This episode is brought to you by House of Macadamia's Delicious and Nutritious Nuts.
Holy hell folks, I tell you, these things aren't delicious, I've been gobbling them all day.
Anyway, I love macadamia nuts and have been enjoying them often since keto expert Dr. Dominic Agostino recommended them way back on the podcast in 2015.
They taste great and they have more healthy, mono-unsaturated fat than both olive oil and avocados.
27% fewer grams of carbs than almonds and more than 50% fewer grams of carbs than cashews.
They're the perfect, low-carb, keto-friendly, nutty snack.
In fact, I just ate a handful of lightly white chocolate dusted, dare I say.
Macadamia's about an hour ago to keep me going through the afternoon until dinner.
It is the perfect snack for me.
And I will say this, House of Macadamia's produces the best tasting macadamia nuts I've ever eaten that I've ever had by far.
That's due, in part, to their location in the Mupumulanga province of South Africa,
which provides the ideal temperature, altitude, soil composition, rainwater, and pristine mountain water for growing, you guessed it, macadamia's.
House of Macadamia's have partnered with the largest macadamia producer in the world, comprising 94 independent farmers in South Africa,
which gets them first pick of the highest quality macadamia nuts in the region to make their one-of-a-kind snacks,
like their vegan, paleo, and keto-friendly chocolate-dipped macadamia's.
They really took their time to get all of this right, and they've done more than two years of flavor testing,
and you can taste that in each packet you consume, and I've had two of those today.
And now, listeners of the Tim Ferriss Show, that's you guys, can use code TIM20, that's T-I-M-2-0 altogether,
to get 20% off of all orders in a free box of their best-selling Namibian sea-salted macadamia nuts.
That's a mouthful, and you want a mouthful.
They are worth $35, and you get them for free.
If these are not the best macadamia nuts you've ever eaten,
House of Macadamias will give you a full 100% refund guaranteed.
So just visit HouseOfMacadamias, that's plural,
HouseOfMacadamias.com slash Tim, to discover some of the most delicious and nutritious nuts on the planet.
That's HouseOfMacadamias.com slash Tim, code TIM20.
One more time, HouseOfMacadamias.com slash Tim, and use code TIM20.
This episode is brought to you by Eight Sleep.
Temperature is one of the main causes of poor sleep, and heat is my personal nemesis.
I've suffered for decades, tossing and turning, throwing blankets off, pulling the back on,
putting one leg on top, and repeating all of that ad nauseam.
But now I am falling asleep in record time.
Why? Because I'm using a device that was recommended to me by friends called the Pod Cover by Eight Sleep.
The Pod Cover fits on any mattress, and allows you to adjust the temperature of your sleeping

environment,
providing the optimal temperature that gets you the best night's sleep.
With the Pod Cover's dual zone temperature control, you and your partner can set your sides of the bed to as cool as 55 degrees,
or as hot as 110 degrees.
I think generally in my experience, my partners prefer the high side, and I like to sleep very, very cool.
So stop fighting, this helps.
Based on your biometrics, environment, and sleep stages, the Pod Cover makes temperature adjustments throughout the night
that limit wake-ups and increase your percentage of deep sleep.
In addition to its best-in-class temperature regulation, the Pod Cover sensors also track your health and sleep metrics
without the need to use a wearable.
So go to eightsleep.com slash Tim.
All spelled out, eightsleep.com slash Tim, and save $250 on the Eight Sleep Pod Cover.
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Eight Sleep currently ships within the U.S., Canada, and the U.K., select countries in the E.U. and Australia.
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Hello, boys and girls, ladies and germs.
This is Tim Ferriss.
Welcome to another episode of the Tim Ferriss Show, where it is my job every episode to interview and deconstruct
world-class performers from all different disciplines.
That could be business, it could be military.
In this case, it is science.
And my guest today is Nora D. Volkov M.D.
Dr. Volkov is director of the National Institute on Drug Abuse,
often abbreviated to NIDA at the National Institutes of Health.
NIDA is the world's largest funder of scientific research on the health aspects of drug use and addiction.
Dr. Volkov's work has been instrumental in demonstrating that drug addiction is, in fact, a brain disorder.
As a research psychiatrist, Dr. Volkov pioneered the use of brain imaging to investigate how substance use affects brain functions.
And there are many stories we dig into there.
In particular, her studies have documented how changes in the dopamine system affect the functions of brain regions
involved with reward and self-control in addiction.
She has also made important contributions to the neurobiology of obesity, ADHD, and aging.
Dr. Volkov is fascinating.
Her life story is beyond wild.

And we get into that pretty early in the conversation.
She has overcome a lot.
We examine the influences that have helped to shape her thinking, the philosophies that have helped to shape her thinking,
the philosophies that have helped to guide her.
We hone in on the tenacity that has helped her to arrive where she is today.
And much, much more, you can find NIDA online at NIDA.nih.gov.
That's N-I-D-A.nih.gov.
You can find them on Twitter at NIDA News and on Facebook, NIDA-N-I-H.
So without further ado, please enjoy this very wide-ranging conversation with none other than Nora de Volkov, MD.
Dr. Volkov, it is lovely to see you.
Thank you for making the time to be on the show.
Thanks for being here.
Team, it's a pleasure.
Thanks for having me.
Absolutely.
And I wanted to say, before we launch into the full conversation, a sincere thanks to you and the entire NIDA team,
because I have found addiction to be very near and dear to me in the sense that my uncle died of alcohol-induced cardiomyopathy.
One of my aunts died of alcohol and percocet as an overdose.
One of my best friends growing up died of a fentanyl overdose.
So this is a subject that I think, not surprisingly to anyone listening, is incredibly important.
And I've just had the opportunity to see it in very close quarters.
So I wanted to start with just thanking you for doing the work that you do.
So that's step number one.
And I thought then I would take a very hard left turn and ask you about cadavers.
Specifically, I read that you, when you were quite young, asked your father if you could bring a cadaver home to disact.
His answer was yes.
And that his answer was generally yes to anything science related.
Could you just flesh this story out a little bit, provide a little more context?
Absolutely.
And first of all, I'm sorry for the loss of your family, relatives, and your friend.
I mean, it is very tragic.
And that's why, I mean, I'm so devoted to the whole subject because it shouldn't be.
I mean, people shouldn't be dying from addictions.
And, and yet they do.
And there are many factors that if we could change, then we wouldn't be losing these lives.
So then let me jump into the question that you call left side or right side.
My father is a scientist.
And so he was obsessed of having his daughters.

He didn't have a son.
So he was obsessed of having the daughters go into science.
And I was the one that I have another sister who was then in high school, but I was the one in medical school.
I wanted to do research and I was absolutely fascinated by the human body and anatomy.
And I just marvel about the beauty of how our bodies are constructed.
So in the classes, we have to take anatomy and we had to dissect a basically the section on people who have died on corpses, but I didn't have enough time.
And I wanted, I'm very obsessive.
Whenever I do things, I do them compulsively.
So I wanted to be able to do that right.
And based on the time limits that we have at school, it was going to be impossible.
We would be able to each one of us dissect, for example, one extremity.
And so I asked my father if I could bring a corpse that I could do autopsy and my father had a laboratory in the house.
He said, yes, but then my mother and my sister's a rebel.
And I said, if Nora brings a corpse into the house for her anatomy classes, then we're leaving the house.
That was very categorical.
I lost.
That's it. No more.
So I'm going to come back to the obsessive focus and following the trail where it leads.
I'm going to come back to that.
But before I do, perhaps you could just describe where you grew up, where you were at the time and how someone or a family with the last name Volkov, which to most people would perhaps bring up connotations of certain types of origins, end up in where you ended up in terms of your formative years.
I was born in Mexico City.
I went to medical school in Mexico City, and it was until I was finishing medical school that I left Mexico to go to Paris, then to the jungle, and then I went to New York for my training in psychiatry.
And the reason why actually I ultimately was born in Mexico City is interesting.
It's driven by, I always say, the belligerent nature of men, because my father is the grandson of Leon Trotsky, and the only place that gave political asylum to Leon Trotsky was Mexico.
And my mother, who was born in Madrid, ended up in Mexico because also Mexico was the place that gave asylum to the children of the people that were fighting against Franco in Madrid.
So Madrid was going to be bombarded by the Franco forces, so the government of Mexico, in an attempt to save those children, offered asylum to the children to be brought from Madrid into Mexico at the care of the Mexican government.
And so that's how the two families came together. My father came to Mexico as an orphan because, and Trotsky basically had taken the responsibility of him.
His mother had committed suicide. His father had been sent to a concentration camp by Stalin, and so the only relative that he had was Trotsky.
So he came to Mexico because that was his family. And he was 12 years old when he came to

Mexico, and that's how he ended up in Mexico.
My mother came to Mexico when she was 18 years of age, coming with her family to look for her two brothers who had come and his little children as part of the asylum to the children that were in Madrid.
That's how fortuitous history is. They met, they fell in love, and then they had four daughters, and I was the second one of them.
And we actually lived in the house where Trotsky had been killed because my father took the responsibility to ensure that the house where Trotsky lived will be left as a museum so that there would be a historical memory of what tyranny can do,
the tyranny of Stalin and basically the extermination of all of his enemies, which of course Trotsky was one of his main ones.
And he had basically aimed to destroy the family of Trotsky up to the third generation, which would have ended with my father.
But it would have ended with us actually, the third generation is us.
And they tried to kill my father, and my father was a little child, but they didn't succeed.
Then by my time I was born, which is the third generation.
No one has tried to kill me, fortunately, not from the Stalin era, but I shouldn't be so flippant about it.
I mean, it's a very serious issue.
And of course it has followed our family.
And at one point when I was a medical student, I wanted to go to Russia to study and I was given a scholarship and my father really freaked out.
And at that point is when I was basically made aware and said, Nora, you cannot do that.
You're also going to be putting your father in a very awkward position because he can be blackmailed.
And there is this curse that Stalin had said that he would persecute up to the third generation.
And that's how I ended up in Mexico City where I went to school and until I did my training in psychiatry.
So I would love to expand on this just a little bit for people who may not recognize the name Leon Trotsky.
So number one, we won't go into a huge Wikipedia page on Leon Trotsky, but people should read the basics and find him online.
Very historically notable, very important, as you mentioned, as opposition of sorts with respect to some very powerful figures in Soviet history.
And he also, based on my reading, please correct me if I'm wrong, but survived multiple assassination attempts and then was finally killed,
but not immediately by someone with an ice axe that penetrated his head by something like seven centimeters,
but still managed to subdue with his guards the attacker.
And he just seems like such a force of nature and such a powerful figure to begin with.
So to have that in your lineage, I would just be so curious to know how all of that has informed, if you feel like it has, the way you relate to the world
or even think about history or voicing your own opinion, anything like that.

There's no way it doesn't influence you and be aware that that's a little girl that was living in that house.
And so I was surrounded by not just the knowledge that it was my father's grandfather and I had until I was seven, eight years old.
I also, his second wife was living in the house, Natalia, who became a very dear person to me.
So when you are born into a house where you know that you have a relative that did something that was very motivated towards improving the next generations,
the chances that next generations had that they were committed to a more just and fair society,
that is ingrained into your brain and both my parents were very systematic as making us aware that we do have a responsibility
that each one of us as an individual should be recognized that we are part of a social system where how you act has consequences
and that your acts can actually significantly improve or negatively affect the life of others.
So we, all of us, my three sisters and I have that very much ingrained into our motivation and how we live our lives.
And so for me, that has been crucial.
So I become very, I mean, particularly, and this is something I've always had, I very sensitive to people the most vulnerable.
I mean, it just generates this drive and trying to help a very intolerant of injustices I've always been.
And so it drives me crazy.
It activates my amygdala when I see someone improperly treated.
And obviously, as you grow up, you find yourselves in positions where you say, what can I do to help?
And that has ultimately led me to take this position of director of the National Institute on Drug Abuse,
because I realized that it would put me in a leadership position where I could influence the knowledge that was derived
in order to affect policies that would lead to a better opportunity for people suffering from substance use disorder.
That's fundamental to me.
And that came from my historical background and upbringing.
What did your father feel the role or responsibility of scientists was?
I'm wondering, I suppose, why he said yes to most things or all things science related.
Maybe he said yes to most things for you.
I have no idea.
But if it happened to be pretty specific to science, why did he do that?
Why was it important in his mind?
I think a lot about it because my father, you know, when we were growing up, he would never ever speak about Trotsky.
And we were not allowed to ask questions because it was felt that it was just too painful for him to speak up.
And the first time he did an interview about his experience with Trotsky was when I was, I think I must have been 17 years of age or 16 years of age.

My father was a turning point for him where he started to speak about it.
And I think my father, an extraordinary individual, I mean, with an amazing resilience, was using certain mechanisms to try to deal with the suffering.
I mean, his mother committed suicide when he was living with her.
I mean, he lost his father to a concentration camp.
Once there was left behind in Russia because Stalin did not allow his mother to take, basically only allowed him to take one of the two children.
And so the mother selected the one that was younger, which was my father.
And then when he loses the mother, he goes and lives with an uncle and the uncle is killed by Stalin while in Paris.
And then he ends up with Trotsky and Trotsky is assassinated.
And basically my father is coming into the house when Merkader, who's the killer, is inside and he hears him.
Don't let Sieva, which is the name of my father, see me.
So he has the clarity of mind to recognize he doesn't want my father to see him all covered in blood.
So if you think about what it must mean for a child to go these, all of these experiences.
I think you have to develop a mechanism of protection.
And in that respect, my view is that science provides it because science tends to be very black and white.
I mean, it's not really black and white.
I mean, the physical sciences, mathematical sciences are black and white.
Biology is more graded, but you can extract objective information that is reproducible.
And I think that gives you a sense of solidity.
And I think that this may be one of the reasons why my father was so attracted to science.
And what I can tell you, he was very categorical.
He did not want any one of his daughters to go into politics.
He was black and white, no politics.
And his perspective was that the family already had paid a very, very big price of politics.
And so he really didn't want to.
So in that respect, of course, science offered this ideal profession where people were driven by looking and trying to understand the truth of things in objective ways,
where there was not that subjective element where things can creep in and rapidly be influenced by one person's perspective.
This is me speculating about why my father was so driven into the science.
It may just be that he loved science because it's a fantastic field.
Science is basically moving your curiosity to try to understand the world and they pay you for it.
So I am making a speculative leap because I have thought about it like to sort of ask me.
But at the same time, I have to recognize that it may also just be that he loved science because he's a curious, very curious person.
I'd love to look at other influences in your thinking and trajectory.
And the name I would like to invoke is Julian Villarreal.
And I did check the pronunciation before we started for people wondering.
And I would love to know who this person was and what influence he had on you, if you could

describe.
Jano Julian was a pharmacologist that was working in a pharmaceutical company.
And he was a physician and a PhD in pharmacology who had gone to Michigan University for his PhD.
I ended up with him because as a medical student, I knew I wanted to do research.
And so I started to volunteer with actually one of the major scientists in Mexico,
Tamayo, who was doing work on autopsies and tissue pathologists.
He was a pathologist.
And he said, Nora, you like behavior, you like drugs, you like the brain.
Let me introduce you to someone that will basically have better background than mine.
And so he introduced me to Julian Villarreal.
And immediately I hit it off with Julian.
And what intrigued me so much about Julian was that he thought outside the box completely.
And that resonated totally with me.
And he was interested at that time.
His research was on trying to understand what were the mechanisms that account for the tolerance to opioids
and the mechanisms that account for the withdrawal that emerges when someone becomes physically dependent to opioids.
And his idea was that if you have these models and you could understand them,
then you would be able to develop an opioid medication that would not be addictive,
that would not produce tolerance, that would not produce withdrawal.
Many pharmacologists went into that whole field.
And certainly what I can tell you as of now,
no one has succeeded on getting an opioid medication that is not addictive
and that doesn't produce tolerance or withdrawal.
But the models that he was using and the way that he was challenging me,
which was very, very quantitative,
he was always trying to figure out a way of quantifying behavior in animals
that then could be used to predict the responses to drugs.
How did Julian encourage you to think differently?
Well, he was introducing me to a lot of the analytical methods to be able to define variables.
I mean, I realized this was very much before its time.
Right now, for example, a lot of the analysis that we do employ vectors,
as a means to actually describe a trajectory of something more than one point.
And he was introducing me to those technologies and says,
Nora, learn about it.
And he would give me books so that you can try to see how you apply them
to the measures you are taking on the animal experiments.
So he opened in my brain the whole curiosity of using quantitative analysis
in ways beyond the traditional, very simplistic statistical methods that we use.
And this is something that now is fundamental for the type of work that we are doing
in many fields of science.

But for me, as someone that is in neurosciences and neuroimaging,
it is crucial to basically enable us to understand and to actually integrate databases
that are very, very diverse and distinct.
So that I owe to Julian.
I mean, he would challenge me.
He would basically give me questions that would make me think.
That's what I like.
And I actually, he taught me that.
And this is something that I, as a mentor now of young scientists,
I basically want, I put them in positions where I force them to think and to think differently.
And I mean, for example, you have students and postdocs and they present me the data
and I asked them, well, what do you make of it?
And they give me an explanation and I said, OK, now I want you to give me the most outrageous explanation that you can get of these data in order to force them to think differently.
Because there is a predictive element in a lot of the things that is a reflection
of the influence of others.
And I want that innovative way, that association that others have not done.
I want to encourage them to play with it.
Right.
Because as a mentor, especially a mentor who is highly respected by your mentees
or postdocs or whatever it might be.
It would be very easy to correct them and perhaps in some respects force your perspective on them.
But that doesn't help them develop the muscle of thinking differently in the way that you're describing
by asking those types of probing questions, which makes all the sense in the world.
Yeah, but there's also a selfish component into it.
I think that for me is totally uninteresting to hear a response that I already would have thought myself.
And I think that brains work better when you expose them to unexpected stimuli.
I think that the scientific creativity is enriched by playing with ideas and concepts.
And I encourage it a lot.
And so we have team meetings where I really probe them for people to get into those spaces.
And so it's crucial that you empower them.
You make them feel confident because otherwise people don't dare.
They feel intimidated that they may say some things that others will think it's stupid.
And that's so very common when you are in groups.
People don't want to be seen as saying something that will make them feel embarrassed.
And to me, I always actually start meetings and says, look, guys, we're here to basically push the limit.
So please do not feel embarrassed.
If you don't speak up, we'll never have an opportunity to understand whether where that idea may go through.
So it's something I always push, whether it is with people are my mentors or I'm organizing it with

experts.
I do like to get that going.
You have a well-established history, I would say, of pushing the limits and knowing when to push.
So I would like to just read something I found from the Washington Post.
It's just a few paragraphs and then I'll ask a question related to it.
In 1984, she, that is you, left NYU for an assistant professorship at the University of Texas Health Science Center at Houston,
expecting to continue her research.
And then they're quoting you.
They had a fantastic imaging center.
Volkoff recalls, but as it happens, quote, there wasn't a single schizophrenic in the university hospital.
End quote.
What the hospital did have was cocaine addicts.
So you adapted.
And I'll summarize a little bit here or just abbreviate, but you said,
I was probably the first person to use these new technologies for the investigation of drugs of abuse, she says.
But her work was ignored initially, especially her seminal paper documenting strokes in the brains of cocaine abusers.
And then this is a quote of you.
I started to present these data at meetings and people didn't believe it because there was no evidence that cocaine was toxic.
She says, that's fine.
I said, because this is what the data show.
She applied for a grant from NIDA.
Of course, everything comes full circle, but she applied for a grant from NIDA to pursue her research and was turned down.
It took three years before the British Journal of Psychiatry finally published her paper.
And then the closing quote from you in this section is, this is what happens when you come up with things before their time.
And my question for you is, what was the experience like?
And what was your inner talk like going through this sequence of events?
And having people dismiss, having people reject over that period of time.
What was that like for you?
And how did you keep going?
Well, I'm a very persevering person and I never give up.
So my perspective is on this issue has always been like that.
And that finding actually, I still working on that to try to understand how cocaine affects and producing these strokes and how we can prevent them and how we can help people.
But at that time I was very young.
And I, you know, you have this sense of you trust the system and you believe, well, maybe I'm not good enough and haven't consolidated the belief in yourself because you are basically recently

trained.
You are using, no one had used that technology.
So at that point, there was this belief that cocaine was safe.
So here comes this person showing these data on images that others had never seen and with the background that cocaine was at that time felt to be safe.
And I submitted it to the New England Journal of Medicine, which is the most important medical journal, clinical medical journal.
They review it and they came back again saying, well, there's really no evidence that cocaine can be damaging to the blood vessels.
They were completely wrong.
And now it's clear.
I mean, all of that is history.
No one will question that cocaine as well as other stimulant drugs produces vascular damage and pathology.
But it is the way that science goes.
And you sort of say science should be guided by data, but science has a religious nature to it also.
And once a model is created, it becomes very difficult to change it.
So and it takes a long, long time for concepts that have been consolidated as accepted as the truth to be questioned.
And I see it.
I mean, it happened to me there, but I see it constantly.
And that statement that I stated there is very, very valid.
If you come up with something that it's ahead of its time, you're going to have trouble getting it accepted.
And you may not actually necessarily be recognized for it when it becomes everyday life.
Then I'll be upset.
Well, what's the big deal?
That's in the nature of the scientific progress.
As someone that is directing and allocating resources for science, I am very sensitive to ensure that if there are situations where there may be something that is very innovative that others are not seeing, that we don't curtail it.
So I tend to, in many instances, say, OK, let's give it the benefit of the doubt, because if it is correct, it's going to be much more transformative than if we just continue doing science that follows the rules of the game very, very precisely,
where basically what you are expecting you've already seen.
So I do think that we need to push the limits with open access to scientific databases.
This is happening more and more, which is very exciting.
Just a quick thanks to one of our sponsors and we'll be right back to the show.
This episode is brought to you by AG1 by Athletic Greens.
I get asked all the time what I would take if I could only take one supplement.
The answer is invariably AG1.
I view it as my all in one nutritional insurance.
I recommended it long ago in my 2010 number one New York Times bestseller, the 4-hour body, and

I did not get paid to do so.
With approximately 75 vitamins, minerals, and whole food-sourced ingredients, you'd be very hard-pressed to find a more nutrient-dense formula on the market.
It has a multi-vitamin, a multi-mineral greens complex, probiotics and prebiotics for gut health, an immune support formula, digestive enzymes, and adaptogens.
AG1 makes it easy to get a lot of nutrition when good whole foods simply aren't at hand or when you just want to ensure you are covering your bases.
AG1 is the ultimate all-in-one nutritional supplement bundle in one easy scoop.
And Athletic Greens is giving you a free one-year supply of vitamin D and five free travel packs with your first subscription purchase.
Go to athleticgreens.com slash Tim. You can check it out.
Athleticgreens.com slash Tim. They also offer a 90-day money-back guarantee.
If you are not 100% satisfied, learn more, try it out.
Athleticgreens.com slash Tim.
Now, as you mentioned, you have perseverance as a superpower.
It is just a statement of reality that you don't stop.
And some people may not have that constitutionally when you are mentoring or having conversations with, say, younger scientists who are facing their first pushback.
They're getting rejected. They're having to try again and again.
Maybe they're feeling demoralized. What do you say to them?
I say, you know, this happened to me. I mean, my first grant was basically just red-lined, totally and absolutely.
And I was very depressed. And at that time, actually, people in the institute at NIDA said, Nora, try again.
And I was in that respect. And again, I do not take no for an answer.
Because sort of like, and this is a message that I say to young people, you should dare to do things.
And no one has the right to say you cannot bring a new perspective into things.
And so I always say, be daring and persevere with all of my postdoc students.
They get rejected on a paper. They get rejected on a grant.
I mean, the answer is just stand up and jump back on the horse.
I mean, it's just like as simple as that.
And for those who aren't watching any video, you are very tough.
You're very physically fit. You're very mentally fit and you walk the walk.
So I want to just give people further evidence that you very much walk that walk.
And I'm going to segue now to perhaps a discussion of the difference between studying compounds and experiencing compounds.
And I was hoping you could tell the story of how you became acquainted with demoral.
It's interesting, you know, because I love demoral.
I probably shouldn't be saying these things.
But what happened to me, I was in a horrible car accident.
I was the passenger and there was one of those hits that the car, it was, I see the car does a 90 degree flip.
And the car in the opposite direction comes in and strikes me in the passenger seat.

Seeing the car coming to me, I did not want my brain to be hit by a car.
And so I said, OK, I put my foot into the car to protect my head and to get my head as far away as I could from the door because I saw it coming.
And so I did not get hit in the head, fortunately, but the door came crashing and I was trapped.
My leg was trapped, it was broken.
I was under a lot of pain and I wanted to lose consciousness because the pain was so intense.
And so they finally, they had to come up with this just of life to open up the door because they couldn't get me.
They get me into the ambulance, take me to the hospital.
And there the doctor says, Nora, we have to try to move the fracture so that we can accelerate the healing.
So otherwise we're going to have to go for surgery.
So we're going to give you demoral.
And they injected me with demoral and it was extraordinary.
I mean, it was not just the intensity of the suffering was disappearing.
Everything was fascinating.
And I hope it makes you sleepy.
And I was forcing myself not to sleep because everything was so extraordinary.
And so it gave me an insight of how powerful that drug was that despite everything that was there, I wanted to be aware of every sensation.
And they admitted me to the hospital and I had to spend there three two nights and three days.
And I recall I was in the terrible pain and they would give me the demoral and it was this sense of well-being extraordinary sense of well-being from the opioid.
And that is the only time I really that I've had a real ability to have a consciousness of how an opioid makes you feel.
And so when they discharged me, they discharged me on Monday.
The accident was on Friday.
I was waiting on the car and I felt all chemical.
Everything felt very unreal.
And the doctor had sent me home with two weeks of medication for the pain and I stopped called Turkey.
And behold, I did have withdrawal over the night and it was so bad.
I didn't understand at first what was happening.
I was restless.
It was worse than pain.
And that's sometimes you need to experience these things to understand that you say what can be worse than pain?
It was just I could not be comfortable no matter what.
So I took one of the pills that he had given me and that was the last I took.
And then the physical dependence that was responsible for that withdrawal disappear.
And that's it.
That's my story with opioids, which made me very aware that I do not want to be exposed to opioids unless I have horrible pain.

Because I can see their allure.
I can see how someone who'd easily fall into that nirvana, that chemical nirvana that they create.
And that's the story of that demiral.
And that's why I say I did.
I have to be honest.
It was an extraordinary experience for me to have been able to feel what it was, but it was also a very scary one.
Super scary.
I had nothing nearly that severe, but I had a terrible shoulder injury that ended up requiring reconstruction.
But in the emergency room when I ended up in the hospital, they were overbooked understaffed.
They had gunshot victims and so on who took precedence, of course.
So I was sitting there with my arm dislocated, sort of sticking out of my chest for hours.
And they gave me morphine.
And I remember thinking two things.
The first was this is incredible.
The number two was I should never, ever touch anything like this again.
And so after my surgery, when they sent me home and they gave me Vicodin and this, that and the other thing, they gave me a whole collection of different painkillers.
And fortunately, some of them I took for just a few days and they made me nauseous.
And I was very happy that they made me nauseous because it made me less likely to use them.
But I do have a, I suppose, a firsthand acquired fear and then a developed fear just from the experience of people in my family and my friends.
What is the current state?
How should people think about the current state of addiction and overdose crises in the U.S.?
It's unfortunate.
I wish it were different, but it is really a state of very severe overdose deaths that are very difficult to control and regulate.
And what we are observing is that we are seeing more and more people die with very diverse demographics from overdoses, which again makes it so very hard to control.
Because at the beginning, the crisis started because we started to over prescribe opioid medications and people diverted them.
And people also who should have not been given them because they didn't have severe pain syndromes became addicted.
And that opened up the door for heroin.
And then we started to see a rise in 2011, more or less of heroin injection and people dying.
And then in 2016, there was a transformative, very malignant change, which was the introduction of fentanyl.
And fentanyl, we all been hearing about it in the news, is a synthetic opioid that was developed in order to have a more potent analgesic, is widely utilized in medicine for breakthrough pain for cancer patients.
For example, when the medications that they have no longer controls the pain, you can use fentanyl.
But it's also widely used by anesthesiologists because when you combine fentanyl with an anesthetic,

you actually can control and regulate much better the level of consciousness of your patients.
So it's a very useful drug.
But it is by its potency, it is highly, highly addictive.
It's also highly dangerous because of its potency.
It can make you stop breathing very, very rapidly.
And it's a drug that is very cheap to manufacture.
You don't need to cultivate any plant.
You synthesize it and the synthesis is very simple.
And because it's so potent, you need a 50 time less volume of drugs so you can bring it through the borders much more easily than with heroin or any other drug that we know of.
And so it has both pharmacological effects that make it dangerous, but also the production makes it actually very enticing for the drug dealers.
So they are incentivized to distribute it.
And that's what we've seen.
Accelerated during the COVID pandemic, basically fentanyl permeated all of the country everywhere.
And so they started to also mix it with other drugs like cocaine or methamphetamine.
And now more recently with counterfeit pills that are so like Adderall, which is an amphetamine, or like Ativan, which is a benzodiazepine that you use for anxiety or sleep.
Or even these guys as Vicodin, which is an opioid medication for pain.
They go and buy it on the web and they are less expensive than the real thing.
So it's not just that people that are addicted to opioids can overdose.
Now those that are taking cocaine can overdose.
Those that can take methamphetamine can overdose.
And students that may buy a pill in order to study for an exam may overdose and die because the pill they got had fentanyl.
Or a person cannot get their physicians to prescribe them a sleep medicine.
They go and buy it on the web and they overdose.
So this is the nature of the major challenges that we have.
And we're seeing more and more new substances emerging, which is like, again, running in a treadmill because we develop antidotes for the overdoses from fentanyl.
But now they are mixing fentanyl with an anesthetic that is using veterinary medicine, silasin.
And that actually, silasin does not respond to Narcan, which is the antidote that we use for fentanyl.
So this shifting nature of the drugs that people are exposed to, the fact that they are increasingly more potent.
And the fact that they are basically disguised in many ways is expanding the number of people that are now overdosing.
In some instances, we don't have good strategies that we can use to help them to revert those overdoses.
It's such a complex, evolving ecosystem of compounds.
And as you mentioned, there are so many incidental or accidental ways to ingest, for example, fentanyl.
And I know of many direct stories where people have gone to a bachelor party, they try a little bit of

some drug that ends up being cut with fentanyl.
I know of two people specifically, one just dropped dead on the floor, one fell into a coma from what would have been considered low doses of illicit drugs.
But they happen to be cut with fentanyl, which is horrifying.
And in fact, my friend who died was not himself an addict.
He was collateral damage.
One of my other friends I grew up with, there are a lot of drug issues where I grew up, was a heroin addict.
He had developed just an incredible tolerance to fentanyl, and he gave it to my other friend to help with his hangover.
And my other friend had never used any opiates, and he fell asleep and just never woke up.
So the sheer ease with which the fentanyl, as you mentioned, sort of permeates different corners and neighbourhoods of society,
which does not discriminate, or I shouldn't say it doesn't discriminate, but it has infiltrated every socioeconomic class.
It's really pervasive and really terrifying.
What is your perspective on the war on drugs and perhaps any other approaches that you think may be more effective?
I'll answer it, but that's actually the story that you just told of your friend.
That how he began taking fentanyl on benoing what it was, it just killed him.
And this is what we are observing a lot.
And I think it's important to educate people that this is a seriously dangerous drug.
And unfortunately, I think that we have cried wolf so many, many times that we've lost credibility.
But if there was a way that we could convey that in very objective, we don't need to exaggerate in any way.
I mean, fentanyl, its two milligrams will kill you.
And the counterfeit pills contain five milligrams, some of them, two doses to kill you.
So it is very, very tragic.
But coming back to your question in terms of the war on drugs,
I think that what it did was it created a mechanism that could perpetuate structural racism.
It is very tragic to see how its enforcement led to the incarceration of young black Americans.
And again, that punitive system where someone could be stopped,
and this will happen if you are black on the notion that you had drugs with you and thrown in jail or prison because you had drugs on you.
It's such an unfair system.
And it didn't work in any way because it did not reduce the amount of drugs that people were taking or the negative consequences to our society.
So it did not work.
And I think one of the aspects that it did show is if you do throw a person that's taking drugs in jail, if you criminalize that person that's using drugs like, for example, we did horribly with crack cocaine.
So if you were smoking crack cocaine, it was like, I don't recall exactly,
but it was at least 10 times greater penalty that if you were just snorting cocaine, snorting cocaine

or injecting cocaine hydrochloride,
it was much more favored by white people, whereas crack was favored by black people.
So cocaine hydrochloride white, crack cocaine black.
Why do you see such a difference?
It is the same cocaine.
Basically it's cocaine is cocaine.
And yet one called noted a much higher penalty than the other.
That's an example of the consequences.
But what science has shown is that when you do throw people into jail or prisons that have a problem with substance use disorders,
then when they leave, they are at much greater risk of, first of all, relapsing immediately into drug taking and escalating their drug taking.
So you are exacerbating the nature of the problem by putting them in jail and prison.
So it doesn't work no matter what you do.
And that's why the whole notion of criminalizing the person that takes drugs is basically very negative
vis-a-vis the outcomes of the person and also in no way the benefit society.
It is actually very costly by itself.
When an issue becomes politicized, then it becomes much harder to change and shift.
I think that we've seen over the past, I would say, certainly five or eight years, an openness to recognizing that the war on drugs did not work
and that criminalizing drug users is basically a negative and it's promoting structural racism.
So I'd like to cover quite a few things.
And I would like to get to harm reduction, but I'd like to do that a little bit later and to hear your perspectives on that.
First, I wanted to go from the problems that you've described to looking at pushing the limits, daring to do things,
some of the, perhaps, novel or developing potential approaches to treating addiction.
And there are several things I'd like to talk about.
Certainly you have recently, I want to say, written about TMS and deep brain stimulation.
I would like to talk about those.
First, I thought we might speak about psychedelics and psychedelic assisted therapy.
And I wanted to congratulate and thank you for being one of the first, if not the first,
institute director to fund psychedelic research with humans after the scientific winter following the Nixon administration,
which interestingly enough, at least I've read that some of the controlled substance act and Nixon's decisions around that were motivated
by controlling certain demographics or having the pretense of being able to search and seize and so on.
That was from, I think it was Ehrlichman in his, might not have been cabinet, but sort of inner circle.
But coming back to the treatment side of things, could you speak to perhaps what we know already about psychedelics as treatments?
What is interesting?

And what milestones, I think this is a question on a lot of minds and you're very qualified to speak to this.
What milestones still need to be reached to instill confidence in these drugs as therapeutics?
I think it's a very interesting, potentially promising area of therapeutics.
The way that I see it is the evidence that exists is very limited, but is sufficiently intriguing that you cannot ignore it.
And behooves you in terms of why we are identifying this as a priority area of research in the whole issue of psychotherapeutics,
of the use of psychedelic drugs.
The data is strongest for the use of psilocybin for depression.
Studies have shown and I think that even though the sample sizes are not very large,
they have consistently shown improved the outcomes on patients with terminal illnesses.
Most of them, I think if I recall correctly, were with cancer in whom the psilocybin allowed them to accept better emotionally
the fact that this was a terminal illness and improve their depression scores.
And that was quite significant.
There's also data showing potential for PTSD, the use of psychedelic drugs.
So these may be the two disease conditions for which there's more data.
The clinical trials are limited in sample sizes and in numbers, but the effect sizes are significant despite the small sample sizes.
There are some studies that have been done in substance use disorder.
Nicotine is one of them.
Alcohol use disorders, alcoholism is another one.
And again, both of them are on psilocybin and for both of them, there is also this positive effect.
And what's intriguing and speaking about it in terms of the nicotine is that the effects actually appear to be larger
than the ones that you see with medications that we use for the treatment of nicotine dependence, just like Chantix or nicotine replacement therapies.
So the number of people that stops smoking is actually significantly greater than that.
That is the percentage that stops smoking with medications that have been approved by the FDA.
But it's study number one, only one study and the sample sizes are small.
So that's why we're funding the researchers.
This is a group at Johns Hopkins University to actually replicate that study.
So the data is quite interesting, but it is very preliminary.
And I do want to emphasize this because sort of people like to make conclusions before the evidence is out there.
And my concern is that, and you already see it, you go into the web and there's a lot of sites advertising treatments with psychedelic drugs,
not just for mental illnesses, but also for well-being when the data is not there.
And so we don't know, first of all, we need to replicate.
But assume that you replicate and it does work.
What are the doses?
How to give it?

What are potential negative side effects?
I mean, what the clinical trials have reported is in a small number of people,
there is a risk of suicidal behaviors and suicidality.
So who is at risk to show that?
How do you actually, if you start to see it, how can you prevent it?
How should you administer the psychedelic drug?
It is believed that the psychedelic drug is adjunctive therapy,
that it is the interaction with the therapist while you are under the influence of the psychedelic drug, that it is therapeutic.
That's one of the hypotheses.
So how you should be administering?
How do psychotherapists get involved?
And all of these are scientific questions that we need to basically explore with research
because we don't have the data there that is needed to build up.
And if we don't build up and people start to use it and they start to have negative effects like suicides,
then that can lead to actually the jeopardizing the future use of these medications.
The FDA may say this is too dangerous or the DEA may say this is too dangerous.
We are not going to agree to its utilization.
And that is where the danger comes around of pushing something too preliminary.
I agree that certainly the positioning of psychedelics as panacea, which we see a lot,
is really putting the cart before the horse in a lot of ways.
And there are risks, which is why there are exclusionary criteria at places like Johns Hopkins
for certain conditions, whether it's schizophrenia or bipolar disorder or others.
And I'd love to chat a little bit about study design and what researchers might do
or consider to make their studies and grant applications more appealing to institutes like NIDA.
And the reason that I'd love to explore that a bit is many smart scientists are now paying attention to this,
including younger scientists who are considering this as a career focus.
And as it stands right now, there is a very small pool of serious independent philanthropists
or foundations who are providing funding.
It's very small.
I would say it may be in the 15 to 20 person range, really,
when we're looking at anyone donating above $100,000 a year.
It's very small.
And then on the other hand, you have...
And I think there's a role, certainly an important role for market-based for-profit solutions and providers,
but you have sponsored research on the other end of the spectrum.
And NIDA has been very forward-looking in the sense that you've provided funding to Dr. Matt Johnson
and so on at Hopkins looking at nicotine addiction.
I would love to know, and I'll just provide a little bit more thought.

I know this is going to be a very long question.
And then to get your thoughts on what people might do to make their applications or studies more appealing,
one of the challenges is certainly that is brought up oftentimes is blinding.
And these studies or these compounds and the experiences associated are really highly discriminable
in the sense that most people know they are either in the control group or not.
You have potential active placebo and people have experimented with niacin.
Some people have considered higher doses of, say, cannabinoids.
But it's difficult, it seems, to find look-alike drugs that do not also bring similar actions or effects.
Do you think there's a place for, say, comparative efficacy studies where you might have, by analogy, psychotherapy versus X, right?
The people who are getting psychotherapy are going to be aware they're getting psychotherapy,
but you could compare it with another therapy or you could compare psilocybin for, say, nicotine addiction to nicotine replacement therapy.
Those are just a couple of, I suppose, a bit of a connective tissue for people who may not have more context.
But what would you like scientists to pay attention to?
What would you implore them to try to do with their studies and designs if they want to try to get more federal funding?
There's no simple solutions, I mean, of how difficult it is to control for a placebo.
But it is an important one.
So one of the recommendations is to use a very low dose of the psychedelic drug.
So you are giving them the psychedelic drug, but a dose that is considered to be subtherapeutic.
And that's what some of the researchers are doing right now.
And to follow all of the guidelines and practices that you're going to be doing a randomized clinical trial,
which are the ones that you basically divide, participants some get the active intervention, others do not, and you randomize it.
And you follow them.
And that's the way that you actually collect data that then allows you to determine if there is a difference or not.
But I think that the grantees that are coming up with proposals are no these.
I mean, how to propose one of the randomized clinical trials.
One of the things that we work with grantees to which is important is that we help them in terms of the interactions with the FDA.
Because the FDA at the end of the day is the one that's going to be able to say what data do they need in order to be able to consider that a clinical trial is done in a way that they make it feel comfortable to approve an indication for a psychedelic drug or not.
So it is crucial that they work with the from the beginning as they are planning to do their clinical trial that they engage with the FDA and we absolutely help them.
I mean, we try to provide them support in if the FDA, for example, wants them to do toxicology X or toxicology Y or look at the bio distribution.

There are certain things that we can, through our contracts, help them obtain.
And we are specifically requesting this and I'm speaking right now of clinical trials, grantees.
There may be other scientific questions that are very valid that are not just a randomized clinical trial that we also would be very interested in funding.
For example, with brain imaging, you can now look at how and there was a paper.
There's one paper that actually look at the effects of psilocybin.
I think it was psilocybin, either LSD or psilocybin.
I don't recall.
And you're looking at we have these brain networks that interact with one another.
And what they showed was that that architecture of network was significantly disrupted during the hallucinations that when the drug was on board.
And so if you can do research that can identify biomarkers of the effects of the psychedelic drug, that's one area that we're interesting.
But also through those studies, can you understand the mechanisms that are responsible for the therapeutic benefits?
So by looking at how the brain changes its operations and then you can determine if that is associated with therapeutic benefit, you can start to understand mechanisms of actions of psychedelic drugs.
We're also funding researchers to develop.
We know what the psychedelic drugs that we currently have.
But with chemistry, you can create other psychedelic drugs, for example, that may have the same pharmacological target, but they don't produce hallucinatory experiences, which would make it much easier to actually implement.
So we are interested on a whole gamut of research that could help advance our understanding of the potential of psychedelic drugs for therapeutics.
The entire category of sort of non hallucinatory psychedelic compounds is very interesting.
I think there appear to be some very interesting indications that might be really favorable targets for these, what are sometimes called the cycloplastogens, like cluster headaches, in the case of LSD or LSD analogs.
What would you make and the answer could be that they're mistaken of researchers who report based on all the documentation from subjects in these various studies, whether at UCSF.
And I think the imaging that you were mentioning may be Robin Carhart Harris and his team, because they do a lot of functional MRI and imaging, looking at the perhaps increased entropy or connectivity or both communication-wise in the brain on these experiences.
In that case, it would be psilocybin or psilocybin.
And what would you make potentially of the importance of meaning making?
And that is to say, beyond the activity signature that you can track or the receptor affinity, the reports from subjects that it's the meaning making in these sessions, which seem to be in part, hand in hand with the hallucinations, the psychedelic experience,
relating to how they see themselves and the world that lead to the behavioral change and the durability of some of these effects, rather than dendritic spine growth or any number of changes that you can observe.
But given that the duration of some of these sessions is four to six hours, let's just say, and the half-

life is pretty short, but some of the effects seem to be quite durable with, say, the existential distress and terminal cancer patients,
and also for nicotine.
Is there a way to include those factors as an area of inquiry, in addition to the sort of mechanistic studies and the basic science and the imaging?
Of course.
And there's been actually papers that have done that that actually have looked at the association between the intensity of the subjective experience and their therapeutic benefits,
and then have shown that those that have the more intense mystical experience had the better therapeutic response.
But that element of meaning and understanding is basically not in any way exclusionary with that of neuroplasticity, because it may be that, in fact, that that experience that you have there while you are living it under the effect of the hallucinogenic drug
may generate a longer lasting memory because of those neuroplastic effects.
And again, highlighting why that combination of the drug itself with a psychotherapeutic intervention becomes crucial.
So you cannot certainly separate them.
To me, if it can be corroborating that there is this neuroplasticity and we learn to use it properly, then imagine how extraordinary it is to be able to generate a window in time where by exposing you to a stimuli under the effect of the psychedelic drug,
if it, in fact, turns to be the case, you could strengthen a particular memory, and that would allow you to actually cover a memory that may be very painful.
So you are competing one memory against the other.
So I think that this is, to me, one of the most fascinating areas about why I think that these psychedelic drugs deserve attention for research.
Because to have a means to monitor, to accelerate learning and memory process, this neuroplasticity long-term potential phenomena that we've been studying in neuroscience, could be a very powerful tool.
Yeah, it's been very exciting to be involved with some of the early-stage science and to see it develop over time.
And to also have a lot of misgivings about the public discussion when it veers into the land of panacea, because these things are absolutely not panacea.
And they're very, I believe, powerful compounds based on the data that we have so far.
One more question, maybe two more questions about this, and then I would love to move to TMS, which I am increasingly fascinated by.
I was a subject in a study involving TMS a long time ago, but the technology was pretty primitive then.
My question is about substance use disorders in the very preliminary hypothesis that psychedelics, and specifically psilocybin, so the same molecule,
appears to have effects across drugs of abuse, meaning or potential abuse.
So if you have, let's say, the work of Michael Bogan shoots and others at NYU looking at alcohol use disorder, psilocybin.
Then you have Matt Johnson, Dr. Matt Johnson, and nicotine.

You also have people like Peter Hendricks looking at cocaine.
If it turns out that those can be replicated, we can hopefully, and I'm very optimistic that there'll be more federal funding for these things,
because there is a bit of a chicken and the egg problem in terms of sample size and funding availability, which is challenging.
But what could it mean if it turns out that something like psilocybin is effective across multiple compounds?
Is that common? I simply don't know in other sort of frontline treatments.
Or would that be something novel that would raise very interesting questions in your mind about the nature of addiction?
I've been studying as a researcher multiple addictions.
I mean, cocaine, alcohol, methamphetamine, nicotine, and more recently, opioids and heroin also.
And I've been intrigued about what all of these addictions have in common.
In fact, I've been intrigued about what something like morbid obesity has in common with addiction if you look at the brain,
because they all share as a common phenomenological presentation the compulsiveness of the behavior and the loss of self-regulation.
So you cannot stop it and you just basically escalate on that behavior.
So I've been intrigued about recognizing the common elements in the brain and then, of course, studying also their uniqueness.
But the neurosurgery is basically very similar.
What is different is the way that you engage it.
So to me, in and of itself, it's not surprising that you have a therapeutic that is going to be valuable for multiple addictions.
And we're funding other type of research with other molecules with the aim of basically targeting just a medication for addiction in general
so that we could also start to address the problem of poly-substance addictions that we have without having to just go specific.
So it doesn't surprise me.
What I would be very intrigued in that notion is if we were to understand the mechanism and the common mechanism across all of the addictions
is that you create long-term potentiation in regard to circuits.
So you are strengthening the signaling on systems that basically are associating the drug with pleasure and regard.
And you are weakening the signaling that's associating pleasure and reinforcement for other stimuli and regard.
So just a strengthening process and a weakening processing.
And you generate it in such a way that you've created an artificial need for the drug.
You have a need for food.
Now you have an artificial need for the drug.
And I'm very much intrigued about the similarities with pain.
When you have pain where the insult is no longer there, but the memory of that pain continues making you feel it.

Just like in the addicted person, the memory of the pleasure leads you to continue wanting it.
So it's not just that I think it could be beneficial for different types of drugs.
But I do think there's value in actually even considering the extent to which if they are shown to be able to modify neuroplasticity,
treatments for these chronic pain conditions, which are devastating and for which you really don't have anything.
I mean, not that I know that there's much research into it, but I'm just telling you where my brain is jumping into.
Yeah, absolutely.
So a few things come to mind.
If you haven't looked at the work of Gould Dullin, G-U-L-D-O-L-E-N, she's at Hopkins.
Her perspective is quite different from, say, Robin Carhart-Harris.
And I think she has some very interesting hypotheses around a reopening of critical windows with respect to, say, plasticity.
And then on the chronic pain topic, I will say this was done at a above board, very well run clinic with proper medical supervision.
But I went through two weeks of ketamine infusion several years ago,
not because I was depressed but because I wanted to be able to speak firsthand to the experience because I knew I would have a lot of questions about it from friends and also audience and so on.
I'm not a doctor. I don't play one on the internet just to be very clear.
But what was fascinating to me is I went in having read a lot of the research related to depression and I've since had Dr. John Crystal from Yale on the show to have a very long conversation about all things ketamine.
What I didn't realize, though, when I went in, because I was not going in with any severe depression, is or I couldn't have anticipated what happened.
And that was, for me, I had chronic back pain in my mid-thoracic back from a long-standing injury, which was very severe,
had daily pain, intense pain for ten years, let's call it.
And when I left my two weeks of infusions, I had no back pain for about six months.
And it turns out one of the other primary indications is chronic pain.
So there's a lot to recommend psilocybin over ketamine at psychedelic dosing,
but it matches very well with what you were saying about the potential overlap of plasticity
and not just for indications like depression but also for something like chronic pain.
I wasn't thinking of ketamine because I wasn't thinking, I mean, ketamine is not considered, as you know, a classical psychedelic drug.
But there is a lot of work on research ongoing for the value of ketamine for the treatment of chronic pain.
I look at it in terms of what has been done.
Again, all of these areas are on their own, they're investigated, but I'm going to check it out because I want to see if anyone has published anything on psilocybin for chronic pain.
So I was jumping into the classical psychedelics, which have very different mechanisms of actions than ketamine.
And I think ketamine was the drug that led us to open up the doors to say, here we have a drug that

nobody, that is a dissociative type of drug,
that is also a drug that can produce addiction, a psychedelic, classical psychedelic stone,
and yet despite everybody's prejudices, show to be beneficial for treatment of depression.
So I think that that is an example about why we cannot just close our eyes and say no.
And we need to look at these classical psychedelics.
So I would like, you made me now curious about it.
Also the fact, as you were mentioning earlier, that there is room for potentially stripping out some of the psychedelic effects.
I think we need to keep in mind that the business motivations may not always be aligned with clinical outcomes.
Of course, it would be much more convenient to work with these compounds if they didn't elicit the types of hallucinations we've discussed.
But even something that is non-classical psychedelic, let's say salvanor and A, right?
So you have a Kappa opioid agonist, may have some really interesting applications for minimizing damage after stroke for vascular problems.
Super, super fascinating.
Of course, more research is needed.
So I wanted to shift to TMS and deep brain stimulation.
And this is very interesting to me.
We were talking about sort of different activity or maybe pathological activity in different neuroanatomical structures.
I don't know if the nucleus accumbens fits into both that prior discussion and the TMS and deep brain stimulation.
But could you speak to what TMS is, what deep brain stimulation is, and why they are of interest?
They are incredibly interesting.
I'm going to introduce you to a new technology that has my brain even more excited than TMS.
TMS goes for transcranial magnetic stimulation and it's a technology that is not invasive.
You actually administer magnetic currents in the scalp and then these magnetic currents actually go into the cortex of the brain
and they are signal transferred as electrical signals.
And it can be used to modulate either at high frequencies to stimulate or sort of lower frequencies to inhibit the areas that you are targeting.
And by understanding how in the cortex, because the brain is a very complicated network and so it links with almost everything else,
but they are hops, they are areas that act as hops.
That is, they have many more connections.
Some of them go deep into the brain.
So as you understand better that pattern of connectivity, you can deliver TMS in such a way that you can start to reach areas that are deeper in the brain,
which are very important for diseases of depression and diseases of certainly addiction.
I mean, you were speaking about the nucleus accumbens, which is the main reward region of the brain and all of the drugs of abuse, all of them stimulated.
And when you stimulate the inanimals with electrical currents or with optogenetics, you generate

rewarding signals.
But the transcranial magnetic stimulation cannot reach deep, but you can reach it indirectly.
And that's what they use it and it's a technology that's approved for the treatment of depression.
Deep brain stimulation then basically is an invasive procedure.
You put the electrodes inside the brain.
It's being used, for example, for treatment of addiction research is being used for research also treatment of depression and other diseases.
And the nucleus accumbens is one of the main targets, both for depression as well as for addiction.
But there are other neuromodulation technologies, so transcranial magnetic.
The other one is direct electrical current stimulation, which instead of giving magnetic signals from the outside to give electrical pulses.
But the one that I am very intrigued and I want to actually introduce you to it, if you haven't heard about it, is low intensity ultrasound.
So it uses ultrasound and if you can use it with high intensity or low intensity and you apply it on the outside of the brain.
If you use high intensity, you can very specifically create an ablation.
So you can do what you could do with surgery, but very precisely without having to open the head.
But that's high intensity.
The beauty of the low intensity is you do not produce damage to the tissue, but you can modify it for a long time.
So they are doing research right now and the high intensity ultrasound was recently approved for Parkinson's disease and they are now doing...
This is the high intensity.
The high intensity, but the researchers are looking at low intensity for neurological diseases and for addiction and other mental illness.
And the beauty is that sound goes through the tissue.
So you can target your nucleus accumbens directly with a much greater precision than with transcranial magnetic stimulation.
That's super interesting.
It's fascinating and you need to apply it for 10 minutes.
And the pilot data is showing that you see it for say, the effects are two weeks or four weeks with a single stimulation.
With a single session of 10 minutes?
Yes, it's very...
The pilot data is very...
It's pilot data.
That's why I say now that you're speaking to me and last time we spoke, I was...
I'm very excited of TMS.
I'm not in any way going to minimize it.
But actually what I like so much and I'm just going to say what you pushed the limit.
And I said, let's push our own thinking.
If you are able to do this long lasting effect through this, as you learn to understand better how these frequencies for ultrasound stimulation affect the tissue.

I think that one day we may be able to cure addiction and no one has ever heard me speak about cure addiction.
So why do I think it is possible?
Because we know that when people have strokes in certain areas of the brain, particularly frequently involving the insula,
there are cases where people just stop taking the drug.
They forget about taking the drug.
They don't care anymore about it.
So there's been instances which have shown that the insult, a stroke in a particular area, cure the person of their addiction.
So what about if we gain that knowledge about what are the relevant circuits and areas?
And we have the tools now to manipulate them in ways that are much more effective than we had in the past.
That opens up the possibility of in the future that we may be able to cure addiction.
Well, that makes me feel much more optimistic.
And I also feel like at some point, and I'm getting ahead of myself, but looking at these novel cutting edge technologies,
or in some cases very old technologies like psilocybin being applied to conditions and novel ways, that at some point there might be polytherapies that combine some of these factors.
Let me ask you a question about the Parkinson's for a second, though, because I have Parkinson's on one, I think now both sides of my family.
So it's of intense interest.
If they're using high frequency, and for those who don't know the term ablation, and I want you to please correct me if I'm wrong,
but that can be surgical removal of tissue, or I suppose destruction of tissue, might be another way to put it.
I want you to correct my definition if I'm getting it wrong, but how would that strength of effect be used in Parkinson's?
It is the high intensity ultrasound, and the high intensity ultrasound becomes ablative.
So you are targeting, for example, the subthalamic nuclei, just like you do with surgery.
But in this case, you are not opening it up, and you can very precisely damage it.
Yeah.
So this brings psychosurgery to a completely new level.
Wow.
And so they applied it, and they're also, I think that one of the targets is a subthalamic nuclei,
but I also think that they've targeted parts of a very small nuclei in the thalamus, too.
So it is fascinating also from that perspective of, in instances where psychosurgery may be valuable, that you can do it as minimally invasive and as precisely and as small at areas possible.
So I think it's quite remarkable.
In the case of, now you got me all excited about this low intensity ultrasound.
I've been following the TMS pretty closely, and in particular the shorter duration, higher frequency dosing of TMS.
So let's just say multiple sessions a day over the span of five days.

There's some interesting work being done.
And certainly, I know the plural of anecdote does not equal data, but anecdotally, I've seen a number of outcomes with friends,
children who are patients that have practically just defied belief.
But on the low intensity ultrasound side, you mentioned, and we'll put links in the show notes for people,
and maybe I'll get some links from you or your team, just where people can learn more about this.
I know it's pilot data, so hold your horses, the jury's still out.
But nonetheless, very interesting place to begin.
Question to the durability that you're mentioning, which I think was two to four weeks.
Let's just say after a single 10 minute session, is the onset of effect immediate or near immediate as well?
It's basically almost immediate.
And one of the consistent findings that they are seeing is that there's a reduction in anxiety.
They see a reduction in craving.
It's pilot work.
I want to reiterate that it needs to be replicated.
But, you know, when I saw that pilot data, I said, oh my God, and it was the group at West Virginia who has been doing the deep brain stimulation for the treatment of opioid addiction.
And they insert these electrodes and then they've basically observed that in three of the four individuals
that they've treated on that pilot study, they were able to, again, very dramatically reduce anxiety and they decreased the consumption of opioids.
So it showed a positive effect in three or four.
They basically told me these effects that we're getting with a low, low intensity ultrasound that if tested eight people
are as dramatic or more dramatic than one we're seeing with the deep brain stimulation of the nucleus accumbens.
So they target also the nucleus accumbens with low intensity ultrasound.
So it's very intriguing.
You know, I'm a scientist and I love and I get excited with data.
But I do want to reiterate it's very pilot.
It's very, very pilot, but it has to be studied.
It's like what we were saying with the psychedelic drugs.
It's very interesting.
It has to be studied.
Everything starts small.
Almost everything starts small.
We all start with the pilot.
So the jury is still out, but it's exciting that you're pushing the limits and you're daring to push the envelope
and experiment with new things.
Of course, I mean, that's part of the charter, but you also have a history of doing this well.

And I don't think you would have arrived where you are today had you not been very dogged and determined.
And it goes all the way back to when you were turned down by Nida.
And here you are as the director.
It's just remarkable.
It's just a remarkable story.
So Dr. Volkov, you've been very generous with your time.
I've enjoyed the conversation.
I could keep going for another two hours, no problem, but you have an incredibly busy schedule.
Is there anything else that you would like to share with people out there?
You know, there are two things that I would have liked to add.
One of them is that addiction is very frequently comorbid with other psychiatric disorders.
And most notable is anxiety, depression, suicidality.
And I bring it up because you need to address these comorbid conditions,
because otherwise it's not going to be possible for the person to be able to recover.
And also from the perspective that if you are depressed, if you are anxious, if you are suicidal,
you are likely to take drugs as a means to auto-medicate, to escape that mental state.
And it is crucial to send this message because it's not as simple as saying that you take drugs because you want to get high and you're taking the drugs.
I mean, people are taking the drugs too many times.
Initially, yes, for curiosity, many times to feel good.
But once you become addicted, it is really to escape a mental state that is very difficult to stay at.
It's very painful.
And the other point that I did want to bring to that we haven't discussed,
which is in understanding how we understand the effects of drugs and addiction
and how we understand also mental illness,
is how important the environmental factors are and how crucial they are,
particularly when you are a child or an adolescent.
I think that we've all become much more sensitized to them with the COVID pandemic
because we came to realize that there are certain people that were at much greater disadvantage.
And that's those that deal with people that are in circumstances of economic inequality,
of trauma during childhood and what we call the social determinants of health
that are really playing very important roles in people's encounter with drugs
and how they respond to it and how they ultimately also may be given an opportunity or not to access treatment
and to how they respond to treatment.
So as you were speaking, for example, with psychedelic drugs,
we are very concerned that if psychedelic therapies,
if they get into mainstay clinical practice, if they are proven to be useful,
that they are equitable and it doesn't end up with like many of the very fancy treatments that we have now
that are only accessible to a very few.
So that's the only other thing that I would want to say.

Yeah, 100% agreed on both.
And that's also part of the reason that I hope we will see whether it's with psychedelic therapies, psychedelic assisted therapies or other modalities in some cases options for group treatment.
And at least the testing of the hypothesis that outcomes can not only be equal to individual treatment,
but potentially even better.
And I think there is the possibility that that is the case,
which would also have the wonderful side effect of decreasing costs quite significantly.
And there's so many questions of insurance reimbursement and ultimately reclassification,
which would be sort of a precursor to a lot of these things happening.
But I agree with you absolutely completely.
And it's also as upsetting and pessimistic as one can become when they look at the compounding of many of the addiction problems in the U.S.
I feel like we are at a point in history also with some of these burgeoning technologies, as you mentioned.
And I think it was obvious in the excitement in your voice.
I mean, there are things potentially on the horizon that could really change how we not only treat addiction,
but how we think about addiction as well, which is very exciting and I think cause for a certain degree of cautious optimism.
Oh, yes, I'm very optimistic.
Tim, I'm going to abandon you at this point.
I'm going to jump off that screen.
But it's been a pleasure speaking with you.
Thank you so much for your time.
Dr. Volkov, I have learned so much.
I have so many things to look into.
And for those listening, you may also have things you want to look into.
We will have links to everything in the show notes as per usual at tim.blog.com.
Until next time, be just a little kinder than is necessary, not just to others, but also to yourself.
And as always, thank you for tuning in.
Hey, guys, this is Tim again.
Just one more thing before you take off and that is five bullet Friday.
Would you enjoy getting a short email from me every Friday that provides a little fun before the weekend?
Between one and a half and two million people subscribed to my free newsletter, my super short newsletter called five bullet Friday.
Easy to sign up, easy to cancel.
It is basically a half page that I send out every Friday to share the coolest things I've found or discovered or have started exploring over that week.
It's kind of like my diary of cool things.
I often include articles I'm reading, books I'm reading, albums, perhaps gadgets, gizmos, all sorts of tech tricks and so on.

They get sent to me by my friends, including a lot of podcast guests and these strange esoteric things end up in my field.
And then I test them and then I share them with you.
So if that sounds fun, again, it's very short, a little tiny bite of goodness before you head off for the weekend, something to think about.
If you'd like to try it out, just go to tim.blog.friday.
Type that into your browser tim.blog.friday.
Drop in your email and you'll get the very next one.
Thanks for listening.
This episode is brought to you by Eight Sleep.
Temperature is one of the main causes of poor sleep and heat is my personal nemesis.
I've suffered for decades, tossing and turning, throwing blankets off, pulling the back on, putting one leg on top and repeating all of that ad nauseam.
But now I am falling asleep in record time.
Why? Because I'm using a device that was recommended to me by friends called the Pod Cover by Eight Sleep.
The Pod Cover fits on any mattress and allows you to adjust the temperature of your sleeping environment, providing the optimal temperature that gets you the best night's sleep.
With the Pod Cover's dual zone temperature control, you and your partner can set your sides of the bed to as cool as 55 degrees or as hot as 110 degrees.
I think generally in my experience, my partners prefer the high side and I like to sleep very, very cool.
So stop fighting. This helps.
Based on your biometrics, environment and sleep stages, the Pod Cover makes temperature adjustments throughout the night that limit wake ups and increase your percentage of deep sleep.
In addition to its best in class temperature regulation, the Pod Cover sensors also track your health and sleep metrics without the need to use a wearable.
So go to eightsleep.com slash Tim, all spelled out, eightsleep.com slash Tim and save $250 on the Eight Sleep Pod Cover.
That's eightsleep.com slash Tim.
Eight Sleep currently ships within the US, Canada and the UK, select countries in the EU and Australia.
Again, that's eightsleep.com slash Tim to save $250 on the Eight Sleep Pod Cover.
This episode is brought to you by House of Macadamia's delicious and nutritious nuts.
Holy hell, folks. I tell you, these things aren't delicious. I've been gobbling them all day.
Anyway, I love macadamia nuts and have been enjoying them often since keto expert Dr. Dominic Agostino recommended them way back on the podcast in 2015.
It tastes great and they have more healthy, mono unsaturated fat than both olive oil and avocados.
27% fewer grams of carbs than almonds and more than 50% fewer grams of carbs than cashews.
They're the perfect, low carb, keto friendly, nutty snack.
In fact, I just ate a handful of lightly white chocolate dusted, dare I say.
Macadamia's about an hour ago to keep me going through the afternoon until dinner.
It is the perfect snack for me.

Now we'll say this, House of Macadamia's produces the best tasting macadamia nuts I've ever eaten that I've ever had by far.
That's due in part to their location in the Mupumalanga province of South Africa,
which provides the ideal temperature, altitude, soil composition, rainwater and pristine mountain water for growing, you guessed it, macadamia's.
House of Macadamia's have partnered with the largest macadamia producer in the world,
comprising 94 independent farmers in South Africa,
which gets them first pick of the highest quality macadamia nuts in the region to make their one of a kind snacks,
like their vegan, paleo and keto friendly chocolate dipped macadamia's.
They really took their time to get all of this right, and they've done more than two years of flavor testing,
and you can taste that in each packet you consume, and I've had two of those today.
And now, listeners of the Tim Ferriss Show, that's you guys, can use code TIM20, that's T-I-M-2-0 altogether,
to get 20% off of all orders in a free box of their best selling Namibian sea salted macadamia nuts.
That's a mouthful, and you want a mouthful.
They are worth $35, and you get them for free.
If these are not the best macadamia nuts you've ever eaten, House of Macadamia's will give you a full 100% refund, guaranteed.
So just visit HouseOfMacadamia's, that's plural, HouseOfMacadamia's.com slash Tim,
to discover some of the most delicious and nutritious nuts on the planet.
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One more time, HouseOfMacadamia's.com slash Tim, and use code TIM20.
Thanks for watching.