[Transcript] The Tim Ferriss Show / #667: Dr. Gül Dölen on Rethinking Psychedelics, New Applications (Autism, Stroke, and Allergies), The Neurobiology of Beginner's Mind, Octopuses on MDMA, and The Master Key of Metaplasticity

This episode is brought to you by AG1 by Athletic Greens,
a true staple of my daily routine,
as it has been for more than a decade.
I take it most mornings and I even travel with it.
Whether I'm skiing, traveling abroad,
going to an event where I'll be around a lot of people,
I just use it to cover all of my nutritional bases.
But let's start with the basics.
What is AG1?
And we'll get to the ingredients,
but I get asked all the time what I would take
if I could only take one supplement.
The answer is invariably AG1.
And as I mentioned,
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 four-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.
I know how much time they put into quality assurance
and sourcing.
It has a multi-vitamin, a multi-mineral greens complex,
probiotics and prebiotics for gut health,
an immune support formula, digestive enzymes,
and adaptogens.
I always do my best, of course,
to get nutrient-rich meals, and that is a top priority.
But 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.
Furthermore, it's also NSF-certified for sport,
making it safe for professional athletes
as what's on the label is actually what's in the powder.
AG1 is the ultimate all-in-one nutritional supplement bundle
in one easy scoop, because let's face it,
if it's not convenient, you're just not going to use it.
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 floor time,
actually two more times.
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.
This episode is brought to you by Helix Sleep.
Helix Sleep is a premium mattress brand
that provides tailored mattresses
based on your sleep preferences.
Their lineup includes 14 unique mattresses,
including a collection of luxury models,
a mattress for big and tall sleepers, that's not me,
and even a mattress made specifically for kids.
They have models with memory foam layers
to provide optimal pressure relief if you sleep on your side,
as I often do and did last night on one of their beds.
Models with more responsive foam to cradle your body
for essential support in stomach and back sleeping positions
and on and on, they have you covered.
So how will you know which Helix mattress
works best for you and your body?
Take the Helix Sleep Quiz at helixsleep.com slash Tim
and find your perfect mattress in less than two minutes.
Personally, for the last few years,
I've been sleeping on a Helix Midnight Luxe mattress.
I also have one of those in the guest bedroom,
and feedback from friends has always been fantastic.
They frequently say it's the best night of sleep
they've had in ages.
It's something they comment on
without any prompting from me whatsoever.
Helix mattresses are American made
and come with a 10 or 15 year warranty,
depending on the model.
Your mattress will be shipped straight to your door
free of charge, and there's no better way
to test out a new mattress than by sleeping on it
in your own home.
That's why they offer a 100 night risk-free trial.

If you decide it's not the best fit,
you're welcome to return it for a full refund.
Helix has been awarded number one mattress
by both GQ and Wired magazines.
Helix is now offering 20% off on all mattress orders
plus two free pillows for you, my dear listeners.
On some mattresses, this can mean savings
of more than $500.
So go to helixsleep.com slash Tim.
This is the best offer that they have made yet,
and it will not last forever.
With Helix, better sleep starts now.
So one more time, check it out.
Helix, H-E-L-I-X, helixsleep.com slash Tim.
Optimal minimal.
At this altitude, I can run flat out for a half mile
before my hands start shaking.
Can I answer your personal question?
No, I would've seen it in a perfect time.
What if I did the opposite?
I'm a cyber-nerdy organism,
living this year over metal and proscemic.
Hello, boys and girls. This is Tim Ferriss.
Welcome to another episode of the Tim Ferriss Show,
where it is my job to deconstruct,
or at least attempt to deconstruct,
interview, shall we say, world-class performers
from all different disciplines.
My guest today, I feel, for me, has been a long time coming.
I'm very excited to have on the podcast Dr. Ghoul Dolan.
Dr. Ghoul Dolan is an associate professor of neuroscience
at the John F. Kennedy University.
I'm a professor of neuroscience at the John F. Kennedy University.
I'm a professor of neuroscience
at the Johns Hopkins University School of Medicine
and a pioneer and world leader of psychedelics research.
Her laboratory has discovered a novel mechanism
that could account for the broad range
of therapeutic applications that psychedelics
are currently being tested for.
Her lab has discovered a novel critical period,
we'll define what these things mean,

for social reward learning and shown that this critical period
can be reopened with psychedelic drugs,
such as MDMA, LSD, psilocybin, ketamine, and ibogaine.
Building on this discovery,
she's formulated the hypothesis that psychedelics
may be the long sought master key
for unlocking critical periods across the brain.
To test this hypothesis,
she's initiated a nationwide collaborative effort
to determine whether psychedelics reopen critical periods
for ocular dominance, plasticity,
birdsong learning, anatomical plasticity
in the barrel cortex, serotonergic neuronal regeneration,
dendritics, spinogenesis, and motor learning.
And if you don't know what those words or phrases mean,
don't worry, we will define them as we go.
Importantly, understanding psychedelics
through this framework,
dramatically expands the scope of disorders,
including autism, stroke, and allergies
that might benefit from adjunct therapy with psychedelics.
An approach she has dubbed the Fathom Project,
that's P-H-A-T-H-O-M,
which stands for psychedelic healing,
adjunct therapy, harnessing opened malleability.
Dr. Dolan earned her MD, PhD at Brown University
and the Massachusetts Institute of Technology,
otherwise known as MIT,
where she carried out seminal work on critical periods,
learning and memory, and the pathogenesis of autism.
You can find her online at dolanlab.org.
Dr. Dolan, welcome to the show.
Nice to have you.
Thank you for having me, it's nice to be here.
So I thought we might start with your undergrad experience.
And I have read that you designed your own major,
and I was hoping you could describe
how one designs one's own major
and how you thought about going about
designing your own major.
You know, I've always been somebody who learns best
by comparing, and originally I thought,

well, I'll just do a triple major of neuroscience
and linguistics and philosophy.
And the university was like, no, no,
there's no triple major.
You can do a double major,
but if you really need all three,
we recommend that you do this design your own major path.
And so I worked with my professors in philosophy
and neuroscience primarily to come up with a curriculum
that would span all of the different elements
that I wanted to incorporate
in trying to ask the question, what is the mind?
What is consciousness?
How do we know that from different perspectives?
And so the major was called comparative perspectives
on the mind, and it was a combination
of neuroscience, philosophy, linguistics, art, religion.
And really the idea was that this is something
that humans care about, and so we've thought about it
from all of these different perspectives for millennia,
and what can we understand from that approach?
Why were those questions,
and hopefully this doesn't sound like a stupid question,
because at face value,
perhaps they should be interesting questions to everyone
since on some level, I suppose consciousness
is fundamental, but why were these questions
interesting, compelling to you at the time,
enough that you would attempt to have a triple major?
I have to say, I'm not really sure why exactly those,
it just compared to everything else
that I saw other people majoring in,
like economics or history.
I just didn't care about those things the same way
as I cared about.
You know, I just found myself,
I've always wanted to only study or think about things
that I think are deeply interesting
that I would wanna talk to with anybody,
whether it be the person sitting next to me on the bus
or my parents or somebody's kid, you know,
I just, I like thinking about things,

and when I'm obsessed with something,
I just think about it all the time in every context,
and so I just never had that with economics or history
or any of the other topics
that seemed to be popular majors.
It didn't cause the quickening.
There are a few terms that may come up later, we'll see,
and I'd love to have you just expand on them
or define them because I was reading in prep for this
and you briefly considered marine biology,
but you were also interested in philosophy of mind
and then a philosophical consideration
called theory of mind.
What is philosophy of mind?
How should we think about it?
What is theory of mind?
Philosophy of mind,
it's not really a branch of philosophy or anything,
it's just a thing that has drawn the attention
of philosophers from a variety of different perspectives,
like you can imagine considering what is the mind
from a metaphysical point of view,
so what are the things that we count
when we say this is what a mind is,
this is what a mind is not,
then there are other considerations like,
well, how do we know mind?
Can we know mind just through introspection
or is there some empirical way
or some way that we can compare different people's descriptions
of those things to get at what is mind
and that would be sort of the more epistemological approach
to mind and I was interested in all of those things,
there continues to be debate about that
and one of the interesting ideas that I came across
was that there was this concept of theory of mind,
which is not really a theory in the way
that we have a theory of light
or a theory of synaptogenesis
or any of the more commonplace theories,
it's more like it's a point of view.
The shorthand way of explaining what theory of mind is

that I like to tell people is it's sort of what you're doing,
it's the neurobiological process that is going on
when you're playing poker,
it's anticipating what somebody else might be thinking
and trying to see the world from their point of view.
So in some sense it's a theory
about what somebody else might be thinking
and this ability to understand
or to have a concept of what somebody else might be thinking
is something that we develop
and we get better at as we mature.
So you can always tell when a kid is starting
to pick up theory of mind,
it first comes on around age four or five
because they start doing these funny pranking behaviors
where they'll reach around your back
and tap you on the wrong side and look the other way
and that's them sort of playing with the idea
that their own point of view
and the person whose shoulder they're tapping
might be different and that they can trick somebody
by playing on that difference.
And so this theory of mind, there was some idea out there,
you know, I'm not sure that it's really a dominant theory
right now in autism, but there was an idea
that this is something that people with autism
are not so good at
and it makes them bad poker players,
it makes them bad at lying, it makes them bad at tricking people.
It's this thing that psychopaths, for example, are very good at.
They have better than average theory of mind
and they use that better than average theory of mind
to manipulate people by anticipating what they may
or may not like and using that information
to try and get whatever it is that they're trying to get.
And so this theory of mind idea was sort of
out there and there was some idea that,
well, you need to have theory of mind
in order to have consciousness,
in order to have a full sense of knowing who you are
compared to other people.
And I like this idea because it was a testable hypothesis.

And one of the things that I found sort of frustrating
about being a philosopher is that
the philosophers were always asking the coolest questions,
the biggest questions, but just felt like, you know,
they were just going around in circles
and never really coming up with an answer
that I found to be deeply satisfying.
And on the other hand, you know, scientists, neuroscientists,
you know, maybe they weren't getting to ask
all the really big questions,
but man, they were coming up with some concrete answers
that felt tangible and like we were getting somewhere.
And so I liked this idea that we could test
the requirement of theory of mind for consciousness
by looking at diseases where that function is impaired
and learn something about the relationship
between consciousness and genes that encode
different proteins that are required
for that theory of mind.
Have many, many follow-up questions.
Theory of mind does not seem to be based on the reading
that I've done entirely human specific.
And is it true that you've observed this in, for instance,
and you're tapping on the shoulder, maybe think of it,
hunting behavior in octopuses?
Those were actually not my experiments.
Those were experiments done
by really imminent octopus researcher, Roy Caldwell.
And he showed me the videos of them.
And as soon as I saw the videos of the octopuses hunting,
it occurred to me that that is exactly a theory of mind
like behavior in an octopus.
And the reason that that was so interesting
is because the way that people talk about theory of mind
is that this is a behavior that evolved
due to the selection pressures imposed by social living.
So when we have to live in a social group,
it serves us to be able to anticipate
what other members of that social group might be thinking
in order to anticipate and either compete or collaborate
or whatever it is that you're trying to do.
And octopuses, by and large, are not social species.

So two octopuses of the same species
into a tank together, they will kill each other.
And there are differences in the amount of aggressiveness
that we observe in octopuses.
Some are so aggressive
that we've never even seen the males of the species
because when they mate,
they leave their hectocautilus arm,
which is their reproductive arm in the mantle of the female
and eject it and escape so that they don't get eaten.
So we've only ever found their hectocautilus arm.
That's how aggressive that species is, okay?
So other species of octopus aren't quite so aggressive,
but they're still a social.
And it was interesting because the species of octopus
that does that hunting behavior
is the only known social species of octopus.
It seems like an interesting opportunity
to test these ideas about what are the selection pressures
that make theory of mind develop across evolution
and what are the species' specific advantages
to having a theory of mind.
But it's interesting also because
even though the larger Pacific striped octopus,
which is the octopus that does that hunting behavior,
is social, it's not using this behavior in a social context,
it's using it in a hunting context,
which suggests that maybe theory of mind originated
from a hunting behavior where you can imagine
it would be useful for the animal to be able to anticipate
where its food might hide if it was being chased
because octopuses eat shrimp and fish
and they're excellent hunters.
And so the idea is that maybe these ideas
that social behaviors are what drive
the evolution of theory of mind is not quite right
and that it emerged by something earlier
like hunting behavior.
It strikes me as a hunter myself,
which really only was adult onset hunting
in my 30s when I was writing about food.
I felt sort of obligated to explore these things

that you would observe behaviors
that you could map to theory of mind
in thousands of species that are really effective hunters.
And I would love to bring up three words
that are in your intro, which I had read earlier,
that people may not associate with the conversation
around psychedelics currently, autism, stroke, and allergies.
Where did your interest in autism begin?
For me, autism was something that I became interested in
when I was an undergrad thinking about these problems
of theory of mind and consciousness
because I was intrigued by the possibility
that autism could be thought of as an impairment
in theory of mind and that it would be sort of a case example
of what happens to your ability to have
a fully conscious experience in the absence of
or under conditions of impaired theory of mind.
And so how that relates to psychedelics
is really sort of a long-ish winding story,
which is that when I was a graduate student,
my PhD work was focused on trying to find
a therapy for autism and we had focused in
on one specific type of autism called Fragile X.
It's the first identified cause of autism.
It's currently the most abundant,
the most common cause of autism is a mutation
in the FMR1 gene, which encodes Fragile X.
And what we had found is that we could do
a biochemical manipulation to correct a cellular imbalance
that in mice corrected many of the symptoms of autism
that we could measure at the time.
And so that was really exciting,
something like 26 other labs followed up on that work.
And several big pharmaceutical companies said,
okay, this is it.
This is the mechanism-based therapy
that we've been looking for.
And ran several very large-scale human clinical trials
for that metabotropic glutamate receptor modulator
that we thought would correct the imbalance in Fragile X.
And when they did those studies,
everybody was hugely disappointed

because we were expecting the drugs to work
and to cure the disease.
And we really got very little evidence to support that view.
And I think at the time,
all the people who were doing human research
and clinical trials were just willing to throw their hands up
and say, well, see, we told you a mouse is not a human.
And that's why the trials didn't work
because all of the human trials were based on mouse studies.
And this was just where we went wrong.
But a few of us kind of took a more circumspect view
and said, well, yeah, okay, mice aren't humans,
but there were a lot of other differences
between the human trials and the mouse trials.
And to me, the one that really stands out
is that while all of the mouse studies that were done,
the clinical intervention, the alteration of the receptor,
were given either right at birth
or a genesis or very early in development.
Whereas all of the human trials,
the drugs were given to adults.
And it occurred to me that because of the timing
of when the therapies were given,
all of the mouse studies would have been trying
to correct the underlying biochemical imbalance
when the animals' critical periods were all still open.
Whereas in the human trials,
the relevant critical periods
would have been closed by the time we gave the intervention.
And so the way that I'm imagining
that a psychedelic might be useful in the case of autism
is not to cure the primary underlying problems
with social behaviors directly with psychedelics,
but rather to pair the psychedelic intervention
with the intervention that we think
is restoring the biochemical balance.
And when we do that,
we feel like we can restore the biochemical imbalance
while reopening the relevant critical periods
so that the patient can learn from their social environment
in the normal way under the conditions
of the restored biochemical imbalance.

So I want to eventually ask you
what reopening the critical period
looks like chemically or neuroanatomically.
But before we get to that,
I would love for you to help me separate
fact from fiction with autism.
It's not a condition that I know much about.
And I am nonetheless exposed to many opinions about autism.
And people say, for instance,
that the prevalence is skyrocketing,
that it may be caused by people having children
when they're older or it's caused by, God knows what,
BPA, you name it.
There's probably a million different theories out there.
And I would be curious to know, as a scientist,
what appears to be most plausible as causes of autism?
Are rates increasing,
or are we just getting better at diagnosing
or looking for that diagnosis, et cetera?
Could you just help give us the ABCs
of fact versus fiction?
This is a great question
and one that I'm only gonna be able
to give you a partial answer for
because things are changing rapidly around this.
So when I first started studying autism 20 years ago,
it was very narrowly defined as a disease.
There was only five or six different genes
that had been implicated in causing autism.
It was incredibly highly inherited.
So if we can give a heritability score
for different diseases
and different inheritance patterns,
hair color and eye color
might give you a heritability score of one,
whereas something like cervical cancer,
which is caused by a virus,
has a heritability score of closer to zero.
And autism had a heritability score
of something like 0.96, so very, very highly heritable.
And it made it different
from almost all of the other neuropsychiatric diseases

out there because things like depression
and anxiety are hovering more around the 0.5 range.
So sometimes inherited, sometimes environmental,
usually a combination of those factors.
And at the time that diagnosis was so narrowly defined
that you got this high heritability.
And then for a variety of different reasons,
some of them scientific, some of them socioeconomic,
the definition of autism got expanded
in the diagnostic and statistical manual
of neuropsychiatric disease.
The expanded definition started including
the spectrum of autism.
And so now rather than having,
you absolutely have to have an impairment
in social behaviors and an impairment
in locomotor stereotypies
and all of these other developmental criteria.
It sort of got expanded
and a lot more things started being included.
And when this happened,
the heritability estimates of the disease dropped.
And so my interpretation of those data
is that basically we stopped defining a disease
that was a sort of unified single disease
and started including a lot more things
that were not what I would consider
to be classical autism.
And so now it feels like to me
that this has gotten so expansive
that we're essentially including things like ADHD
with social anxiety or all kinds of other things
that while they might be in the realm of autism,
it makes it much harder to identify it
and say this is what's being caused.
And as a scientist, I find this to be something
that makes my life much more difficult
if we are no longer defining the disease
in a very narrow way.
And so when this happens, it's a little bit frustrating.
And so I have tended to focus
on those early identified genes like FMR1,

which have been known to be a cause of autism
for a long time.
And more importantly, when we look at all of the other genes
that have been implicated in autism,
so now we're somewhere in the approximately 1,000 genes
have been implicated in autism.
FMR1 seems to be a node.
So in other words, the protein that FMR1 encodes
regulates roughly 25% of all the other autism genes.
And so to me, that's a good place to start
to try and understand autism.
And then I will leave it up to the epidemiologists
to sort out how to redefine the category
so that we're capturing the right subset of patients
and excluding the subset that are not going
to respond to therapy if we're targeting the subset
that are defined in one specific way.
If we look at FMR1 as a node and a focal point,
I apologize that I don't know the answer to this in advance,
but does that mean that in the same way
that if say a couple are planning on having children
or someone were looking at say, surrogacy,
you could do genetic screening
that it's possible for people to currently do genetic screening
for the probability of sort of autism
as an outcome in offspring?
I believe, I mean, it's been a long time
since I was in medical school, but last time I was,
I looked into that, I believe it was still the case
that FMR1 was rare enough that it wasn't worth it
to do the screening test to try and find it
because you have to balance doing a screening test
against the possibility that the test itself
is gonna cause problems with the pregnancy.
And so there is a sort of a judgment call there.
And unless you had a family history of Fragile X,
I think that it's still the case
that people don't actually test for it beforehand.
It's not like Down syndrome also
where there's any strong indication
that in Down syndrome, there seems to be,
there is a correlation between the age of the mother

and the likelihood of getting Down syndrome.
For schizophrenia, there seems to be a correlation
between the age of the father and getting schizophrenia.
But for autism, as far as I know,
there is no age dependent correlation
with your likelihood of getting it.
And all of the causes of autism
are each individually so rare
that there's no screening test
that is generally applicable that would be worth doing.
Let's just revisit, as promised,
the reopening of the critical period.
The idea of critical periods first came in 1935
by Conrad Lorenz, who was a ethologist
who was studying imprinting behavior in snow keys.
So this is the behavior that shortly after hatching,
the animals will form a long lasting attachment,
typically to their mother,
but if the mother isn't around
and instead it's sort of a motorized airplane
or the scientist, in that case, Conrad Lorenz himself,
then they'll form that attachment
to that other moving object in their vicinity.
And there are all these funny pictures online
of Conrad Lorenz being followed around by little snow geese,
because they form this attachment.
But what are snow geese?
They're just a type of geese.
Okay, there we go.
I just wanted to figure out.
Sounds like a little Scandinavian dwarf or something.
No, no, no, they're just like type of geese.
Type of geese, birds, okay?
So they're just followed around by these birds.
They're really cute pictures.
And this imprinting behavior, though, if you wait,
so if you wait until 48 hours after hatching,
then they don't form this behavior, right?
So this attachment is only possible
within the first 48 hours of hatching.
And Conrad Lorenz called that period of time
when the animals are extremely sensitive

to their environment and can form these long-lasting memories.
He called that window of time the critical period.
And critical periods, since then,
have been described for so many different things.
So probably the one that most people will be familiar with
is the critical period for language learning.
So it's so much easier to learn your first language
that you learn as a child
than if you later on try and pick up another language.
It's harder.
You always have an accent.
It's not easy to incorporate that into your first language.
And so that's a critical period for language.
And what my lab did is that we knew
from the human literature
that there was probably a critical period
for social learning, right?
Because we know, for example,
that teenagers are much more susceptible to peer pressure
than adults are.
We know that they prioritize learning from their environment,
from their social interactions,
much more so than adults do.
And that whatever social environment you grew up in
is sort of your native social environment.
So that, for example, when I go to Japan,
I always feel like a bear in a china closet
because I feel like I'm always insulting somebody
without really realizing it.
Because I didn't grow up in that social environment, right?
And so I don't know that it's extremely rude
to hand somebody something with one hand instead of two.
These are the kinds of rules
that I didn't grow up exposed to.
So it's a foreign social language to me.
So we had this intuition
that there was a critical period for social reward learning.
And that's what my lab discovered.
So we discovered that in mice, just like in humans,
there is this window of time
where the animals are learning from their social environment
much more strongly than when they are as adults.

And we figured out a bunch of different mechanisms
relating to that.
Critical periods, typically the long, long arc
of trying to understand critical periods
has really been focused around this idea
that critical periods are great,
but the fact that they close means that
it's really, really hard to treat brain disorders in adults
because the brain is no longer flexible
and able to learn from its environment
in the same way as it was as a child.
And so if we can understand the mechanisms,
maybe we can figure out ways
to reopen them for therapeutic benefit.
That's been sort of the goal of neuroscience
for the last 100 years or so, right?
Is to try and find that.
And three Nobel Prizes have been given
for mechanisms trying to figure this out
because it's understood that this would be so important.
But I gotta say, when I was a graduate student,
this idea of finding the master key
for unlocking critical periods, I never believed in it.
And in fact, my lab and another lab at Harvard
were kind of in a intellectual debate with one another
over this idea of can there be a master key?
And I was always like, no, obviously anything
that could do that to the brain
would either cause massive amnesia,
would cause seizures
and possibly could cause the whole brain to melt.
And I was like, there's no master key, stop it,
forget about it, Harvard, you're just wrong, okay?
And so what we've kind of come up with now
is we started with the idea that, well,
MDMA is sort of different from other psychedelics
in that it has this very prominent pro-social component to it.
People take MDMA and they wanna cuddle,
they wanna be sociable.
Some people talk about like this incredible feeling
of empathy and being able to see other people's pain.
It's just a very pro-social type of psychedelic.

In fact, some people even wanna call it an empathogen
rather than a straight up psychedelic.
And so we started with that idea that, okay,
we're trying to reopen a social critical period.
We know it follows a lot of the same rules
as other critical periods,
but maybe MDMA is the way to do it.
And in fact, we did find evidence that MDMA
reopens the social critical period,
and it does so by restoring oxytocin metoplasticity
in the nucleus succumbens.
And we love this idea that that was the story
and whatever psychedelics, other psychedelics
probably wouldn't do it.
That was our original idea.
But then again, mother nature, tricky.
So when we did the control experiments
to look at what other psychedelics are doing,
we found that all of the psychedelics
reopened this critical period,
even though nobody is taking LSD
and doing a 60-person cuddle pedal,
not that I've seen anyway, right?
The LSD is not prominently a pro-social type of psychedelic,
neither is Ibogaine, neither is ketamine,
and yet all of them are reopening this critical period
for social reward learning.
And so what this suggested to me immediately
was that the whole social part of the MDMA story
was a little bit of a red herring,
and that really what psychedelics are
are this master key for unlocking critical periods.
There's not just one critical period.
There are lots of different critical periods,
but we are beginning to get a sense
that many of the critical periods close
using the same sort of governing principle,
the same kind of molecules,
if not the exact same molecules,
have been implicated in the closure
of say the visual critical period
or the touch critical period

or the motor critical period.
And what's different is that the social critical period
is kind of different from those
in that it's not a sensory motor,
it's an emotional critical period
that we think is encoded in a different part of the brain,
the nucleus succumbens,
which is part of the limbic system.
It's a different type of brain region
than the classical critical periods
which have all been defined in the cortex.
And so we don't know, still don't know
whether or not the rules are the same.
But what we did figure out
is that when we did RNA sequencing
or genetic profiling, transcriptional profiling
of what happens to this brain region
when we give psychedelics
and we reopen this social critical period,
the molecules that get up and down regulated
in response to psychedelics but not cocaine
share a lot of overlap
in terms of their molecular identity
with the molecules that have been implicated
in the closure of other types of critical periods
like vision, somatosensation, motor.
And so beginning to see lots of sort of
circumstantial evidence that the psychedelics
are all doing the same thing,
they're reopening this critical period.
And they're doing it in a way that suggests
that the social critical period,
the social part of it is irrelevant
and that this is really tapping into molecular mechanisms
that are conserved across all the different types
of critical periods.
And if that's true, then it suggests
that these drugs might be useful
for reopening all kinds of critical periods,
including the visual critical periods,
including the touch critical periods,
including the motor critical periods.

And so that's kind of the next direction
that the lab is heading is testing the idea
that psychedelics are in fact this master key
for unlocking lots of different critical periods.
Question back to autism.
And man, must you get a lot of questions about autism?
So my apologies, but I want to use that example
because, and this will underscore my ignorance
in so many of these topics.
But if we're looking at a narrow definition of autism,
so we're not succumbing to the scope creep
in the DSM or elsewhere,
where suddenly everything and its cousin is autism.
But focusing more on the fragile X
and that type of narrower or more specific definition.
When I then think of a critical window,
what is the interplay of the genetics
and the critical window when it is untreated, right?
When you don't have an intervention.
Does that mean that there is a critical window,
but it's narrower or for whatever reason,
the child is less adaptive in that critical window.
So it's not genetic determinism.
It's not like if you have this particular phenotype,
you're destined to get autism
and that you can unwind the clock
or rewind the clock in a sense
with potentially something like psychedelics
to give them a second shot on goal.
I know I'm asking this in probably a very clumsy way
because I don't understand exactly why it would work.
But why would reopening the window
help someone potentially with autism
if they weren't able to capitalize
on a similar window earlier themselves?
Autism is a little bit complicated
because it's a multifactorial disease.
So let me just give a different example
to help clarify and maybe make it clearer
why what we think is the way that psychedelics
could be used for autism and that's with vision.
So one of the early observations of critical periods

is that if a child is born with bilateral cataracts, okay?
And then you remove those cataracts and they can see.
But if you wait and you don't remove those cataracts
until they're aged six or seven,
then even though the physical impediment to vision is gone,
the brain cannot adjust to the visual inputs anymore.
And so the child remains blind forever.
And that's because there is a critical period
before setting the strength of the synapses
or visual inputs.
And once that critical period is closed,
even though the primary impediment
or the primary injury has been resolved,
it missed its opportunity to wire properly
for the visual environment.
And so they'll be blind forever.
So the idea there is if you miss the window
and the child didn't have their cataracts removed
until they were seven or eight years old
and you paired cataract removal surgery with psychedelics,
then the idea would be that if psychedelics
can reopen visual critical periods,
then the idea would be that you would be able
to restore vision because you would be pairing
the primary intervention, which is the cataract
removal surgery with the reopening of the critical period
to give the opportunity to learn
from the visual environment in the natural way.
And so with autism, it's the same idea.
We're saying, okay, there's a genetic impairment
that causes autism, which we think is related
to an imbalance at this one specific receptor,
which we can correct by targeting that receptor.
But if we just do that alone
after the social critical period has closed,
then they still remain socially blind, if you will,
because we missed that window.
So the idea is if we could pair that M-Gluar therapy
with a psychedelic, then we could restore the imbalance
and also restore the ability to learn
from the social environment so that they can,
under those corrected conditions,

have a shot at learning the ways of social interaction,
the way they would have during natural development.
Got it, thank you.
That's very helpful.
Just a quick thanks to one of our sponsors
and we'll be right back to the show.
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Check it out.
I want to just perhaps mention,

and this is actually from the microdose,
which is a great newsletter.
You were featured in the microdose from UC Berkeley
not too, too long ago.
And some people listening may wonder
why we shouldn't always leave our critical windows open.
Wouldn't that be great?
We could learn everything and anything.
And I just want to read something here
and then we can move on,
although we could expand on it.
When you talk to people around psychedelics,
it's like hurting kittens.
They're paying attention to everything.
Look at this leaf.
The shoe won't fit, et cetera.
And they're in full explorer mode,
which is wonderful, but it's not very efficient.
Habits get a bad rep,
but you couldn't get out the door if you didn't have them.
Living in a world where you're trying to learn
and pay attention to everything
is emotionally and energetically costly.
And we could certainly expand on this,
but needless to say, there is a lot to be said
for a stable version of reality
with certain scripts that run reliably.
Is there anything you would like to add to that?
I would just expand on that a little bit
by pointing out that, you know,
the reason that we have critical periods at all
rather than being sort of genetically encoded
with everything that we need to survive in the world
is because the world is big and varied.
And if you genetically encoded everything,
you probably would be very limited
in how you could navigate that world.
My parents are Turkish.
If I was genetically encoded with Turkish, you know,
the fact that I grew up in the United States would be,
it would make my life very difficult
because I wouldn't speak English, I would speak Turkish.

But because I have a language critical period,
I am genetically, what's genetically encoded
is that the ability to learn a language,
not the language itself,
that ability to learn from our environment
is why we have them.
But as everybody knows,
being a teenager sucks, it's hard, it's painful.
It's really very emotionally draining
to constantly be checking yourself,
trying to figure out how you fit in.
And sometimes you wanna just get on with it.
And if the environment that you're in is stable,
then you don't need to necessarily be adapting
or adjusting your model of the world
every single move that you make.
And so that's why we think that critical periods close.
But then another question is,
why does the brain have a sort of ready-made mechanism
that psychedelics can tap into
for reopening critical periods, right?
Like why can we reopen them so easily
if the brain wasn't already built to do this?
And this is, you know, really me speculating,
but I suspect it's because when we have these habits,
they're adaptive so long as the environment is stable.
But then there's a radical shift in the environment,
then you can imagine that it would be adaptive
to be able to reopen critical periods
and relearn from your environment.
So going back to the language example, you know,
as long as everybody around you speaks English,
it's probably not all that adaptive to be learning Spanish.
But if you move to Spain or you move to Central America,
then suddenly nobody's speaking English
and you wanna be able to learn the language
that everybody's speaking around you.
And so we have a little bit of other evidence
that this deprivation technique
of reopening critical periods,
which has been described for things like the visual system,
the sensory system, a little bit in the motor system,

there's evidence for this,
that this deprivation induced, you know,
can also reopen our social critical period.
So here's another rule that kind of applies
across critical periods is that deprivation is a technique.
And so this might be the explanation, for example,
for why it's easier to learn Spanish
if you go to Guatemala than if you go to Costa Rica,
because in Costa Rica, everybody speaks Spanish,
but everybody also speaks English, right?
So it's very hard, you're not deprived of English,
you're just exposed to Spanish.
Whereas in Guatemala, almost nobody speaks English,
and so you're deprived and you get the language.
So that's one idea that we have, we haven't proven it.
But the other part of that is that it's an interesting
to note that historically religious practices
across many, many different cultures
have used deprivation techniques
to get to that mystical state
that people talk about Zen Buddhists call it beginner's mind.
If you were looking for a neurobiological description
of beginner's mind, reopening critical periods would be it.
And so what we think possibly is that,
remember how I said that I was, as an undergrad,
I was really interested in getting around
to using neuroscience to answer the really big questions
that philosophers seem to have exclusive domain for?
Well, this might be it.
It might be that if what it feels like
to be in that altered state of consciousness
or that mystical experience
that we think of with psychedelics
is just what it feels like to reopen critical periods,
then this explanation, this critical period explanation
gives us a mechanistic handle
to start answering those big questions like,
well, what is consciousness?
Well, what is that mystical experience?
What does it mean to feel like you're an altered state?
In the course of my reading,
and feel free to correct anything that I misstate here,

but part of what makes catalyzing prosocial behavior
in octopus is so interesting with the use of, say, MDMA,
is that the nervous system of an octopus
and the anatomical structure, sorry,
as compared to humans, are so different, right?
So in humans, we might attribute some of the outcomes
that we see or therapeutic effects
to, I believe, the nucleus of Cummins,
but then you look at an octopus, no Cummins, no amygdala,
no default mode network, no prefrontal cortex.
What have you gleaned from the octopus work
as it relates to critical periods
and or interesting characteristics of MDMA?
Tim, I'm really glad that you asked that question
because I think that possibly a lot of people
in your audience know a little something about psychedelics
and they've seen the studies
where people have been given psychedelics
and they take an fMRI image and they point to, you know,
this brain region or that brain region and say,
ah-ha, this is where psychedelics are working
and they get this sort of warm and fuzzy feeling
like, I understand now what's happening.
And as a neuroscientist, I am susceptible
to that interpretation as well.
I don't do it with fMRI.
I do it with circuit mapping and viral mediated gene transfer
and look at it at a much higher resolution
than fMRI imaging allows.
So my lab, we do wholesale patch clamp electrophysiology
so we can do single neuron resolution
of these kinds of anatomical maps
of what neurons are getting turned on by psychedelics.
And from those types of analyses,
we get this satisfying feeling like, ah-ha,
MDMA is causing the nucleus accumbens neurons to light up.
It's causing the oxytocin neurons
and the hypothalamus to fire and release oxytocin.
We got it.
We understand how these work.
And I think the really, really compelling thing
about the octopus study and why so many people

who are not lay people, just regular scientists
who are a little bit shaken by this octopus paper
is because it challenges that very comfortable place
that we've all been sitting with circuit mapping
that we have an answer.
And what it says instead is that, yeah, okay,
those anatomical results matter
and they're telling us something,
but they're not telling us the general rules
of how you build complex behavioral functions
from synapses, circuits, brain regions.
And instead what they're telling us is something
like the historical accident or the evolutionary byproduct
of one animal's history of how they came up
with this solution.
But we haven't really learned anything about
what are the generalizable principles?
What are the motifs?
What are the rules governing those circuit level rearrangements
that enable complex behavior?
What are some other ideas in your mind
that need challenging or that could be challenged
just writ large in psychedelics
or psychedelic related science?
I think the two big ones that I have,
let me start with, since I'm already beating up
on the people who do human research a little bit,
let me just challenge the idea
that we can only understand what psychedelics
are doing in humans.
I think for the early part of,
well, the last decade and the early part of this one,
there has been this idea
that really the cool and interesting part of psychedelics,
you can only understand by studying it in humans
because humans are the only ones who do the
behaviorally complex enough things
that you would wanna know about what psychedelics are doing.
I consider Alexander Shulgen to be an elder
in this field for me.
I met him when he came to visit MIT.
I have this goofy picture of myself

as this young little neuroscientist,
all enamored of Alexander Shulgen,
and I think he was very much a proponent of this view
that he needed to take the psychedelics himself
because really the interesting part
of what psychedelics are doing,
you can only know on a personal level.
And I wanna push back against that idea
because I think that as we start to get a better handle
of what they're actually doing in mice,
we may be able to come up with things that generalize
because after all, humans didn't just emerge out of nowhere.
We weren't plopped here on earth by aliens.
We evolved just like all other animals on earth.
And so we were subject to a lot of the same rules
and we came up with some mostly overlapping solutions
and some unique ones.
And so I think we will eventually get to a point
where we can study the really cool and interesting parts
of what psychedelics are doing in animals
as well as in humans.
And I think that our critical period idea
is one step in that direction.
I think that many people in your audience
may have also heard of the idea
that psychedelics are inducing plasticity.
And I'm very careful not to use that word
if I can avoid it because plasticity is a word
that is thrown around a lot
and it means a lot of different things
to a lot of different people.
So for a synaptic neurophysiologist,
it has a very specific meaning.
It's about the something that you can record
from doing wholesale recordings
or patch clamp recordings or even unit recordings
in the brain, but it's an electrophysiological property
that is defined between two synapses.
Whereas the clinicians basically use plasticity
to mean anything that changes over time,
which is so general it sort of loses meaning.
And so I try not to use that word as much as possible.

And especially in the context of psychedelics
because some people have tried to make the argument
that what psychedelics are are so-called psychoplastogens
or drugs that induce plasticity.
And this is an inaccurate and confusing terminology
that I would really hope we could abandon
because there are drugs that cause plasticity
in the way that that word implies
and they're all drugs of abuse.
So heroin, nicotine, cocaine, amphetamine,
these are all psychoactive drugs
that cause robust bi-directional plasticity.
They cause the neurons to sprout,
they cause the neurons to shrink,
they cause robust changes.
And it's that very plastic or hyperplastic property
that we think underlies their addictive potential
because that exaggerated sprouting
or that exaggerated plasticity,
we think is what enables drugs of abuse
to kind of override the breaks on learning and memory
that are normally part of naturally rewarding stimuli
that allow memories to be sort of encoded
in a way that are driven by limitations on association.
So let me give an example
because I'm sort of fumbling a little.
So the example I like to give
is that a natural reward like food, for example,
we like food and if I like a, let's say a turkey sandwich,
I might remember the memory that I formed
to a turkey sandwich that I just ate and loved
would be something like,
oh, I love that turkey sandwich.
Next time I'm hungry and I'm in this neighborhood,
then I'm gonna go to that store
and buy that sandwich again, I loved it.
But for drugs of abuse,
we override those kinds of associative constraints
on when we want the thing.
And a drug of abuse like cocaine or nicotine,
it sort of doesn't matter if you're hungry
or you're in the right neighborhood

or it's not out of your way, you just like it always.
And that very ability to override that constraint
is what we think the hyperplasticity
is encoding and enabling
and making those drugs so much more addictive.
And so I wouldn't want people to confuse that property,
that hyperplastic property
with what we think is actually happening with psychedelics,
which is that psychedelics, we believe,
and there's starting to be other evidence
to support this view,
are enabling what's called metoplasticity,
which I know that it's confusing terminology,
hyperplasticity versus metoplasticity,
but metoplasticity is an idea that's been around
for over 20 years now
that says that the ability to induce plasticity
also can change over time typically.
So when you're young, your ability to induce plasticity
is greater than when you're older,
the ability to induce plasticity declines.
And there are molecular things that control that.
You were mentioning that plasticity
can mean a lot of different things to different people.
So in this case, the ability to induce plasticity,
what does plasticity mean to you in this use?
So the metoplastic definition,
I mean, it's a very specific definition,
plasticity of plasticity.
And in that case, it was defined by Mark Bear
and Cliff Abraham, and it was a synaptic physiology.
So it's, you know, synaptic plasticity,
the change in response of stimulating one synapse
and the magnitude of the response changing
when you're recording the post-synapse.
So very narrowly defined again.
So metoplasticity originally was used
to define what happens in the reopening or the closure
of the critical period for ocular dominance plasticity.
And it was defined primarily in terms of the change
in the subunit composition of the NMDA receptor,
which is one of the receptors

that's been so heavily implicated in learning and memory,
and specifically also learning and memory
with regards to visual processing.
Does that mean that ketamine
would have any particular applications
to studies involving visual processing?
I'm just thinking, given the,
seems like there's a decent effect
at the NMDA receptor level with ketamine
when you look at chronic pain and other things.
Is that the case, or is it not so much?
There are a variety of things
that have been attributed to the NMDA receptor.
For a long time, it was my favorite receptor,
and I guess why.
I know it's super nerdy to have a favorite receptor, but...
I'm into it, I'm into it.
So NMDA receptors are fast neurotransmitter receptors,
but they're different from AMPA receptors,
which are the other major subtype of glutamate receptor,
because they have something
that the way the receptor is designed
is that it's blocked, usually, by magnesium.
And only when the neuron is active
or the membrane potential changes
and the magnesium no longer wants to sit in there,
that magnesium comes out.
So because of that property,
the NMDA receptor is thought to be
a natural coincidence detector.
So it can detect when two neurons
are firing at the same time.
And that has gotten neuroscientists
super excited about the idea
that this is exactly the type of coincidence detection
that would be necessary at a cellular level
in order to encode memories, okay?
And this idea has been around for a while now.
It's why people are excited about the NMDA receptor.
Incidentally, it's also thought to be
why ketamine and PCP interfere with memory.
They do cause impairments in memory

because they mess with the receptor
that we think is super important for encoding memories.
Now, in terms of this critical period idea,
NMDA receptors, they're made up of different subunits,
and the composition of those subunits
changes over development, right?
So very early in development,
the NMDA receptors have the subunit,
the B subunit is more predominant.
The way I remember that is that that's the NR2B subunit
is for baby, and then the A subunit is for adult.
So as the brain matures,
then the subunit switches out and it goes from being
to B heavy to being to A heavy.
And what that does to the receptor
is it makes it more or less likely
to be able to induce that synaptic plasticity
when the glutamate binds to that receptor.
And that is the sort of original first classical
understanding of what a meta-plastic change
would look like.
It would be the change in the subunit composition
of the NMDA receptor that enabled the baby receptors
to induce plasticity more readily
than the adult receptors do.
And just to try to recap my understanding,
which will hopefully help the audience track as well,
jumping back to the autism example
and the fragile X or FMR1,
the joint therapy would look like using the compounds
such as possibly a psychedelic
to increase the meta-plasticity
followed by or maybe simultaneous
with the administration of the drug
that was so disappointing in human trials
because it was administered to adults
who had already switched to a different dominant subtype.
I'm getting close.
I'm not quite there, but you see.
You're very close and you're actually sort of picking up
on something that is a hesitation I have
about using psychedelics and autism.

So there's another, a third type of glutamate receptor
that I love.
It's called the metabotropic glutamate receptor, the M-glue R.
And the metabotropic glutamate receptor
we think is the one that whose signaling
is so altered in fragile X.
And the metabotropic glutamate receptors
are also implicated as their brain matures,
their expression goes down.
And so we think that that coincides
with the closure of the critical period.
And what we think is, is that in fragile X
that M-glue R signaling is exaggerated.
It's kind of not being curtailed in the right way.
And so we have some evidence to suggest
that autism might be caused by a failure
to properly close the critical period.
So even though theoretically I like the idea
of combining negative allosteric modulator of the M-glue R
with a psychedelic that can reopen,
say the social critical periods through metoplasticity,
in this case of a different receptor,
I think in this case it would be the oxytocin receptor
that would be the relevant one.
I am a little bit hesitant to jump into human trials
for that without first testing the safety of this
in mouse models because again,
there's this tension between there's some idea
that the pathogenesis of the disease is related
to a failure to close the critical periods properly.
So I'm not sure that reopening them later
is going to be necessarily the right way to go.
So it's still a hypothesis that we're testing.
How does allergies or how do allergies fit into this?
I've become very, very interested in allergies
and all sorts of not to paint with too broad a brush
sort of autoimmune questions,
specifically as related to psychedelic compounds.
How do allergies fit in?
Well, first I should premise this by telling you
that my mom is an immunologist and she hates this idea.
So she and I spar.

So we spar over this and we have a very different view
of the relationship between the immune system
and the nervous system.
She basically lives in an immune centric world
where the nervous system is just like a downstream effector
of the immune system,
which is the primary controller of everything.
And obviously I think it's the other way around.
So the idea with allergy is this.
There is some epidemiological evidence to suggest
that allergy has a higher prevalence in countries
where the food and the water is largely parasite free.
And so that part of the immune system,
which is ordinarily used to fight off parasitic infections
is left jobless.
So the idea is that in that state of joblessness,
it sort of goes out looking for another threat
to fight against, to protect the body against.
And in this formulation, I am thinking,
well, what if how that threat gets assigned
is really through the brain?
The brain is saying, okay, well, that dog is barking at you
and your immune system is left jobless, that's threatening,
go fight against the dog proteins, right?
If that's true, at least in a subset of patients with allergy,
then you can imagine that reopening
that learned sort of threat,
that critical period for the learned threat
that's misassigned would enable people to unlearn
the association between dog and allergy.
That's a very different way, for example, of looking at it
than the way that some people focus on psychedelics
to think of it as they have these anti-inflammatory properties
which I think are true,
independent of this critical period explanation.
And that property might be beneficial
in allergy sort of independent
of this learned association framework
that I'm proposing around the critical period.
So we just don't know yet.
I like the idea though, because there are a few anecdotal
stories of, I think Andrew Weil has a story

where he cures himself of-
Yeah, I was gonna bring him up.
Cats. Yeah.
And I mean, I love the idea because I actually
kind of wanted to be a veterinarian,
but I'm allergic to horses, dogs and cats.
So I would love to take psychedelics
and cure myself of those allergies.
And while I love this idea, I don't believe it enough yet
to take a bunch of psychedelics and go snuggle up to a horse
because I think we could be looking at anaphylactic shock
in that situation.
So I don't believe it yet,
but I like the idea as something that we could test.
Okay. So I'm glad you brought up Andy
and not the sole example.
I mean, I have an understanding
the plural of anecdote is not data,
but nonetheless, sometimes helpful
for generating hypotheses.
This is something that's been in the conversation
with numerous anecdotes for a while.
And I guess what I want to ask next
is whether it's autism, stroke or allergies,
and I do want to come back to stroke.
When we are talking about reopening critical windows
and in the introduction, in your bio that I read,
we had MDMA, LSD, psilocybin, ketamine and Ibogaine,
which act on quite a number of different receptors.
LSD seems particularly promiscuous,
maybe Ibogaine as well.
But broadly speaking, are we talking about
increasing postsynaptic sensitivity
in which case they could be hitting different receptors,
but as long as it's eliciting that type of sensitivity
that is associated with earlier critical windows,
it fits the description of reopening the critical window.
Let me back up for a second
and just explain that there's sort of a debate
going on in the field right now
because there are, if you look back in the textbooks
written in the 70s and 80s about psychedelics,

textbooks written by people like Solomon Snyder
who started my department at Johns Hopkins
and discovered almost every neurotransmitter receptor
you've ever heard of, including, by the way,
the serotonin 2A receptor,
their definition of what a psychedelic is was very broad.
So they basically said it's anything
that causes this altered state of consciousness,
altered perception of time, space, body, cells.
These were all sort of things that psychedelics do
and they included psychedelics ranging from ketamine, PCP,
what people are now trying to call
the classical serotonin psychedelics
like LSD, mescaline, psilocybin, DMT.
And then also the weird ones like MDMA and Ibogaine.
And both Snyder and Alexander Shulgen
considered all of those drugs to be psychedelics.
More recently, there has been this push,
mostly led by the chemists, to say, oh, no, no, no, no, no.
If we look at the receptor binding properties
of these drugs, the classical psychedelics,
the hallucinogenic psychedelics,
they're all serotonin 2A receptor binding.
And even though they're promiscuous,
even though they're binding to a bunch of different receptors,
the psychedelic effects seem to be mediated
by this receptor using pharmacology studies in humans.
And they are really pushing hard to kind of exclude MDMA
and Ibogaine and ketamine
from the definition of classical psychedelics.
But I personally feel that this is putting the cart
before the horse because we don't know
that that is necessarily a good boundary
for defining psychedelics.
First of all, because we know that most of the psychedelics
are very promiscuous in their binding.
Second of all, we don't really understand
whether or not the 2A receptor is required
for the therapeutic properties, right?
So there is some evidence that there are antidepressive
properties that may or may not be blocked
by serotonin receptor antagonists.

There's two papers that have exactly opposite results
about this right now.
I am not entirely convinced that those antidepressive properties
that they're measuring have anything to do
with the durable, context-dependent, long-term therapeutic
effects of psychedelics that we see in humans.
And so, I think it's up for debate
whether or not the serotonin 2A receptor is required.
But what we do know is that psychedelics
that have primary binding at, you know, NMDA receptors,
serotonin transporters, serotonin 2A receptors,
kappa-opioid receptors, ones that span
the diversity of receptors all show some therapeutic effect.
And so, our lab has really been focused
in trying to understand, well, what's the commonality
across all of those receptors?
And so to kind of in a long-winded way
get back to your original question,
what we wanted to know is what's downstream
of those receptors that's common
to all of those psychedelics?
We don't have the complete answer yet,
but the answer that we're coming up upon
is that it's not the receptor,
it's not even one step downstream of that.
People have been excited about the possibility
that changes in biochemical signaling
at the level of beta-arrested might be the next step
after the receptor that might be common.
We don't see that to be the case in our studies.
And what it seems to be is downstream of that even more,
which is regulation of the extracellular matrix,
which we think is sort of the final common pathway
that happens.
And the working model that we have is that psychedelics
bind to their receptor.
And when they sit in that receptor for too long,
it signals to the cell,
oh no, oh no, excited toxicity is coming,
hit the reset button.
And what that does through a variety
of different mechanisms is we think,

and we don't have strong evidence to support this,
but this is our working model,
is that that hit the reset button involves
calling in all of the receptors,
internalizing them, cleaning up the synapse,
degrading the extracellular matrix
that is sort of holding the synapse together
and the last step of making a synapse mature and stable.
And that sort of hard reset is enabling
the reintegration of those baby receptors
that are more sensitive and able to induce plasticity.
That's sort of our working model.
So I'm curious just to revisit Kappa opioid for a second,
because the only Kappa opioid agonist
that I'm familiar with is salvanorin A.
Some people may know salvia divinorum,
which from a phenomenological perspective
to get real fancy, subjectively,
people find it typically pretty dysphoric.
And I'm just wondering how perhaps it's not salvanorin,
but any Kappa opioid agonist might be used therapeutically
what applications might exist.
I mean, people have been excited about Kappa opioids
because it's sort of thought to be
that's going to be the one that's going to make you
not be addicted to it and it's not very pleasurable,
but because it's not very pleasurable,
you know, nobody wants to take it.
I don't want to overstep the Kappa opioid stuff.
The reason that we got interested in it
is because Ibogaine also has high affinity
for Kappa opioid receptors,
but it also acts as serotonin transporters.
So I really don't know what the answer is there.
I thought the beta arresting story
was going to nicely sew everything up and it just didn't.
What is beta arresting?
I'm going to plead ignorance.
I don't know what that is.
So basically most of the psychedelic drugs
except for ketamine and PCP
are acting at what are called G protein coupled receptors.

Okay, so when I was talking about NMDA receptors
versus M. gluar receptors,
the differences M. gluars or G protein coupled receptors
and NMDA receptors are ion channels.
So they're inotropic receptors, right?
So metabotropic, inotropic,
it has to do with how they're coupled to internal signaling.
So all of the G protein coupled receptors,
including this almost all of the serotonin receptors,
they work by when the drugs binds to their binding pocket,
they induce a series of biochemical events,
either excitatory or inhibitory biochemical changes
downstream that are sort of the second messengers,
if you will, of the receptor binding, okay?
Now that's just how they normally signal.
But when a drug like LSD binds to the serotonin 2A receptor,
Brian Roth's group has shown
that when it sits in its receptor,
it has an unusually long off rate.
So normally when transmitters get in their receptor,
they jump in and they jump right back out.
So they pop in, pop out really, really fast, okay?
Less than a second time scale.
LSD, when it sits in the serotonin 2A receptor binding pocket,
a little lid kind of comes down and locks it into place.
And when that lid locks the LSD into place,
its off rate goes to four and a half hours,
which is like insane, right?
It's gonna be a long night.
It's gonna be a long night, exactly.
So, and that's the half off.
So only half of it comes off in four and a half hours, right?
And so this was like a really important insight
into why it is that LSD's effects last so long.
But when it sits in that receptor for too long,
instead of signaling through the normal
G protein coupled signaling pathway,
what happens is it starts sending signal to the cell,
no, instead of G protein,
you need to hit a different biochemical pathway,
we need to trigger beta arrestant.
And beta arrestant is just another biochemical pathway

that gets triggered by that receptor
being activated too long.
And what is thought that beta arrestant does
is rather than do the second messenger signaling,
it says to the cell, pull that receptor out,
we're about to get toxic damage
from too much receptor activation.
So beta arrestant signaling historically
has been thought to be a signal to the cell
that says, pull in the receptors.
I really loved the idea that even though
not all psychedelics bind to the serotonin 2A,
most of them, you could imagine a scenario
where they were triggering beta arrestant signaling
over G protein coupled signaling,
and that if you knocked out the beta arrestant protein
that you could block the ability of psychedelics
to reopen critical periods.
And while that was true for some of the psychedelics,
it turned out not to be the universal mechanism
that spans across all of the psychedelics.
So that was a little bit of a bummer, I have to say.
Cause I thought, all right, we'll solve it, it'll be done.
And, you know, I can rest easy,
but it didn't work out that simple.
And Mother Nature always likes to trip us up like that.
Yeah, then the Mother Nature curve balls
seem to come more often than not.
I do want to get to strokes and how they fit in,
but before we get there, I have to scratch an itch
because I've been wanting to ask you for a while now.
First, a bit of background.
You mentioned Alexander Shulgin,
also known as Sasha Shulgin,
for people who don't recognize the name.
Incredibly adept, incredibly prolific biochemists,
very much recommend people check out Pekal and Tikal,
which he wrote with his wife.
But the contrast you drew earlier
was one of, say, maybe human centricity.
So he not only created or resurrected
hundreds, maybe thousands of different psychedelic compounds,

but also was a very dedicated self-experimenter.
And the tasting parties were very famous, of course.
Where do you most strongly perhaps agree or align with Sasha?
What are things that you perhaps have in common
if anything comes to mind?
I got to tell you a funny story
of when he came to visit MIT
when I was a graduate student.
It was sort of the opening party for the new building.
And I won't name any names, but there were,
everybody had invited a bunch of Nobel Prize winners
who had discovered every cool thing in biology.
And they all got up there
and not necessarily knew anything about neuroscience.
They were all sort of older
and they kind of gave a little biography
and then sat back down.
And then Sasha got up on stage
and he was just basically the same age as everybody else,
the only person without a Nobel Prize on that stage.
And yet he was so alert and so adept.
And he was like, oh,
and then we added this methyl group over here
and this happened and the behavioral response.
And then we did this and we got ego this
and we put that on there.
And all of the neuroscientists were just like
wrapped attention, right?
Because this is it.
This is what we all dream of as neuroscientists
is to have some manipulation that we can give,
in this case, a drug that is dramatically altering
the way that the brain is functioning
and interpreting the world around it.
And here is this chemist sort of explaining to us
how this could be done just by adding a methyl group
in this position versus that position.
And we were all just like blown away.
I don't think there was anybody who walked away
from that lecture thinking, gosh, you know,
psychedelics should just stay in the backwaters.
We shouldn't care about this as neuroscience.

Obviously not, right?
And in fact, it's how I got excited
about neuroscience to begin with.
I took this class when I was an undergrad
called Drugs Brain and Behavior.
And in that class, you know, the first day
I saw the photograph of the molecule of LSD
sitting right next to the molecule of serotonin
and the similarities between them.
I was like, this is it.
This is how we're going to crack it.
This is how we're going to get
at those hard questions of neuroscience
because here are chemicals that can alter
our entire sense of reality, consciousness, perception,
time, self, space, everything, right?
And I am not alone.
I think most neuroscientists who have tried psychedelics
would have exactly the same response.
And the difference between me and Sasha really
in terms of our approach is that Sasha comes
from an older tradition in science,
which was very much prioritize the
do the experiment on yourself idea.
And that has a long and glorious tradition in science.
So for example, we have a cure for ulcers
because there was a biologist who was convinced
that those were caused by a bacteria,
but nobody believed him.
So he drank a vial of bacteria, gave himself ulcers
and then took a bunch of antibiotics
and cured himself of the ulcers.
And he won the Nobel Prize for that.
The difference is with psychedelics
is that that's a little bit trickier to do
because psychedelics have this property,
which William James pointed out over a hundred years ago
of creating this sense of what he called
the noetic property, this feeling that
now that I've had this experience, I know the really real.
The true truth has been revealed to me
and everything before this moment was just a facade

or some lesser truth or some limited access to the truth.
But now I really know.
And so for a scientist, that's pretty dangerous.
For a scientist, you always wanna be able
to have a little bit of skepticism
about what it is that you have discovered.
You always wanna keep your ideas as sort of provisional
until the next test comes along,
until it should always be a working model,
never this is the 10 Commandments of Neuroscience.
That's not the way that we do science.
And so the noetic property I think does mean
that that experiment where you take a bunch of bacteria
and give yourself ulcers is a little bit harder
to justify in this Neuroscience now.
So that's how I...
Hard to be an objective or strive
to be an objective scientist
if you turn yourself into David Koresh accidentally.
How do strokes fit into this?
For a long time now, clinically, we have known
that right after you have a stroke,
you have this very short window of time,
really, really closed by three months,
but really you wanna get in there
within six weeks to two months or so,
where physical therapy is going to have
its maximal effect or benefit for helping you
to recover the motor function that you lost
because of the stroke, okay?
And that window of time,
we don't exactly know why it closes,
but it seems to be that it's not that
the damaged part of the brain
suddenly resprouts neurons,
it's that the brain regions immediately adjacent
to the damaged part of the brain become flexible again
and able to perform or control the motor functions
that were lost by the brain region immediately next to it.
And that window closes,
just like all other critical periods close.
And so far, the best way that we have

for reopening that critical period
is to give another stroke,
but nobody wants to cure stroke by giving another stroke.
That's just not a clinically useful way.
Hard to sell, hard to sell that.
Yeah, definitely hard to sell.
Even harder, you know, we like the idea
that maybe we could branch out into other critical periods
like this one to see whether or not psychedelics
can reopen that critical period for stroke.
And we have a collaboration with Steve Zeiler,
who's a neurologist at Johns Hopkins,
who has developed a rodent model
for that critical period of motor recovery following stroke.
And he also has a stroke clinic at Hopkins.
And so we're working closely with them
to see whether or not this idea
really can help these patients,
which basically it's a 400,000 patients a year
in the United States who have debilitating,
lasting impairments because of stroke.
So it's a huge number of people.
And it's super exciting because, you know,
here's something that we started out with,
ooh, I'm just curious what MDMA will do in an octopus.
It was totally curiosity-based science.
And to see it evolve into something
that can potentially help so many people
is, as a scientist, just super gratifying.
It's pretty rare.
Nobody really gets to have those kinds of woohoo success stories.
And so that's very gratifying to me on a personal level.
But also I think that for all of the psychedelics
enthusiasts out there,
it's a lesson in how important it is to never stop learning,
never stop questioning.
You know, I think there was an intuition a few years ago
that, well, you know,
indigenous people have been using psychedelics forever.
We don't really need to understand their mechanisms.
We don't really need to dig into
how it is these things work

because we know they're gonna work
because they've got this long history behind them.
But I think that if this ends up being true,
that this mechanistic explanation
can really open up whole new avenues
that people hadn't been thinking of before,
then I think that that's a testament
to the importance of always keep an open mind,
always look for more answers, more questions,
and keep searching.
Absolutely.
And I would also say,
even if, let's just say hypothetically,
these various indigenous cultures have figured it out,
let's just take that as an assumption for a second.
They figured out how to use these things,
but the scale at which they're used
and the context within which they're used
are on the order of, say, max 100 or several 100 people
within the safety net of certain rituals
and familial and social support structures
that it cannot be replicated at scale
in, say, a Western treatment paradigm,
you need new tools.
And that requires exploration and testing.
Let me just riff on that for a second
because I think that that's a really important point
about the context.
So the context of disease is also different
in this culture versus other cultures
and how a disease is defined is different across cultures
and how you might approach a disease
is defined differently across cultures.
And so a good example is the way
that Ibogaine is used traditionally.
In these cultures that using Ibogaine
for traditional healing practices,
it's not just that the person taking it
has a disease and they're being treated.
It's sort of a mix between they have a disease
but they also have something to share
with the rest of their community.

And the whole Ibogaine experience is encapsulated
in a bunch of things that we as Western doctors
might dismiss as just ritual,
but include things like face painting and social touch
and the whole community is involved
for this three day long trip
that the person goes from one house to another.
And it turns out that a lot of those elements
that we might not necessarily recognize as important
that we might dismiss as ritual in a mouse,
we can recapitulate.
We know that MDMA's ability to reopen
the social critical period is social context dependent.
If we give it in isolation, then it doesn't reopen.
So it turns out that there are all of these elements
that go beyond just the molecule
and we can't just import, take the thing that we decide
is the most important element, the molecule
and import it into our medicinal practices
and our cultural history without understanding it
because many of those elements of the ritual
might be actually really important
to how these drugs are working therapeutically.
And unless we understand it from our context,
we won't be able to readily adapt.
100%.
And to maybe clarify the point I was trying
to make somewhat in elegantly,
I think all of these practices are worth studying,
especially the things that have had some degree
of longevity and persisted over time
that seemed to be adaptive
or could potentially plausibly be helpful
in the therapeutic effects.
And I push back, maybe it's because I'm in Austin
and you can't throw a rock without meeting someone
who did a weekend online course
and is now a self-proclaimed shaman.
So I have a certain sensitivity to it,
but this romanticized, I think very naive notion
that you can just copy and paste things whole cloth
from one area to another is not just naive

but also quite dangerous.
And I appreciate you saying what you just said.
If you flash forward in your mind,
I recognize there's some imagination
and speculation required here.
But if this critical period work
and maybe the offshoots of that work
continue to gain support through rigorous science
and evidence, what might therapeutic interventions
or treatments look like 10 years from now?
I'm pulling that number kind of out of nowhere,
but I'm curious to know sort of in your mind's eye
what you think things could look like
if this continues to develop in the direction
that at least now you're pursuing research.
If this ends up being true,
then it's gonna be a pretty big paradigm shift
for neuropsychiatric treatments
because let me just back up and say,
I have to give a little bit of credit to Maps here
because Maps did a lot of really hard work
to convince the FDA that the way
to design clinical trials around psychedelics
was to abandon the sort of one variable at a time test model
and say, look, we really need to pair these drugs
with psychotherapy because the drugs
are not doing the magic by themselves.
It's really this combination that's working.
And so that I think was a big shift in the way
that the FDA wants us to test drugs in clinical trials.
I think that we're beginning to see more and more evidence
that that context is really what matters.
So for example, the clinical trials
where context is sort of secondary,
where the psychotherapy is essentially there
in case somebody has a bad trip,
but it's not really front and center to the intervention.
Then I think those trials for psilocybin, for example,
aren't working as well as the trials where it's really seen
as an adjunct to the primary therapy,
which is the psychotherapy.
Now, if we're right in the critical period reopening

explanation is this shift in the framework
for how we understand these therapeutic effects,
then in 10 years from now,
the way that psychedelics are gonna be used
is going to be trying to identify that right context
for the right disease.
So while an inter-directed trip with a lot of psychotherapy
makes a lot of sense for PTSD and addiction and depression,
it's probably the wrong context for stroke.
Whereas doing a lot of physical therapy and movement
and playing virtual reality motion games
might be the right context
for giving the psychedelic for stroke.
For allergy, maybe the right context is snuggling up
to that horse or that dog or that cat
that you're allergic to, right?
And so I think the future, the therapeutic potential for this,
the opportunity is huge,
but the devil is gonna be in the details
in terms of identifying the right context
and figuring out how to get activation
of the right neural circuit that's relevant
for the sort of brain transformation
that you wanna see happen.
If we take the case of stroke patients, for instance,
if we just assume for the moment
that we're using human subjects,
how might you think about currently
what type of experimental design you would use
with respect to dosing?
Because if you have this less inter-directed,
say higher dose experience with the potential
for these noetic qualities that you described,
but rather your following instructions,
your practicing skills using potentially VR,
do you have any thoughts on how you design the study
or what the minimum effective dose might look like?
There are two questions in there.
Let me just pull them apart for a second.
So the dose issue, our studies that we've done so far
suggest that there's a pretty narrow dose response
for reopening critical periods

that matches what we see in humans
for the acute subjective effects,
but we don't see any evidence
that increasing the dose necessarily increases
the opening of the critical period
or how long the duration of the critical period open state.
So basically what we find is that
if the acute subjective effects are short,
like with ketamine, then the window only stays open
for a very short amount of time, like less than a week.
If the acute subjective effects last a really long time,
like with Ibogaine, which lasts 36 to 72 hours,
then the window, the critical period window stays open
for much longer in mice that's four weeks
and humans that may translate to four weeks
or four months, we're not sure.
But it's not the case, for example,
and then psilocybin, MDMA and LSD are in the middle there
between those two extremes,
but it's not the case that if you double the dose of LSD,
then you can get LSD to open the critical period longer,
for example, and so that dosing business,
I think is gonna be a little bit of a heartbreak
for all of the pharmaceutical companies out there
that are essentially trying to engineer out
the psychedelic effects by shortening the duration
of the psychedelic effects to get less side effects
in a shorter journey that will be easier
to manage in a clinical setting.
And again, what can you do?
Nature is nature, but I do think
it changes the model of how we approach these
rather than thinking of these
as next generation anxiolytics or next generation
antidepressives or SSRIs.
What we really need to be thinking of these
as is more like surgery.
If you have a heart attack,
you go and you have open heart surgery,
it lasts for eight hours,
you have maybe two or three weeks afterwards
where you are required to be on bed rest

and take things easy, but then you're cured, right?
And so who wouldn't rather be cured of a heart attack
than have to be on a medicine for the rest of their lives?
I think most people see that
as the major promise of psychedelics.
So in terms of the therapeutic approach,
I think the way I'm framing this stroke trial
is really like, I'm not worried about the fact
that they're gonna have to do a psychedelic
and potentially the maximum benefit is gonna be
from these long acting psychedelics
because I think that these motor critical periods
are pretty strong closes and so you wanna reopen them
for as long as you possibly can to get the maximal effect
and we'll have to work out how to do them back to back to back
but that's sort of how I'm thinking about it there.
The second sort of thing I wanna unpack
about your question is that you mentioned for the stroke
that you were imagining that we would be giving
a psychedelic and the person would be practicing
a bunch of things in a very specific, directed way
and actually that's not how I'm imagining that this will work.
I got it, it would be more sequential, not concurrent.
No, no, no, it would be concurrent
but I would say it's not gonna be practice-based.
So one of the things that I would want to emphasize
is part of the reason that I paired up with Steve Zeiler
and John Krakauer at Hopkins is that their approach
for treating stroke during the normal
while the critical period is already open, right?
Is that they've said, well, you know,
most of the physical therapy that patients receive
is very goal directed.
It's, you know, I need to learn how to zip my pants
with the other hand.
I need to learn how to comb my hair with the other hand
and so it's very much practical
solving the problem another way.
Whereas the way that we learn those motor patterns
when we're children is much more sort of goal undirected,
kind of play, wandering, don't care if I fall down
a million times.

I mean, there's this great idea that children walk
when they're learning how to walk
will walk the equivalent of seven football fields
in an hour.
Now, the only time I've ever seen an adult do that
is on MDMA.
So they will, they will just dance
and they don't care if they look like fools.
They don't care if they're not good dancers.
It's not goal directed.
They're just enjoying the play of doing the motion.
And so what I like about Steve and John's approach
to motor rehabilitation sort of without psychedelics
is that their virtual reality system that they've built
is very much capitalizing on this
non-goal directed play like behavior.
And I think that's gonna be the key.
And so I think if we can get people on psychedelics
plus put them in this motor play context,
then we can maximally recapitulate the conditions
that we learn how to do motor function
when we're developing his children.
So speaking of fun,
I want to go back in time to Bear's lab at MIT.
And this is from Spectrum News reading a section of this.
He had stressed the importance of science being fun.
And the quote is,
if you lose sight of the fun in science,
it's hardly worth continuing end quote he used to say.
Dolan decided that if she was indeed going to give up
a life of science, she would go out on her own terms.
So could you unpack that last sentence?
Were you considering giving up a life of science?
And then how did that lead to octopuses?
Because it seems like that focus
then opened up Pandora's box in the most positive way, right?
So I want to go back and do a little bit of postmortem
on what exactly happened.
So please, if you wouldn't mind,
just tell the story of that period.
When you start your own lab,
you get a bunch of money and that startup package is great

to kind of get you started, hire some people,
buy some equipment, get your lab established
without having to worry too much about the funding.
But when I started my lab, I got a nice startup package.
I immediately got a couple of private foundation grants,
which were very helpful to help me establish the lab.
But you really can't in academia survive
unless you can also get funding from the NIH.
And these big NIH grants have in my career
and my lifetime have gotten harder and harder to get.
And it used to be that people who were young
and had a lot of creative ideas
had much higher success rates
than people who were older
and kind of just redoing the same experiments
with a different, whatever,
very conservative kind of rinse and repeat type of experiments.
And over my scientific career,
I have seen that situation essentially reversed.
So people over the age of 65
are getting most of the NIH grants.
Junior people are really struggling.
And there have been some attempts to correct that,
but they just haven't worked.
And it's just incredibly difficult to get funding
and then if you add on top of that,
the funding has gotten so conservative
that basically the way that I write NIH grants right now
is like once I have all of the results
that are gonna make a cool nature paper,
I write a grant on all of the sort of boring experiments
that I didn't do it for that paper,
but that I think that the reviewers might ask me for
and I package that together and I send that to the NIH.
That's how conservative my grants really are
when I apply to NIH funding.
And that's been successful,
but there was a moment sort of a few months
before the octopus paper,
before we even did that experiment
where I was just beginning to feel like,
you know, I'm not gonna make it.

I applied to the NIH 17 times
before I got my first NIH grant.
And I think part of it was because I was proposing
these crazy ideas that people were like,
there's no critical period for social behavior.
What? Nobody's ever gonna use psychedelics clinically?
What? No, that'll never work.
Oh, you made those mice too bad.
You didn't use them for the experiment
that I would have used them for.
You're just a junior person.
You have no established track record.
No, no, no, no, no, no, no, no, no.
And I was feeling really demoralized.
And I was like, I can't do this.
I thought I was becoming a scientist
because I was gonna get to pursue these big questions
and be creative and steer my own ship.
That's what I had worked so hard for
as a graduate student, as a postdoc,
and as a medical student.
That was the dream that I was sold.
And I was pretty devastated by how many rejections I got.
And so, in that moment, when I was like,
all right, I'm gonna try a couple more times,
but if I don't get it, that's it.
I'm out as soon as I, you know,
my department was very supportive.
They're like, you'll get there,
you'll get there, you'll get there.
We'll cover you, don't worry,
don't fire anybody, you're good.
But still, it's a blow to your ego
if you can't convince your peers at the NIH
to give you that money.
And so, going out on my own terms,
I was just like, look,
I've always wanted to study evolution.
I've always wanted to do something
to do with marine neuroscience.
I have this opportunity to look at
what happens to this behavior in an octopus.

I'm just gonna go for it, and it'll be fun.
And even if it doesn't work,
even if it is not useful for my career in any way at all,
like, I mean, I would go to these meetings,
faculty meetings, and meetings with my department chair,
and I'd tell them we were planning
to do this octopus stuff, and he'd be like,
Gull, what are you doing?
We hired you to cure autism.
What is this octopus stuff?
Like, what?
And I'd just be like, look, you gotta back off.
This is what I wanna do.
This is what's gonna make me feel like science is fun.
Like, I'm doing it not in a goal-directed way,
in a kind of playful, just out of curiosity.
I just wanna know what happens.
And then it worked, and it revived my sense of play
and joy and feeling like you can do those crazy experiments
that everybody thinks are crazy.
And just to have fun with it.
So you, I wouldn't say bet the farm,
but you were willing to go out
and sort of a blaze of glory and meaning,
just focusing on fun and trying to break new ground.
It worked.
How do you think about, if you do,
sort of preserving that type of willingness?
Maybe the octopus work kind of bought you a golden ticket
to now continuing to do work that is not rinse and repeat.
But perhaps I'm just spinning a story here,
but I can imagine as you get more established,
maybe you feel like you have more to protect.
So maybe there's an inclination to take fewer risks.
How do you think about risk taking moving forward?
First of all, I don't wanna oversell
how big of a risk it was for me to do that experiment.
We were already working on MDMA.
We already had reasonable response from nature
about the MDMA critical period experiment.
The octopus thing was really kind of like,
well, we had the MDMA around and I've always been curious

and I just wanted to see what would happen.
And then a collaborator was like,
well, we have seven octopuses that we can lend you for,
you know, a week.
And I was like, come on down.
He flew down.
He slept on my couch.
We stayed up until like two o'clock in the morning,
every night, like just doing it mad scientists
because we had to send the octopuses back
by the end of the week.
And, you know, it's just like this mad scientist fun time,
right?
And so how do I preserve that?
Well, I guess part of, I think the reason that we as scientists
are seeing less and less of that kind of crazy stuff
is really the funding.
I mean, the funding, just to give a sense of this,
I think this is a really missed point and especially with tech.
So in the fifties and sixties,
the NSF, the National Science Foundation and the NIH
were sort of funding all kinds of crazy stuff
that they just never thought would ever be useful
or have a goal.
They were just funding it.
And so when, you know, Thomas Brock was like,
there are these weird bacteria that live
in these thermal vents in Yellowstone National Park.
Give me some money to go figure out
how they can survive those temperatures.
NSF was like, yeah, sure, here you go.
If they hadn't given him that money,
the PCR test that we all learned
about during the pandemic would not be possible
because that enzyme that is required for that test
is made by those bacteria
that live in those weird thermal vents.
And so I think this non-goal directed curiosity based science,
it doesn't show any usefulness for 40, 50 years.
So it takes that long for something meaningful
to come out of that kind of discovery based,
curiosity based science.

And I think that the way that funding constraints
and the way that tech and even private foundations
are very goal oriented, right?
It's like, well, how can we sell this?
How can we market this?
And the private foundations have names like pure autism now.
They're very goal directed.
And I think that that sort of kills the motivation
or the impetus to just do the weird stuff
that's just for fun and curiosity.
And I would say every person who becomes a scientist
at one point or another had that as their motivation.
And the strain of the funding crisis
is essentially what has forced people
to get more and more and more conservative.
So I don't think I'm unique for wanting to just see
what happens when you give octopuses MDMA.
In fact, I think the reason that everybody responded
to that paper, so well, worldwide is because
every single one of us has that curiosity,
has that, I wonder what would happen, you know?
And it resonated with people.
And I just think it mostly gets beaten out of us
because of funding constraints.
Is there any solution there?
I mean, if you could wave a magic wand,
are there any structural changes
that would help to alleviate that?
Are there any policies?
I'm just wondering if anything comes to mind,
aside from just like, come on guys, come on.
We need the exploratory stuff, the weird stuff.
Otherwise, we're not actually investing
in the sort of long-term serendipity
that has produced all of these world changing technologies.
Aside from just like having drinks with people at NIH
or NSF or elsewhere and having this conversation,
are there other levers that could be pulled
or other changes that could be made?
This is sort of venturing off into politics,
which is a hobby, not my area of expertise.
But I would certainly say that if we look at the percentage

of taxpayer money, well, first of all,
in the 50s and 60s, we collected a lot more taxes.
Today, we give away more in tax breaks
than the entire discretionary budget,
back to big corporations as incentives and tax breaks.
But really, most of those corporations,
the thing that they are making and selling right now,
especially in the tech industry,
are possible because the taxpayers in the 50s and 60s
made those investments in the science and technology areas
to develop all of the computing and software-building
science and research that that stuff was built upon.
Facebook and all of these tech ventures
that we, and Google and cell phones and computers,
they didn't just happen to arise out of America
for no reason.
They came because the United States for years
understood that this was an investment for the wayway future.
And so I think changing our tax structure
to sort of reinvest in the future of science,
it's either gonna happen or it's not.
It's gonna move to other countries and places like China
that are investing in science and technology
in this sort of non-goal directed,
just throw money at it and eventually something cool
will pop out attitude.
I mean, that's just my two cents.
So how about an insult like half your audience, but...
No.
That's what I think.
I don't think you've insulted half the audience, but...
I think, I mean, I do think it's important to say
that the priorities of the government and nation-state
affect so many different components of life
and the future of innovation in this country.
And if you do look back, as you mentioned,
to many of the innovations that came out of, say, DARPA
and other organizations that were fundamentally
funded by taxpayer dollars.
I mean, it is remarkable to look back
at how fundamental many of these technologies have become.
Switching gears, just to ask a few more questions.

Do you have any books that you have shared, recommended
or gifted the most to other people
or recommended often to other people?
Any favorite books that come to mind?
How did we wander into this political sphere?
Probably the ones that I have gifted the most
is a book called Invisible Women by Carolyn Criado Perez.
You know, I really love it because I think it's a book
of feminism that is accessible and I think resonates
with people whether or not you're a man or a woman.
It's just data.
It's like, all right, well, you know,
here's how much it costs to keep ignoring women.
And if you fix it, your city can save a million dollars a year.
It's all about the structural stuff.
It's not about your feelings about whether women deserve
to be in the kitchen or not.
It's not about that.
It's just here's how ignoring data about women's body sizes,
women's travel patterns ends up costing society at large.
And I think it's an excellent way of kind of getting that.
And then the other book that I love the most,
it's a very grandiose title.
It's called The Dawn of Everything,
A New History of Humanity by David Graber.
I actually love everything that that guy wrote.
I started with this book called Bullshit Jobs,
which, you know, I was dealing with like the bureaucracy
of academia and feeling very frustrated.
And I read that book and it was very cathartic.
And then I just kind of went down the rabbit hole
and have enjoyed all the other books.
But The Dawn of Everything, it's a big book
and it's pretty thick,
but the last chapter has some really cool stuff
about psychedelic uses in other cultures.
And then the third one that I really love
is The Immortality Key by Brian Morescu.
I love that book so much.
Like I designed my entire Halloween decoration this year
all around that book.
And, you know, I sent pictures of it to Brian

and he was like, oh my God, you nailed it.
I gotta up my Halloween game.
So yeah, those are the three books that I would recommend.
The Immortality Key is the only of the three that I've read,
but fantastic book, really, really exceptional.
And it has made me want to try to meet archaeochemists
and have more conversations about recreating
the elixirs of Midas and many others.
So we'll see if I ever get around to that.
I have to maybe cut back on my podcasting
to make time for that.
Well, I loved that book also
because my family's from Turkey
and one of the places that he mentions is Ephesus,
which is, you know, an hour and a half drive away
from my mom's house.
And, you know, I'm definitely,
next time I go to Turkey, I'm visiting Ephesus
to try and figure out those Hecate carvings
and maybe take a little soil sample.
Just a little soil sample.
Customs love soil samples.
So, cool.
This has been a wonderful conversation.
We've covered a lot of ground.
Is there anything else that you would like to add?
Any closing comments, anything we didn't discuss
that you'd like to make mention of
or draw attention to before we wind to a close
for at least this initial conversation?
Oh, God, I can't think of it.
I think this has been one of the most fun,
meandering conversations.
I feel like we covered everything.
I look forward to doing it again sometime
because I really do think that in the next few years
we're gonna have some pretty
ground shifting stories coming out
and I would love to come back and share them with you.
Absolutely.
Things are moving quickly.
Things are developing quickly.

And I think we're gonna have a lot of very exciting,
interesting and provocative questions
on the forefront of science in the next few years,
which I'm looking forward to.
And I'm glad that you are very willing
and capable of challenging the,
maybe dominant beliefs or the beliefs to get traction
and are willing to take risks
with the science that you pursue.
So thank you for doing the work that you do.
And it's the best place for people to find your work,
DolanLab.org, is that where you would point people?
Yes, yes.
Perfect.
Well, teshikuradirim, thank you for taking the time today.
Oh, wow, excellent pronunciation.
Thank you.
Teshikuradirim, okay.
Yeah, I love Turkey.
I love Turkey.
The language I'm fascinated with,
that's a conversation for another time,
very similar grammatically to Japanese, oddly enough,
which is where I've spent more time.
But I really appreciate you taking the time today
and being willing and so game
to explore so many different subjects.
And to everybody listening,
we'll have links to the various terms,
stories, people, names, books, et cetera,
that we discussed, including studies.
In the show notes, as always, at tim.log slash podcast.
And until next time, experiment widely,
be just a bit kinder to yourself and others
than is necessary.
And thanks 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

subscribe 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.
It often includes articles I'm reading, books I'm reading,
albums, perhaps, gadgets, gizmos,
all sorts of tech tricks and so on
that 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.vlog.friday, type that into your browser,
tim.vlog.friday, drop in your email
and you'll get the very next one.
Thanks for listening.
This episode is brought to you by Helix Sleep.
Helix Sleep is a premium mattress brand
that provides tailored mattresses
based on your sleep preferences.
Their lineup includes 14 unique mattresses,
including a collection of luxury models,
a mattress for big and tall sleepers, that's not me,
and even a mattress made specifically for kids.
They have models with memory foam layers
to provide optimal pressure relief if you sleep on your side
as I often do and did last night on one of their beds.
Models with more responsive foam
to cradle your body for essential support
in stomach and back sleeping positions
and on and on, they have you covered.
So how will you know which Helix mattress
works best for you and your body?
Take the Helix sleep quiz at helixsleep.com slash tim
and find your perfect mattress in less than two minutes.
Personally, for the last few years,

I've been sleeping on a Helix Midnight Lux mattress.
I also have one of those in the guest bedroom
and feedback from friends has always been fantastic.
They frequently say it's the best night of sleep
they've had in ages.
It's something they comment on
without any prompting from me whatsoever.
Helix mattresses are American made
and come with a 10 or 15 year warranty
depending on the model.
Your mattress will be shipped straight to your door
free of charge and there's no better way
to test out a new mattress than by sleeping on it
in your own home.
That's why they offer a 100 night risk-free trial.
If you decide it's not the best fit,
you're welcome to return it for a full refund.
Helix has been awarded number one mattress
by both GQ and Wired magazines.
Helix is now offering 20% off on all mattress orders
plus two free pillows for you, my dear listeners.
On some mattresses, this can mean savings
of more than $500.
So go to helixsleep.com slash Tim.
This is the best offer that they have made yet
and it will not last forever.
With Helix, better sleep starts now.
So one more time, check it out.
Helix H-E-L-I-X, helixsleep.com slash Tim.
This episode is brought to you by AG1 by Athletic Greens,
a true staple of my daily routine
as it has been for more than a decade.
I take it most mornings and I even travel with it.
Whether I'm skiing, traveling abroad,
going to an event where I'll be around a lot of people,
I just use it to cover all of my nutritional bases.
But let's start with the basics.
What is AG1?
And we'll get to the ingredients.
But I get asked all the time,
what I would take if I could only take one supplement?
The answer is invariably AG1.

And as I mentioned,
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 source ingredients,
you'd be very hard-pressed to find
a more nutrient-dense formula on the market.
I know how much time they put into quality assurance.
And sourcing, it has a multi-vitamin,
a multi-mineral greens complex,
probiotics and prebiotics for gut health,
an immune support formula, digestive enzymes,
and adaptogens.
I always do my best, of course,
to get nutrient-rich meals.
That is a top priority.
But 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.
Furthermore, it's also NSF certified for sport,
making it safe for professional athletes
as what's on the label is actually
what's in the powder.
AG1 is the ultimate all-in-one nutritional supplement bundle
in one easy scoop.
Cause let's face it, if it's not convenient,
you're just not going to use it.
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 one more time,
actually two more times, 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.