Welcome to the Huberman Lab Podcast where we discuss science and science-based tools for everyday life.
I'm Andrew Huberman and I'm a professor of neurobiology and ophthalmology at Stanford School of Medicine.
Today my guest is Dr. Robert Malenka.
Dr. Robert Malenka is a professor of psychiatry and behavioral sciences at Stanford University School of Medicine.
He is both a medical doctor and MD and a researcher, a PhD.
His laboratory is famous for having discovered some of the key components allowing neuroplasticity, that is the nervous system's ability to change in response to experience.
In addition, Dr. Malenka's research is considered central to the textbook knowledge about how reward systems in the brain are organized and function.
Indeed, Dr. Malenka's research over the last 10 or 15 years has merged what was once two disparate fields,
the first being the study of neuroplasticity, again the nervous system's ability to change in response to experience,
and the other field being the field of dopamine as it relates to pleasure and addiction.
His laboratory has shown for instance that when we seek out particular forms of pleasure,
regardless of whether or not they are healthy for us, that changes the way that our reward circuitry works
and actually changes the way that dopamine is released and how it impacts the brain.
And his work has also informed how we seek out healthy pleasures, including healthy food and social connection.
Today's discussion explores all of these topics and by the end of today's discussion,
you will have a rich understanding of how neurochemicals like dopamine and serotonin work in parallel to reinforce,
that is to increase the probability that we will engage in certain types of thinking and behaviors.
So if you are somebody interested in neuroplasticity, that is how the nervous system can change in response to experience,
and or you are interested in reward systems, what motivates us and what we are likely to pursue in the future given our choices of past,
and if you are interested in things like social connection and empathy or lack thereof,
today's discussion encompasses all of those topics.
It is worth mentioning that Dr. Malenka is a true luminary in all of the fields I just mentioned,
as well as several other fields. In fact, when you look out on the landscape of modern neuroscience,
what you'll discover is that a very large percentage of the top laboratories studying neuroplasticity and reward systems and so on,
all stemmed from having trained in Dr. Malenka's laboratory.
So it's a real honor and pleasure to be able to host him today,
and I'm sure that our discussion is going to greatly enrich the way that you think about brain function, neuroplasticity, and reward.
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.
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Roka makes eyeglasses and sunglasses that are 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 an enormous number of challenges in order for you to be able to see clearly.
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and others whose aesthetic really allows you to use them for sport as well as out to dinner or to work, etc.
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Today's episode is also brought to us by Levels.
Levels is a program that lets you see how different foods and behaviors affect your health
by giving you real-time feedback on your diet using a continuous glucose monitor.
One of the most important factors impacting your immediate and long-term health
is the way that your body manages its blood glucose, or sometimes referred to as blood sugar levels.
To maintain energy and focus throughout the day, you want to keep your blood glucose steady without big spikes or dips.
Using Levels, you can monitor how different types of foods and different food combinations,
as well as food timing and things like exercise, combine to impact your blood glucose levels.
I started using Levels a little over a year ago, and it gave me a lot of insight into how specific foods were spiking my blood sugar
and then leaving me feeling tired for several hours afterwards,
as well as how the spacing of exercise and my meals was impacting my overall energy.
And in doing so, it really allowed me to optimize how I eat, what I eat, when I exercise, and so on,
such that my blood glucose levels and energy levels are stable throughout the day.
If you're interested in learning more about Levels and trying a continuous glucose monitor yourself, go to levels.link.huberman.
Right now, Levels is offering an additional two free months of membership.
Again, that's levels.link.link.huberman to get two free months of membership.
And now, for my discussion with Dr. Robert Malenka.

Dr. Malenka, Rob, welcome.
Yeah, thanks for having me.
Delighted to have you here, both for sake of your medical knowledge and training as a psychiatrist and, of course, as a luminary in the field of neuroplasticity, dopamine and reward systems, social systems, your knowledge of autism and social interactions,
a newer interest in, or perhaps old interest in psychedelics and what they're doing and potential for mental health.
There are just so many things that you've done in this field.
I've been a long, long time fan of your work since your days as an assistant professor.
I've tracked your career.
I've learned a tremendous amount from you by observing you and from being your colleague.
So really delighted to have you here.
You're making me blush, and I don't blush easily.
Well, it's all true.
And I will say as well, you've also trained an enormous number of incredible scientists, Carl Diceroth, the Carl Diceroth.
Anna Lemke always speaks incredibly highly of you as a mentor and somebody she's learned a tremendous amount from.
And pretty much anyone that's worked on neuroplasticity, on dopamine and reward systems, addiction.
And now in the fields of autism and soon psychedelics as well, references as you often, and you've been mentioned many times before in this podcast, if not by name, by work.
So again, thank you for being here.
I'd love to kick off the conversation by talking about something which is very fundamental to everything we're going to talk about,
but certainly fundamental to our daily lives, which is dopamine.
We hear so much about dopamine.
People talk about dopamine hits.
People think about dopamine as pleasure, dopamine reward.
For the novice, how would you frame the dopamine system?
I mean, it does a bunch of different things in different areas of the brain and body.
But to you, what does dopamine represent as its major function in the brain?
And could you give us a kind of general contour of the neural circuits that allow this chemical to more or less put value on our experiences?
Yeah, that's very well put.
As you point out, dopamine is one of the major what we term neuromodulators in the brain, a chemical signaling messenger that the brain uses to mediate a complex array of actions.
Its best well-known function is in what we call the brain's reward circuitry.
So this is a circuit in the brain.
And when we use the term circuit, what we really mean is one part of the brain communicating with another part of the brain.
Because the brain is this very complex, you know, it's the most complex organ in the universe with lots of different nerve cells talking to each other simultaneously.

And as neuroscientists, we try to parse what different brain areas are doing and what different neuromodulators might be doing.
And dopamine was discovered, oh, I should know this many decades ago.
And it's, as I said, the major chemical messenger molecule in the so-called brain's reward circuitry.
And what is the brain's reward circuitry?
This is a part of the brain that tells us something is reinforcing in our environment, some stimuli, or in quotes is rewarding, makes us feel better or good, although that's a gross oversimplification.
And before getting into the details of dopamine and its function in the reward circuitry,
I think it's useful to talk about why do we need a reward circuitry?
Why do we need something in our brain that tells us this feels good or this feels bad?
And it goes back to evolution.
I am a biological scientist, that means I believe in evolution.
And if you think about the evolution of our species, everything is driven by developing mechanisms that increase our survival.
And it's really useful, you need something in your nervous system that tells you some stimuli in your environment is important for your survival,
or some stimulus in your environment is dangerous.
So it's not magic that sugary, high-fat, laden foods are highly reinforcing and rewarding.
It's not an accident.
There has to be a mechanism in the brain that tells us that.
It's not an accident that most of the time, for most of us, a sexual experience is pretty reinforcing, is pretty rewarding.
It's not an accident that warmth feels really good when you're cold, that water tastes much better when you're really thirsty.
What evolved is a mechanism to tell our nervous systems and tell our brains, this feels pretty good.
I should repeat the behavior that leads to that rewarding experience.
And similarly, it's really important when there is an event in your life that's highly dangerous for some mechanism in your brain to say,
whoa, I don't want to go back to where that line was and we can get into that.
So this was a long-ruined way of saying what the reward circuitry tells us is this event, this stimulus, it could be an external stimulus.
Like I said, a Krispy Kreme donut, which I happen to love and I have to be very disciplined so I don't eat too many of them.
It could be a drug of abuse and maybe we'll talk about that a little bit.
All of these stimuli seem to activate and cause the release of dopamine in this brain's reward circuitry.
So now we need to get into a little bit of detail.
Neurosciences use these very unfriendly terms to describe different brain regions.
So the home of dopamine cells or brain cells are called neurons.
So the home of dopamine neurons are in a part of the brain, sort of what we call the lower midbrain.
The dopamine neurons are part of the reward circuitry are found in this area called the ventral tegmental area,
which I'm sorry to have to use such technical jargon and we call it the VTA.

That's the acronym.
I think the roof of the midbrain is the tectum.
It means roof and the base of the midbrain, it means floor, which is tegmentum.
So there's a rationale but it doesn't help much at all to know the names.
And in fact, you are absolutely correct and I always forget that.
So thank you for pointing that out.
It's a side effect of teaching your own atom.
And then, which I once did back in the early 80s, but I've forgotten everything I taught.
Anyhow, so these dopamine neurons, and we can talk about other types of dopamine neurons,
they send messages, what we call projections, using telegraph wires that we call axons.
They send projections to many different brain regions.
The key one in the brain's reward circuitry being an area, again, with a very complicated name called the nucleus accumbens.
And maybe, Andrew, you know, I actually don't know how that name evolved, the nucleus accumbens.
I don't know.
And I'm sure I should know because I've been studying it for 30 years, but I have never looked up the genesis of that name.
The fortunate thing about this podcast is it's both on audio platforms like Spotify and Apple, but also on YouTube.
And so now we can be absolutely sure that somebody has put it into the YouTube comments underneath this episode,
and therefore everyone will learn, including us.
So I don't know the origins of the word nucleus accumbens.
And it's a gross oversimplification, but it's the activity of these dopamine neurons in the ventral tegmental area
that then cause the release of this powerful neuromodulator dopamine in the nucleus accumbens,
which is part of another brain structure with a tough-to-remember name called the ventral striatum.
And then magic happens.
And when I say magic happens, even though we've been studying how dopamine modifies the properties of cells in this nucleus accumbens,
the truth is we don't have a deep mechanistic understanding why when dopamine is released in the nucleus accumbens,
we experience that as, I'm being very cautious here.
The simple way would be to say as highly rewarding, but it's a little more complicated than that.
What it tells us is that there's something really important happening in our environment.
So could we say that it cues the arousal system?
It gets the arousal system going, there's close ties to our memory systems,
which hopefully intuitively makes some sense if something really important is happening in your environment.
Because again, I think what's helpful for your audience is to always be thinking about how these systems evolved from an evolutionary perspective.
And if dopamine is signaling something really important and salient is happening in your

environment, you want to remember that.
It could be a highly rewarding experience, like a source of food.
I like all donuts, so I don't want to emphasize any one manufacturer of one donut versus the other.
I like sugar laden, fat laden foods. That's why I never eat them because I like them so much and I use that as an example.
But because that was an important event for my survival, this reward circuitry, yes, it stimulates my arousal system.
It gets me to pay attention. It also has very close ties to memory systems.
And to go off on a little bit of a tangent, I think the one, I don't want to say it's a mistake.
I think perhaps somewhat oversimplification of how people conceptualize dopamine's role in the brain is,
even though it's a major important role, is for it to be active and released during highly reinforcing experiences,
like sex, like really good food, like drugs of abuse.
It also can get activated subdivisions of the system during painful stimuli and during aversive stimuli,
which again are really important for you to be aware of to say, oh my God, that's really bad for me.
And so the dopamine system, this reward circuitry and its subcomponents that maybe perhaps signal more salience or aversion in the environment
are closely tied to arousal systems and memory systems.
Again, hopefully for somewhat obvious reasons, you want to remember powerfully reinforcing events in your life,
as well as powerfully emotionally or physically painful events in your life.
So I hope I answered your question to a modest degree.
No, far better than a modest degree.
That's an excellent description of the dopamine system from a true expert.
And the question I have is about some of the context and nuance of the system.
But in sort of real world terms, how should I think about this?
Even in my training as a neuroscientist, I know neurons can be a little active, a lot active,
everything in between that can be active over long periods of time or short periods of time.
But let's use the example of the donut.
I like a glazed old fashioned donut.
I actually don't have a craving for sweet things, but donuts is an exception.
I like the glazed old fashioned donut.
But if I were to see just a little piece of a glazed old fashioned donut versus a full glazed old fashioned donut,
could I expect that more dopamine is released to the anticipation of the complete donut?
And then the other question is, how does context influence the dopamine system?
For instance, if I'm very full, a glazed old fashioned donut might be aversive to me.
Whereas if I'm just a little bit hungry, or if I'm actually more on a schedule of rewarding myself for abstaining from sweet fatty foods, then abstaining from the food might be its own form of reward.
And so to me, the dopamine system seems incredibly simple and yet incredibly prone to immediate

context
and the kinds of nuance that I mean, we're constantly juggling.
I'll interrupt myself to say that we're constantly juggling a bunch of different reward contingencies.
We want to have good health metrics and maybe have a certain aesthetic qualities to our body, but we also want the donut.
And so how does a system as simple as a one neuromodulator system and the VTA to nucleus accumbens
and with some connections to the memory area, how does it balance all of that information in real time?
To me, that's just like staggeringly complex, but also incredibly interesting.
I think you beautifully put, very eloquent description.
You just said it, it's staggeringly simple, simultaneously staggeringly complex.
And you asked several different questions.
So context makes an enormous importance.
And that's one of the reasons I became interested in the dopamine reward circuitry is, as you know, as a colleague in the academic neuroscience world, but your listeners probably don't.
I started out my career studying very basic mechanisms of plasticity.
How does the brain modify itself?
And what makes the brain different than compute the computer hardware is the physical connections
in the brain are constantly changing the strength of the communication.
Similarly for the dopamine reward circuitry, it's highly plastic and it's highly contextually dependent.
And so you gave the example of donuts and feeding and I'll answer your question about the cues.
Yes, it's I used to give the example of Thanksgiving.
So let me give that example.
You know, in the morning of Thanksgiving, all for most of us in the United States,
the morning of Thanksgiving, if you're at home visiting your parents, the smells of the apple pie,
the smells of the turkey cooking are highly appetitive, highly reinforcing.
You're anticipating that fun event.
You're anticipating Uncle Joe coming to visit you for Thanksgiving.
And that's all because these cues, the smells, the anticipation of Uncle Joe's your previous experiences
are part of your memory system sort of talking to in a simple way, your reward circuitry.
So you're building up this anticipation.
One could almost say this craving, which maybe we'll talk about in the context of addiction.
And then make a long story short, think about that evening at the end of Thanksgiving,
those exact same cues, the exact same smell of the apple pie, turkey and Uncle Joe himself.
At the very least, they're no longer a petitive, meaning they might actually be aversive.
The last thing you want is a piece of apple pie.
You can't wait for Uncle Joe to leave your Thanksgiving dinner.
And I always argue that does not happen magically.
That happens because your brain has been modified by the context in which it sits.
And this very important modulatory system, this reward circuitry is responding to the exact same

stimuli with a very different response.
So that I'm just telling you, I'm repeating what you said, the phenomenology.
And again, my other favorite example is any of us who have been in an intimate relationship knows that the love of your life can turn to the bane of your existence in 20 seconds.
And again, that doesn't happen magically.
This person who you crave, who you love, does something.
And two minutes later, your brain is saying, oh my God, I may have to break up with this person, or this is an incredibly painful emotional experience.
And what fascinates me about the brain is how does the brain mediate that rapid change?
So now back to, so yes, context makes, is everything about how this powerful neuromodulatory system that uses dopamine works.
And the truth is we don't know.
It's because the inputs onto these dopamine neurons, the other nerve cells that are driving the activity of the dopamine neurons.
And I've actually studied this in my lab at Stanford University with a colleague, you know, well, Lee Chun Luo, who's a world-class neuroscientist.
We've studied the complexity of the neuroanatomy of the dopamine system.
And these dopamine neurons in the ventral tegmental area, the source of the reward circuitry dopamine, are receiving inputs from all over the brain.
They're receiving, you know, indirectly or directly inputs from visual areas, from somatosensory areas.
And I'm not giving you a really good answer because that's one of the goals of my research to try to understand how context, how the history that you've had with these cues,
which we're going to get back to of the donut or of a drug, how has that modified how this neuromodulatory system responds.
Similarly, the nucleus accumbens, the target of this powerful modulator dopamine is receiving communications, what we call inputs from all sorts of brain regions that you know about, Andrew.
Your audience may not. It receives inputs from an area called the hippocampus, which you may have covered in previous podcasts, which is very powerfully, very important for memories, both establishing new memories.
And again, remember, that makes sense. You want this system, this dopamine reward circuitry to be very connected to memory systems.
So the nucleus accumbens, the activity in the nucleus accumbens is modulated by dopamine while it is receiving information from the hippocampus, which helps encode new memories while it's receiving information from a brain area called the amygdala,
which tells is a part of the brain involved in our emotional experiences. The accumbens also receives inputs from the prefrontal cortex, which is this brain area as you know better than me.
Andrew is important for decision making, for planning our activity, and I could go on and on.
Could we talk about prefrontal cortex for a moment? Because it always was surprising to me that prefrontal cortex is talked about as this higher executive function area.
But then when you look at the neuroanatomy, it's, as we say monosynaptically, as you and I know, one connection away from structures like the amygdala, one connection away from structures like the nucleus accumbens.

In other words, prefrontal cortex to me is every bit as ancient as some of these other structures that we think of as more ancient.
And really the whole ancient evolved thing gets a little bit dicey because certain areas like the prefrontal cortex are more elaborated in humans.
But to me, the prefrontal cortex seems to be especially important in the context of this thing of scaling the reward response or context of the reward response because it can set rules.
It seems to know, okay, we're recording a podcast now, and there are certain rules, there are certain things that we're going to do and not do.
But what's fascinating about the, and I'm so glad you gave a bunch of different examples, because what's fascinating, for instance, about the relationship example is that, yes, at one moment we can adore somebody,
and another moment later, if they do something or don't do something, we can be incredibly frustrated with them.
They can even become aversive to us.
Hopefully that doesn't happen too frequently.
Hopefully.
But I think we've all had the experience of a donut, an event, or a person actually looking different to us from one moment to the next.
Hopefully not at random, right?
And so to me, it seems like the prefrontal cortex is uniquely positioned to really say, okay, right now we are in a mode of, for lack of a better word, love and loving.
Like be in the verb tense of loving, be in the verb tense of arguing.
We're now arguing.
We know we're in the verb tense of reconciliation, you know, kind of somewhere in between or something of that sort.
And how a structure in a circuit as simple as the dopamine system, right?
One molecule could suddenly say, oh, you know what, now getting over my anger is rewarding, whereas five minutes ago, being right and being the most angry was rewarding.
And then five minutes before that, again, we're accelerating this movie, but five minutes or five days or five years before that, this person could do no wrong.
The dopamine system is just cranking out dopamine saying, whatever you do, I'm just delighted by it.
Incredible.
Like to me, I can't think of a more interesting system in neuroscience.
Well, I mean, that was eloquently put.
I agree with pretty much everything you said.
I don't have much to add because what you're pointing out is the challenges of studying these systems, the importance of studying these systems and the challenge of presenting these systems.
The challenge of presenting how the brain works to this podcast audience, because on the one hand, you have done a fantastic job over the last few years in your podcast of making complex subjects accessible to a lay audience.
And get them to be thinking about how our modern view of how the brain works may could be used to enhance health, could enhance mental well-being.
But as neuroscientists, academic neuroscientists ourselves, we know, you know, you are

oversimplifying things and the actual functioning of a system like the dopamine reward circuitry.
As you just eloquently point out, it's so much more complex.
It's modified by these prefrontal inputs, which are simultaneously telling our memory systems, you know, pay attention here.
I'm repeating what you just said, the context makes a big difference, the history you have with the person or stimuli with whom you're interacting.
Like to bring this back to your, you know, which I never, the initial question is a small piece of a donut activate the cue that that small piece of a donut activate the reward circuitry and cause release of dopamine to the same extent as the full donut.
Depends on your experience with donuts.
I mean, I think for you and me, because we seem to both have, you know, like donuts, they're highly appetitive for us.
Probably doesn't matter because we have learned even a little piece of a donut activates all of our memory system saying, man, that's an old fashioned glazed donut.
I want to eat that.
I want to get one or I want to have the discipline not to eat it.
So I hope I'm answering your question and I'm shifting topics completely, but that's why addiction is so challenging.
Well, let's talk about that.
Let's talk about that because you've done a ton of important work in this area of addiction.
I mean, one of the basic questions I have about addiction is, you know, we hear that certain drugs are more addicting than other drugs or certain behaviors.
We also hear that we can become addicted to anything when Anna Lemke was on this podcast.
I said, what's the most unusual addiction you've ever seen?
And she talked about a patient who sadly committed suicide at some point later that she told us had been addicted to water, to drinking of any kind, first alcohol, but then water eventually.
And so my question about addiction in the dopamine system is, you know, let's pick a drug like cocaine.
I've never done cocaine.
But people who have done cocaine tell me that it feels very good.
And one of the more salient features of the cocaine high is that it comes on very fast and it ends pretty quickly too.
Is the rate of dopamine increase related to the addictive property of a drug or behavior as much as how much dopamine is released?
And that's a very sophisticated question.
And the answer is yes.
And that's usually the lecture I give.
The way I think about addiction and obviously my friend and colleague Anna Lemke is one of the world's experts in terms of the understanding the human experience of addiction.
I have studied it as a cellular molecular neuroscientist trying to understand how addictive substances modify reward circuitry, modify the connections in the reward circuitry, modify how dopamine neurons act.
And the way I, you know, like any what appears to be a simple term, it's layered with complexity.

Addiction is somewhat of a continuum.
And I like to think about whether you're talking about substances like cocaine and I will explicitly answer your question soon.
Or opioids, as we, as you know, we're going in this country, there is an opioid epidemic.
I do like to think about addictive liability.
And it is, in my view, it is pretty clear that when we're talking about drugs, they have different degrees of addictive liability.
I mean, I had a cup of coffee this morning.
And many of us listening to this podcast, it's really hard to start our day without getting that hit of caffeine.
But are we addicted to caffeine?
That's a tricky question, because I've never heard of anybody robbing a bank to get caffeine, destroying their personal life to get caffeine.
So I would say caffeine causes tolerance.
But I would not say it has a particularly high addictive liability.
Whereas drugs like psychosimulants like cocaine have a very or opioids have a very high addictive liability.
To answer your mechanistic question, there have been some famous studies done by the director of the national suit on drug abuse, Nora Volkov.
Simultaneously, there have been studies in animal models of addiction where you nailed it.
In a rough way, the addictive liability of a substance is directly correlated with two aspects of dopamine.
How much dopamine is released in the Cummins and the kinetics of the dopamine release?
As you said, how rapidly it's released?
To get a little technical, even with the drug like cocaine or opioids, it's not only the drug itself.
It's the root of administration, because the root of administration influences the kinetics.
Meaning how fast that drugs gets into your brain influences the reward circuitry and how fast it causes a big rapid release of dopamine.
And some of your podcast listeners may be old enough to remember the crack cocaine epidemic or freebase cocaine.
And cocaine does have, like methamphetamine, a very high addictive liability.
I give lectures to students at Stanford about neurobiology of addiction as part of a team taught course.
I have kids who I had to deal with.
And what I always say is, it's not that if you use this drug, you're automatically going to become an addict.
But you're taking that risk.
And it is impossible to become addicted to a substance if you've never used it by definition.
But back to the root of administration.
That's actually an interesting statement.
Because I think we may have heard that in high school, although I, to be honest, wasn't the most attentive high school student.
And I regret that high school students pay attention.

Eventually I came around, but there was an uphill battle there.
But you that you can't become addicted to something that you've never done, which I just want to earmark that because I think it's a profound statement because it points to the importance of the memory system, but also plasticity.
And so I want to make sure that eventually we get around to talking about how the amount of dopamine released in the kinetics, how that might influence plasticity.
This is what I'm asking here, queuing up in the back of your mind is whether or not addiction is just related to the sensation that we have when we indulge in a behavior or when we are under the influence of a drug, or whether or not it actually modifies neural circuitry in a way that makes a broader range of drugs or experiences attractive to us.
It's probably the latter, but so let me get back and I will answer that in a second to the point I was making.
So it's not only the substance, it's the root of administration.
So, you know, as I said, you can't develop a problem with a substance and develop a substance abuse problem if you never take it.
But snorting cocaine is a different experience than smoking it or injecting it.
And one of the reasons the crack cocaine epidemic was so powerful is it gets into when you're smoking it or injecting it, and people do this now with methamphetamine.
I mean, meth addicts, most of them, and that is another epidemic in our country, most of them smoke it.
And the danger of that is the drug, whether it's cocaine, methamphetamine, gets into your brain almost instantaneously, causes a very rapid, powerful surge of dopamine in the accumbens in this reward circuitry.
And that the feeling you get, which, and we're going to get into this, is not necessarily a happy feeling.
And it only lasts, it can last for tens of seconds or a few minutes.
And it's a feeling that gives you this overwhelming compulsion and urge, I want to do it again.
So even though it may not actually feel all that good, and again, this gets into, you know, we didn't have an addiction problem for any substance other than alcohol.
You know, for most of humanity's existence, because these substances like cocaine, methamphetamine, synthetic opioids like fentanyl, they didn't exist.
And our brain, you know, the truth is, our brains are not designed to handle those kinds of very powerful substances.
As many of you know, I've been taking AG1 daily since 2012.
So I'm delighted that they're sponsoring the podcast.
AG1 is a vitamin mineral probiotic drink that's designed to meet all of your foundational nutrition needs.
Now, of course, I try to get enough servings of vitamins and minerals through whole food sources that include vegetables and fruits every day.
But oftentimes I simply can't get enough servings.
But with AG1, I'm sure to get enough vitamins and minerals and the probiotics that I need.
And it also contains adaptogens to help buffer stress.
Simply put, I always feel better when I take AG1.

I have more focus and energy and I sleep better and it also happens to taste great.
For all these reasons, whenever I'm asked if you could take just one supplement, what would it be?
I answer AG1.
If you'd like to try AG1, go to drinkag1.com slash Huberman to claim a special offer.
They'll give you five free travel packs plus a year supply of vitamin D3K2.
Again, that's drinkag1.com slash Huberman.
So where do you want to go from here?
You asked a question about, you know, the neural mechanisms of what we call addiction.
Yeah, I'd like to know about the role of neuroplasticity and addiction.
I do want to highlight something you said and I apologize for interrupting a moment ago.
No, absolutely.
But it was an interruption based on real excitement because a person I know quite well who is a recovered cocaine addict told me,
and then by the way, folks, this isn't, I have a friend and I'm actually, you know, I truly have never tried cocaine.
And this person said that the first time they did cocaine, his thought was, I hate this and I can't wait to do it again.
And that's exactly how you described it.
And I think that is a fairly common experience with people suffering from an addiction disorder.
We're not supposed to use the word addicts anymore because that's a little bit judgmental.
That's the new nomenclature.
That's something along those lines.
Calling someone an addict as opposed to being addicted.
Yeah, being and that is a beautiful description.
I hate it, but I want to do it again.
And again, it just shows the power of this system, which remember evolved for our survival.
So a very simple way of thinking about it is these drugs are tricking the reward circuitry to say this stimulus.
This experience is really important for my survival.
I have to go do it again and again.
And again, a side question is the huge question is why does some people develop an addiction problem and others who have used this substance just don't.
And again, as a world-class neuroscientist yourself, you know the answer.
It's always a complex combination of underlying genetics, the environment in which they find themselves, the environment in which they grew up and how that modified their reward circuitry.
So to get at your question, one set of experiments my lab did, which other labs did too.
I don't deserve the sole credit for this is showing that drugs of abuse cause powerful plasticity in the neurons that make up the cells that make up the reward circuitry.
And in fact, drugs of abuse like cocaine, methamphetamine, opioids like morphine, heroin, change the synapses.
The synapses are the connections from other nerve cells onto dopamine neurons, onto the nerve cells in the accumbens.
And these connections, these synapses can change.

And drugs of abuse cause powerful changes in those connections and therefore powerful changes in the activity of the dopamine neurons and the neurons in the nucleus accumbens.
And in fact, the types of changes that occur appear to be similar to the types of changes that have evolved for good uses, for adaptive forms of learning and memory.
So again, this is an example that this superficially simple dopamine reward circuitry is changing all the time.
It is highly plastic and can become more sensitive to certain experiences, et cetera, et cetera.
Well, could I ask a question about some of the general contours of the plasticity in the dopamine system?
You said before, and I love this statement, even though it's very simple, but in its simplicity, it's really elegant that we can't become addicted to a substance or a behavior that we haven't taken or partaken in.
So is there data to support the idea that just one exposure to cocaine or one exposure to some sort of behavior can lead to a lasting change in the dopamine system such that one's propensity to be addicted to that substance?
Again, if one were to indulge in the future or behavior again in the future is increased.
I have a very particular reason for asking this, but I'm very curious what the answer is.
In the work my lab and other labs have done in preclinical rodent models, the answer is yes.
A single administration of a drug of abuse like cocaine, like morphine, can cause relatively several days, several weeks of changes in the connections onto dopamine neurons
and onto the neurons in the nucleus accumbens.
Those changes, that does not mean these changes are permanent or irreversible, but the changes last a long time.
And again, the big question for understanding the neurobiology of addiction is those changes are probably happening in most people who take the drug in this case.
We can talk about other stimuli, non-drug stimuli that can become in quotes addictive.
Again, why in certain individuals?
To be honest, it's not a big deal.
Yeah, I did cocaine at this party.
It was nice, but I don't feel any craving or urge to do it again.
Whereas other individuals, it sets them down a very bad path and really badly affects their life.
And that's a huge question in the research field, because obviously if we could make predictions on which individuals are more susceptible and not to get to political here.
But whether you become a developer problem with addiction or not is influenced by the other parts of your life.
You have other ways of getting reinforcing stimuli, getting satisfaction, having an outlet that other ways of activating your reward or dopamine circuitry.
Healthy ways.
Healthy ways.
As you have articulated, I think, in your podcast, getting exercise, you and I both like to get exercise.
I feel really good.
Sometimes it's painful during the exercise, but afterwards I feel great.
Very almost the inverse of the cocaine response.

The desire and then that I hate this, but I can't wait to do it again.
It seems like exercise is often the opposite.
I hate this.
I don't want to do this.
And then afterwards, gosh, I always feel better and I'd be happy to do it again.
I mean, yes, I mean, I like to exercise chasing a ball because that gets me off thinking about this hurts.
So anyhow, back to addiction.
So yes, these drugs can cause.
I don't want to definitely not permanent changes from a single exposure.
You know, and the types of studies I'm talking about, we're all done in, you know, experimental animals.
So how that relates to what happens in our brains and human subjects brains is it's not completely clear, but I think there are parallels.
So the changes might last, you know, a few days a week or two, but one can see if somebody.
There have been studies done where in an animal model, if you give repeated administration of a drug like cocaine, the changes get stronger and they last longer, which is kind of intuitively obvious.
But again, the big question is why in human subjects, there are people who can use these substances and not develop a serious problem and there are others where they're very, very damaging.
And, you know, and then that's why I still make the point.
If you're a young person, if you're, do you want to take that risk?
Is it worth it to have that experience?
And that's an individual decision.
We've done some podcast episodes about alcohol, cannabis, etc.
And there does seem to be a pretty wide variation in people's response to the information.
I think because there are people out there who, well, I've got friends who are recovered alcoholics who will tell me the first drink they took.
They use language like, you know, it combined with the chemistry of my body in a way that nothing before ever had.
And they felt like it was like this magic elixir, right?
That has not been my experience.
And I have heard the same stories and it's hard for me to relate because like you, alcohol does not have that effect on me.
And that's where it's hard to believe that kind of immediate response to alcohol is due to the environment in which they grew up.
Although that can have an influence.
That just feels almost more genetically encoded.
And there is evidence that issues with the use of alcohol and developing alcohol use disorder does run in families.
And obviously if it runs in family, you have to worry about how the environment of that family influences it.
But there's a lot of studies saying there is a genetic component.
Maybe like you, if I have a drink or two in the afternoon, I just fall asleep.

And it does not have that effect on me.
And anyone could imagine similar things for other drugs of abuse.
There are people who have used cocaine, have used methamphetamine, who find it modestly enjoyable, but it's not the be all or end all.
It isn't this incredibly powerful experience.
And you just talked about, I think, a friend or a colleague who said, I hate it.
I hate that, but I want to do it again.
And that's fascinating.
They're now a recovered alcoholic and cocaine addict.
And they've, they've abstained for many years, but still get a little bit of a gleam in their eye when they talk about alcohol or cocaine in a way that I just can't relate to.
I can relate.
I mean, can I tell you a little vignette about me, which I love to tell.
Sure.
And it gets into how the reward circuitry is so closely associated with memory systems and how cues associate it with powerful experiences, develop their own reinforcing or aversive quality.
So long story short, when I was a young kid in, I can't remember in my twenties, maybe 20, I spent a few weeks in Paris.
I started smoking cigarettes.
I mean, this is a long time ago.
And I got it.
Cigarettes are very interesting.
Nicotine is highly addictive as are as the tobacco companies were fully aware of high addictive liability, very high addictive liability.
People will rob people for the money to buy cigarettes.
They may not rob because although they're my understanding is to become quite expensive.
But I guess that's a vote.
Significantly counterfeit cigarettes are a huge market for organized crime.
There are parts of our of our in the world, third world countries where organized crime produce counterfeit cigarettes and are making hundreds of millions or billions of dollars.
And so I think nicotine as it is delivered in cigarettes, as you know, I mean, tobacco companies put in a lot of work to figure out the exact dose of nicotine that will make you get that kind of feeling that only lasts for a few minutes.
So you want to do it again and again.
So we can talk about the nicotine, you know, what becomes a problem in a specific society with addiction is not only based on the neurobiological actions.
If we're talking still about drugs or substances of that substance, it's heavily influenced by the availability of the substance to but my my little story is I smoked some cigarettes in Paris.
I learned why people like to smoke.
It was very satisfying to have a cigarette in a Parisian cafe.
It just, you know, it's very interesting because the first few times you inhale tobacco, you get dizzy, it's kind of aversive, and it's exactly what you articulated.
Despite that, you want to do it again.

So it was just a lot of fun for me.
I enjoyed it and I was disciplined, you know, at some point, whenever this was I came back to the United States.
I didn't smoke because I knew it was bad for you.
But to this day, 40 years later, every time I go back to Paris, I get cravings.
I actually just want to get a pack of cigarettes.
I want to have that feeling again of inhaling the smoke.
But the point is of how powerful these rewarding experiences can be or reinforcing experiences.
And for your audience, technically, you know, what I have been taught by some of my psychology colleagues is we use the term reinforcing in a very behaviorally defined way.
Something is reinforcing is if the behavior that led to that stimuli, it makes you want to do that behavior again.
Rewarding means it actually felt in quotes good.
It's an important distinction.
They actually can be different again as you define by your friend who is, I forget, I think it was cocaine.
The cocaine was highly reinforcing, but it was not necessarily enjoyable or rewarding.
And isn't that fascinating?
I have some colleagues in the addiction field.
One of them is retired now Kent Barrage and Terry Robinson.
They distinguish between the terms wanting and liking.
And think about that.
It's something you like, you enjoy.
Wanting means you want it, but you don't necessarily like it or enjoy it.
And that's a description of your friend's experience with cocaine.
Some of us have been in destructive relationships where you want that individual, but you're not sure you necessarily like that.
Sometimes people will be in relationships where they actively dislike the other person, which is a bit foreign of a concept to me.
It's interesting this separation of reinforcing and rewarding, wanting and liking because one of the things that's very prominent in 12-step programs is to create rewards around abstaining from the drug or behavior.
And I should mention that programs like 12-step when followed seem to have very high success rates.
That's what Anna Lemke tells me, that in some ways they are modifying the wanting and liking.
They're splitting the wanting and liking of alcohol, for instance, creating a liking of sobriety more than the wanting of alcohol, for instance.
That's beautifully put.
And I think that's right.
How that plays out in the neural mechanisms that as a neuroscientist, I'm interested in.
Man, that's a tough one.
But I think that's why those programs are pretty successful.
It's helping the person make those dissociations.

And I don't know that much about those programs because I have not seen patients myself for whatever it's been 27, 28 years.
But I think part of them are to help that individual find, as you see, both other sources of liking and reward getting some satisfaction and reward from the actual abstinence.
Being able to cognitively teach themselves that I deserve a pat on the back.
I deserve credit.
I feel good that I did not take a drink at that party, that I did not use that substance again.
And how that plays out in our brains is a really tough one.
The way you described it is exactly right.
Those programs are highly reinforcing for abstinence behaviors, everything from the social connection, which we're going to get to social connection as we know, to the way that people start to conceptualize their addict self versus other self.
It actually involves a splitting of the self in interesting ways.
As long as we're talking about donuts, cigarettes, alcohol, cocaine.
I'm curious, before we move to a bit more on neuroplasticity, is there anything that people ought to know about how different substances and behaviors that are addicting might impact the dopamine reward circuitry differently?
So for instance, we talked about cocaine is having this very rapid onset, big increase in dopamine than a crash, as we know, a certain pattern of kinetics as you describe it.
The opioid crisis is an incredibly serious problem right now, as is methamphetamine, but it sounds like methamphetamine functions a bit like cocaine and in terms of its kinetics.
So an opioid is a very different chemical than cocaine, but it sounds like it impacts the dopamine system.
Is the dopaminergic activity caused by opioids responsible for the addictive properties of opioids, or do people also like the feeling of being under opioids?
I personally hate it coming out of surgery.
They gave me Vicodin once, and I hated it.
I'd rather have the pain, post-operative pain, than take something like Vicodin or Valium or Fentanyl or anything like that.
To me, it's just completely aversive, but I realized that there are many millions of people that feel quite differently.
It's a great question.
So I think all the studies, both in human beings and preclinical animal models, yes, would suggest that the addictive liability of opioids and psychostimulants, which are cocaine and methamphetamine,
have the common final action of causing massive release of dopamine in this target of the dopamine neurons and nucleus accumbens.
They do it, if we want to get a little scientifically technical here, via very different mechanisms.
So cocaine and methamphetamine, the drugs known as psychostimulants, actually bind to a protein in the brain or a molecule in the brain that is responsible for sucking up the dopamine after it's been released.
And cocaine prevents that dopamine from being vacuumed up so the cocaine hangs around longer.
Meth not only prevents the dopamine from being vacuumed up, it actually causes the reverse.

It actually causes the direct release of dopamine from what we call nerve terminals from the site where dopamine is released.
Opioids work very differently.
They actually primarily, not solely, work where the dopamine neurons live.
And it's a little complicated if it's not that critical, but they indirectly increase the activity within the dopamine neurons themselves, causing a big, massive, bigger than normal release of dopamine.
So that's one commonality.
But anybody who has used these drugs or read about these drugs, the subjective experience of the drugs are dramatically different.
And that's because of the actions they're having, not only in the reward circuitry, but throughout the brain.
So, and it's interesting you talked about Vicodin.
I've taken Vicodin because I've had several knee surgeries and things like you, I didn't like it.
I've gotten other opioids for pain relief that were great.
I mean, they took, they took away a lot of pain after my ligament repair.
And that's a different question that even when you're talking about opioids, all drugs are not, they're not identical.
Fentanyl has a much larger addictive liability because of its molecular properties and how it's interacting with the opioid system in our brains and the receptors, the actual proteins in the brain that it interacts with.
But the subjective experience of opioids, I mean, it's interesting.
Some people love it.
That's, you know, if we go back in history, as you know, there were the opium dens throughout Asia.
There were wars about opioids, the famous opioid wars between China and the United Kingdom.
I mean, showing you how powerful the availability of a substance like an opioid can be.
So I'm going off in a tangent.
No, I think these are important.
But commonality is dopamine release in the accumbens.
But it's a, if you remember what a Venn diagram is, all these drugs have some common actions, usually on directly or indirectly causing the massive release of dopamine in the accumbens.
But then they have their own individual actions because obviously when you take cocaine or methamphetamine, it's a stimulator.
People are grinding their teeth.
They're hyped up.
For most people, opioids are the exact opposite.
I mean, an opium dense from the movies I watched and watching Narcos and all those TV shows, you're often, you're lying down.
You're kind of in almost a dreamlike state.
So very different subjective experiences.
I'd like to just take a brief break and thank one of our sponsors, which is Element.
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And while I do any kind of physical training and after physical training as well, especially if I've been sweating a lot and certainly I drink Element in my water when I'm in the sauna and after going in the sauna because that causes quite a lot of sweating.
If you'd like to try Element, you can go to Drink Element.
That's LMNT.com slash Huberman to claim a free Element sample pack with your purchase.
Again, that's DrinkElementLMNT.com slash Huberman.
Yeah, I had an experience with the opioid recently, not voluntarily over the Christmas holiday.
We went to visit friends and before going to sleep, I wanted some tea and I asked if they had any non-caffeinated tea.
So they gave me this tea and that night I had the most bizarre dreams I've ever had and I slept for 14 hours.
The next morning I was like, what was that tea?
And I felt off in the morning and it was actually a blue lotus flower tea that is actually illegal in the United States, but it is sold and it has morphine-like compounds in it.
I am one of those people that's very susceptible to even low doses of any kind of novel drug.
So I'm interested, have you ever taken cough syrup with dextromethorthane?
No, I avoid that stuff.
Well, I have a tendency when I get a cold, it gets into my lungs, I cough a lot and I think this has been reported.
This is my anecdotal experience.
I'm confirming what you said.
Dextromethorthane is a different sort of opioid and actually some people develop a problem with it.
For me, it gives me really bizarre dreams, really similar to what you were describing.
Yeah, it was a very unusual experience.
And that's a whole different conversation about what makes us dream and what are the meaning of dreams.
Fascinating.
I hope you've covered, maybe you've covered that.
We have not yet, but we are intending to do a whole series on sleep and dreaming and we will definitely get into it.
I started out in sleep research, so I have a fondness for it.
Well, drug research and sleep research have a long history of overlap with Alan Hobson's work on LSD.
I worked with Alan Hobson.
Okay, by the way, folks, if you're interested in the relationship between hallucinations and dreaming,

Alan Hobson is a good name to start your rabbit hole.
Oh my God, I'm dating myself, 1970.
I can't remember who it was, 76 or 77.
I worked with Alan Hobson as an undergraduate.
At Harvard Medical School.
No, as an undergraduate at Harvard.
He was at Harvard Medical School.
Amazing.
I love his writing and I heard a lot from it.
He was really ahead of his time.
Yes, he was.
Nobody would, anybody who knows me won't believe this, but back then I was a very shy, insecure, 20-year-old kid.
And even in medical school, I literally was not confident of my opinions at all.
I was very shy, thought all of the ideas I had must be obvious and I should never save them out loud.
Do you mind if I ask, since you raised this, I think it's really important.
I mean, you have this incredible career track record.
You're adored by your colleagues.
You're highly respected.
You won just about every award there is to win in neuroscience.
So was there something in particular that was in an overnight thing or one day you woke up and thought, you know, I actually believe in myself.
But if you wouldn't mind sharing that, because before we get back into some of the science, you know, science is a human endeavor and most people listening are probably not scientists.
But I think everybody deals with these issues of self-doubt and people appear to have varying levels of confidence.
But what happened?
Thank you for asking.
No, for me, it was a very gradual process and I'm not as an undergraduate, as a medical student, even as a postdoc.
Yeah, I was very unsure of my ideas, of my intellectual abilities, of whether what I was thinking was really worthwhile.
So it was a very gradual process.
I think the increase in my confidence, I think, began when I was a postdoc, which is a training period after you've received a PhD or an MD where you get additional research training.
And I worked with a guy named Roger Nicolette, UCSF.
And Roger was a very intellectually intense, very forceful individual.
And I got involved in a field where, I mean, people, a little bit of a tangent.
Your listeners may think that scientists are these geeky individuals wearing white coats with no passion or emotion and nothing could be further from the truth.
The most successful scientists I know are pretty passionate and pretty intense about what they're working on and driven.
I mean, and this is a gross generalization.

So anyhow, during my postdoc, I started getting involved in a topic where there were vigorous arguments about phenomenology we were studying.
So I had to develop a tougher and thicker skin.
I had to be able to argue my side of the hypotheses we were generating.
So it started developing as a postdoc, and then it slowly evolved as an assistant professor.
And for your listeners who don't know, I don't like to admit this, but I'm in my late 60s.
I have been running my own lab for almost 40 years.
So I have been so gradually as an assistant professor, I realized, hey, I can do this.
I can do science.
I can write papers that my colleagues seem to be interested in.
And then gradually over the next 10, 20, 30 years, I gained more and more confidence.
So for me, it was this very gradual buildup of many different experiences where I developed some confidence that, you know, not all of my ideas are great.
Of course they're not, but it's okay to voice my opinion.
It's okay to state my ideas and why I believe this and why I don't believe that.
So that was my experience.
Thank you for sharing that because I think, you know, people struggle with that very issue.
And clearly showing up again and again over a long period of time is helpful.
But as you said, you know, learning to trust one's ideas, just a brief anecdote.
When I was coming up in neuroscience a few years behind you, not too many.
Two decades behind me.
But I recall the incredible number of high profile papers on neuroplasticity and long-term potentiation, long-term depression.
These are terms related to the modification of synapses that Rob Malenka and Roger Nicole pioneered a big segment to that work.
And I remember seeing your names on papers and I thought Roger worked for you.
Sorry, Roger.
I'd love to hear that.
I love to hear that.
I was under the impression we worked for you and only later did I learn that you were his postdoc.
And then we collaborated as equals.
You became peers very quickly.
Very quickly.
Yeah.
So you've had a...
And Roger, you know, I...
Roger's wonderful.
I did have the confidence even as a postdoc and actually even as a grad student,
even though I was a little insecure about my ideas, I wanted to be treated as an equal.
That's the one thing I did have.
I never felt that I was working for somebody else.
I always felt that I was working for myself and that we were colleagues,
even though my mentors had more experience and I could learn from them.

I like that you're working for yourself even though you have mentors.
I think there's some real gems in what you just described.
So thank you for taking the time to do that.
Sure.
I'd like to discuss one aspect of reward circuitry that I don't think most people think about.
Fairly straightforward nowadays.
I like to think when more people know what dopamine is and understand it thanks to your work and Anna's work and some discussions that have taken place on our podcast, other podcasts.
But, you know, it's all too often we think dopamine, reward, wanting, liking, drugs.
Okay.
All of that is great.
But what about the truly adaptive stuff, right?
Because it's easy to fall into a discussion around dopamine of, you know, the things that are bad for us.
But what I'm thinking about here is social interaction.
Clearly, we are a social species and a lot of your work in the last decade and a half or so has focused on the relationship between the reward circuitry, which you beautifully described for us and social interaction and connection.
And where I'm going with this is ultimately this has huge implications for autism and autism spectrum disorders.
I don't know if nowadays is it okay.
What's supposed to call autism a disease?
Is that right?
You hear about neurotypical and neurotypical, but is, but I have friends who have children who are severely autistic and I don't know many parents who would elect to have a severely autistic kid.
And so those people often will talk about it as autism or a child having autism.
So first of all, before we get into the social piece, maybe because I just tabled it, what is, how are we supposed to talk about autism nowadays?
I am very interested in the pathophysiology of what the medical profession terms autism spectrum disorder, as you pointed out, the individuals living with an autism spectrum disorder are quite heterogeneous and it can range from individuals with severe intellectual impairments and quite severe impairments in social interactions, impairments in sensory processing, impairments and lots of different aspects of our behaviors that are important.
And I think nobody would say would argue those individuals on the severe spectrum do not have some sort of in quotes disorder.
The issue we have to be sensitive to is it's a heterogeneous disorder, like many brain issues that psychiatrists deal with, like depression, we all like obsessive compulsive disorder, like various anxiety disorders, it's always on a continuum and a spectrum.
So for autism spectrum disorder, there are individuals who are high functioning, who one could argue have a different style of interacting socially, may have a different way of processing sensory information, but who would prefer not to be viewed as having an illness, but rather

would be viewed as having a different style of living and interaction and I think we need to respect that. So the challenge is, again, not oversimplifying a complex heterogeneous disorder and both being respectful of the people who don't want to be defined as having a neuropsychiatric or brain disorder, while equally being respectful of people like your friends with severely impaired children who deserve help, who deserve research, and it's a tough one because my understanding from, to be honest, just reading articles in the lay press and going to websites from organizations that philanthropically support research related to autism, within that community of individuals who are not researchers, but who have family members or are themselves dealing with some degree of autism spectrum disorder, there's disagreements about what terminology to use, how to deal with them and it's complicated. I think we just have to respect everybody and if you're interacting with individuals, I think it's appropriate. What do you prefer? I do know as a medical professional, and especially when you're dealing with children, there are children who need help and we're not doing them a service by saying they don't have an issue that we should be helping them with and working on. So I hope that answers your question.

Yeah, beautifully. I think it beautifully answers it and encompasses all sides so that we can move forward. So as we use the term autism or children or people with autism, that's what we're referring to.

I think people are very sensitive, especially those individuals who are neuro atypical, who previously might be diagnosed as autism spectrum disorder, but would prefer to not be labeled as having a brain illness. That's fine. It's kind of, once you are an adult, you can make that decision for yourself.

We certainly have colleagues at Stanford and elsewhere who, at least by my non-clinical assessment, seem to fall somewhere on that spectrum.

And again, it's a continuum, just like the experience of depression is a continuum.

Right, and as with depression, you wouldn't love a child or an adult any less because they have depression, nor would you love a child or adult any less because of expression of some autism symptoms.

I know the point. People don't, you know, and so we are being trained in the medical profession to be very, you know, and our society is going this way too, very careful with the terms we use and the labeling of individuals.

So, you know, I've been taught you can say individuals living with an autism spectrum disorder. Some people don't like using a term of that individual is autistic because that has some, can have some, I don't want to say derogatory meaning, but some labeling kind of, but, you know, sometimes this gets out of control too, as we both know.

Well, for sake of fluid conversation, we will do our best, but we will acknowledge from the outset that we are

well-meaning, but far from perfect in how we'll handle this.

Well-put, well-put.

So, in thinking about social interactions and leaving aside anything related to autism for the moment,

it appears that the circuits in the brain that mediate the desire to spend time with others of the same species,

maybe even with other species like a dog, are fairly hardwired but modifiable.
We were born with the capacity to build them up and that social behavior is highly rewarded.
Is it rewarded through the dopamine system?
And what if any involvement is there of the serotonergic system?
And we haven't talked about serotonin yet, but I'd love to bring up serotonin at this point.
Maybe you could educate us a little bit about serotonin because gosh, if dopamine is fascinating, serotonin is at least as incredible.
Yeah, great question.
So I think for me, the easiest way for me to answer it is actually just tell you my research history and how a lab like mine at Stanford that at one point was studying what you and I would call fairly hardcore molecular mechanisms of neuroplasticity.
How do connections between nerve cells change and what molecules are changing
and pretty hardcore molecular stuff?
How did I end up studying social behaviors in mice and what I hope we'll end up talking about, even developing behavioral models of what I will define as empathy in mice?
The answer is very simple.
My lab was working on the roles of classic dopamine reward circuitry and how it changes in models of addiction.
We haven't talked about depression models of depression because just intuitively,
hopefully your listeners can understand if one component of depression is what we call anhedonia, the inability to experience reward.
Eating a donut is no longer satisfying, having sex is no longer that much fun,
which is a component of depression.
If there's a mechanism in the brain that tells you something is rewarding,
by definition that's not functioning normally in severe depression.
So we were doing models of depression to figure out how the dopamine reward circuitry was changing.
As were many other labs, we were studying addiction.
Those were the obvious ones.
It might be entertaining to your audience to learn how academic scientists think.
I was thinking those are fascinating topics.
They're pretty competitive.
Lots of other labs were working on it.
I started thinking what other experiences might be modifying the reward circuitry.
I actually made some attempts to look at feeding behavior,
but we actually never pursued that for a variety of reasons.
That's obviously important because there is an obesity epidemic in this country.
We can talk about how the reward circuitry and some of the things we've learned from our studies of addiction
may be helpful to understanding obesity.
But back to social interaction, I started thinking,
well, for most of us, what I call a pro-social, non-sexual experience is highly reinforcing.
Andrew, you're a pretty social guy.

I'm a pretty social guy.
Most of the time, I'd rather go to a movie, a sporting event, a dinner with friends.
Actually, for me, the most meaningful component of my life other than spending time with my children
is spending time with my close friends.
I started thinking, well, why is that?
Why do I have such a good time going to a ball game with my best friend
or going out to dinner with another couple and interacting?
It's because while it's highly reinforcing,
and if it's highly reinforcing, it must involve the reward circuitry.
And then I started thinking evolutionarily.
It makes a lot of sense because if you are part of a social species,
there's a lot of evolutionarily, a lot of advantages for your survival
to be hanging out with other members of your species in a non-aggressive way.
It can increase your likelihood to find a mate and reproduce.
It can protect you from predators.
I mean, that's why any of your listeners who ever watch, you know,
wildlife shows or national geographic shows,
there's a reason all these animals hang out together.
It's for protection from predators.
There are all these reasons.
About whenever it was 13 or 14 years ago,
my lab decided to start looking at how the reward circuitry may play a role
in what I am going to call positive pro-social, non-aggressive interactions.
Another word we use is just sociability.
And for a variety of reasons, back then, this is at least 13 years ago.
Maybe 15 years ago.
A post-doc joined my lab named Gould Dolan.
She's now a professor at Johns Hopkins.
And she had an interest in oxytocin.
And as your listeners know, oxytocin is this evolutionarily conserved neuropeptide
that's very important for parturition, having a baby born from milk being produced.
And it's gotten a lot of attention as a potential love neuropeptide
as something that is released in our brains during a positive social interaction.
There's a well-known researcher in social behavior and bonding research called Larry Young.
And he did some very important, now somewhat classic work studying a species called the vole,
in particular the prairie vole.
And prairie voles are a species where they mate for life.
It's called pair bonding.
So one vole will find another vole.
They basically get married.
They have kids.
And they hang out together for the rest of their life.

No divorce.
No 50% divorce rate.
No 50% divorce rate.
And what Larry elegantly showed, in early days in collaboration with a guy named Tom Insel who is a famous academic psychiatrist,
they showed that oxytocin action within the nucleus accumbens, within this reward circuitry was required and really important for this monogamous pair bonding.
Having said that, there was just a paper that called into question that.
But there's 30 years of research prior to that.
I'm glad you brought that up because we'll keep this contemporary.
And the reality is that that recent paper got a lot of attention.
You know the paper I'm talking about.
Yeah, that maybe oxytocin isn't playing as prominent role in pair bonding as people had thought.
And yet, folks, that could be true.
We have to be scientific about this and be open-minded.
But there's three decades of work that speaks to the contrary.
So I think we want to weigh the evidence.
Yeah, exactly.
And again, the investigators who presented the work saying oxytocin may not be as important.
There are limitations to the manipulations they did, which they would agree with.
So I'm just telling you, so Gould Olin was a postdoc in my lab.
And we formulated a project to look at the actions of oxytocin in the nucleus accumbens in mice.
And the reason we study mice is they're what are known as a genetically tractable organism.
We have all sorts of really cool and sophisticated tricks we can do to probe brain circuitry,
the actions of neuromodulators like dopamine and serotonin and oxytocin in ways that we can't do in other species.
And I'm going to get back to dopamine in a second.
And what we found was that oxytocin action in the nucleus accumbens was indeed important for promoting sociability,
probably for promoting the reinforcing component of a social interaction.
And that surprised us.
So it was like, wow, it's oxytocin seems to be causing enhancing the release of serotonin in the nucleus accumbens.
And that, well, perhaps we'll get to this.
That led me off on a whole series of experiments trying to figure out how serotonin works,
studying this drug we may talk about called MDMA, which is ecstasy or molly, which actually causes release of serotonin.
So we did that work and that got us working in serotonin.
Simultaneously, there were some other papers reporting that dopamine release in the accumbens, that dopamine is released in the accumbens during a social interaction, a positive non-aggressive social interaction.
Truth be told, it may also be released during an aggressive interaction.
Some people like to fight.

Some people like to fight.
And the difference here is the dopamine release and its role in social interactions.
It's not specific only for a social interaction, as we have talked about.
But nevertheless, that led my lab and other labs to do a series of papers.
I'm talking about the field now showing that.
And I'm giving you a lot of information here.
How might dopamine release happen during a non-aggressive social interaction?
It turns out that oxytocin is not only released in the nucleus accumbens,
it's released in the home of the dopamine neurons in the VTA.
So my lab and another lab from Northwestern showed that oxytocin can actually modulate dopamine neuron activity in the ventral tegmental area.
So I hope I'm making sense here.
I don't want to get too technical, but it just shows how we discuss these neuromodulators like dopamine.
I just brought in oxytocin.
We're going to talk about serotonin in a second.
Unfortunately for your listeners, they don't work in isolation.
They influence each other in ways that I think it's important for us to understand and elucidate.
Not too much technical detail.
And I think it's wonderfully rich with areas for us to discuss.
And I'm so very glad that you brought up that neither dopamine nor serotonin nor oxytocin work in isolation,
because all too often and admittedly, sometimes even on my podcast,
I'll talk about these things in isolation as a way to try and simplify them a bit,
but there's just no way that the brain works that way.
For instance, turning on dopamine and turning off serotonin.
It's a weighting of inputs.
I think that serotonin, perhaps I should frame it this way,
just as often as dopamine is framed as this reward molecule and pleasure and dopamine hits,
all too often, I think, in the popular press, serotonin is discussed and oxytocin too, for that matter, as this kind of warm feel good, everything's mellow, not really associated with reward and reinforcement.
And of course, it's not that simple.
So when it comes to social interactions, it sounds like oxytocin and serotonin are playing a prominent role,
also in the accumbens, and that dopamine is activated too.
Do I have that right?
Okay.
So I don't want to take us too far down the rabbit hole of neural circuit function,
but that to me makes at least a brief discussion about the nucleus accumbens itself.
Interesting.
Okay, so I'm thinking nucleus.
I know that means a pile of neurons, an aggregation of neurons.

It's talking to this ventral striatum.
So we got a bunch of neurons.
It's a part of the ventral striatum.
It's a subdivision.
Excuse me.
I misspoke.
Yeah.
It's part of the ventral striatum, and the neurons there can be active and communicate with other brain areas,
but we're talking about a lot of nuance of function.
Oh, man.
So I'm not smiling.
I don't know if your audience is going to see me smile because it's so...
I sometimes go to bed feeling.
It's so complicated.
Oh, my God.
It is.
And yet could we say that within the nucleus accumbens, there are neurons that are acting as accelerators and brakes.
I mean, is there a simple analogy that perhaps while not exhaustive can still be true?
Because that's always the goal on this podcast.
There's no way we can be exhaustive, but we want to be as accurate as possible.
So a very influential hypothesis, which has guided my thinking.
And again, the trick, I mean, you know, you have done a wonderful job of communicating complex scientific topics to your podcast audience.
And I congratulate you on that.
And it's a really important role.
But as you know, it's always more complicated than we want it to be as scientists, especially when you're dealing with brain activity issues and how the brain mediates all its amazing functions.
So historically, we have thought about the nucleus accumbens and other components of this ventral stridal brain area as primarily being composed of two different cell types.
And as you pointed out, one being sort of an accelerator, something that promotes certain behaviors.
And then the other cell type, somewhat being a break saying, don't do that behavior, don't perform that motor action.
And it is true that there are these different cell types.
It is true that they are modulated by these modulators like dopamine and serotonin in different ways.
And that simplistic hypothesis or heuristic we call it has been very useful in making models about how the accumbens does all its wonderful things.
What I'm leading up to is it's unfortunately, it's a little more complicated.
But yes, there are two different cell types.
And at least for your audience, we can think about dopamine driving the activity of one,

promoting certain behaviors and inhibiting the activity of the other cell type and being
a sort of break on certain behaviors.
As long as you and I as scientists appreciate, it's not quite that simple.
It's a little more complicated.
So using that as a framework to think about social behavior, as you said, you know, pro-social,
non-aggressive, non-sexual interactions involve the choice of a lot of behaviors,
but also the suppression of a lot of behaviors.
And so maybe you're starting to sense what I'm doing here.
I think for people to understand how a single structure like the accumbens could mediate social
interaction and reward it, what it sounds like it's doing is rewarding a certain category
and catalog of behavioral options and punishing or at least reducing the probability
of the occurrence of other behavioral actions.
Because when I go to dinner with friends, if I know them really well, I might hug them,
I might even say something mildly inappropriate.
And if I know the context to be safe, right?
But at a dinner interview or a discussion with somebody I barely know,
I might watch my words a little bit more, for instance.
And I think the accumbens and its associated circuit, I love the way you just put that,
probabilities.
My probability of having this behavior in a certain context is increased,
the probabilities of not doing certain behaviors.
And I think there's little doubt that this brain area called the nucleus accumbens
and all of its associated circuitry play a very important role in what behaviors
you choose to do, pursue, play a very important role in these making the decision
and performing these pro-social, non-aggressive, non-sexual interactions.
I actually also think it plays a role in empathy and I'm leading you there.
I want to have a discussion about that.
Please.
Well, again, as a mechanistically driven neuroscientist, what is frustrating for me
is I know a lot of the connections it's making and the other brain areas it's communicating with,
but I can't give you a coherent hypothesis or diagram of how it all happens, you know, yet.
You're still going.
What I can say is even at our current level of understanding, it is leading to novel hypotheses
that are allowing the development, you know, perhaps, you know, if we bring it back to autism,
that are allowing the development of novel, at the moment, pharmacologic therapeutics
that might be helpful for people who are not having normal pro-social interactions
and would like to have them, would like to be able to function in that domain
in a more adaptive and productive and meaningful way.
And that's the importance, in my view, of the kind of mechanistic work my lab
and many other labs around the country are doing.
Even if we don't have a detailed understanding of how it's all happening,
we can identify drugs and drug-able targets or even behavioral interventions
that might actually help people.

For example, suffering from autism spectrum disorder of the sort that they actually want
and need interactive, need therapeutic help.
I think looking at the social connection circuitry through the lens of autism
is going to be very interesting for us to do.
I do have a question about what is being selected for in rewarding social interactions,
because obviously we are living in a time where, you know, we don't have to aggregate in groups
necessarily to protect ourselves physically.
It helps in certain ways in certain circumstances,
but certainly to support ourselves in each other emotionally.
You know, having people that we can call on when we're not feeling so well
that we can look to for resources and that they can look to us.
But when we go out to dinner with friends or we go to a ballgame with friends
or we interact with friends, I'm very familiar with the feeling of like,
well, that felt really good.
It just felt good.
It gives me energy.
It actually gives me energy to go back and do other things like spend four days alone
with a bunch of papers and lectures preparing for a podcast,
which I also really enjoy.
But when I do that, when I go out to dinner with friends or see friends,
I'm not thinking about buffering myself against loneliness.
When I do it, I just like the interaction.
So what sorts of evolutionary hypotheses can we come up with
as to why the human brain is so tuned for these social interactions?
Why it's rewarded by not just one dopamine, but also serotonin.
Serotonin and oxytocin, three prominent neuromodulatory chemicals in the brain
are devoted at one site in the brain and others that it's connected to, of course,
but to making sure that we do this as often as possible
without giving up the rest of our lives.
Well, I mean, again, I think the answer I'm going to be able to give,
I hope it's not tried and it may be a little bit obvious is,
and in some ways it's analogous to why drugs of abuse and addiction
are also a problem is that the circuitry that is telling us
a prosocial positive interaction is so highly reinforcing
evolved over millions of years or hundreds of thousands of years,
whatever that is.
And the only hypothesis I can come up with, and Andrew,
you may be able to come up with better ones, is what I alluded to earlier,
is it was very adaptive when we were more primitive organisms,
never mind non-human primates, but when we were whatever we were
to be a social species for basically primarily two reasons
for reproductive purposes.
It increased your likelihood of reproducing if you were hanging out

with other members of your species in a non-aggressive way
and for protection against predators.
There may be other reasons.
Probably child-rearing too.
In your absence, you aren't trusted friends that can watch your offspring.
Thank you.
Very good point.
So the circuits, the modulators, we used that evolved over millennia
and as you pointed out, eventually, depending on the society in which you live,
you didn't need those social interactions for protection against predators.
Although if we look at our world now, one can make arguments both ways.
If you're in a war zone, is it better to be off by yourself?
Is it better to be with a group of people?
The mechanisms evolved for one purpose and they don't just disappear
because there's no disadvantage to having this mechanism that tells us
a social interaction is reinforcing.
And I would still argue there's benefit for reproductive purposes.
You can't have kids if you're by yourself all the time.
As far as I think it's impossible, at least currently,
you can't find a partner with whom to have kids if you're socially isolated
or it makes it much harder.
So I hope I'm answering your question.
And then as you pointed out, for many of us,
there's a lot of positive aspects to having friendships and hanging out with your friends.
Emotional support, emotional buffering.
There's something about this notion of feeling connected,
and later we'll talk about psychedelics,
but this notion of feeling connected has a lot to do with buffering loneliness
when we are alone.
The memories and the energy, for lack of a better word,
that we feel in recalling social experiences
and anticipating social experiences is really powerful.
You mentioned that people can't have children if they spend all their time alone.
I realize you're not on social media and more power to you,
but there's actually a prominent discussion on social media.
There's an entire culture of young people,
in particular young men these days who,
at least from what I understand in the research literature about this,
are socially isolated, spending other time online,
maybe not even on social media,
but are spending a lot of time online,
video games, hiding in electronic landscapes, digital landscapes.
And concern about mental health issues there, et cetera.

Concern about porn overuse and addiction there, et cetera.
But social media itself is an incredible phenomenon
to consider in light of everything we're talking about.
I can't say, even though I am on all social media platforms,
and I'm quite active there,
I can't say that I've ever been on social media
and experienced the kind of delight and thrill and persistent energy
increase that I experienced with in-person interaction.
And yet, social media, I have to assume,
is capitalizing on some of these same reward mechanisms
in presumably the nucleus accumbens.
So are there any data,
I realize this is a hard experiment to do in mice, maybe impossible,
are there any data that you're aware of
that shows that social media has a high addictive liability,
or do we even need an experiment?
I'm not sure we need an experiment.
I think it clearly does.
I agree with the point you're making,
although your podcast audience probably doesn't know who I am.
I am in my late 60s.
I grew up...
Well, they know who you are now.
I grew up before computers, before cell phones.
So I still am a believer, perhaps in an old-fashioned way,
that physical interpersonal reactions are really important.
Obviously, there are advantages to being able to interact over social media.
And I mean, for all sorts of reasons,
there's a lot of positive and good from that.
But back to your question, can we get addicted?
I can't speak to social media.
I can speak in analemki, you know,
I think is much more able to eloquently describe
the issues around you.
I can just talk from my own experience that my cell phone is...
This is in social media, but checking my email messages,
checking my text messages,
for me, has a compulsive addictive quality.
It's like a lever press, isn't it?
It's like a lever press for a mouse.
And part of that is my own personality.
Part of that is the immediate feedback.
So you get from a social media post from seeing your name mentioned,

getting a message from one of your friends.
Sure, you know, I like getting messages from my friends.
It means they're thinking about me.
It means I'm part of their world.
I have no doubt it's activating my reward circuitry,
not nearly to the degree that a hit of cocaine or an opioid would do.
So I don't know what else to say about it.
I think as a society, we have to be aware of these issues,
and it's really complicated how we manage,
especially, you know, once you're an adult,
you make your own decisions for better or worse.
But, you know, it's a huge issue, obviously, for anybody who has children
or is planning to have children.
And adults on social media.
I mean, I see lots of accounts of people that are 18 and older
who they spend a lot of time on there.
And I'm not necessarily saying that's a bad thing.
A lot of people have entire careers that exist on social media.
It just seems to me that Instagram, Facebook, LinkedIn, Twitter
have capitalized on this hardwired circuitry.
To make it really reductionist, the release of serotonin, dopamine and oxytocin
by virtue of someone saying something to us,
maybe not even a positive thing.
Maybe it's a negative thing.
But as you said, they're thinking of us.
There's something about being recognized by others.
And maybe this is a good segue.
We're heading towards empathy here, a discussion about empathy.
I think that's very well put.
It is capitalizing on these more primitive neurobiological mechanisms
that evolved for purposes of reproduction and survival.
I think that certainly has to be the case.
And I think it's important.
I mean, thank you for bringing that up for us as a society
to be at least aware of this.
And it doesn't mean it's like many things.
It's not all good.
It's not all bad.
It has, there are positive uses of social media I can see.
But mostly we read about the dangers of it.
We read about these kids who are socially isolated,
who make bad decisions based on what they're seeing with social media.
But anyhow, back to the neuroscience, you're absolutely correct.

It's capitalizing on these mechanisms that evolved for physical interpersonal interactions.
Because our evolution didn't anticipate it.
Right.
Just as pornography is capitalizing on the sexual arousal reward circuit,
associate reward circuit.
No question about it.
And just as the gambling industry does, I mean, as you know,
the Vegas casinos have full-time people developing algorithms
for how frequently should a slot machine pay off?
What's the perfect amount of payoff to keep certain individuals coming back?
So pernicious.
You could tell I've been spending a lot of time around addicts and former addicts.
I've been researching some things for the podcast.
And a gambling addict told me something interesting.
They said the real stinger with being a gambling addict is that the next time really could change everything.
Whereas no alcoholic says that, that the next drink could change everything for the better.
Or, you know, the cocaine addict doesn't think, oh, you know,
the next line of cocaine could make all of life better now and forever.
Whereas the gambling addict actually holds in mind the infinitesimally small and yet real potential that the next time really could wipe out their debt and perhaps wipe out.
And yet we know they would lose that too.
Right.
Whatever winnings they have.
And casinos are fully aware of this.
I have been told by friends who know they employ, you know, full-time quantitative, you know,
for lack of a better term.
I was going to say computer geek.
I don't mean to that be.
And probably neuroscience too.
I would be amazed if they don't have neuroscientists who have expertise in what's called neuroeconomics or behavioral economics.
I'm 95% sure that has to be the case.
I occasionally sit down to the roulette table because I just so passive and easy.
And not long ago, actually, I had the experience of winning, not a large sum, but a meaningful sum of money.
And I'll tell you, my sole mission at that point was to get up and go back to my room and not stop at another table.
And I confess I pulled one brief stop and another table played one hand and then lost it and then just got back to my room as quickly as possible
and then left Las Vegas as quickly as possible.
Yeah, gambling is fascinating.
But they'll probably get me the next time.

Yeah, gambling is, you know, again, it all gets back to this reward circuitry and the intermittent rewards are very, very powerful.
Well, and you mentioned earlier that the reward system is powerfully tuned to remember what were the behaviors that led up to the rewarding experience.
And nobody ever won at the roulette or craps table or poker table by getting up and leaving.
Yeah, yeah, exactly.
And so I guess my brain was just thinking, well, how did I win?
I won by sitting down and putting chips on the table, not by going back to my room.
Exactly, exactly.
And yet I have, you know, a fair number of degrees and I like to think my prefrontal cortex is working and yet it was still challenging in that moment.
No, gambling is really interesting.
I mean, yeah, another human activity that's quite complicated.
It can be enjoyable or it can be incredibly damaging.
And now people are going to think I was that gambling addict that I was referring to, but I swear I'm not fortunately feel very blessed that that's not my addiction.
I'd like to talk about empathy and use that as a framework for eventually returning to our discussion of autism.
But you have this perhaps longstanding interest, but recent research interest in empathy.
Tell me about this work.
I'm not familiar with it yet.
Okay.
So I am going to, I'm going to, I hope it's okay, drag in the some work I've done on this drug called MDMA because it is related.
So we were working on in my lab, social behaviors, positive pro social behaviors that stimulated me to start thinking about what are components of a positive pro social non aggressive interaction.
A common key component of that is having some empathy and compassion for the individuals you're hanging out with.
And it is a topic I've been interested in for many, many decades.
I was once a psychiatrist.
And to get on my whatever the word is hobby horse.
I look at the world today, I try to be optimistic.
Again, I am a child of the 60s and 70s.
When I look at the world, and I actually just did a trip to Israel to give a series of lectures and I look at the Israeli Palestinian conflict.
What always enters my mind is I've felt this way for decades is what is more important for the survival of the human species, then empathy and compassion, then actually being able to look at another human being.
Even if they look different than you, even if they have a different belief system than you, what is more important than actually understanding that 98% of your life is very, is very similar.
You know, you have some differences in how you look and the beliefs you have, but there's so much in common.
So what's more important than understanding that when another person is suffering, their suffering

is the same as your suffering with and having compassion for somebody.
So I started thinking, what is more important?
And I'm not a politician.
As you know, Andrew, I have no social media presence.
I figured the only way I might be able to contribute to efforts that might help you, the human species, enhance empathy and compassion is by studying the neurobiological underpinnings of it.
And I didn't realize I might be able to do that until I started studying sociability or prosocial behaviors in mice.
And then I was able to have a young woman scientist and I want to give her credit, Monique Smith.
You might want to have Monique on your podcast.
She's a dynamo.
She's now an assistant professor at UCSD.
And Monique introduced me to a series of behavioral assays that I like to use the phrase, they are measurements.
They are behavioral antecedents of empathy because in the world of psychologists and people who use the term empathy, it has a lot of different meanings to different people.
I'm using it basically to mean one member of a species manifests some behavior that indicates it is being influenced by the emotional state or what we call the effective state, effective with an A, of another member of that species in its immediate environment.
And for human interactions, I just think of, you know, any of, we were talking about friendships, any of us who watch a close friend suffer, it's hard.
You want to do anything you can to help them.
That's empathy, a mother with their child, a good mother, hopefully, you know, when you have a kid who is sick, there's nothing worse as a parent.
You just want to take that pain and suffering away.
That's how I'm defining empathy.
So it's my belief that like any complex human behavior, there are evolutionary reasons why that has been adaptive and important and maintained.
And if it's evolutionarily evolved, there are ways of studying it in more primitive organisms like mice.
So I'll tell you some of the behavioral assays we're doing.
One is, and I get a kick out of this because it's pretty new for me.
So one assay, and we published a paper in a journal called Science about this, which is if you take one mouse and in a ethical way, you put it in pain.
You make its hind paw, one of its paws, one of its feet hurt a modest amount.
And you take another mouse and you let that, what's known as the bystander mouse, just hang out with the mouse that's in pain for one hour, just one hour.
The bystander mouse who has experienced no physical injury whatsoever will manifest behaviors indicating it is now in pain.
And it lasts maybe four to 20 hours.
But think about that.
A mouse that is normal hanging out with another mouse in pain starts feeling pain itself.
And the mice are able to see one another and hear one another.
Good point.

So you're getting to how is that communication happening and a lot more work needs to be done on it.
Monique and her previous colleagues and others, one component of it is probably an olfactory cue or what we call a pheromone.
So the mouse that's in pain is secreting an odor.
Probably, probably, because you can take bedding from mice in pain and expose the bystander mice.
So that's one thing.
And I had never heard of these behavioral assays.
We developed our, and this is pretty cool.
And then I'll tell you two others and then I'll tell you how it connects to reward circuitry.
We developed a novel assay, which is the social transfer of pain relief.
Pain relief is called analgesia.
And I thought this was pretty cool.
So you take, and this is in this paper that was published in Science a year ago, you take two mice and they're both in pain.
Modest pain.
I don't want your listeners to get upset.
We are not hurting these mice too badly.
And it is a tricky issue.
Is it, you know, is it okay to put a mouse in pain so you can, the goal is to develop better treatments for human beings in pain, obviously.
So you have two mice and modest pain.
You give one mice mouse morphine.
So it's now analgesic.
It is no longer experiencing pain.
You take another mouse that's in pain and you just let it hang out with the mouse that is no longer in pain.
And the mouse that is in pain will show behaviors indicating it is experiencing analgesia.
It is no longer in as much pain.
Now think about that.
And there's actually evidence from human studies that I can't speak to in any comprehensive way where, I mean, it's called social buffering of pain.
If you are, I mean, to be honest, I've been having some neck pain just because I'm an old guy and I woke up on the wrong side of the bed.
And if I'm by myself, I focus on that pain and it bothers me more if I'm in a social socially engaged.
I think it's not only that I'm not paying as much attention to the pain, but I think there's actually some relief from what's known as the social buffering of pain.
Well, I'm no hippie, but I actually think that all species, including humans, are secreting molecules, mainly odorants that are perhaps even acting directly as analgesics.
And I can make that statement without worrying too much that people think I'm completely crazy because we had a gnome sobo on the podcast from the Weissman who shared with us, you know, not one, not two,
but at least a dozen ways in which humans are making molecules, typically odors, and

communicating those to one another to powerfully impact their testosterone levels, their vasopressin levels, their immune molecules, you know.
And of course, gnome works on olfaction, so he's going to be biased toward that system, but that's just one slice of the sensory array.
I mean, what about the way that somebody can look at us in a way that makes us feel good on a normal day?
Well, when we're in pain, just even the touch to a shoulder can mean a lot.
I remember going to meetings when I was an early neuroscientist, and I would probably at that point have, you know, not been the type to just walk up and say hello to you because I wasn't in your field and you're this luminary and stuff.
But what I remember is I started with cancer.
I'm a good guy by the way.
You are. Very, very good.
I always say hi to everyone.
I know you are.
And that statement was a reflection on you, not a reflection on you.
But as I advanced through my career, what I found was, you know, you'd give a talk or something, and someone in your field more senior to you who you respected would give a nod or something.
Those nods mean a lot.
Absolutely.
I mean, those nods could carry you a long distance.
I mean, obviously we want to be intrinsically driven to do the work we do.
But the social communication stuff, I think there's a whole landscape of things.
So what you're describing is incredible, but I think it makes a ton of sense.
Yeah.
So we have the social transfer pain and vanities here.
We're working on, and there's a little bit of evidence in the literature suggesting this might work.
And then I'll talk about reward circuitry and maybe MDMA and is it an empathogen or not, and how that might influence therapeutic efforts for autism.
We're working on behavioral models.
We're asking the question, will one mouse behave to give another mouse a reward?
So it's the mouse that's behaving that has to press a bar or nose poke or even experience a shock.
Will the mouse do that simply to give one of its buddies a reward?
Pure altruism.
And yeah, it's pure.
It's what we call a generosity, a generosity assay.
And early days, it looks like it might be working.
And that's a generosity assay.
We can also ask the question, will a mouse work so another mouse doesn't get a shock, doesn't get hurt, which is compassion.
And I think these things are going to be working.
And whether you want to call that empathy, I would call that those are behaviors.
I like to use the term behavioral antecedents of how we define empathy in human beings.

And the connection to reward circuitry and in the little bit of work we have done on this is we presented evidence that these behaviors we call the social transfer of pain.
One mouse experiencing pain just because it's hanging out with another mouse, the social transfer of analgesia.
A mouse in pain getting some pain relief from hanging out with another mouse in pain who has that pain relief.
It seems to involve one component of the complex brain mechanisms.
Seems to involve a part of the brain called the anterior cingulate cortex, which human brain imaging studies suggest are is activated during empathic human responses.
And the projections of that area into the nucleus accumbens, that's the connection.
And we're interested in whether neuromodulators like dopamine and serotonin may influence these circuitry, these connections that are involved in these, in quotes, empathic behaviors, etc, etc.
And we think drugs can be used as probes of those kinds of neuromodulatory mechanisms.
I hope this is all making sense.
It makes an excellent sense and is fascinating.
I'm not one to suggest experiments to colleagues in areas where I don't work, but I'm going to anyway.
Yeah, please.
You're a really smart guy, so I will value your suggestions.
You know, I love the motivational backbone to what you're describing here because I agree the world has a lot of issues and what it could be more important than to increase the amount of empathy and compassion in the world.
But one thing that we know inhibits empathy and compassion is one's own challenges and struggles.
And so I'm wondering if there's a way to introduce something to this behavioral paradigm such that the working to provide another animal relief from pain.
Or a animal working to provide pleasure, reward for another animal, you know, if it could be scaled with how inconvenient that work is.
If I'm very hungry, I mean, we're all taught to put our own oxygen mask on first in some way too so that we don't all die, so to speak.
But, you know, I grew up, for instance, with one parent, my mother, it was the kind of person who would see, at that time, there were far fewer homeless people on the street.
Maybe they were all institutionalized, I don't know.
But if she saw a homeless person on the street of the town we lived in, she would literally pull over, give them money, find hotels.
She had homeless people living in hotels all over the town we lived in.
It was crazy.
I mean, we couldn't get anywhere.
That was the problem is we would never arrive anywhere on time and that's my excuse for always being late.
I was positively reinforced for being late.
I always run late and I always run incredible, right?
Just a very strong sense of social connection.
That kind of thing.

But in any case, you know, some people are like that, like she could not experience any even modicum of inconvenience for helping others.
Whereas I think most of us feel like if I'm rushing to catch a flight and I see someone who's struggling, I'm probably going to help them if they're in acute pain or it seems like a dire circumstance.
But let's be honest, most people are probably going to prioritize their own stress and priorities, for lack of a better word.
When the situation often calls for us to set those aside and tend to people that are suffering.
So if there was a way to introduce the probe of the interplay of circuitries that involve how convenient or inconvenient it is.
Like if we're well fed, it's pretty easy to go out and gather and distribute food for others.
But if we're hungry, we tend to focus on our own hunger.
So first, in full disclosure, even though I'm studying empathy and compassion, I can look in the mirror and say I probably don't practice it nearly as much as I should.
I'm thinking of your example.
If I was late for a plane, I'm not sure I would stop and help somebody.
And I'm not saying that.
It depends on what sort of software.
Yeah, exactly.
I mean, if they're emerging on the side of the road, we all would.
Of course.
But on tire, right?
You might think, oh goodness, like, do I have time for this?
Yeah, yeah, exactly.
So I'm not proud of that statement.
But back to your question.
Yes, I think absolutely we can design experiments where after we've established the basic phenomenology, then we can take our subject animal or mouse and put it in just certain circumstances.
If it's hungry itself, will it work as hard to give another animal?
I mean, it's a good question because I'm not sure what the outcome will be.
One could predict it might work harder because it understands the hunger in quotes more or it could be.
Of course, it's not going to work hard for another animal to get a food reward because it's starving itself and it needs to take care of itself first.
It's a great question.
We're also asking questions about, do you have to know your buddy mouse?
Right?
Are you more likely to behave in a generous or compassionate way?
If you grew up with that mouse, you know, in the way our mice grow up in academic environments, and if it's a stranger, how will you behave?
How will you behave if you had a fight with that mouse previously?
And what if you had, and it also matters, did you win the fight or did you lose the fight?

Right?
Intuitively, as we probably would all guess, I'm more likely to help somebody I defeated in a fight previously because I'm the hierarchy.
I'm the dominant one.
I'm probably less likely if that person beat me up.
So all these are great questions.
I think we can study them.
I also think there are ways we can study these kinds of interactions in human subjects.
Not that I am going to do that myself.
Someone at Stanford will.
Yeah.
So I think there's also an opportunity and I'm happy to discuss how neuromodulators like in particular serotonin, but also perhaps dopamine and oxytocin may influence the brain, the circuitry in the brain mechanisms that are mediating what I term empathic behaviors.
Let's return to autism.
Right.
Does autism involve a lack of empathy?
Does autism involve a restructuring of the reward system around social interactions?
Maybe considering the second question.
First, I could imagine, for instance, that there are variations in brain wiring that would make it such that a kid who then becomes an adult gets a tremendous amount of reward from, I don't know, math, designing mugs, any number of activities.
But that through some variation in brain wiring, social interaction, spending time with friends is just not as socially rewarding.
It just doesn't feel good in the moment.
It doesn't necessarily feel bad, but it's not selected for.
And is there any evidence that that's the case in children who are classified as autistic or having autism?
I want to be clear.
I'm not a world expert on pathophysiology of individuals with autism spectrum disorder.
I have read some of the literature.
I do study mouse models of genetically based autism spectrum disorder.
So the answer is yes.
There have been imaging studies.
And again, so your audience, certain members of your audience, don't get mad.
Remember our earlier conversation, we made the point that autism spectrum disorder is a highly heterogeneous set of behavioral symptoms with wide variation in how these symptoms manifest in each individual.
So we cannot make blanket statements that individuals with autism spectrum disorder are this or that.
But there are studies, both in human beings and mice, that suggests that the reinforcing component of a social interaction is much less or lacking in our models of autism spectrum disorder and certain individuals.

An important point is, is that just genetically wired?
Was that because in their early experiences, they weren't able to get the sensory stimuli that tell them this is a reinforcing social experience unknown?
Or at least those are topics that I think are worthy of investigation.
Do individuals or mice with autism spectrum disorder lack or do not have the capacity or the same experience of empathy?
Again, a very complex topic in question.
And it's very likely for some individuals, the answer is yes, meaning they do lack some of the neuro mechanisms that allow them.
But that probably doesn't apply to everybody.
I can say in our mouse models of social interactions and our mouse models of end quotes, empathy in these are my show deficits.
And those deficits can be rescued, meaning improved upon by manipulations of certain neuromodulatory systems, in this case, the serotonin system, by giving drugs, including a drug called MDMA or ecstasy.
So I hope I'm answering your question.
I think these are worthwhile subjects for investigation.
I think there's a lot of value in studying them.
Let's go back to serotonin in the nucleus accumbens.
We will get into this in a bit more detail when we discuss MDMA, but I've now spent a lot of time with a recent paper of yours that really really which one of the MDMA paper.
The Boris Heifetz one?
Yeah, that parsed the relative roles of dopamine in the nucleus accumbens versus serotonin in the nucleus accumbens.
By the way, folks, by the time this episode comes out, an episode all about MDMA itself and its modes of action will have already aired and you can find that.
But even if you haven't heard that, MDMA is an amazing molecule because it profoundly increases dopamine.
And that's why the word methamphetamine is actually in MDMA.
Still a surprise to many people to hear that, but it also robustly increases serotonin transmission.
And what I love about the paper from your lab that explored this is that, at least by my read of the data, it showed very convincingly that it's serotonin released in the nucleus accumbens that's responsible for the pro-social effects of MDMA.
Whereas oxytocin, this thing we talked about earlier that everyone assumes is the pair bonding molecule, the molecule of love, both in humans now, there's a study in humans and in the mouse work that you've done doesn't seem to play as prominent a role in the social enhancement that MDMA causes.
The reason I'm asking this in the context of autism is that for a long time there was excitement about the idea that oxytocin nasal sprays might make autistic kids more excited about social interactions, more tuned to social interactions.
First question is, is there any evidence that increasing oxytocin in a child or adult with autism makes them somehow more social or desiring more social connections?
I'm not aware of any.

I don't think the, I think it is a worthwhile, it has been studied.
I don't think we can close the door on the potential therapeutic uses of oxytocin.
From the people I know who are much more expert in this than I am, I think most of the clinical trials have been pretty disappointing.
With a lot of hope that intranasal oxytocin would promote more positive pro-social experiences.
I don't think the door is shut yet.
There may be different ways of administering it.
There may be ways of making a different type of oxytocin that might be beneficial.
I have a colleague at Stanford who's actually looking at a related neuropeptide called vasopressin, and she's finding some potential benefit from that.
And vasopressin and oxytocin are closely related to each other.
They can even activate some of the same, what we call receptors in the brain.
So I don't think the door is closed on the possibility of oxytocin or related therapeutic agents having some therapeutic potential.
The evidence as far as I'm aware is not there yet.
In terms of MDMA, again, complicated story.
As you pointed out, MDMA, its major molecular targets, don't want to get too technical here, are the serotonin vacuum cleaner, the molecule that vacuums up serotonin, and the dopamine vacuum cleaner,
the molecule that vacuums up, excuse my language, sucks up dopamine when it's released.
Because it's an amphetamine derivative, as you point correctly pointed out, it not only prevents these proteins we call them, these molecules, these vacuum cleaners, from vacuuming up the dopamine and serotonin when it's released,
it actually causes it, I don't want to use the term, the terminals to vomit out dopamine and serotonin.
That's what I say on the, when I talk about synaptic release, I'm known for, in my solo episodes, when I talk about synaptic release, I'll say that they vomit out.
So what amphetamine derivative?
You work on synaptic transmission, so it's almost an insult to a biologist.
What MDMA does is it actually calls what's known as a reverse transport, it actually causes, it not only prevents the vacuum cleaners from sucking up the dopamine and serotonin, it causes it to spew out dopamine and serotonin.
So imagine if your vacuum cleaner started, the pressure in your vacuum cleaner reversed and all the dirt you collected started being spewed out.
Now the one difference for MDMA, and it's a fascinating topic, I hope we have time to talk about, is why does MDMA qualitatively, for most people, give human subjects a different experience than cocaine or especially methamphetamine.
Presumably it's the fact that there's so much serotonin.
Exactly.
And so if you actually get into, and this is why, for your audiences, this is why hardcore molecular science can actually teach us something about complex human behavioral phenomena such as social interactions and addiction.
At least the hypothesis we propose and others in the field, it's not just, you know, science is not done in isolation, so I want to give credit where creditors do.

We did not define the following that MDMA affects the serotonin system more than the dopamine system.
So it's not equal, it's not 50-50, maybe it's 70-30, 80-20, and that's because the molecule itself of MDMA, again, I'm trying not to use language, has a, it binds to, it has a higher affinity.
It likes to bind to and influence the serotonin vacuum cleaner more than the dopamine vacuum cleaner.
It's still affecting both, but it's not 50-50, it's more, whatever, 70% serotonin, 30% dopamine.
And then it does influence oxytocin in very complex ways, which is a further technical discussion.
It was just a nice paper that came out that reported that serotonin release in a hypothalamic structure, which again, the hypothalamus, you can explain to your listeners.
Yeah, look, a marble-ish size structure above the roof of your mouth responsible for sex, temperature control, feeding and satiety and a bunch of other things, critical.
And, yeah.
And it's a home of oxytocin, neurons that produce oxytocin.
Thank you.
And this paper reported that when serotonin is released in the hypothalamus, it activates and causes the release of oxytocin.
That's in the hypothalamus.
Our work in the reward circuitry suggests that oxytocin, so that's serotonin upstream of oxytocin in the hypothalamus.
And where we were looking in the accumbens, it was the opposite.
Oxytocin caused the release of serotonin.
The point to your listeners is the brain's unfortunately complicated.
You know, we like it's tractable.
We like to come up with general hypotheses and principles, but sometimes the devil's in the details and we really need to probe deeper.
So back to your question about our previous paper and dopamine and serotonin.
So what we proposed, which is far from nailed down, is that MDMA, because it is an amphetamine derivative, does influence dopamine release and dopamine, the dopamine system.
And some of my colleagues in the MDMA field, who I respect enormously, don't like me to say this, but I'm going to say it anyhow.
Remember earlier in the podcast, we talked about different substances having addictive liabilities.
Does it mean that substances automatically addictive doesn't mean it's automatically not.
It's a continuum.
And I would argue that MDMA does have a some addictive liability because it is an amphetamine derivative.
It feels good.
And it feels good.
And so there are individuals that especially, you know, as your listeners may know, MDMA has gotten a lot of attention because it's in a therapeutic trial that looks very promising for as an adjunct to psychotherapy for post-traumatic stress disorder.
And the FDA, the part of our government that approves or disapproves the legal distribution of therapeutic drugs may end up approving MDMA for certain uses.

The point being is that once it, if it gets approved, my personal feeling is it will have some addictive liability.
It also has this very powerful, what you and I might term, Andrew, a pro-social effect.
Some people even call it an impathogen.
That's a little controversial, meaning it enhances your capacity for empathy to experience the emotional state of another individual to want to understand that person's experiences in emotional state.
And what we've suggested is that the addictive liability is mostly, although not solely, being mediated by its actions on the dopamine system, whereas its positive, more pro-social effects and perhaps its impathogenic effects are more likely to be mediated by its interactions with the serotonin system in this reward circuitry.
And we're actually doing a lot of work to test that hypothesis.
We're actually testing MDMA in these behavioral models of empathy in mice.
And it looks like our hypothesis is being supported.
The other thing to drive your listeners crazy about, sorry listeners, how complex the brain is.
Neither you nor I were consulted at the design phase, and so we don't have to apologize for the brain's complexity.
Because I don't, trust me, as a scientist, I wish I could keep things as simple as possible.
That's what good science is.
It turns out the serotonin is produced by neurons in another part of the brain with this wonderful name called the dorsal raffae nucleus.
And it turns out the serotonin neurons talk to the dopamine neurons and influence the dopamine neurons.
And so it's again the point we made earlier in your podcast, even though it's fun and useful both for your listeners and as scientists to think about these powerful chemical messengers in isolation.
Because that's how we can make progress scientifically.
It's how your audience can understand some of the concepts that have been elucidated from brain research over the decades, but they don't work in isolation.
They influence each other.
They communicate with each other.
We're actually doing studies showing that serotonin release in the Cummins actually modulates dopamine release.
So it gets crazy complicated.
But you can still develop simplistic hypotheses, like as I was saying about MDMA, where abuse, addictive liability, and some of its reinforcing qualities, which you just mentioned.
MDMA, a lot of people find it fun to take it.
It's probably mostly being mediated via the dopamine system and some of its social effects are being mediated by the serotonin system.
We're actually doing studies to figure out whether the reinforcing component of a social experience requires that dopamine release.
Probably does.
What I'm most interested in really in the context of MDMA, and we should just mention because we do like to mention these caveats.

Yes, and I can say this because I participated in a trial with MDMA.
It is a very pleasant experience.
It's certainly not for everybody.
It still is a Schedule 1 drug at this moment.
Absolutely.
So you can go to jail for possessing or selling.
In fact, there was a big bust recently in Canada and another one in Brussels.
Large amounts of MDMA collected.
Those people are probably going to prison for a long period of time.
So you don't want to take it or possess it.
It's illegal.
We're talking about clinical trials here, but also the fentanyl issue.
There's a lot of fentanyl contamination.
And I was just going to mention to your listeners.
So we'd be remiss if we didn't mention a lot of people are dying thinking that they're taking one drug when they're taking another.
So we are not encouraging the use of these, but I will say that the subjective experience of MDMA provided.
It's done in the appropriate clinical setting.
It's actually MDMA.
It doesn't contain other things, dosed correctly, et cetera, is a pleasant one for sure.
And my sense is that the dopamine release is reinforcing the experience that the context that serotonin is providing with the social context.
And the word context there becomes important when we think about back to the 90s when there were a lot of raves.
And people were also getting, I guess, positive feedback from the interactions they were having dancing all night, parting with friends, et cetera.
I mean, I think that returning to the issue of autism and the role of serotonin.
So in autism, there seems to be less of a reinforcement pathway for certain kinds of social interactions in some individuals with autism.
And I'm aware that there are some prescription treatments for autism that capitalize on the serotonergic system and dopamine system.
So is it fentamine?
To my knowledge, the only FDA approved pharmacologic therapeutic for individuals with autism spectrum disorder is actually, oh God, I'm just blanking.
It's not a serotonergic drug.
I have to look it up.
I want to say resperidone for agitation.
There is no drug for lack of a better term, the social deficits.
There's no FDA approved drug.
If you look at the literature, psychiatrists and individuals with good intention have tested the utility of traditional serotonergic drugs like Prozac SSRIs.
There are drugs known as SNRIs, drugs that influence serotonin release and another

neuromodulator that you know well, norepinephrine.
And at least well done clinical trials, which in my view, as an academic are very important, none of them have showed efficacy.
Having said that, there are several companies and full disclosure here.
I am the founder of a small biotech called Maplite Therapeutics and I'm not advertising for Maplite.
I'm just doing a full disclosure.
It was founded with Carl Deiseroth, who you've had on your podcast and an entrepreneur in San Francisco named Carolee Nicolich.
And we have a phase two trial.
Phase two trial means it's a safe drug.
We've done all the safety work and it's a drug that targets a subtype of receptor for serotonin.
Serotonin works on many different, I don't know, what word can I use other than receptor?
No, listeners of this podcast probably be familiar with receptors.
It's sort of parking spots for molecules.
Yes, the paper I was referencing earlier from your lab, it talked about serotonin 1B receptors being particularly important.
The point being is, I do have an interest in this on can you use the type of discoveries we've made in mice.
Might it actually have any relevance to human beings, in particular those who some of which have some sort of sociability deficits.
Other companies are pursuing this too.
So MDMA itself, there has been, I don't know if it's ongoing, there's a well-known organization.
I don't know if you've ever had anybody from MAPS, the Multidisciplinary Association for Psychedelic Studies.
MAPS deserves a lot of credit for being a pioneer in saying, in particular with MDMA,
promoting the idea that this drug deserves rigorous and ethical study.
That's at least my view.
And MAPS, which was founded by an individual named Rick Doblin,
has deserves enormous credit for their 30-year effort to make it allowed and legal to actually study MDMA.
The point I'm making is, I know MAPS and perhaps others have done some small trials studying MDMA in individuals,
high-functioning individuals with some form of social anxiety.
I'm saying this because this is public.
There's another company called MindMed, which is one of the publicly traded psychedelic companies.
And this is on their website, full disclosure.
I am on their Scientific Advisory Board.
They are gearing up to do a trial of a, I don't want to get too technical, of a certain form of MDMA.
There are two different types of MDMA that they have these horrible names called enantiomers.
So the MDMA that is used for clinical trials at MAPS.
MDMA is a molecule and it has mirror images of itself.
And one has the name R-MDMA and one has the name S-MDMA.

And they're called the enantiomers because they're mirror images of each other.
And other labs over the years, not my lab, I deserve no credit for this,
have done some studies to suggest that the S enantiomer is the one that has a higher interaction with the dopamine system.
And the R enantiomer has a higher interaction with the serotonin system.
Interesting.
If you look at the literature on autism spectrum disorder in human subjects,
there's a bunch of papers suggesting serotonergic systems are malfunctioning in individuals with autism spectrum disorder.
And if you look at reviews I've written or any of my papers, we probably cite some of their reviews.
It's clear that serotonin is playing some role in social interactions, at least in mice and almost certainly in humans as well.
It's hard to imagine based on data from everything from SSRIs to neurotoxic lesions of the human brain, et cetera,
that it's not also playing at least a similar role in humans.
Right. And I fully agree with that.
And as we were discussing, there's a modestly extensive clinical literature,
meaning literature from human subjects,
suggesting that some aspects of brain systems that utilize serotonin as one of their signaling molecules,
one of their neuromodulatory mechanisms may not be functioning in some populations of individuals with autism spectrum disorder.
So based on that, based on my lab's work on the role of serotonin in modifying reward circuitry, its role in pro-social behaviors.
And the biggest clue, which I think you would agree with, Andrew, is this drug, MDMA.
I mean, this is why I am not a druggy myself.
I am a child of the 60s and 70s.
So I did, which means I'm 20 years older than you, Andrew.
I did experiment like everybody of my generation with psychoactive substances in the 70s.
So I don't want to lie about my experiences.
I also would say like many neuroscientists, my experiences with psychoactive substances stimulate at my interest in neuroscience.
How do these substances work?
Why, when I was a young kid, the first time I got drunk on beer, why is that happening?
But more seriously, I use drugs in my research as powerful probes of brain function with the advantage that,
and now I'm talking scientists to scientists with you, Andrew.
They have molecular targets that we can manipulate in rigorous ways.
We can figure out where in the brain they act using the modern tools of neuroscience, which your audience may not know about.
I'm saying this to you, conditional knockout mice, rescue experiments.
We can do all those fancy stuff and we can use drugs to study.
Even things as complicated as empathy.

And I really do believe, that's why I've been interested in MDMA for decades, is there's a clue there.
How does a drug that has molecular targets in the dopamine neuromodulatory system, in the serotonin neuromodulatory system,
have such a powerful effect, which is relatively specific on social interactions?
It doesn't make you want to go eat more donuts.
It doesn't, I don't know, for me there's a clue there.
There's something really important from that phenomenological observation in the human experiences that we can learn from.
I completely agree about MDMA and we've done a couple of podcasts about psilocybin and by extension LSD,
because even though there are differences there, psilocybin and LSD, as far as we understand, largely work through activation of the serotonin 2A receptor,
broadening of a brain network connectivity.
So again, it's serotonin, serotonin, serotonin, but different receptors, very different subjective experience.
And I guess perhaps the best way to describe it is that LSD and psilocybin are almost always considered mystical in their subjective effects,
whereas MDMA can be an impathogen and actogen.
And so serotonin acting through different receptor systems impacting and creating very different subjective experiences.
I also agree, I think MDMA is particularly interesting for the neuroscientist.
Perhaps also because, at least to my knowledge, there is no substance in nature, no plant, no mushroom, no ergot, no mold that creates this increase in dopamine and serotonin simultaneously.
MDMA is a synthesized molecule.
And so it may be one of the, again, highlighting all the safety issues and things we talked about before,
but it may be one of the great, at least experimental probes of the brain that humans have developed,
and it may be one of the great therapeutic probes that folks like MAPS are now doing such fantastic work on.
So I'm very excited about what's happening with the research on MDMA,
and I'm so glad that your laboratory has parsed some of the relative roles of serotonin, the receptors involved.
Since we mentioned serotonin 2A for psilocybin and LSD, we'd be remiss if we didn't say that this wonderful paper that we will provide a link to in the show note captions,
by the way, folks, that Rob Malenka here's lab, it's focused on the serotonin 1B receptor.
So even just differences in receptor subtypes leading to profoundly different subjective outcomes,
I find that to be just one of the most important areas that one could even think about, let alone work on.
Thank you, I appreciate the compliment.
I will also say, like everything we're finding, it's not all about only serotonin 1B,
but that's, as you know, there are, again, pointing to the amazing and powerful complexity of the human brain or the mammalian brain.

There are 16 different serotonin parking spots or receptors that are distributed in different brain areas in complex ways,
and so that's daunting, but it also offers possibilities for developing very novel therapeutic agents that activate or inhibit these in complex ways, hopefully for therapeutic benefit.
So before we conclude, I'm very curious to get your opinion on what you see as the landscape of the work on psychedelics and MDMA,
which isn't really a classic psychedelic, but all these drugs that, as you pointed out during your youth, were used recreationally
and for mind exploration and expansion and are now being probed as potential therapeutics for various mental health challenges,
as well as potentially expanding consciousness, empathy, and all of that.
I mean, not getting into the details of the legal issues that have to be overcome,
not even necessarily talking about the clinical trials or the people doing the work in different laboratories,
but just have to imagine this must amuse, tickle, surprise you.
I mean, how do you feel about what you're seeing now?
Because it is a very exciting time for these compounds.
It tickles me and excites me with the appropriate caution.
So I do think drugs are very powerful probes of brain function.
I think this class of drug, which as you correctly pointed out, people use the term psychedelics scientifically
when pursuing their understanding, their therapeutic potential, their mechanism of action.
It's more useful to divide them up into different categories.
The classic hallucinogens, which are LSD and psilocybin.
The intact or empathogens, which is MDMA, which is really a qualitatively different drug.
There are other substances, which we don't have time to talk about like Ibogaine and ayahuasca, which are very complex and peyote.
But nevertheless, I am tickled and excited as a child of the 60s and 70s,
but I am also not evangelical about their use and their therapeutic potential.
So as you can imagine what I'm going to say, I think they should be the subject of rigorous, sophisticated,
and most importantly, ethical research.
I think we could learn a lot about how the brain works and its amazing capabilities.
I think they may, notice I say may, have therapeutic potential,
but I do not think they're going to be miracle cures.
And I do worry as somebody who lived through the 60s and 70s and watched because of the leery, the history with Timothy Leary and his colleagues and the political landscape of how they were being used and promoted.
I am cautious that these substances need to be studied scientifically and rigorously.
And I hope that's the case.
And I want to caution your audience that not everybody should take these substances.
They are not miracle cures.
And while they certainly may be a benefit to certain individuals who are suffering and they certainly

may provide unusual and in quotes,
mystical experiences for certain individuals,
I am very concerned that there are individuals out there that will gain access to these substances and have very bad experiences.
Because anybody who grew up in the 60s and 70s knows all about bad trips and truth be told,
I have had a bad trip or two in the 70s.
And I'm glad I did because it made me,
I have no idea what a suicidal depression feels like where you are experiencing such a darkness, such a lack of hope that a rational decision is to end one's life.
And I think the closest I ever came to that experience is a bad trip on LSD.
And I do have concerns that if you look at the clinical trials that have been done,
the well could done, not the anecdotal.
I went and saw some psychedelic therapists that a friend recommended and it did wonders for me.
But the well controlled clinical trials that are being done by certain biotechs,
some academic institutions, they have very strict what are known as inclusionary and exclusionary criteria
about who is allowed to participate in the subject and may rule out a lot of people.
So I don't mean to be overly cautious, but I do worry that if some people take these substances and bad things happen,
it will slow down the excitement that's currently happening and it will make it more difficult for serious human subjects,
researchers, preclinical researchers to study these substances in the way they deserve to be studied.
So I hope that articulates my viewpoint.
I think it does and thank you for that viewpoint.
It's an important counterbalance on a lot of the excitement that we hear about these days.
I think the state of Kentucky just recently decided to give $42 million from the opioid lawsuit settlement
with Purdue Pharmaceuticals to the study of Ibogaine.
So there's a lot happening here.
Just to be clear, I think there's no problem with that.
And I actually would support that as long as the studies of Ibogaine are done thoughtfully, carefully, and ethically.
I see no problem with testing its efficacy in certain mental illnesses and addiction.
And it's actually a topic I know a little bit about that we'll save that for another time.
Well, first off, I want to thank you for coming here and sharing your knowledge with all of us.
For me, it's been a real thrill.
And I also just want to thank you for the incredible amount of work that you've done over the years.
I know it's still ongoing here by no means retiring.
I certainly hope not, but I'm sure the listeners have now a clear picture of the enormous number of contributions and errors
that we've worked everywhere from, as I mentioned earlier, neuroplasticity at the cellular level, molecular level, addiction,
work relating to social cognition and social interactions rather as it pertains to autism models and

now psychedelics
and empathy and on and on and again trained so many prominent scientists in our field.
And to take time out of your schedule to come sit here with us and share some of that knowledge and stimulate our thinking.
And as you mentioned, raise still more questions that need to be resolved is a real privilege.
So thank you ever so much.
And indeed, as you just mentioned, we'd love to have you back again for all I can say is I want to thank you for having me.
I was a little hesitant or nervous about coming here and now I want to come back.
So that was a blast when I just did with you and I'd be happy to continue this conversation anytime.
So thank you for your very sophisticated and thoughtful questions to be continued to be continued.
Thank you for joining me for today's discussion all about neuroplasticity, reward systems, social connection and empathy with Dr. Robert Malenka.
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Thank you once again for joining me for today's discussion with Dr. Robert Malenka.
And last but certainly not least, thank you for your interest in science.