been tried and failed for successful treatment of bipolar disorder, because some of those things are often talked about and suggested, especially in online communities, and while it's not clear that any of them are particularly hazardous on their own, although some of them do carry some hazards, I do think it's important because of the critical time sensitive nature of bipolar disorder and the urgency of getting treatments early to try and prevent some of the longer lasting neural circuit changes that if people can avoid some of the less effective or demonstrated to be ineffective treatments, that they stand to combat bipolar disorder much more successfully. First of all, a key point about drug therapies versus non-drug therapies or talk therapies, without question, drug therapies are going to be most effective when done also with talk therapies. And we'll talk about which talk therapies have been demonstrated to be most effective. There is some argument about what I'm about to say next, but in general, most psychiatrists will tell you, or certainly the ones I've spoken to

have told me, that talk therapy on its own is rarely, if ever effective for bipolar depression and bipolar disorder, whether or not it's BP-I or BP-II. That's just the reality of it. Contrast that with our discussion about obsessive-compulsive disorder, which we talked about a few episodes ago, if you haven't seen that episode, We have an in-depth episode all about OCD and obsessive-compulsive personality disorder. There it seems that drug therapies and talk therapies can be done independently or in combination. As expected, combined drug and talk therapies are more effective there than either one alone, but there are pretty impressive effects of talk therapy alone provided that they're initiated at the right time, and it's the right form of talk therapy. That's OCD, but in terms of bipolar disorder, it really seems that the drug therapies are necessary, at least in most all cases. That said, talk therapies are terrific augment or support for those drug therapies and sometimes can allow people to take lower doses of those drug therapies, which turns out to be important because of the side effect profiles of a lot of drug therapies and sometimes the cost as well. I guess we can think of cost just as another side effect really. There are both established and more novel forms of talk therapy being used, again, in concert with drug treatments for bipolar disorder. Cognitive behavioral therapy is the one that seems to be best, at least by way of the statistics and papers that exist. It's also the one that's been explored the most. So one of the reasons why it's often considered the most popular or effective is 'cause it's also been around longer and it's been explored the most. Cognitive behavioral therapy in general is a progressive exposure of the patient in a very controlled way, in a clinical setting, to some of the triggers or the conditions that would exacerbate bipolar disorder. Now, earlier I said borderline personality disorder has all these triggers and triggered elements from the external environment, whereas bipolar disorder does not. And that's still true, but it is the case that somebody with bipolar can have worse symptoms if life conditions get worse or more stressful. So cognitive behavioral therapy, I mean the discussion about and sometimes the direct exposure to anxiety provoking elements of life can be very helpful for adjusting the responses to those otherwise triggering events and sometimes making the drug treatments more effective even at lower doses. There are also forms of therapy including family-focused therapy, which is especially important in terms of bipolar disorder because family members, provided that they are not themselves in a manic episode due to the close heritability of bipolar disorder, but family members can often be excellent windows into whether or not somebody is doing well or poorly, or is veering toward or is emerging from a manic or depressive episode because they understand that

person, they have a lot of data, it could be purely subjective data, but they have a lot of exposure to how long or well somebody's been sleeping or eating, et cetera. So family-focused therapy involves other members of the person suffering from bipolar disorder's family, as well as conversations about family members in a way that helps patients with bipolar disorder navigate, not just through manic episodes and depressive episodes, but start to learn to predict what are the conditions psychological, physical, and otherwise that can trigger bipolar episodes. And then there's a category of therapy called interpersonal and social rhythm therapy. This is deserving of its own entire episode really. Interpersonal and social rhythm therapy, it's sort of an expansion on family-focused therapy, although it's distinct in certain ways as well, and really focuses on how people are relating to others in their life, and in the workplace, and in the school environment, and also within the family, et cetera. And I should say that a overall theme that's emerging in psychiatry and psychology is to start wherever possible to incorporate more of the social aspects and the interpersonal aspects. In other words, not just talking to and examining a patient as one biological system, one nervous system, one set of chemicals, and one life, but rather a set of chemicals, neural circuits, and a life that's embedded in the chemicals and neural circuits and lives of other people. Just by way of example, you can imagine that if somebody is in a very healthy relationship or a very abusive relationship, that that's going to strongly impact the outcomes of manic episodes. You can imagine that if the financial situation is one in which people can recover from manic episodes, I didn't mention this earlier, but I should have, forgive me, that oftentimes people who are in a manic episode will go out and spend immense amounts of money that they simply cannot afford to lose. And then the depressive episodes that, in many cases, follow are made far worse by the financial anxiety and the financial stress that results from those manic episodes of spending, et cetera. And then of course, this carries over to sexual promiscuity where people might be dealing with unwanted pregnancy or STIs, or very fractured interpersonal dynamics with existing or new relationships. I mean, you can imagine how these manic episodes, as well as the depressive episodes can really wick out into an enormous amount of destruction, which brings us back to the initial criteria of BP-1 and BP-2 is that these manic episodes are not a good thing. These depressive episodes are not a good thing. They create this sense of euphoria in the person experiencing mania, or they create this sense that anything is possible. But at the end of the day, and actually every day, these episodes are quite maladaptive. They really destroy people's lives. And it's not just the life of the

person that's suffering from bipolar disorder. And so hence cognitive behavioral therapy, family-focused therapy and interpersonal and social rhythm therapies are the primary three talk therapies that are most often combined with drug therapies in order to try and really reduce the harm.

01:43:18 Electroconvulsive Therapy (ECT), Transcranial Magnetic Stimulation (rTMS)

It's really all about harm reduction from manic episodes and depressive episodes. One very exciting and emerging treatment that does show great promise, and in some cases, great outcomes, for bipolar disorder is, believe it or not electric shock therapy. Electric shock therapy may sound barbaric, and in fact, it tends to look barbaric, although this is done in the controlled setting of a hospital. If any of you have seen *One Flew Over the Cuckoo's Nest*, the final scene or near final scene in that movie was Jack Nicholson with the sort of bite protector in his mouth and getting electric shock therapy, and it's as the name suggests, it's a kind of inducing a global seizure, either low level or grand mal type seizure in the patient's brain and nervous system. You might ask, well, why would one want to do that? Well, it turns out that this is a well-established, and in many cases, very effective treatment for major depression. Electric shock therapy is generally used for treatment-resistant depression. So these are people that have no positive response or ongoing positive response to drug therapies or other therapies. Electric shock therapy is thought to work primarily by stimulating the massive kind of indiscriminate release of things like serotonin, dopamine, acetylcholine, a huge variety of neuromodulators, as well as things like BDNF, brain-derived neurotrophic factor which then allows neuroplasticity to take place. Again, BDNF being permissive for neuroplasticity. The problem with ECT is that it's really only useful for treatment-resistant depression, it doesn't actually target the manic aspects of bipolar depression and bipolar disorder, but nonetheless, is used when drug treatments don't work. Some of the negatives of electric shock therapy or electric convulsive therapy, ECT, is the proper acronym and way it's described is that it's quite invasive, right? This is something that you need to go to the hospital for and oftentimes there's some inpatient care required after the electric convulsive therapy. It's a fairly high cost, especially for those that don't have insurance. And of course it requires anesthesia. For most people, that's not going to be a problem, but for many people that could be a problem. And there's often some associated memory loss. And so the memory loss, the invasive nature of ECT and the cost

oftentimes rule out ECT for most patients, and that's why it's sort of a late stage or kind of last resort type thing for treatment-resistant depression. Nowadays ketamine type therapy is done repeatedly or other treatments, for instance, transcranial magnetic stimulation which is basically non-invasive, it's a coil that's placed on the outside of the skull, excuse me. And we can more accurately refer to it as repetitive or rTMS, repetitive transcranial magnetic stimulation. Transcranial magnetic stimulation is a tool that allows researchers and clinicians to reduce the amount of activity in specific neural circuits. So they can actually target the magnetic field to particular neural circuits to reduce activity in those neural circuits. Again, it's minimally invasive. It has been shown to be effective in both increasing neuroplasticity in positive ways, as well as reducing depressive episodes and in a few instances in reducing the amplitude or the intensity of manic episodes in people with bipolar disorder. The problem is it's still a very early technique. There aren't a lot of clinics and labs doing it. I'm starting to see more advertisements, literally commercial clinics that are advertising rTMS or TMS. I encourage you to approach those clinics with caution. I'm of the mind that if those clinics are not either closely or maybe even distantly associated with a research institution that's really up on the latest of rTMS, you'd be wise to at least do your research, and explore, talk to other patients who've done these treatments, but certainly in university hospitals and in clinical settings and research settings, rTMS is being used as a way to, for instance, reduce the activity of certain limbic circuitries so that people are just overall less excitable and manic or to activate because it can also be used for activation now of certain neural circuits. Activate, for instance, the parietal inputs, the top down control over the limbic system. This is all happening right now. So we have ECT, repetitive TMS or rTMS, and then as I mentioned earlier, ketamine therapies, most of those are targeted toward the depressive aspects of manic depression. So for people with bipolar disorder that doesn't include depression, those are going to be less effective, but overall, it's going to be the talk therapies of the sort that we discussed earlier, or a moment ago. Plus drug treatments, almost always lithium will be explored,

01:48:01 Psilocybin, Cannabis

plus some treatments for the depressive episodes in particular if those depressive episodes are present. Nowadays, there's a lot of excitement about psilocybin which is a psychedelic. In the US, psilocybin is still illegal. It is not legal, meaning you can get in a

lot of trouble for possessing it, certainly for selling it, et cetera. But psilocybin is being explored as a clinical therapy in certain laboratory settings in particular, at Johns Hopkins School of Medicine. It's being explored in human patients for the treatment of major depression, for OCD I believe as well, but certainly for major depression and for eating disorders. And it seems from the initial wave of publications from that work done by the incredible Matthew Johnson or Dr. Matthew Johnson, who was a guest on this podcast before, he's also been on the Tim Ferris Podcast, he's been on the Lex Fridman Podcast. Dr. Matthew Johnson came on this podcast, he's talked about some of the work with psilocybin for the treatment of depression. Very impressive results there. And as you can imagine, very impressive results for the major depressive episodes for bipolar. However, at least to my knowledge, again, to my knowledge, there have not been any controlled clinical trials exploring psilocybin for the mania associated with bipolar disorder. If someone out there is aware of those clinical trials, please let me know. I'll do an update in a future podcast, but right now, no knowledge from me about psilocybin clinical trials for the manic component of bipolar disorder. A number of people are probably also going to wonder about whether or not cannabis or medical marijuana is useful for bipolar disorder. To address this, I looked to some previous lectures and some clinicians at Stanford Psychiatry. This question was asked of them, and as it turns out, cannabis does not seem to be effective for the treatment of the manic phases of bipolar disorder or for the treatment of the major depressive component. The only treatment perhaps, or I should say the only situation perhaps in which it might be useful, and this is what was relayed to me, is that it may help with sleep in certain people that are having trouble with insomnia, though nowadays, it's far more common for people in manic episodes to be prescribed things like Trazodone or other benzos, benzodiazepines in order to try and get sleep within the manic episodes. And benzodiazepines and Trazodone, et cetera, work largely through the so-called GABA system. This is a neurotransmitter that causes reductions in excitability of neurons, hence why it's being used to try and calm people down and allow them to sleep during their manic episodes. So not a lot, or essentially no data, supporting the use of cannabis for the treatment of bipolar disorder, per se, nor data supporting the use of psilocybin for the treatment of bipolar disorder per se. But I realize, as I say that, that there are going to be a number of people that may have had positive or negative experiences with cannabis or psilocybin as they relate to bipolar disorder. So please, if you're willing or comfortable, put that, if you're comfortable, into the comment section on YouTube. And

of course, if you are aware of any studies on cannabis or psilocybin showing positive outcomes for the treatment bipolar disorder, please provide links or PubMed ideas to those, I'd love to peruse those studies. There are two naturopathic, or I should say, nutrition, supplement-based approaches to bipolar disorder. They get talked about a lot, and one of them shows some interesting promise, or effectiveness even, in a limited context. Before marching into this description of these two compounds, in fact before even mentioning these two compounds, I do want to emphasize what's been said and written about over and over again and what was relayed to me from expert psychiatrists.

01:51:50 Lifestyle Support, Supplements: Inositol & Omega-3 Fatty Acids

It is not wise to rely purely on talk therapy or on natural approaches to the treatment of bipolar disorder given the intensity of the disorder and the high propensity for suicide risk in people with bipolar disorder, it is a chemical and neural circuit disruption, and it needs to be dealt with head on through the appropriate chemistry and prescription drug approaches from a board-certified psychiatrist. I don't say this to protect me, I say this truly to protect those who either suffer from or think they may suffer from bipolar disorder or if you know someone who you think might suffer from a bipolar disorder. Now, all that is not to say that there aren't useful lifestyle interventions that can support people with bipolar disorder. So I just briefly want to mention those. And again, I'm lifting the statements I'm about to make from some excellent online lectures from psychiatrists at Stanford and elsewhere, which essentially say that, of course, of course, of course, getting better sleep, getting adequate exercise, getting proper nutrition, having quality, healthy, social interactions, even getting regular sunlight in the day and avoiding bright light at night, all of those things are going to braid together to support the nervous system and the psyche of somebody with bipolar disorder, but they braid together to support the psyche and the neurochemistry and the neural circuits of anybody and everybody. So they have generally a modulatory effect that is they're indirectly shifting the likelihood that somebody might have an episode, or the intensity of an episode, in particular, the depressive episodes. You can imagine how someone who's heading into a depressive episode, maybe they're on a lower amount of medication or they haven't yet medicated for the depressive episode of bipolar. And now they're making sure or their family is making sure that they're getting exercise, sunshine, eating correctly, social engagement, et cetera. Of course it makes perfect sense why they would have perhaps

a shallower drop into depression or maybe an offset of depressive episode. That said, most all, if not all people with bipolar disorder are likely to need some sort of drug therapy intervention in order to help them. So lifestyle factors are always important in all individuals, those suffering from psychiatric conditions or not. But in some conditions of the mind and body, those lifestyle interventions can have a greater effect in offsetting symptoms, whereas in bipolar disorder, I think it's naive, and in fact, wrong to say that lifestyle interventions alone are going to prevent, especially the extreme forms of mania and depression. Again, bipolar disorder being so serious and carrying such high suicide risk, we just have to point this out again and again. Now with that said, there are two substances generally found as supplements, although there are other sources of them as well, including within nutritional sources that have been shown, at least in some studies, to be pretty effective in adjusting the symptoms of bipolar disorder, and those two things are inositol and omega-3 fatty acids. Now inositol is a compound that is taken for a variety of reasons. It's something we've talked about on the podcast before. I personally take inositol not because I have bipolar disorder, in fact I am quite lucky that I don't have bipolar disorder, but I take inositol, a 900 milligrams of myo-inositol every third night or so in order to improve my sleep. It's something that I've added to my sleep stack. It's something that I found greatly enhances the depth and quality of my sleep. And if I wake up in the middle of the night to use the bathroom, et cetera, it's greatly enhanced my ability to fall back asleep when I want to go back to sleep. It also seems to have a fairly potent anti-anxiety effect during the day. And as I discussed in our episode about obsessive-compulsive disorder, inositol has been used at high dosages, again, I should say myo-inositol has been used at high dosages, at levels of even 10, 18 grams, those are massive dosages by the way, to deal with certain symptoms of OCD to limited success. And I should mention that high dosages of 10 or 18 grams of inositol can cause a lot of gastric discomfort, et cetera. If you want to learn more about inositol and its various uses, I encourage you to go to examine.com where there's the so-called Human Effect Matrix, and that Human Effects Matrix will describe the many places in which myo-inositol and other forms of inositol have been shown to be effective in, for instance, reducing anxiety, enhancing sleep and on and on. Myo-inositol is important because myo-inositol, and we can just say inositol, is related to so-called second messenger pathways. I don't want to get too deep into second messenger pathways, but when certain substances bind, like neurotransmitters to a receptor on a cell surface, oftentimes those receptors themselves will open and allow the passage of ions and other things into

a cell. Oftentimes they will engage what are called second messenger systems that is they will trigger mechanisms within the cell to then go do other things. This is probably something we should get into in real detail in a future episode for those of you that really want to nerd out on cell-cell signaling, which is a favorite topic of mine. In any case, inositol is related to a number of so-called second messenger systems, this handoff, or this kind of stimulating of changes within a cell that can inspire changes in what's called membrane fluidity, can actually make the membranes of cells, the outside fence around a cell, which is made up of fatty stuff, it can change the fluidity, meaning how readily things can float around in the membrane. You know, we think of cells as very rigid, like there's a cell, there's a neuron, or there's a immune cell, but actually those cells have a fatty outside, in particular neurons have a fatty outside. It's a thin fatty outside, it's called the cell membrane, and things are floating around in that cell membrane, but it's kind of like jello that hasn't quite fixed. And so things like receptors moving into the synapse or moving out the synapse for homeostatic plasticity, things like the ability for certain genes to be turned on in a cell or not turned on, can depend a lot on things that are happening in that cell membrane and how readily things move around in the cell membrane. One way to think about this whole picture of membrane fluidity is that just imagine that everyone of your cells has this layer, it's kind of a gelatinous-like layer and there are lots of little rafts floating around in there, but those rafts are able to move more quickly from one place to another, or get more stuck at one place or another, depending on how set that jello is. Inositol and lithium, and as we'll talk about next, omega-3 fatty acids seem to change the fluidity of those membranes, in other words, they allow things to move in and out of those membranes more readily or not. And this is no surprise given that those membranes are made out of fatty stuff. In particular, the membranes of neurons are what called a lipid bilayer, it's two layers of fat, bi means two, lipid, fat. And omega-3 fatty acids of the sort that are found in certain fish, and that fatty fish in particular, and that are found in fish oil and cod liver oil, et cetera. Omega-3 fatty acids, when we ingest them are used for a lot of different things, but they can be readily incorporated into pathways or directly incorporated into cell membranes, changing the way those cell membranes work and if those cell membranes are the cell membranes of neurons, changing the way that neurons work. So the ability for fish oil, and in particular, the omega-3 fatty acids, which come in varieties like EPA and DHA, we'll talk about that in a moment, have been explored at relatively high dosages for their ability to offset some of the effects of mania and to offset the effects of depressive episodes in bipolar disorder.

And actually, the data there are pretty impressive, although, although they are varied, meaning you will find several studies, and I'll mention a few, that found no effect of omega-3 supplementation through fish oil, usually it's capsuled fish oil, although fish oil can also be taken, excuse me, in liquid form. Oftentimes taking in liquid form is the more cost efficient way to do it. Taking in capsule form is the more palatable way to do it, because fish oil for a lot of people doesn't taste good. But nonetheless, there are several studies that have shown that supplementing with fish oil or omega-3 fatty acids at levels of, for instance, four grams per day for a period of time, this is a study that we will link in the show notes, This is Murphy at al. 2012. This is a fatty acid supplementation of 70% EPA to DHA actually worsen symptoms of mania over a period of about 16 weeks, which on the face of it makes it seem like, okay, omega-3 fatty acid supplementation, very likely to not be good for bipolar disorder. And yet that was the manic phase. When one looks at some of the other studies of omega-3 fatty acid supplementation, there is, for instance, a study published in 1999, this is a much higher dosage supplementation with omega-3 fatty acid, this is a 9.6 grams of fish oil per day for four months. And then actually greatly reduced symptoms of bipolar depression compared to the control group which received olive oil, olive oil is a different form of fat, monounsaturated fat but doesn't contain as much of the omega-3 fatty acids and so forth. So 9.6 grams of fish oil per day over four months is a lot of fish oil to be ingesting on a given day. This was a double blind study. This was only carried out, I should mention, in 30 subjects, but it was males and females. And the age range was pretty broad, anywhere from 18 all the way up to 64 years of age, which is important given the sort of longitudinal or changes over time, that one sees in bipolar disorder. Here's the major takeaway, supplementing with high dose omega-3s does seem to be beneficial for a good number of people with bipolar disorder. However, again, I want to highlight, however, it should not be viewed as the only treatment approach for bipolar disorder. This goes back to what I was saying before about the essential need, in most every case, for high potency prescription drug treatments prescribed by board certified psychiatrists for bipolar disorder. However, omega-3 supplementation does seem to improve or reduce the depressive symptoms in the major depressive episodes of bipolar. And there are a couple studies, and we'll link to these in the show notes as well, that show that it may even improve some of the manic episodes as well, meaning it reduces some of the manic symptoms. Now I say all this from a place of great caution, because I know, especially for listeners of this podcast, there's a lot of interest in the behavioral tools, the supplement-based tools, the

nutrition tools that can support bipolar disorder, but I don't think I can overemphasize enough that especially for bipolar disorder and the great risk of suicide and suffering and inappropriate spending, or I should say maladaptive spending and impulsivity that's associated with bipolar disorder, that it's hard to imagine a scenario in which just talk therapy and fish oil and lifestyle interventions are going to completely suppress or treat bipolar disorder. People with bipolar disorder really need to consider the full picture of treatments, the drug treatments, the talk therapy treatments, and lifestyle treatments, and nutraceutical, or we can say supplement-based treatments such as omega-3 supplementation as a full and necessary picture

02:03:31 Omega-3s, Membrane Fluidity & Neuroplasticity

for dealing with their illness. I'd be remiss, however, if I didn't emphasize that the omega-3 fatty acid supplementation is very interesting, not just in terms of the subjective effects, people saying they feel less depressed or able to sleep better, or maybe even some reduction in manic symptoms, there's actually been some really good brain imaging to try and understand how omega-3 fatty acid treatments are actually changing the brains and neural circuits of people with bipolar. And I will put a reference to this. This is a paper that was published in the American Journal Psychiatry. It's entitled, Omega-3 Fatty Acid Treatment and T2 Whole Brain Relaxation Times in Bipolar Disorder. I don't have the opportunity to go into a lot of detail right now about what T2 whole brain relaxation times are, but basically when people go into a MRI or f, functional MRI scanner, excuse me, magnetic resonance imaging scanner, what they're getting essentially is pulses of magnetic fields and the way that brain structures and neural activity can be evaluated has a lot to do with the sort of spinning, or not sort of, it has to do with the spinning and the relaxation times of different elements, literally the protons and electrons within the neurons, so it gets really detailed there, and the relaxation time is essentially looking at how quickly some of that spinning returns to rest. And in particular, the fact that the relaxation times are different for aqueous, that is liquid, versus lipid, fatty versus other components of brain tissue. And basically what this study shows is that the membranes of neurons within the brains of these people with bipolar disorder, showed more fluidity, more ability of things to move in and around the membranes, which we know is an important component of neuroplasticity in bipolar subjects that were treated with omega-3 fatty acids as compared to bipolar subjects that

did not receive omega-3 fatty acids. And fortunately this study also include a healthy comparison group where they could essentially find that people with bipolar disorder who supplemented with omega-3 had changes at the cellular level and the neural circuit level that brought their brains and neural circuits closer to that of the healthy comparison subjects. So while I don't want to point to omega-3 fatty acid supplementation as the be-all end-all of treatment for bipolar disorder, certainly it is not, it does have a strong mechanistic basis for its possible support of neural circuitry, of neuroplasticity, and in particular, the ability to make changes in cell membranes that are very reminiscent of some of the neural circuit changes and changes in membrane fluidity that are seen with lithium treatment and other known prescription drug treatments that have been established now for decades to be very effective for bipolar disorder. So what that says is that omega-3 supplementation, while not the only intervention that one should consider is something to consider and talk about with your doctor and it's operating in powerful ways. It's not just that it's changing, for instance, your gut microbiome, which is powerful,

02:06:44 Mania, Creativity & Occupations

but is indirect to the brain, it does seem to be having direct effects on neurons and neural circuits. Before we begin to conclude our discussion about bipolar disorder, I want to talk a little bit about this word, disorder, and this is a theme that doesn't just relate to bipolar disorder, but other psychiatric disorders as well. And when we think of a disorder, we think of something that is really detrimental to us. Something that really impairs our ability to function in work, in school, in relationships, and really starts to pull down our health status in a variety of ways. And certainly bipolar disorder meets those criteria. However, there is this idea that things like bipolar disorder, even things like schizophrenia in some cases are responsible for some of the creative aspects or the creative works that have been observed and carried out by human beings for many centuries. And believe it or not, there are good data to support the fact that certain aspects of mania are associated with creativity. Now, we are long overdue for an episode about creativity, its neural circuit basis, its chemical basis here on the Huberman Lab Podcast, and certainly we will have that conversation. But in the meantime, I'd like to just briefly touch upon this idea that certain occupations are associated with a higher incidence of bipolar depression. And in fact, it's been explored

at a research level. There are data pointed to the fact that certain individuals of certain occupations tend to be more creative and that creativity is associated with, again, associated, this isn't causal, it's associated, correlated with higher levels or incidents of bipolar depression and maybe even other forms of depression. So this is a study looking at mood disorders in eminent individuals. So these are people that are not just good at what they do, but are exceptional at what they do, and explored the percentage of people in given professions with either depression or mania. And this was actually a data set gleaned from more than a thousand 20th Century Westerners based on their biographies that were reviewed by other people. So it's a bit of an indirect measurement. This isn't psychiatrist data, this is data, or I should say these are data that were compiled from self reports or from reads of self reports. And they explored a number of different professions. So for instance, they looked at people in the military or people who were professional athletes or natural scientists or social scientists, people who occupied positions in public office, or were musical performers, artists, nonfiction writers, poetry, et cetera. There are a lot of professions here. I will post this or I'll post a link to it in the show note captions for you to peruse, but I'll just give you a sense of the extremes on this graph because they're very interesting. Turns out that if you were to look at the profession or I should say among the professions they looked at in this study, 'cause they didn't look at all professions, those in the military and those who are professional athletes or had jobs in the social or natural sciences, of those, there was a lower percentage of those that had depression or mania. In some cases like those who were professional athletes didn't seem to have, there was no incidence of mania, at least in this dataset, whereas at the opposite extreme of the graph, those that were poets, so these are eminent individuals, people that were exceptional poets, exceptional fiction writers, exceptional artists or non-fiction writers, well there, especially for the poets, you find that as many as 90% of these very successful poets had either depression or mania. As high as 90%, that's incredible. Contrast that with military where it's as few as 10% or professional athletes where it's as few as 20%, and for the professional athletes, as I mentioned before, none of them had mania. So does this mean that being a poet will make you manic or depressed? Well, first of all, let's look at the poetry category. It turns out that 75% of these eminent poets, these highly accomplished poets had major depression, whereas only about 20% of those poets had manic episodes. So again, it's not that being a poet is going to give you mania, certainly we're not saying that, it's not that being a poet is going to give you depression, but it turns out that people with

depression and people with depression and mania seem to gravitate towards poetry or at least are very successful at poetry. Again, associative, correlative, no causal relationship here. But it is really striking to see how the creative occupations, poetry, fiction, art, non-fiction writing, even though non-fiction writing is about non-fiction, it's still creative, music composition, theater, much higher incidents of things like mania. In fact, for the people in theater, the actors, even though the overall occurrence of depression and mania is lower than that in poets, the fraction of those individuals that have mania is exceedingly high. It's about 30% of those that they looked at who are actors, have manic episodes or have full blown mania. So I'm referring to these data because first of all, I find them incredibly interesting, right up until now we've been talking about bipolar disorder and other mood disorders for their maladaptive effects. And again, they're extremely maladaptive, much, much higher instance of suicide, et cetera, but we'd be wrong to say that certain aspects of manic episodes don't lend themselves well to creativity or that certain aspects of major depression don't lend themselves well to creativity or to the performing arts or to poetry. That said, in no way, shape or form, do I believe that being depressed is a good thing or that being manic is a good thing. Again, we return to the basic foundational criteria for bipolar disorder, major depression which is that the pressured speech, the not sleeping, the incredible increases in energy and the flights of ideas are generally not going to lead, or I think it's fair to say, are not going to lead to good places. In fact, often lead to bad places. But we would also be wrong if we didn't consider the fact that there is a somewhat inextricable relationship between mania and creativity. And it could be that hypomania or brief periods of mania, maybe even an hour a day or 30 minutes a day of composing or writing poetry, maybe even some of the lows that we feel, some of the sadness, some of the grief, some of the nostalgia that we feel provided that it's not pathologic, that it's not persistent for the four or seven days that are diagnostic of bipolar 2 and bipolar 1 disorder respectively, well, then we can start to view emotional states as something that can actually lend themselves to positive outcomes and maybe even to creativity and to improved occupations. So it's important that we have a nuanced view of what sadness versus depression versus major depression are, it's important that we distinguish between being erratic, being very energized, and full blown bipolar disorder. And I raise this for another reason as well. Nowadays, it's very common to hear people saying, ah, you know, that person is OCD. Well, on the episode about OCD that I did a few weeks back, that you can find if you like at hubermanlab.com, in that episode, I pointed out that OCD, obsessive-compulsive

disorder is very maladaptive. I think it's number seven, as I recall on the list of debilitating diseases, all diseases in terms of lost time at work, suffering relationships, et cetera. So it's a really serious condition. And yet we often hear, oh, that person is obsessive. And as I pointed out, there is obsessive-compulsive personality disorder. And then there is obsessive-compulsive tendencies, which actually benefit people, but that is distinct from obsessive-compulsive disorder as a clinically diagnosed thing. Similarly, we hear that, oh, somebody's being bipolar. You know, they're all over the place. They're bipolar. Well, that's a very subjective label that people give one another in passing, more and more often I'm hearing this, and yet bipolar disorder, whether or not it's BP-1 or BP-2 are extremely maladaptive and extremely associated with high suicide risk. So while I'm not here to police people, I'm not certainly not the word police or the nomenclature police, I do think that whether or not you refer to people as OCD or as bipolar, et cetera, that's up to you, it's not my place to say, but I do think it's important that all of us understand

02:15:33 Bipolar Disorder: Diagnosis, Neural Circuits & Treatment

that these psychiatric conditions carry with them tremendous maladaptive weight. So today we've really done a deep dive into bipolar disorder and to both the manic and the depressive components that are present or can be present in bipolar disorder and the different forms of bipolar disorder and some of the major treatments for bipolar disorder, in particular lithium and its underlying mechanisms and some of the neural circuit and chemical basis and neuroplasticity basis of the treatments for bipolar disorder, in particular homeostatic scaling or homeostatic plasticity. All of that, of course, is relevant to bipolar disorder and I hope will be useful in your understanding and maybe even in your pursuit of treatments for bipolar depression, bipolar disorder for you or other people. I also hope that it will be useful in your understanding of how brain circuits work in normal conditions or in conditions where there is no disease state or maladaptive conditions. Homeostatic plasticity is present in all of us. Membrane fluidity due to how easily things move around in the surface, the fatty layers on the outside of neurons and the movement of receptors in and out of neurons that is present in all of us. The influence of omega-3 fatty acids is central to that discussion. As is the discussion about various drug treatments because even if you're not somebody who's taking a drug treatment or who is pursuing a drug treatment for bipolar disorder or another psychiatric

condition, your serotonin levels, your dopamine levels, your acetylcholine levels, all of these play into what we call your mental and physical health. In fact, if any of you are interested in the various categories of neuromodulators and tools to adjust those neuromodulators under more standard non-disease conditions, we did an episode on neurochemicals and how to control them. You can find that at hubermanlab.com along with all other episodes of the Huberman Lab Podcast. I should mention everything is timestamped So you can navigate to the specific topics and tools of interest to you. And meanwhile, I just want to thank all of you for joining me on this voyage through the biology and the treatments for bipolar disorder. I do hope you found it beneficial both for yourself and for others. I just want to remind people that bipolar disorder is an extremely serious condition. If you suspect that you have bipolar disorder or you know somebody who does,

02:17:45 Zero-Cost Support, YouTube Feedback, Spotify & Apple Reviews, Sponsors, Momentous Supplements, Instagram, Twitter, Neural Network Newsletter

please make sure that you or they talk to a qualified health professional. If you're learning from and are enjoying this podcast, please subscribe to our YouTube channel, that's a terrific, zero cost way to support us. In addition, please subscribe to the podcast on Spotify and Apple. And on both Spotify and Apple, you can leave us up to a five star review. If you have suggestions about topics you'd like us to cover or guests you'd like us to interview on the Huberman Lab Podcast, or if you have questions about material already covered on the Huberman Lab Podcast, please put that in the comment section on YouTube, we do read all the comments. In addition, please check out the sponsors mentioned at the beginning of today's episode, that's the best way to support this podcast. During today's episode, and certainly on many previous episodes of the Huberman Lab Podcast, we talk about supplements. Once again, while supplements aren't necessary for everybody, many people derive tremendous benefit from them for things like enhancing sleep and focus and hormone support and other aspects of mental and physical health and performance. As I mentioned at the beginning of today's episode, the Huberman Lab Podcast is happy to announce that we partnered with Momentous Supplements. If you'd like to see our supplements and the ones that we designed in concert with Momentous, you can go to livemomentous.com/huberman. Please also check out Huberman Lab on social media. We are [hubermanlab](https://www.instagram.com/hubermanlab) on both

Twitter and Instagram. In both places, I cover science and science-related tools, some of which overlaps with the content of the Huberman Lab Podcast, but much of which is distinct from the information covered on the Huberman Lab Podcast. We also have a newsletter, it's called the Neural Network Newsletter. It's completely zero cost and it contains summaries of podcasts and some actionable protocols from each podcast. You can sign up for it by going to hubermanlab.com, go to the menu and click on Neural Network Newsletter. You can also see some examples of previous newsletters there. I should mention that by signing up, you do provide your email, but we do not share your email with anybody. And again, it is completely zero cost. So once again, thank you for joining me today for our discussion about the biology and treatment of bipolar disorder. And last, but certainly not least, thank you for your interest in science. [upbeat rock music]