Welcome to the Huberman Lab Podcast where we discuss science and science-based tools for everyday life.
I'm Andrew Huberman and I'm a professor of neurobiology and ophthalmology at Stanford School of Medicine.
Today we're discussing stimulants, in particular stimulants for the treatment of ADHD or attention deficit hyperactivity disorder.
As many of you know, there is tremendous interest in drugs like Adderall, Ritalin, Vivants and other stimulants as well as non-stimulant prescription drugs
that have been shown to improve the symptoms of ADHD such as Modafinil, Armodafinil and Guanfacine.
Today I'm going to discuss all of these compounds in the context of how they work to improve the symptoms of ADHD.
I'm going to address common questions about these compounds such as are they just speed?
Are they similar to meth or methamphetamine?
I'll talk about their addictive potential as well as their potential to cause psychotic symptoms both in the short and long term.
And of course I will talk about the scientific literature surrounding the most frequently asked question about these compounds
which is what are the long-term consequences of taking any of them in childhood or in adulthood?
Now today's discussion centers around the use of these compounds both for childhood and for adult ADHD.
But of course I'd be remiss if I didn't acknowledge that there are a tremendous number of people that use these prescription drugs without a prescription
in order to improve their ability to focus and indeed also use them recreationally.
In fact some surveys reveal that as high as 80% of college age young adults have used one or several of prescription drugs
such as Adderall Ritalin Vivants or similar at some point and are doing so without a prescription
so they are either obtaining those drugs from those that do have prescriptions for them for ADHD
or they are obtaining them through black market sources which of course carries an additional and very serious risk
related to the so-called fentanyl crisis that is as high as 75% of black market drugs nowadays of various kinds
but certainly including the sorts of drugs we're going to talk about today are contaminated with fentanyl and therefore are very deadly.
So today I'm going to describe what these various drugs really are, how they work at the level of neurons and brain networks
and how they change those brain networks in ways that really can allow people with ADHD to be able to focus better.
I will answer the common question which is why is it that giving children speed because indeed several not all
but several of the compounds I'm going to discuss are speed, they are amphetamine.
Why would that cause a reduction in hyperactivity if speed is a stimulant?
So I'll answer that question for you and I will also answer questions that are commonly asked such

as how these drugs impact things like sleep,
hormone health, reproductive health, as well as what is their impact on height.
Indeed it was one prominent hypothesis that these ADHD meds could actually restrict the height of children.
I'll tell you whether or not that's actually true or not and I'll discuss the data surrounding whether or not these drugs predispose people
to becoming addicts to other substances even if people cease or continue taking the stimulants that can help them in the clinical sense for ADHD.
Before we begin I'd like to emphasize that this podcast is separate from my teaching and research roles at Stanford.
It is however part of my desire and effort to bring zero cost to consumer information about science and science related tools to the general public.
In keeping with that theme I'd like to thank the sponsors of today's podcast.
Our first sponsor is Maui Nui Venison.
Maui Nui Venison is the most nutrient dense red meat available.
Maui Nui spent nearly a decade building a USDA certified wild harvesting system to help balance deer populations on the island of Maui.
The solution they built turns the proliferation of an invasive species into a wide range of nutrient dense products from fresh butcher cuts and organ meats to bone broth and jerky.
I'm a particular fan of their bone broth which has an unmatched 25 grams of protein per 100 calories and I also love the ground venison and the venison steaks.
I've talked many times before on this podcast with expert guests and nutrition who make it clear that we should all be getting at least one gram of protein per pound of body weight each day.
With Maui Nui Venison products that's extremely easy to do and they're extremely delicious as well.
If you'd like to try Maui Nui Venison go to MauiNuiVenison.com slash Huberman to get 20% off your first order.
Again that's MauiNuiVenison.com slash Huberman to get 20% off.
Today's episode is also brought to us by Roka.
Roka makes eyeglasses and sunglasses that are the absolute highest quality.
I've spent a lifetime working on the biology of the visual system and I can tell you that your visual system has to contend with an enormous number of different challenges in order for you to be able to see clearly.
Roka understands all of those challenges at the level of the eye and the visual system within the brain and they've designed their eyeglasses and sunglasses so that no matter what environment you're in you can always see with crystal clarity.
Originally their glasses were designed for sports and as a consequence all of their glasses are extremely lightweight and as well they won't slip off your face even if you get sweaty.
However despite being designed initially for performance Roka eyeglasses and sunglasses include a lot of different styles that are designed for you to wear to work or out to dinner as well as the what I call the cyborg style that designed for cycling etc.
If you'd like to try Roka eyeglasses or sunglasses go to Roka that's Roka.com and enter the code Huberman to save 20% off your first order.
Again that's Roka Roka.com and enter the code Huberman at checkout.

Today's episode is also brought to us by HVMN ketone IQ.
Ketone IQ is a ketone supplement that increases blood ketones and most people have heard of the so-called ketogenic diet but most people including myself are not on the ketogenic diet.
That is I and most people eat complex carbohydrates fruits and things of that sort in addition to quality proteins etc.
It turns out that even if you're not following a ketogenic diet increasing your blood ketones can still have benefits.
So for instance I use ketone IQ anytime I want to do extended bouts of focused work preparing for podcasts research writing grants and if I ever want to exercise but I don't have time to eat or I don't want to have my gut full of food.
Taking ketone IQ and thereby increasing my blood ketones allows me to do cognitive work or physical workouts without getting hungry and with plenty of energy and cognitive focus.
If you'd like to try ketone IQ you can go to HVMN.com slash Huberman to save 20% off.
Again that's HVMN.com slash Huberman.
I'm pleased to announce that I will be hosting two live events in September of 2023.
The first live event will take place in Toronto on September 12.
The second live event will take place in Chicago on September 28.
Both live events will include a lecture and a question and answer period and are entitled the brain body contract during which I will discuss tools and science related to mental health physical health and performance.
I should mention that a lot of that content will have absolutely no overlap with content covered previously on the Huberman Lab podcast or elsewhere.
If you've been attending either or both of these events please go to HubermanLab.com slash tour and enter the code Huberman to get early access to tickets.
Once again that's HubermanLab.com slash tour and use the code Huberman to access tickets.
I hope to see you there.
Let's talk about treatments for ADHD and why stimulant treatments in particular can be so effective.
First of all it's long been known that there are specific brain networks involved in what we call attention.
Now attention is not one thing actually.
It involves several different cognitive operations including the suppression of noise that is turning down the background chatter in our heads and turning down our attending to things outside us like noises or visual cues that are not relevant to what we want to do.
And it also involves ramping up or attending or focusing on particular things that are happening either in our immediate environment or in our head or both.
So if that all sounds rather complex indeed it is it involves several different networks operating in parallel.
But what we know for sure based on a lot of clinical and scientific laboratory data is that the so-called prefrontal cortex the region of neural real estate in your brain just behind your forehead is critically important for orchestrating which neural circuits are going to be more or less active at a given moment
in order to bring about what we call focus or attention or task switching or our ability indeed to multitask because we can actually multitask to some extent.

In fact if you were to look at somebody and focus on perhaps the expression on their face you could do that while also attending to a conversation that's happening nearby.
It's energetically demanding it's hard to do but we can do that.
That's actually referred to as covert attention you're covertly paying attention to something else and then you can switch that attention back to just one thing or one small collection of things.
The point being that attention is a powerful resource.
It's what allows us to navigate through life with efficiency and to be adaptive in our behaviors.
It's what allows us to learn and to build relationships and have successful school careers and professional careers and so on.
But it is indeed expensive.
It takes metabolic resources just at rest if you were to think about essentially nothing or whatever just pops into your mind with no dedicated effort toward paying attention to anything.
Your brain would consume about 25% of your daily caloric needs and then when you lump on top of that your need or your attempts to focus on things to pay attention to specific things.
It should come as no surprise as to why that often can make us feel tired as if we've been working really hard and we've been running a quote unquote mental marathon when trying to learn and attend to things.
It's hard work for the brain and yet we can pay attention because of that very precious real estate just behind our foreheads the prefrontal cortex.
Now in people both children and adults that have ADHD their prefrontal cortex is not necessarily deficient in any specific way except that it is not as good at orchestrating the activity of other brain networks operating in parallel with it.
What do I mean by that?
Well, if we take a step back and say what is the prefrontal cortex really doing?
The prefrontal cortex has this amazing ability through what's called top down inhibition to quiet other brain areas.
So for instance, if you are feeling agitated, but you need to sit still, your ability to sit still, even if it takes a bit of work is coordinated by your prefrontal cortex sending inhibitory suppressive electrical signals to the networks of your brain that are trying to generate physical action.
In addition to that, if you are in a conversation that's either a difficult one or a boring one or you are tempted to interrupt and you are actively holding back your desire to walk away or to yawn or to blurt something out.
It's your prefrontal cortex that is controlling that active suppression.
So in many ways, you can just think of the prefrontal cortex as an orchestra conductor that is essentially saying shh or not right now, be quiet.
This is not the time to many different brain networks all at once.
Now, in addition to that, your prefrontal cortex is coordinating with other brain networks that are involved in generating what's called salience or attention to particular signals.
So the prefrontal cortex in many ways is like a teacher or an orchestra conductor.
It can point to in the neurochemical sense that is point to a given brain structure and say, you I'd like to hear more from you right now.
Yes, you the student in the back speak up and a moment later point to a collection of small students chattering in the back.

Again, I'm presenting all this by analogy and say, hey, hey, hey, you guys quiet down right now.
So and so is going to come up to the front of the room and help us work through this particular math problem.
So when we hear that the prefrontal cortex exerts what's called executive function, what that refers to is the prefrontal cortex's ability to quiet the activity of particular neural circuits
and to enhance or increase the salience of other neural circuits that are involved in creating our spotlight of attention.
And what we know for sure based on many, many brain imaging studies is that ADHD is not necessarily a deficit in prefrontal cortical function,
but rather the prefrontal cortex's ability to communicate with other brain areas in the proper ways.
And so what results in the brain of a person either young or old with ADHD is that a lot of the background chatter becomes very, very loud.
So for instance, we have a brain network called the default mode network.
This is a fascinating brain network.
This is the brain network that is active when you just sort of sit in place and don't think about much.
And then you start having ideas about what you might do next week.
It tends to be very autobiographical.
So you might remember an experience from the past.
You might think about some of your desires, some of your dislikes.
This default mode network, as it's called, is also involved in our imagination or in our spooling together of different experiences that we've had.
It doesn't tend to be the thing that's really focused on anything external in particular all at once.
The default mode network is always active, but it's when we start to attend to something, especially things external to us,
like something written on a page or a conversation or something that we really need to learn, something we need to pay attention to, that the activity of the default mode network is suppressed somewhat.
And that suppression occurs not just by accident, but because the prefrontal cortex is actively suppressing it.
In kids and adults with ADHD, the default mode network is often still active at a very robust level even while we're trying to attend to things.
And that's why someone with ADHD will sit down and try and do some focused work
and they'll start thinking about something they want or something they dislike.
Their internal state will start to distract them.
And of course, there are other networks in the brain.
There's actually what's called a true salience network.
There's the dorsal attention network.
There are a bunch of different networks and brain areas.
But again, when thinking about ADHD and especially when thinking about how the drugs that we're going to talk about today work
to alleviate the symptoms of ADHD and in thinking about why so many people use or even abuse these drugs for sake of learning
or recreationally, we might say, you start to realize that everything centers back to the prefrontal

cortex
and the prefrontal cortex is ability to actively suppress and actively enhance the activity of these multiple brain networks
including default mode network, salience network, dorsal attention network, etc.
So rather than overwhelm you with a bunch of names of brain areas and brain networks, today I'd really like our discussion to focus on first
what the various drugs that are used to treat ADHD are.
That is how do they work at the level of neurons.
Second, how they create a certain set of conditions that allow the prefrontal cortex to be a better conductor.
Third, how that can be leveraged during development to actually teach the prefrontal cortex of a young child
to learn to be a better conductor because that's really the hallmark of the use of these drugs.
It's to try and enhance the activity of particular circuits to create a sort of learning so that the prefrontal cortex is much more efficient
at doing its job of conducting.
And then fourth, we're going to talk about the various things that I think most people out there ask about when they hear about drugs
like Adderall, Vivance and Ritalin, etc.
Which is, you know, are they addictive? Why are they addictive?
Can one use them briefly or even from time to time and still be okay?
What if I use them as a child and I don't want to be on them anymore?
Should I put my child on these drugs, etc.?
It is, I believe, only by understanding the biology of how these drugs work
and their potential both to improve brain function, but also some of the dangers associated with these drugs
that one can really answer those questions for themselves or for their children.
Okay, so let's start with a very basic but critical question, which is why in the world would amphetamines, speed
or other stimulants improve the symptoms of ADHD?
That's so critical to answer because if you think about it, the prefrontal cortex needs to coordinate the actions of these other circuits.
And so just increasing the amount of activity in prefrontal cortex, you can imagine, would create a state of hyper focus perhaps.
But actually, that's not the case. If you just were to ramp up the activity of prefrontal cortex,
what you would find is that somebody would become even less efficient at paying attention to what they wanted to.
Rather, they would pay attention to whatever was presented in front of them with laser focus.
They would lock on to essentially anything and that's not good.
One of the key things about prefrontal cortex is that it needs to be flexible.
It needs to be able to pay attention to this, then it needs to be able to pay attention to that.
Then it needs to go back to paying attention to the thing it was paying attention to previously and so on and so forth.

Life, that is an effective adaptive life, a good life, consists of self directing one's attention most all of the time.
So why would stimulants do that?
Well, almost all, not all, but almost all of the drugs used to treat ADHD fall under the category of stimulants or what are called sympathomimetics.
Sympathomimetic refers to the fact that we naturally have a component of our nervous system called the autonomic nervous system.
The autonomic nervous system has two major components.
One is called the sympathetic arm of the autonomic nervous system, has nothing to do with sympathy, has everything to do with ramping up our level of attention and arousal.
It is the so-called fight or flight aspect of our nervous system, or rather it mediates fight or flight, but it mediates a bunch of other things too, including sexual arousal,
including excitement and focus about something that we want to learn or somebody that we want to learn more about or remembering a phone number or anything that puts us into a state of alertness and focus.
The other arm of the autonomic nervous system is the so-called parasympathetic arm of the autonomic nervous system, and that's often referred to as the so-called rest and digest component of our nervous system.
And yes, it controls rest.
Indeed, it puts us into sleep.
And yes, it's involved in digestion, but it's involved in a bunch of other things as well, including sexual arousal, including rates of digestion, including salivation, including all sorts of things that don't just have to do with it.
That don't just have to do with resting and digesting.
The way to think about the autonomic nervous system is it's a sort of seesaw.
So it's always at a balance someplace between either predominantly sympathetic or predominantly parasympathetic, but both the parasympathetic and the sympathetic arms of the autonomic nervous system are always active all the time.
It's not as if one is completely active and the other shut off.
Even in sleep, your sympathetic nervous system is not completely turned off, and even during a panic attack, your parasympathetic nervous system is not completely turned off.
Drugs to treat ADHD, which fall under the category of stimulants, are sympathomimetics because they trigger the release of neurochemicals and the activation of components of our nervous system that very much resemble the activation of the so-called sympathetic nervous system, the one that makes us more alert and more aroused.
So that's why they're called sympathomimetics.
And the word stimulant refers to a general category of drugs that are sympathomimetics.
Now, the most commonly discussed sympathomimetic is one that fortunately is not prescribed for ADHD, and that's methamphetamine.
These days, we hear a lot about meth.
Meth, which is methylated amphetamine, is an extremely potent sympathomimetic, and it has tremendous abuse potential.
Believe it or not, meth or methamphetamine is actually available as a prescription drug, but it is

used very rarely because of its high abuse potential and all the terrible things that it can do in terms of cardiovascular health,
in terms of oral health, right?
There's this stereotype that meth users have very degraded teeth, and indeed they do.
There's a reason for that related to how meth impacts the brain and body.
I'm going to talk a little bit about methamphetamine a little bit later, but let's just place methamphetamine high on the shelf as the most potent sympathomimetic that's out there.
Because even though it's not often prescribed for ADHD, there are a class of compounds very similar to it that have a very similar pattern of action that is not quite as potent, but that leverages the same underlying mechanisms,
and they are very commonly prescribed for ADHD, namely, Adderall and Vivants.
So first, let's talk about Adderall and what Adderall is.
Adderall is a combination of what are called amphetamine salts.
Amphetamine salts refers to the fact that there are two major forms of amphetamine.
There's a D amphetamine or dexer amphetamine and levoamphetamine or L amphetamine.
So I'll refer to these as D and L amphetamine.
And for you chemistry-minded folks out there, the D and the L also refer to the fact that there is a L left-handed version of the molecule and there's a D or right-handed version of the molecule.
This is only important to understand insofar as you know that the D and the L forms of the molecule look very similar, but they're mirror images of one another, and yet they can have very different actions in the brain and body.
So Adderall is a three-to-one ratio of D amphetamine to L amphetamine.
You should know that L amphetamine tends to be less potent in increasing certain neurochemicals in the brain.
I'll talk about which neurochemicals there are in a moment.
Then is D amphetamine.
So D amphetamine is potent stuff, not as potent as methamphetamine, but very potent stuff.
L amphetamine, a little bit less potent.
L amphetamine tends to be the amphetamine that increases blood pressure and heart rate, what we call peripheral effects, because it happens in the periphery outside the central nervous system.
Peripheral effects like increased heart rate, increased blood pressure, sweating, etc.
Are mostly activated by L amphetamine, whereas D amphetamine tends to work mainly on receptors in the brain and therefore have effects mainly restricted to the brain.
What are these effects that I've been referring to?
The major effect of Adderall and other sympathetic stimulants is to increase the activity of two neurochemicals.
The first of those neurochemicals is dopamine, and the other of those neurochemicals is norepinephrine.
First off, I want to be clear that when I say norepinephrine, I could just as easily say noreadrenaline, because those are the exact same thing.
Forgive me, even though I wasn't the one to name the same thing two different things.
I'll try and stay with norepinephrine, but I may say noreadrenaline. They are the same thing.
There's a whole story as to how they got named two different things, but it's the same thing.

The major effect of Adderall and other sympathetic stimulants is to increase the transmission of dopamine and norepinephrine.
So what is dopamine and what is neuropinephrine?
Well, both dopamine and norepinephrine are what are called neuromodulators.
That is, they have the ability to increase or decrease the firing patterns, the electrical activity of particular brain circuits.
Both dopamine and norepinephrine have separate roles in creating certain states within our brain and body, but they like to collaborate,
meaning they tend to be released at similar locations in the brain in order to deliver us to a particular state of mind and or body.
So if we were to take a look at just dopamine, we would find that dopamine is released at sites within the brain and increases the activity of brain networks
that for the most part lead to increases in motivation, pursuit, and to some extent, mood.
If we were to look at norepinephrine and where it's released in the brain, it tends to be released at many, not all, but many of the same sites where dopamine is released.
And the main function of norepinephrine is to increase the activity of neural networks that are involved in attention and focus to particular things in our environment.
Okay, so think of dopamine and norepinephrine as collaborators because indeed they are, and actually they're very neurochemically similar as well.
It actually just takes one chemical conversion to turn dopamine into norepinephrine.
So they are very similar.
They're like close cousins that work together to help us achieve a common goal that involves increased motivation, focus, and alertness.
So when we talk about attention in ADHD or we talk about quieting the hyperactivity or impulsivity of ADHD,
one of the reasons why drugs that are effective in treating ADHD are so effective is because they increase motivation, focus, and alertness,
and they tend to do that at very focal locations in the brain.
It's worth taking a couple of minutes to think about how sympathomimetics such as Adderall actually increase dopamine and norepinephrine.
They do so by affecting a couple of specific operations at the so-called synapse.
What are synapses?
Synapses are the communication points between neurons.
They're actually the spaces between neurons, but that's where a lot of the action is when neurons, as we say, are stimulating the next neuron
or activating the next neuron or inhibiting the next neuron.
The word neuron just simply refers to nerve cell.
And so what nerve cells have is they have a cell body that contains their DNA and a bunch of other stuff.
They have a long wire-like process, which is referred to as an axon.
And at the end of that axon, there are a bunch of proteins in there that do really interesting things.
So for instance, there are proteins down at the end of the axon that package neurotransmitter into little spherical things that we call vesicles.

Those vesicles confuse with the end of the axon and vomit the contents, those neurotransmitters, into the synaptic cleft, into that little space between neurons.
And then if enough of those neurotransmitters bind to receptors on what's called the postsynaptic side, which simply means the neuron on the other side,
well, then the next neuron will become active and then the signal will propagate from one neuron to the next.
Now, I just described that whole process pretty quickly and I like to think pretty simply,
but it actually involves a lot of different protein bits and some pretty complex machinery in order to make that happen.
I don't want to overcomplicate our conversation, but what I will tell you is that down in the synapse, in the presynaptic terminal,
the neuron that is going to release neurotransmitter, there are what are called transporters which sit there and suck up or suck back up some of the neurotransmitter that's been released.
There are dopamine transporters and there are norepinephrine or noradrenergic transporters down in the synapse.
What Adderall does and what other sympathomimetics do is to inhibit or disrupt the action of those transporters.
And the net consequence of that is that when dopamine and norepinephrine are released into the synapse, more of it is allowed to stick around
and to bind to receptors on the postsynaptic cell than would be the case if Adderall or the other stimulant were not present in the system.
So one way that Adderall increases dopamine and norepinephrine is by disrupting the activity of these presynaptic transporters for dopamine and norepinephrine.
The other way that Adderall increases dopamine and norepinephrine is that it disrupts the activity of a different piece of machinery in the presynaptic neuron,
which is called a VMAT, the vesicle monoamine transporter 2 if you really want to get specific.
You don't have to remember these names, but what these VMATs do is actually really cool.
What they do is they actually take whatever transmitter has been brought back up into the cell by transporters and they package it into those vesicles that are then going to be released
by disrupting the transporters that vacuum back up some of the dopamine or norepinephrine that's been released
and by also disrupting the packaging of dopamine and norepinephrine into vesicles themselves.
What ends up happening is that there's a buildup of a lot more dopamine and norepinephrine in the presynaptic terminal
so that when an electrical signal travels down the neuron, now the total amount of dopamine and norepinephrine that's released is increased.
What's happening when you take Adderall is that you're getting more out of the dopamine and norepinephrine that you're releasing
and you're releasing more dopamine and norepinephrine altogether.
There's a third mechanism by which Adderall increases the amount of dopamine and norepinephrine present in synapses and therefore can act on other neurons.
That has to do with disruption of the entire network between these different proteins.
I'm not going to go into that in any detail because it gets somewhat complicated in terms of the cell

biology
and some of the biochemistry down at the tips of these axons,
but suffice to say that Adderall is such an effective sympathomimetic that it can increase dopamine to such a great extent,
especially compared to other treatments for ADHD,
because of its ability to increase dopamine release and transmission and therefore action,
as well as noradrenergic release and transmission and action down there in the synapse.
And it's worth pointing out that most of the effect of Adderall is an increasing dopamine as opposed to norepinephrine.
It does increase norepinephrine, but its major effects,
we should say the major effects that have made it such an attractive drug to so many people,
both for the treatment of ADHD and for people to take recreationally or off prescription
or for sake of studying or work simply because they want to focus more and longer
is because of its ability to increase dopamine to such a great extent.
I'd like to take a quick break and acknowledge one of our sponsors, Athletic Greens.
Athletic Greens, now called AG1, is a vitamin mineral probiotic drink that covers all of your foundational nutritional needs.
I've been taking Athletic Greens since 2012, so I'm delighted that they're sponsoring the podcast.
The reason I started taking Athletic Greens and the reason I still take Athletic Greens once or usually twice a day
is that it gets to be the probiotics that I need for gut health.
Our gut is very important. It's populated by gut microbiota that communicate with the brain, the immune system,
and basically all the biological systems of our body to strongly impact our immediate and long-term health.
And those probiotics in Athletic Greens are optimal and vital for microbiotic health.
In addition, Athletic Greens contains a number of adaptogens, vitamins, and minerals
that make sure that all of my foundational nutritional needs are met and it tastes great.
If you'd like to try Athletic Greens, you can go to athleticgreens.com slash huberman
and they'll give you five free travel packs that make it really easy to mix up Athletic Greens
while you're on the road and the car on the plane, etc.
And they'll give you a year supply of vitamin D3K2.
Again, that's athleticgreens.com slash huberman to get the five free travel packs
and the year supply of vitamin D3K2.
Now a bit earlier, I mentioned that L-amphetamine, levoamphetamine is present in Adderall,
but at one quarter the amount of D-amphetamine.
Okay, so there's a little bit of L-amphetamine and a lot of D-amphetamine in Adderall.
Many of you are probably familiar with Vivance.
Vivance is a commercial name for what many people think is extended release Adderall,
but actually Vivance is not extended release Adderall.
Vivance is a drug in which the pharmaceutical industry has taken one component of Adderall,
just the D-amphetamine component and attached to it an amino acid called lysine.
The amino acid lysine is a big amino acid and the attaching of lysine to D-amphetamine,

what we call Vivance, makes it what's called a prodrug.
It actually can't have any effect on its own, but when one takes Vivance and it's broken down in the gut,
but to a greater extent actually in the bloodstream, the lysines are cleaved off slowly over time
and as a consequence, Vivance is basically timed release D-amphetamine.
This is important because I think a lot of people think that Adderall, which again is D-amphetamine and L-amphetamine
and those two things operate quite a bit differently at the level of norepinephrine and epinephrine and cardiac versus brain effects.
A lot of people think Vivance is just slow release Adderall, but it is not.
What Vivance is is D-amphetamine only, but in time release form.
And Vivance was actually developed as a way to try and get around or rather prevent some of the abuse potential
of Adderall and other drugs that contain D-amphetamine.
D-amphetamine stands for dextra-amphetamine and in the 70s and 80s, there were a fair amount of movies
and there was a lot of trafficking and there was a lot of criminal activity related to what was called dexadrine.
Dexadrine is pure D-amphetamine.
So if we're going to be very direct, if I were going to just frame these things in the context of their neurochemistry,
what I can tell you is that Vivance is time-release dexadrine.
It's not time-release Adderall.
Now, just because there were movies and reports of criminal activity related to dexadrine,
that doesn't necessarily mean that dexadrine is not an effective and useful pharmaceutical.
In fact, Vivance, which is time-release dexadrine, has proved to be very effective in the treatment of ADHD for a lot of people.
And the reason for that is this time-release does indeed prevent abuse in the sense that despite people's many attempts from what I hear
to increase the rate of entry of the D-amphetamine into their system by either snorting it or God forbid even injecting it and things of that sort,
the attaching of that lysine to D-amphetamine really does slow the absorption.
So when somebody takes Vivance and hopefully people are taking it responsibly,
when they take Vivance, what they're really getting is a slow trickle of D-amphetamine into their system
and therefore a slow, long-lasting increase in dopamine and norepinephrine.
And indeed, that's what happens.
The effects of Vivance can extend over anywhere from 12 to 16, sometimes even 18 hours, depending on how quickly somebody metabolizes it.
And I should say that there is no way to predict how quickly one will metabolize any of these drugs except by trying them.
That's one of the downsides of the state of things these days.
There's no blood test or enzymatic test that will tell you whether or not you're going to be a fast

metabolizer or a slow metabolizer.
And that's why people just have to sort through different dosages, which we'll talk about in a little bit.
They have to sort through different types of sympathomimetics.
Some people try Adderall and they find that the quick time course of Adderall,
or at least quick for them of about six to eight hours, is just too fast.
And then it wears off and they get into a slump in the afternoon.
Other people will find that one Adderall taken at 6 a.m. will have them going all day long and into the night.
And it's just too much stimulation and they need to come way, way down in dose,
or they need to think about other sympathomimetics for ADHD.
And we'll talk about what some of those other options are in a little bit as well.
So the important thing to understand is that Adderall is really two drugs, Dnlmphetamine.
Vivance is DMphetamine, which is also called dexadrine,
but with this time released aspect created by lumping a lysine on there.
And you may notice that I haven't mentioned one of the major drugs used to treat ADHD.
And that's Ritalin, or what's sometimes also called Concerta,
depending on, again, the time release forms, et cetera.
Ritalin was very commonly prescribed for the treatment of ADHD early in the days of using sympathomimetics in order to treat ADHD.
So for instance, I went to college in the early 90s.
I started college in 93 and I graduated in 98.
It was one year in there as a, let's call it a transition year.
I can recall hearing that Ritalin was being prescribed for ADHD in kids.
And I, like many other people, were wondering what are the long-term consequences of this going to be?
I also, like many other people, was very perplexed as to why a stimulant,
sympathomimetic like Ritalin, was being prescribed for hyperactive kids.
That will become clear in a moment.
We don't hear so much about Ritalin nowadays.
And I think that's because Adderall and Vivants and things like them have become so popular for the treatment of ADHD.
It's worth noting that Ritalin is not actually amphetamine.
Ritalin is what's called methylphenidate.
And methylphenidate works in a lot of ways that are similar to the way that Adderall and Vivants work.
But there are certain ways in which it's different.
Now, Ritalin, methylphenidate does increase dopamine transmission at synapses.
And it does so also by inhibiting the function of that presynaptic dopamine transporter
that would otherwise suck more dopamine back up into the presynaptic cell.
Methylphenidate, Ritalin, also disrupts the activity of the noradrenergic transporter,
leading to net increases in the amount of norepinephrine at the synapse.
But it is not as much a potent inhibitor of the noradrenergic transporter.

And therefore, most of the effect of methylphenidate is to increase dopamine at synapses.
A lot of people don't realize this.
A lot of people think that Ritalin is just very short-acting Adderall.
And that's not the case.
It is true that Ritalin, at least in its standard form, tends to have a pretty short half-life.
And therefore, its effects basically kick in about 20 to 40 minutes after taking it,
sometimes a little bit sooner, sometimes a little later.
And they last about four to six hours, as opposed to the six to eight hours typical of Adderall.
But Ritalin is not short-acting Adderall.
Ritalin is mainly increasing dopamine and to some extent norepinephrine at synapses,
whereas Adderall and Vyvance are increasing both dopamine and norepinephrine to a much greater extent.
And for those of you that are interested in the underlying cell biological reason for that,
it has something to do with Ritalin's relatively lower affinity for the noradrenergic transporter.
But it's also because, remember, I listed off three mechanisms by which Adderall and by extension Vyvance
increased dopamine and norepinephrine transmission.
Disruption of the transporter, disruption of the V-MAT2, as well as a disruption of the whole kind of complex of communication between those proteins.
Well, Ritalin is really only tapping into the drug's ability to disrupt the dopamine and noreadrenergic transporter.
So it's three mechanisms of increasing dopamine and norepinephrine for Adderall and Vyvance and by extension dexadrine.
And it's only one mechanism for Ritalin to increase dopamine and norepinephrine.
And they're in mostly dopamine.
So if we take a step back for a moment from all these drugs and all this cell biology of neurons and so forth,
and we go back to the brain networks involved in attention, remember the orchestra model or the teacher model
where the prefrontal cortex really sits in top seat in terms of coordinating the actions, both the shh, the quieting
and the yes, please speak actions of the brain really bringing about what we think of as focused attention and task switching.
All the stuff that goes along with learning and focus and cognition.
Well, what we know is that dopamine and norepinephrine, which are differentially increased by these different drugs that we've been talking about,
also differentially impact the various aspects of executive function of the prefrontal cortex increasing our attention for specific things.
And while there is a lot of nuance in the literature about this, we can safely say a couple of things.
First of all, increasing dopamine at particular synapses and networks in the brain can serve as what's called noise reduction.
It can help further enhance the quieting of all that background stuff.
That background stuff can be attention to things in your environment like noises or visual cues.

It could be some internal narrative that you had about yesterday or something that somebody said about you or something that somebody you like,
would like to say about you or whatever it might be that's happening in your head that's distracting you, as well as your representation of your internal bodily state,
what we call interoception.
This is a really important aspect of attention that we don't often hear about, which is that we have the ability to attend to things outside of us,
which is called exteroception, as well as an ability to attend to things inside of us, which include things like thoughts,
but also includes, for instance, how empty or full our gut feels, whether or not we're comfortable in our chair.
And when we think about the practice of focus and learning or focusing as a verb, it involves often forcing ourselves to sit still.
It often involves us suppressing the fact that our foot is a little bit cramped or that we might need to use the restroom for, you know,
we might want to delay that for 10, 15 minutes, even though it might be fairly urgent.
All these sorts of things are central to our ability to attend and focus.
And so dopamine, while it does many different things in the brain, many, many different things,
one of its main functions in the context of all this prefrontal cortex and attention stuff is to quiet the amount of noise.
That is, it helps the prefrontal cortex suppress the signals that would otherwise distract us into thinking about,
oh, yeah, I'm kind of thirsty right now or I need to use the restroom or I really want to make this call or I really want to pick up my phone.
All of that stuff, all of that suppression, that quieting down of all the background chatter related to things external and internal to us in our head
and our body is greatly facilitated by having more dopamine present in the synapses that allow for what we call noise reduction.
Now, in parallel to that is norepinephrine.
Norepinephrine is released from multiple sites in the brain and body.
But within the brain, there's one major site of neurons that manufacture norepinephrine.
And the name of that site is locus ceruleus.
It sits in the back of the brain.
It's actually a relatively small collection of neurons, but they are very, very powerful.
They extend their little axons, their wires to multiple locations in the brain and they release norepinephrine at those locations.
So think of them sort of as a sprinkler system that originates from one very focal location, but that can sprinkle norepinephrine at multiple locations in the brain.
And the amazing thing about locus ceruleus and that sprinkler system is that indeed the sprinkler system can be pretty widespread where everywhere there's a sprinkler head.
Somebody's getting norepinephrine, but it also can fairly vocally release norepinephrine at particular sites.
So while in the context of today's discussion, dopamine is acting largely to impart noise reduction.

Norepinephrine has the ability to boost signals at synapses to increase the amplitude and frequency of communication between neurons.
And in that way, in the context of today's discussion, norepinephrine, when released at the particular synapses,
in the particular brain networks that are related to attention and learning is largely serving to increase signal.
So what we have in the context of a drug like Adderall or Vivance, or to some extent Methylphenidate, Ritalin does this as well,
is an increase in dopamine and norepinephrine that is leading to two things, both a reduction in noise,
a quieting of the circuitry that we don't want to hear so much from, and an increase in the signal of the networks that we do want to pay attention to.
And the net effect of that noise reduction and signal amplification is what the engineers refer to as increased signal to noise.
And the consequence of that is a heightened subjective sense or ability to decide what we want to focus on, sit down or stand there and just focus on it.
So the way that we've been discussing drugs to treat ADHD and their ability to increase dopamine and norepinephrine,
and thereby to reduce the amount of noise, so to speak, in the brain and to increase the amount of signal related to things that we want to attend to,
all presumes that the amount of dopamine and the amount of norepinephrine that's being increased is perfect for what we want to accomplish,
which is increased focus and reduced hyperactivity and impulsivity.
But of course, in the real world, that's not always the case, depending on the dosage of the drug, one sensitivity to the drug,
even what stage of development across the lifespan a person is at, things can really go haywire pretty fast.
And what I'm referring to when I say haywire is, if you think about dopamine and its ability to reduce noise,
well, dopamine does a bunch of other things as well.
And in fact, we know that if dopamine is increased too much in the brain of somebody that has ADHD or somebody that doesn't have ADHD,
people can become euphoric, people can become manic, people can even become psychotic.
Likewise, if norepinephrine is increased too much, people won't just become alert.
They will become very anxious, have panic attacks.
And depending on the drug they're taking, they may even experience very serious peripheral symptoms,
meaning elevated heart rate and sweating that is super uncomfortable and on and on.
So everything I've been discussing up until now is true,
but I want to make it clear that it's true in the context of appropriately dosed prescribed drug for a given condition,
which leads us to the next question, which is why would it be that giving these drugs, which are in fact stimulants,

why would that calm a kid down?
Why would that calm an adult with ADHD down?
And the answer to that is not completely straightforward.
And it is worth pointing out that not everyone with ADHD has impulsivity and hyperactivity and therefore an inability to focus.
Some kids and adults with ADHD do have challenges with impulsivity and hyperactivity.
Some do not.
Some just have challenges with focus.
And I did an entire episode about ADHD and we are going to have an expert guest on this podcast who specializes in the treatment of ADHD
to talk about some of these issues further.
But I just want to remind everybody that as in the general population,
children and adults with ADHD are capable of very concentrated periods of focus.
The pattern, however, tends to be that children and adults with ADHD have a harder time getting into that state of focus.
And perhaps most importantly, they have a very hard time getting into a forced state of focus for things that they don't enjoy doing.
I'm sure many of you are also thinking, wait, I don't like to do certain things and it's harder to focus on those things than on the things I like.
Of course, does that mean I have ADHD?
And the answer is not necessarily so.
Kids and adults with ADHD exhibit an extreme variation in their ability to focus such that if there's something they really, really like doing,
they can indeed focus.
However, for many, many other activities that are required in order to develop, I guess we'll just call it normal life advancement.
So sitting still, listening to conversations that we may or may not be particularly interested in, that's where the challenges come about.
So the point is that these brain networks and these neuromodulators like dopamine and norepinephrine that we've been talking about in fairly straightforward terms,
as it relates to a drug's ability to increase their transmission and therefore an improved ability to focus, presumes two things.
It presumes that the dosing is right.
That is that the levels of increases in these neuromodulators is just right.
And I also just want to acknowledge that ADHD is first of all, not an inability to focus at all.
It is immense challenges in focusing on lots of different things as required for normal life progression.
And it's also the case that there is no one specific pattern of ADHD that applies to everyone with ADHD.
Some people, both kids and adults, will exhibit the hyperactivity, but not the impulsivity, although those two things tend to go hand in hand.
Some people will have a challenge in focus without hyperactivity, impulsivity, and so forth.
And all of this just really speaks to the complexity of ADHD and yet, and yet, we can confidently say

that there are more drugs to treat ADHD
than any other psychiatric condition.
We've talked about a few of those now, but among those, Adderall, Vivance, Ritalin, also called methylphenidate, there are time-release versions.
There are different variations on those time-release versions.
There's even straight dexadrine, which is prescribed for ADHD in some cases, and on and on.
And you might also find it interesting to know that that very large kit of drugs, all of which, at least the ones we've talked about so far,
are sympathetic mimetics, are stimulants, are more effective at treating ADHD than are any other collection of drugs for treating other psychiatric disorders.
So what all of that diversity of symptomology in ADHD, as well as differences in sensitivity to drugs and individual variation,
and what all of that speaks to is that the large kit of drugs that's out there is designed to be assessed with the careful consult of a very qualified psychiatrist
in order to allow the child or adult to arrive at the specific drug and the specific dosage that's ideal for their particular pattern of ADHD.
And that issue actually gives rise to the answer to that now somewhat age-old question as to why giving stimulants to a kid that is hyperactive would calm them down.
And the answer is that the hyperactivity, impulsivity, and focus issues present in ADHD in children and adults are the consequence not necessarily of deficient activity of neural circuits in the prefrontal cortex
or deficient activity of the default mode network or deficient activity of the salience network, etc.
What appears to be the case based on a lot of high-quality neuroimaging data is that the brains of children and adults with ADHD have all of these networks functioning,
but those networks are actually hyperconnected. That is, they tend to be coactive at times when ordinarily, meaning in kids and adults without ADHD, they would not be coactive.
So that's an important point because it's easy to get the impression that ADHD is just a deficiency in dopamine and norepinephrine, and that's simply not the case.
If you recall, dopamine and norepinephrine are neuromodulators. They modulate the activity of other neural circuits and they can both increase and decrease activity within those circuits.
So you don't necessarily want to think about dopamine and norepinephrine just as molecules that increase neural activity.
And you certainly don't want to think about ADHD as just a deficiency in dopamine or deficiency in norepinephrine.
The way these drugs work when they are used effectively to treat ADHD is to tune the amount of dopamine and norepinephrine that are present in particular brain networks
in order to allow the person to arrive at just the right balance between the activation of these different neural circuits, causing them largely to be less synchronous in their firing.
So this takes us back to this question of why giving stimulants to a kid would calm them down.
It's not so much that you're giving a stimulant to a kid to place them into a state of calm.
I think that's a common misconception. Rather, by increasing dopamine and norepinephrine, these drugs, yes, increase levels of overall autonomic arousal.
They are, after all, sympathomimetics. But more importantly, to the treatment of ADHD symptoms,

you are activating the prefrontal cortex in a way that allows it to be more of a coordinator of that orchestra conductor.
Or if you prefer the analogy to a teacher in the classroom to ramp up the activity of certain neural circuits in a given moment and quiet down the activity of other neural circuits such that the default mode network can still perform its incredible actions.
After all, the default mode network is involved not just in self-referencing and kind of daydreaming, but also creativity and imagination.
It's been well described in the literature as well as the salience network and these other networks that are designed to drop us into very narrow trenches of attention.
These drugs for the treatment of ADHD are indeed stimulants.
But the goal of prescribing these drugs to a child or adult with ADHD is to adjust dosage, timing, and the duration over which somebody takes it in their lifespan in order to allow those neural circuits to work in the proper way.
Meaning for the conductor to activate the instruments in that little symphony or band in the appropriate order in order to arrive at the right music as opposed to all the instruments playing at once, which would just be complete noise.
Or again, if you prefer the classroom teaching analogy for the teacher to call on one student while the others are quiet and then to call on a different student, have one student return to their seats to have the students work in small groups.
Again, all of this by analogy, the point being that dopamine and norepinephrine are all allowing these networks to be activated to the precisely correct levels and in the precisely correct sequence.
Now, the other key aspect of drugs like Adderall, Vivants, Ritalin, and similar to treat ADHD has everything to do with these neuromodulators, dopamine and norepinephrine.
But it has to do with their other incredible feature besides just their ability to reduce noise and increase signal within these brain networks.
And that incredibly important feature is what we call neuroplasticity or the brain and nervous systems ability to change in response to experience.
I've done entire episodes of the Huberman lab podcast on neuroplasticity, what it is and how to access it at different stages of development and in adulthood.
By the way, you can find those episodes at Huberman lab.com by simply searching plasticity in the search function.
But the important thing to understand about plasticity in the context of today's discussion is that while there are many different ways to induce neuroplasticity, almost all of them.
Almost all of them involve strongly activating certain brain networks and in that case also strong or elevated release of certain neuromodulators.
Now, we've talked about dopamine and norepinephrine.
They are but two of many neuromodulators.
Others include serotonin, acetylcholine and each of the neuromodulators does different things that difference synapses in the brain.
And there's some global statements that can be made about each of them.
We've made some of those earlier, like dopamine is broadly involved in motivation, craving and pursuit and norepinephrine in signal detection and drawing a focus or salience to something in our environment or in our body or inner experience.

Serotonin does other things, acetylcholine does other things.
But what's really important to understand is that anytime there is a dramatic elevation in dopamine and norepinephrine relative to baseline, relative to what was happening with dopamine and norepinephrine just prior to that.
That has a tendency to promote neuroplasticity at particular synapses.
So here is where it's appropriate to remind everybody that neuromodulators are different than neurotransmitters.
Neurotransmitters are chemicals that just like dopamine and norepinephrine are released between neurons and they are what actually contribute to the electrical signals going up or down between different neurons.
And again, dopamine and norepinephrine modulate that activity causing a given amount of neurotransmitter to have an even greater effect, for instance.
So when we hear about dopamine and norepinephrine and we hear about motivation or focus, etc., that's all fine and good.
But it's also important to remember that when dopamine and norepinephrine are increased, there is a higher probability of strengthening connections where dopamine and norepinephrine are increased.
And what that means is that later, even if levels of dopamine and norepinephrine are not increased, if they go back to baseline, it's often the case that if in our prior history or the history of a given set of neurons in our brain,
there was more dopamine or norepinephrine around, it's very likely that the connections where that took place are strengthened and therefore more easily activated.
And this takes us back to the really original purpose of prescribing these sympathetic stimulants to children with ADHD during development.
It was, yes, designed to try and help them focus, to reduce their hyperactivity and help them focus.
But it was also designed to help the brain networks that are responsible for focus to undergo neuroplasticity.
That is, for the synapses involved to strengthen so that those networks could function more efficiently later on, even after cessation of the drug.
This is an absolutely crucial point that I think is not often discussed when people, for instance, say, should I put my kid on ADHD meds?
Or should I take my kid off of ADHD meds as they transition from adolescence to their later teen years and into college?
I mean, after all, no child or parent or adult, for that matter, wants to achieve a bunch of benefits with a drug and then lose those benefits later.
Nor does any parent or child want to take a drug that they don't need to take when they could access other routes to improving the neural circuitry or the function of some health system in the body.
Because I don't think anyone really wants to medicate their kids unless they have to. I would hope not.
And I don't think any kid wants to be medicated unless they absolutely need to be medicated.
So increasing dopamine and norepinephrine with these drugs like Adderall, Vivants, Ritalin, and similar is causing several things.

And some of those things actually provide some general answers as to whether or not parents should put their kids on these compounds in the first place.
Obviously, they're going to do that under the careful consult of a qualified psychiatrist, I would hope, and only under those circumstances.
But also whether or not the child should stay on those drugs over time.
And here's what we do know for sure.
I did a vast search within the literature in order to arrive at what is very clear, which is that children with ADHD, true ADHD, who are diagnosed with ADHD and are treated with appropriate doses of drugs like Adderall, Ritalin, or Vivants.
Far better both in childhood and later in life when it comes to performance in school, performance in terms of focusing on anything, and in terms of general outcomes.
So for instance, a lot of people have wondered and worried about whether or not treatment with these drugs early in life will set up a predisposition for illicit drug abuse or craving an addictive potential later.
And it is very clear from the studies that have emerged over the last really 15 years, but mainly within the last five years.
That's when most of the data have arrived that children with ADHD who are not treated correctly, both with drugs and behavioral treatments, because really the combination of drugs and behavioral treatments is the optimal situation.
So kids with ADHD who are not treated with drugs and behavioral treatments to deal with their ADHD have a much higher tendency towards illicit drug use and addictive drug potential in their adulthood.
Okay, so there is a real danger to not treating ADHD during childhood.
And the reverse is also true, which is that children with ADHD who take prescription drugs that are sympathomimetics.
So yes, as you've heard, they are speed. Amphetamine is speed.
Although I should say if they take methylphenidate, Ritalin or Concerta or something of that sort, that's not amphetamine.
Nonetheless, it's a stimulant. It's a sympathomimetic also.
These are kids that are taking these drugs during development and therefore levels of dopamine levels of norepinephrine are being increased in their brain and body.
And you might say, well, wouldn't that lead to a craving for these things later in life?
And that does not appear to be the case.
In fact, there's some very nice neuroimaging studies, mainly positron emission tomography studies that I'll provide a link to in the show note captions that showed that early treatment with these drugs actually leads to
combinations of increased dopamine transmission in the forebrain later in life at a lower level or a lower threshold, I should say, in a way that essentially says there's normalization of the circuits across time by the application of these drugs early in life.
Again, in the case of children that have diagnosed ADHD, I in no way shape or form want to imply that all children should be treated with these drugs is quite clearly not going to be a good idea.
So all of this really speaks to the critical importance of getting an accurate diagnosis of ADHD.
You know, diagnostic criteria include many things in children.

There are multiple, there are more than nine diagnostic criteria for each of the categories relating to impulsivity, hyperactivity and so on.
So a well qualified psychiatrist will do several things.
Well, first of all, do a careful diagnostic evaluation of a child.
And in addition, one would hope that they would think about prescribing both appropriate pharmacologic treatments for ADHD, but also be aware of and prescribe the various other types of prescriptions, meaning behavioral prescriptions.
So there are clearly certain learning tools and things that kids can do in order to improve their ability to focus and to be less impulsive that combine especially well with drug treatments as well as new advancements in the realm of nutrition and supplementation that are constantly coming online.
And the best psychiatrists are going to be tuned into all of those aspects of treatment for ADHD, not just prescription drugs, but also behavioral treatments, also nutritional guidelines, also supplementation.
And also updating each and all of those things as a child matures from each stage of development to the next.
I'd like to take a quick break and thank our sponsor, Inside Tracker.
Inside Tracker is a personalized nutrition platform that analyzes data from your blood and DNA to help you better understand your body and help you reach your health goals.
I've long been a believer in getting regular blood work done for the simple reason that many of the factors that impact your immediate and long-term health can only be assessed with a quality blood test.
The problem with a lot of blood and DNA tests out there, however, is that they'll give you information about certain lipid markers or hormone markers, but no information about what to do with all of that data.
Inside Tracker makes it very easy to look at your levels of hormones, metabolic factors, lipids, etc.
And then to assess what sorts of behavioral, nutritional, supplementation, or perhaps other interventions you might want to use in order to bring those numbers into the ranges that are optimal for your health.
Inside Tracker's ultimate plan now includes three new hormone markers that are critical to measure during a woman's reproductive and menopausal years.
These are estradiol, progesterone, and thyroid-stimulating hormone.
If you'd like to try Inside Tracker, you can go to insidetracker.com.huberman to get 20% off any of Inside Tracker's plans.
Again, that's insidetracker.com.huberman to get 20% off.
Now, the other common question is, if a child has been treated with these ADHD meds during development, do they need to continue on those drugs indefinitely?
And the short answer to this is it depends.
And that can be a somewhat frustrating answer, I realize.
But the good news is it's something that can be assessed in a fairly straightforward way.
Let's recall that the use of these drugs to treat ADHD is designed to accomplish two things.
It's designed to improve the function of those neural circuits that allow a child to focus.
And it's also designed to increase the strength of those circuits to effectively teach the circuits how to learn what focus is.

In other words, these drugs are designed in some cases to be used and then withdrawn later because the circuits that they helped build up are functioning well.
In some cases, however, the circuits that underlie focus are not going to be able to function at the level required for normal, healthy life progression
unless there's continued application of the drug.
So how would this work in the real world context?
Well, I think any child or adolescent or person younger than 25 that's taken these drugs has no doubt achieved some level of neuroplasticity of the neural circuits related to all the things we call focus.
And I want to be very clear, there's no single brain area or set of brain circuits for what I'm referring to as focus.
Because after all, focus involves test switching, focus involves all sorts of different cognitive operations depending on what we're focusing on.
The focusing on a sport is basically a practice of directing one's attention in different locations at different moments.
Focusing on studying is an entirely different pattern of focus altogether.
But the point being, if a person 25 years or younger takes a drug that increases dopamine and norepinephrine and assuming that things are working, meaning the dose is right, they're achieving better ability to focus, etc.
Those circuits are going to get stronger.
And it seems entirely reasonable.
In fact, it was supported by the psychiatrist that I spoke to prior to this episode that people who have been on ADHD meds for any point of time prior to 25 talk to their psychiatrist about what tapering off those drugs in order to examine whether or not they still need those drugs would look like.
Now, I mentioned the word taper because there is a withdrawal potential of simply stopping these drugs very quickly because they do ramp up dopamine and norepinephrine.
Even though they increase plasticity of the neural circuits for focus and mood and motivation, if one very abruptly ceases taking any of these drugs, it does not feel good.
That drop in dopamine that one inevitably experiences is almost always associated with lethargy, with depressed mood, with feeling not good in a number of ways.
And of course, challenges in focus.
So anytime one is going to go off one of these drugs or sample what it is to even reduce dosage, that has to be done in close communication with a board certified psychiatrist.
At the same time, it was made very clear to me from ADHD expert psychiatrists that reductions in dosage over time often are optimal for a patient.
And this gets to the whole issue of dosage generally.
I spend a good amount of time talking to somebody who prescribes these drugs both to children and adults about dosage ranges.
And I don't want to spend too much time on this from the perspective of how much one should take.
In fact, I don't want anyone to think that what I'm about to say should dictate what they should take specifically because that's something that really has to be worked out on an individual basis.
But it is worth noting that if you look at the studies on Adderall and methylphenidate, you'll see is a

pretty broad range in those studies.
And that's because some of the studies used people that were already taking these drugs and asked them to participate in neuroimaging studies.
Other studies actually put people on these drugs for the very first time or adjusted their dosage.
And so you'll see a tremendous range of drug doses explored.
For instance, you will see anywhere from 10 to 40 milligrams of Adderall per day.
You'll see anywhere from 10 to 60 milligrams of Ritalin per day.
And here we could easily be talking about studies on children or adults.
With respect to VIVANTS, you'll see that the dosages tend to be much higher.
In part, that's because VIVANTS has, if you recall, it's that lysine, which is a big molecule stuck on DMphetamine, which is a smaller molecule.
And so the dosages of VIVANTS tend to be in the hundreds of milligram ranges.
But most of that 100 milligrams of VIVANTS is not going to be the DMphetamine.
It's going to be the lysine, which doesn't do anything in the context of treating the brain.
It's just there to control the slow release.
So it's thought that 100 milligrams of VIVANTS translates to roughly 9 milligrams of Adderall and on and on.
And actually it's pretty hard to translate between dosages of different drugs in any direct way.
And in speaking with a psychiatrist expert in ADHD in preparation for this episode,
he made very clear that it is extremely, extremely difficult to predict how a child or adult will react to a given dosage of any of these drugs.
So much so, in fact, that he anecdotally reported to me that one of his patients is a male 300 pounds diagnosed with ADHD
and who achieves tremendous relief from just 2.5 milligrams of Adderall per day.
And at the same time, he has two patients, both of whom are sisters, so they're genetically related, who are in the 120 to 140 pound range, who did not respond well at all for the treatment of their ADHD until their dosages were very, very high.
And if I tell you these dosages, I just want to warn you in advance.
I'm not suggesting anyone explore these dosages without, of course, the approval of their psychiatrist.
Turns out that neither of these two young women responded at all to ADHD medication until they achieved dosages in the range of 180 in the case of one sister
and 240 milligrams in the case of the other sister per day, which is an astronomically high dose on the face of it.
But this physician, again, board certified physician expert in ADHD verified for me that indeed neither of them experienced any discomfort or side effects
that led them to not want to take the drug.
But of course, that amount of Adderall could send somebody else into an absolute psychotic fit could potentially even cause cardiac arrest.
I mean, it's remarkable the ranges of Adderall that are used effectively in children and adults.
And this is true for a lot of the other sympathomimetics used to treat ADHD.
And of course, a good psychiatrist will always assess dosage as it relates to positive benefits, you know, relief of symptoms.

So relief of impulsivity, relief of hyperactivity, improvements in ability to focus.
And of course, they are going to consider side effects, any uncomfortable adverse effects that come from taking the drug at a given dosage or taking the drug at all.
Now, of course, this all begs the question of why such tremendous variation is this due to genetic differences in the amount of dopamine or neuroepinephrine that people make.
It appears that the major underlying factor for why people require such vastly different dosages of these sympathomimetics for the relief of ADHD has to do with the different enzymes
or levels of enzymes that people make, which metabolize these drugs both in the brain and body.
And unfortunately, there is no simple blood test or saliva test or test of any kind that can predict how someone will respond to these drugs.
So the most logical and safe way to assess dosage is to start with the lowest possible effective dose and to increase only as necessary in order to achieve the positive benefits while of course paying attention to any side effects that might arise.
A question that comes up from time to time when discussing the long term effects of drugs like Adderall, Ritalin and Vivance is whether or not they can negatively impact height or growth or development in some other way.
This is a logical question to ask because after all, these drugs are effectively mimicking stress in the body.
And most everyone has heard by now that while stress can help us in the short term, it helps us deploy immune molecules to protect us against infection.
It sharpens our visual focus and our ability to respond to things for survival, chronically elevating our stress over long periods of time.
We know reduces the effectiveness of our immune system and can actually cause certain forms of brain degeneration.
And while there aren't a lot of longitudinal studies on the heights of kids with ADHD and of course we never can tell how tall someone would have grown to be if they were treated with a drug because we don't have a perfect control experiment.
Even in the case of identical twin experiments and there and there aren't that many of those examples where one twin was treated for ADHD and the other wasn't etc.
But here's what we know. It does not appear that treatment with sympathomimetics during development provided the dosages are kept in the appropriate ranges is going to limit overall height.
In fact, if you look at the data, it appears that children with ADHD who are treated with ADHD meds actually arrive at slightly higher BMI's body mass indexes compared to age matched peers.
Now, of course, body mass index doesn't necessarily correlate with height, right?
Someone could not achieve a full height but could be heavier either through bone or fat or muscle or combination of all three.
But what we know is that the appropriate use of ADHD meds during development is not stunting development in any kind of overall way.
It's not preventing maturation of the body in ways that are leading to reduced weight or somehow impaired growth overall.
With that said, long term elevations of sympathetic nervous system activity does carry some risk.
And one of the primary risks that people have wondered about is cardiovascular risk.
And this makes perfect sense, right? When you increase the activity of the sympathetic nervous

system, you increase blood pressure, you increase heart rate, you increase in some cases peripheral sweating,
all the things that we associate with stress.
So you can imagine that a child or adult with ADHD that takes these sympathomimetics every day, even if the dosage is kept in a range that doesn't allow them to experience any immediate untoward side effects.
So they're not feeling miserable. They're just feeling like they can focus better.
But one always wonders what's going on under the hood, so to speak.
There is, as far as I know, one major study that's addressed this and the conclusions of that study were a little bit hard to put into a single category.
It did point to a subtle increase in cardiovascular risk.
But the results did not point to anything so dramatic that the authors of the study warned against taking these drugs or encouraging people to cease taking these drugs.
Again, provided they're being prescribed by a board certified physician for ADHD and at the appropriate dosage for that person.
That said, I think this all again speaks to the importance of arriving at minimal effective dosage.
And it stands to reason that if you're somebody who's taking ADHD meds or if your child is taking ADHD meds,
that one would want to do all the other things that they could do in order to try and improve cardiovascular health or at least not put it at additional risk.
So those are going to be the obvious things like avoiding smoking or vaping nicotine.
Regular exercise is going to be encouraged and things of that sort.
And that dovetails into a bunch of other questions that are often asked anytime the topic of Adderall or Ritalin comes up,
which is what about alcohol?
Is drinking alcohol at the same time or at different times even going to be problematic if one is taking these drugs,
is taking benzodiazepines going to be a problem, et cetera, et cetera.
There's a very straightforward answer to this, which is it's very clear that alcohol, certainly in children,
but also in adults, is best not consumed.
I did an entire episode about alcohol.
She got into this and the data for this.
If you've heard that having some alcohol in particular red wine is better for you than no alcohol, that is simply not true.
Sorry, it's not true.
Most adults who are not alcoholics can probably have up to two.
That's right, two drinks per week and still be on the safe side of health, although zero is better than two.
And once you get past two, you start seeing effects on various systems, including increased cancer risk,
especially brain neuron loss and degeneration risk.
I covered all of those data in the episode on alcohol that you can find at hubermanlab.com.

Combining alcohol with sympathomimetics, even though they reside in very different pathways within the brain,
in fact, the sympathomimetics are driving up sympathetic nervous system activity,
whereas alcohol is actually doing the opposite.
It's depressing it.
And yet all the data point to the fact that combining alcohol with sympathomimetics, such as vivants, Adderall, Ritalin, or any kind of amphetamine, is going to be more detrimental to the brain and body than simply taking those drugs on their own.
Put differently and more directly.
If you are taking any of the drugs that we've been talking about to treat ADHD,
or if you just happen to be taking them for whatever reason,
you are going to want to avoid drinking alcohol at any time.
And you're going to want to avoid benzodiazepines and similar unless they've been prescribed to you by your physician.
In advance of this episode, I put a call out on social media for questions about Adderall, etc.
And I got a lot of questions about whether or not there are impacts of these drugs on the hormone systems of the body
and if they impact the reproductive system in particular.
I also got questions about whether or not these drugs impact sexual behavior or libido or anything of that sort.
In reviewing the literature, what I can tell you is that there are very few studies, unfortunately,
of the long-term effects of these drugs on the endocrine or hormone systems of the body.
But we do know a few things for sure.
First of all, when you increase the activity of the sympathetic nervous system for long periods of time,
you are very likely increasing levels of cortisol.
Cortisol is a quote-unquote stress hormone, but cortisol also plays some really important positive roles in your body.
In fact, do you want cortisol released, especially early in the day?
You don't want cortisol released so much late in the day.
This actually relates back to timing and schedules of taking drugs.
This is something, again, that needs to be worked out with your psychiatrist or your child psychiatrist.
But one of the reasons why there are so many different drugs for the treatment of ADHD is that each and all of them has a different time course of action.
So Ritalin is very short-lived, which might sound bad because then you have to take it multiple times throughout the day.
But if you think about from the perspective of sleep and the importance of having low cortisol at night
and these drugs increase cortisol and the importance of getting sleep,
after all, sleep is the foundation of mental health, physical health and performance in kids and adults.
It's responsible for growth. It's when neuroplasticity happens. It's just so vitally important.

A lot of the drugs that we've been talking about can severely limit one's ability to fall and stay asleep.
And so a short-acting drug like Ritalin is actually attractive from the perspective of being able to take it in the morning and still get to sleep at night
or taking it in the morning and in the afternoon and maybe even again in the evening depending on the person
and then still being able to fall asleep at night.
Whereas long-duration release of DMphetamine, which is what you get when you take vivants,
for some people is going to inhibit their sleep.
They'll get a nice steady rise and improvement in focus and reduction in hyperactivity,
but they might have a lot of trouble falling asleep at night.
And Adderall having a somewhat intermediate time course of action between Ritalin, which is short-lived and vivants, which is very long-lived,
perhaps is going to be the best solution for somebody else where they can take it early in the day,
perhaps at a low dose, maybe again later in the day, low dose and then still fall asleep at night.
But I've spoken to people and I spoke to this clinician expert in ADHD
who told me that some people will take as little as 2.5 milligrams of Adderall at 6 a.m.
and have a hard time falling asleep later that night at 11 p.m.
So again, vastly different sensitivities to these drugs,
leading to vastly different requirements of dosage and timing of intake
and which particular drug somebody might choose to or choose not to take.
So how does that relate to hormones and sex and reproduction?
Well, cortisol itself is a hormone.
It can act as a bit of a hormone and a neurotransmitter in the brain,
but for the most part it's acting as a hormone in the brain and body
and it does a number of things.
First of all, it can enhance your levels of focus and alertness.
It can activate your immune system.
I know the immunologists out there just cringe when I say activate the immune system.
Your immune system is always doing various things,
so it's always active just as your nervous system is always active,
but it can, to be specific, it can amplify or mobilize the release of anti-inflammatory molecules
in your brain and body to combat different types of bacterial, viral and fungal infections.
It's doing an enormous number of positive things.
It's also involved in setting mood.
It has interactions with thyroid hormone pathways.
I've done entire episodes about cortisol and cortisol regulation.
To paint all of that with a very broad brush and briefly now,
it's advantageous to have your cortisol release high in the early part of the day
and to taper off toward the end of the day.
In fact, late day elevations in cortisol are a strong correlate of depressive symptoms.
This was demonstrated by my colleagues, David Spiegel and Robert Sapolsky at Stanford School of Medicine.

But that is not to say that cortisol is bad.
It's to say that the timing of cortisol release is key.
So do these sympathetic drugs disrupt the endocrine system?
Well, they can.
If you are very awake and very alert, regardless of whether or not you're taking your sympathetic treatment for ADHD early in the day or late in the day,
you are very likely experiencing elevations in cortisol late in the day.
So it is important, even for those of you that like to study and need to focus in the evening and nighttime hours,
that you try and limit your levels of overall alertness and certainly stress late in the day.
Because doing that day after day after day for several weeks or months or years
can indeed disrupt other hormones in the endocrine system.
And again, that's because cortisol is interacting with thyroid hormone and testosterone and estrogen.
In fact, cortisol in many ways competes with or can outcompete for the production of testosterone and other so-called steroid hormones.
Remember, cortisol itself is a corticosteroid hormone.
So when we hear the word steroids, oftentimes people just think about athletes and steroid abuse in sports.
But steroid hormones includes a lot of different types of hormones, which are good for us.
Our endogenous steroid hormones are vital for all sorts of things, vitality, reproduction, etc.
And the way this works in general terms is that the cholesterol molecule is used to create testosterone and cortisol and estrogen.
If we make too much cortisol, we in many ways are reducing the total amount of testosterone that we make or that is active.
It's not exactly that straightforward, but we can make that statement with confidence.
For instance, if you spike your cortisol just briefly during the day because you have some sort of stressful event,
that's not going to inhibit your testosterone.
In fact, it probably is going to boost your testosterone levels somewhat.
However, if your cortisol levels are chronically elevated, yes, indeed,
it's likely that you're going to suppress your total and or free unbound forms of testosterone.
And downstream to that, you will experience effects such as reductions in libido,
reductions in muscle and bone mass, reductions in all sorts of aspects of testosterone related psychology and bodily biology.
This is true for both males and females.
And the same thing could be said for estrogen.
Now, what's impossible for us to say is whether or not taking a given treatment for ADHD is going to, for instance,
prevent a woman from ovulating.
That could happen through chronic elevations in cortisol, but there's no direct link,
meaning there are no studies at least that I'm aware of showing that people that take Adderall have irregular ovulatory cycles

or that they cease menstruating entirely.
I don't think there's any evidence for that whatsoever,
nor is there any evidence that people that take Adderall or other sympathomometics for the treatment of ADHD have lower overall testosterone.
In fact, you can imagine all sorts of instances in which the opposite was true,
that a child or young adult or adult who has ADHD but then goes on these meds to improve their symptoms
is now focusing and achieving more in life.
We know that happiness can impact dopamine and vice versa and testosterone levels
and productivity itself and reaching our goals can feed back on the hormone system.
So anytime there's a discussion about hormones or a study that shows that doing X or not doing Y impacts hormone levels of a given type,
we have to be very careful to make sure that we're talking about causality
because all of these hormones are in a very intricate crosstalk with one another.
We can, however, make a very general statement, which is that when you are in states of stress for long periods of time,
that is not a favorable condition for your immune system, your hormone system,
or frankly any other system in the brain and body.
So the treatment of ADHD with these drugs should never be done at the expense of these other critical biological systems.
Another common question and concern is whether or not kids, and I suppose for that matter adults, that take medication for ADHD are basically being predisposed to psychosis and or other forms of addiction.
And earlier we talked a bit about the risk for addiction and the take home message there is very clear
that kids and adults that are treated for ADHD appropriately.
So with the appropriate dosage of the appropriate drugs under the supervision of a board certified qualified psychiatrist
are at less risk for forming addictions to other substances in adulthood or other substances generally.
I think a lot of people also wonder whether or not those kids and those adults that take these ADHD meds become addicted to the medications themselves.
That's a bit of a tricky issue to resolve.
Anytime one stops taking a drug or even tapers off a drug that's used to treat something where they feel better on the drug,
they're going to experience two sets of effects and these two sets of effects are often confounded with one another.
One is the withdrawal effects.
So the effects of removing the drug that makes somebody feel less good than baseline.
So for instance, a kid that takes ADHD meds until their late teens or early 20s decides they're going to taper off.
They do that and they're feeling lousy during the taper or when they reduce their dosage to zero.
They're foggy brain, they can't focus, they feel a little bit depressed mood.

It's unclear whether or not those are withdrawal symptoms or whether or not those are the consequence of not having the systems in their brain
activated the way that those systems were activated before.
I realize that for some of you that might seem like the same thing, but that's not necessarily the same thing.
And probably the best analogy would be something along the lines of a hangover, right?
If somebody drinks too much on a given night, the next morning they have a hangover.
The hangover makes them feel lousy.
It is actually a withdrawal from alcohol effect.
But then when they recover from the hangover, they realize that their sober state, it feels pretty good.
It doesn't obviously feel the same as being on alcohol, but that sober state is not a state of withdrawal.
If we were to look at removal or tapering off of ADHD meds, there's going to be a period of withdrawal symptoms.
But then the real question is how does somebody feel after they get through those withdrawal symptoms?
So that's an important issue to highlight.
Now, in terms of psychosis, this is a very interesting and very important literature.
First of all, any amphetamine, whether or not it's D-amphetamine, L-amphetamine, and also methylphenidate, for that matter, Ritalin, can induce psychosis.
Now, there are a number of different factors that are going to predispose somebody to psychosis.
Having a first relative who's had psychotic episodes, either schizophrenic episodes or bipolar episodes, is certainly a strong predisposition.
Of course, if an individual themselves have had psychotic episodes, that's the strongest predisposition that one could imagine.
So having a first relative with schizophrenia or with bipolar depression or sometimes called bipolar disorder,
sometimes it's also just called bipolar these days, is going to be a strong predisposition for psychotic episodes made much greater
anytime one takes a sympathetic drug such as amphetamine, but also methylphenidate, Ritalin, is going to increase that likelihood of psychotic episodes.
Then comes the question of if somebody has a psychotic episode as the consequence of taking any of these drugs, whether or not it's been prescribed for ADHD or not,
will those psychotic symptoms go away after the person stops taking the drug?
There appears to be a divide in the literature or rather a divide according to drug such that people that take Ritalin, methylphenidate and have a psychotic episode,
often not always, but most often if they stop taking methylphenidate, the psychotic episode will cease.
Not always the case, but most often times it will cease, whereas in individuals who have a predisposition to psychosis or even if they're not aware of a predisposition to psychosis
and they take Adderall, which as you recall is a combination of D and L-amphetamine, they can have psychotic episodes that sometimes are very long lasting even after the cessation of the drug.

And while that might sound kind of shocking and really scary and indeed it is scary, it perhaps shouldn't shock us that much because if you recall D-amphetamine,
which there's a lot of in Adderall, it's a very potent way of increasing dopamine and anytime you potently increase dopamine in a person who has a predisposition to psychotic episodes,
you are shifting the whole system toward greater propensity for psychosis. This would also be the appropriate time to talk about meth, methamphetamine.
Again, methamphetamine is considered an illicit drug, a drug of abuse. It is responsible for a lot of the misfortune and tragedy that you see on the streets of major cities and even outside of major cities and rural areas.
It has all sorts of negative effects on health, including oral health, cardiovascular health. It is neurotoxic to serotonergic neurons.
So it kills serotonin neurons. That is absolutely clear. It kills dopaminergic neurons. That is absolutely clear.
One of the ways that methamphetamine creates so many of the problems that it does, any effects on the body, abuse potential, addictive potential.
The fact that methamphetamine can spark psychosis in those that have a predisposition to psychosis, but also that it can create psychosis in individuals who have no predisposition to psychosis.
All of this points to methamphetamine just being a terrible drug all around, and yet, if you recall back to the beginning of the episode, there is one form of prescription methamphetamine,
but its uses are extremely narrow, and it's probably best left out of this conversation because its uses are so, so narrow in the clinical sense.
I managed to talk to one expert. This is a board certified psychiatrist who's expert in ADHD who was also very familiar with the psychosis symptoms induced by methamphetamine and by various ADHD drugs and people who have the predisposition.
They made it very clear that any of the sympathomimetic ADHD drugs that are of the amphetamine variety, so that would be Adderall and extended release Adderall would be pure dexadrin, or any variants that include amphetamine are going to have higher likelihood of inducing psychosis and people that have a predisposition to psychosis.
And yet, they did assure me that at appropriately prescribed and safe dosages that the total incidence of psychosis in people that take those drugs is still fairly low and not that much greater than in the general population, although there is an increased risk, it's not that severe.
And they also highlighted the fact that methylphenidate Ritalin carries a lower potential for inducing psychosis, not zero, but a lower level of inducing psychosis than for the amphetamine type sympathomimetics.
Now, one exception is a VIVANCE, that long release deamphetamine that we talked about earlier. There does seem to be something protective about that long duration release of deamphetamine that occurs with VIVANCE, which is not to say that there's zero abuse or addictive potential with VIVANCE.
I was told by this same individual that indeed they've had knowledge of patients trying to increase the rate of absorption of VIVANCE and release of VIVANCE or technically of the deamphetamine in order to get more of a high from VIVANCE as opposed to just the extended release.
But they did assure me, however, that VIVANCE seems to be associated with fewer psychotic episodes and less abuse and addictive potential overall, which again is not to say that it's a perfectly

safe drug.
But really, this just highlights the fact that the kinetics or the time course of dopamine and norepinephrine release that's caused by a given drug is going to correlate very strongly with its abuse potential and addictive potential and its potential to induce psychotic episodes.
And this is where the discussion about meth becomes especially relevant.
One of the reasons why meth is so dangerous in terms of its addictive potential and its potential to induce psychotic episodes is first of all, how much dopamine it releases.
Again, five times more than any of the other drugs that we've been talking about, but also how fast that peak comes on.
It's a very fast onset and that's true whether or not people are snorting it, whether they're taking it orally or especially if they inject it intravenously.
But meth, because it increases dopamine so fast and to such a great degree, and then the peak in dopamine comes down very fast as well and it drops below the baseline levels of dopamine that were present initially.
That's one of the reasons why methamphetamine is so dangerous in terms of addiction and in terms of psychotic episodes.
This gets back to a bunch of issues we've talked about before on the Huberman Lab podcast about dopamine kinetics.
And I've done two episodes on dopamine that I'll refer you to.
One is called Dopamine Motivation and Drive, which is all about dopamine and regulating dopamine.
And the other one is about optimizing dopamine.
It's more of a toolkit focused episode, both those you can find at Huberman Lab.com.
But the general takeaway that's relevant for what we're talking about now is that with dopamine, it's not just about the absolute levels of dopamine that are reached,
but how long lasting those increases in dopamine are.
So with vivants, even though vivants is DM-phetamine, it's fairly potent, not as potent as meth, but fairly potent at increasing dopamine and norepinephrine.
It's a long extended release in dopamine and norepinephrine, which reduces its overall abuse potential because it doesn't tend to create that immediate euphoria and high and then crash below baseline.
A lot of you will hear that it increases dopamine a lot and then stays up as translating to, okay, well, then you're just euphoric for 16 hours, but that's not the case.
When it comes to dopamine, it's an issue of how high that peak is and whether or not that peak is stable or whether or not it comes down again.
And when it comes to psychotic episodes or addictive potential, it seems that any drug or behavior that increases dopamine very quickly
and then brings dopamine down very quickly is what sets the high potential for addiction and abuse and for inducing psychotic episodes.
So that's why I'm talking about these two things in parallel.
And now it should be very clear why vivants doesn't have so much addictive and abuse potential and has at least lower potential for inducing psychotic episodes.
It should also be clear to you that for people who do not have ADHD as a child or for people that do not have ADHD in adulthood, if they were to take any, truly any of the compounds that we're talking

about thus far, methylphenidate,
Ritalin, Adderall, Vivants, Dexadrine, and certainly methamphetamine, what we observe from neuroimaging studies is that these people get enormous increases in dopamine.
They're not familiar with these drugs, so the increases in dopamine are just cosmic for them.
They experience a lot of euphoria, even if the dosages are low, the euphoria is associated with a very heightened degree of focus they've never really felt before.
Here what I'm talking about is a lot of the recreational and off prescription use of Adderall and things like it.
And what we know is that that sets in motion both a potential for abuse and addiction to that feeling and substance, as well as a higher potential for psychotic episodes down the road.
Okay, so put differently, children who have ADHD and are prescribed any of these drugs or adults who have ADHD and are prescribed any of these drugs who take them for some period of time are actually at lesser risk to all of the issues related to having chronically elevated and greatly elevated dopamine as a kind of first time event or as a rare event, whereas anyone who takes these drugs without a prescription and decides, okay, I want to focus more, I'm going to use this to stay up for a couple of days.
In other words, using it recreationally or using it for quote unquote performance enhancement is that far greater risk for addiction to these substances because of the amplitude and the time course of dopamine that results when one takes these drugs just out of the blue.
And so for that reason, I really want to caution everybody against using any of the compounds that I've discussed thus far, unless it's been prescribed to you by a physician for the specific purpose of ADHD.
Now, I'm sure someone out there is screaming from the back, wait, if a kid takes these drugs because they're prescribed them for ADHD the very first time they take them, they're going to have a huge amplitude dopamine response.
Or if an adult goes in and talks to their psychiatrist and says, you know, I'm having issues with focusing and they're prescribed one of these meds for ADHD and they take it, they're going to have a huge amplitude dopamine response.
Isn't that going to set in motion all the same things that somebody who is using these drugs recreationally would have.
And indeed, that's one of the reasons why a lot of psychiatrists will start with a very low dosage or the lowest possible dosage to see how somebody responds to that low dosage.
And then over time might or might not increase that dosage.
In fact, they might even bring it down further, depending on how sensitive somebody is to the drug.
But equally important is the fact that it is the repeated taking of that drug by the child with ADHD or by the adult with ADHD that actually leads to lesser and lesser peaks in dopamine each time.
Which is not to say that the person becomes entirely desensitized to the effects of the drug, but rather that the system equilibrates through what's called homeostatic plasticity.
Sometimes referred to broadly as habituation to a drug, but there are systems in the brain and body that regulate the connections between neurons so that if dopamine and norepinephrine are elevated above baseline levels for a while,
the system normalizes so that instead the connections between neurons become stronger and there isn't the critical requirement for all that increase in dopamine and norepinephrine.

I realize that might sound a little bit technical, but basically what I'm saying is the response that somebody has to taking a drug for the first time is far and away different than the response to a drug that somebody has if they are taking the same drug day after day after day.
This gets to another issue, which is not discussed that often these days, but that is really important.
If you go back to the original clinical literature on the sympathomimetics, what you'll find is that the original use of these sympathomimetics to treat childhood ADHD suggested that children not take these drugs every single day.
Now, I'm not recommending that kids take drug holidays because I'm not a clinician.
I'm not promoting any specific dose or dosing regimen, but in speaking again to a psychiatrist expert in ADHD, who by the way is going to be a guest on this podcast in the not too distant future.
What he told me was that many of these drugs were designed to be taken during the school week for children with weekends off or during the school year with weekends off, but then also with vacations during the summer holidays.
And that these days rarely, if ever, is that the pattern of intake that these kids are following and why that is has interesting sociological and financial explanations.
I'm not alluding to any kind of conspiracy here, but this is an aspect of the dosing with these drugs that has sort of fallen away in recent years, but I think is really interesting.
And it's something that actually was supported for the treatment of adult ADHD as well.
Again, there is a very different biological and neuroplastic response to taking a drug once versus taking a drug for say five days and then taking weekends off to taking a drug over and over again every single day for a pattern of years.
And when exploring the literature in preparation for this episode, I confess it was a bit dizzying to find answers to what are the long-term effects of taking Adderall or what are the long-term effects of taking vivants, et cetera.
In fact, most of the literature on the long-term effects of taking drugs to treat ADHD has focused on methylphenidate on Ritalin.
There are studies on vivants and Adderall and actually those were the studies that I will link in the show note captions primarily because that's where most of the interest is these days.
The reason why so many of the studies have focused on methylphenidate on Ritalin is largely because that was one of the first drugs used to treat ADHD.
So in terms of addressing long-term effects of kids treated with ADHD meds, those kids are now adults and therefore can be neuroimaged and assessed.
Whereas a lot of kids that have been prescribed Adderall or Viveans or similar have not yet made it to stages of life in which we can answer that question directly.
There are a few studies and I've made it clear to include those studies in my description of results today.
In particular, the results I talked about earlier where there's an improvement in executive function in kids that have taken ADHD meds or adults that have taken ADHD meds for a longer period of time, anywhere from months to years.
Those studies did include both Adderall and Viveans and methylphenidate.
And again, I'll link to those studies, but by and large, most of what we know about the long-term effects of any of these drugs has to do primarily with studies of methylphenidate.
I'd like to spend a little bit of time talking about some compounds that are not considered

amphetamines at all, but that are now being used to treat ADHD both in children and adults more frequently.
The major drug in this category of non-amphetamine treatments for ADHD is Modafinil, which is also called by its commercial name, Provigil.
There's a variance on this, which is Armodafinil, which goes by the brand name NuvaGil.
The major difference between Modafinil and Armodafinil, aside from having a slight chemical difference, is that Modafinil was released first.
Armodafinil is the second in the generation of these drugs.
And Modafinil tends to be very expensive.
That's one of the reasons why it's prohibitive for some people to take.
It can be as expensive as $25 a pill or more, so more than $1,000 per month.
And Armodafinil tends to be far, far less expensive.
I've talked to a couple of experts about whether or not there are any genuine differences between these two drugs, and they report no.
Although consumers of these drugs, for whatever reason, whether or not it's placebo or not, report yes, there is a difference.
When I say placebo, I in no way mean that these drugs are just acting as placebo.
I just mean that people tend to get very attached to certain drugs and whether or not the brand name or the generic version works better for them.
There's all sorts of lore about this.
In fact, there are a lot of people out there who strongly feel that brand name Adderall works better than generic Adderall for them.
There are a lot of people out there who say the same thing about Vivants.
There are a lot of people out there who say the same thing about Ritalin and all sorts of drugs.
Whether or not that's true or not is unclear.
It is clear that generic versions of drugs can use binders and other things that are in the pill or capsule that are different than what the brand name pill or capsule uses as binders to hold the drug together.
And that can impact rates of release and metabolism, etc.
But a lot of this is just lore.
In fact, I went into the literature to try and find any real concrete support for the idea that generic Adderall is less potent or less effective than brand name Adderall.
And despite the tens of thousands of people who will say to the contrary, I could not find any peer-reviewed published data about that.
So who knows?
Maybe it's a belief effect, as it's called.
Maybe there's a real difference there.
Nowadays, modafinil and armodafinil are prescribed for a huge range of daytime sleepiness issues.
We were talking about narcolepsy, but there are also people who suffer from daytime sleepiness related to dementia.
Daytime sleepiness related to post-surgery anesthesia.
So there's this thing where people have surgery and then they come out of surgery and they feel better for a few days.

But then they find that they aren't recovering their normal levels of wakefulness.
So it's prescribed sometimes to try and get people back into a normal state of wakefulness.
It's been prescribed for traumatic head injury after stroke.
Again, all of these prescribed uses have to be carried out by a certified physician.
You really don't want to start cowboying the use of modafinil or armodafinil or any other prescription drug for that matter.
I must say that in discussing all these different drugs during today's episode, I have zero knowledge of any of these drugs from a firsthand experience except for armodafinil.
Back in 2017, I was prescribed a very, very low dose of armodafinil for jet lag for daytime sleepiness issues, really, when I was traveling overseas to give a talk.
So armodafinil was given to me in a 25 milligram tablet.
It was advised to me that I take a half or even a quarter of that.
So I started with a quarter. I am a believer in minimal effective dose.
I'm also somebody who's fairly hypersensitive to most medication.
So I took what I measured out to be five to seven milligrams of armodafinil.
And what I experienced was pretty profound.
Certainly it relieved any daytime sleepiness.
In fact, it made me feel extremely alert for a period of about four to six hours.
I can't say it was the most comfortable state, although I did not feel as if I had racing heart or anything of that sort.
I basically felt as if I was in a narrow tunnel of attention for that entire period.
One thing I did not like about the experience is that it was a very hard experience to come down from.
There was no crash, but I found that that high arousal state didn't taper off for many hours later, even though it was most heightened for four hours.
I would say anywhere from eight to 12 hours later, I still felt like I was, you know, blinking once every four minutes or so.
And I've certainly been accused on this podcast and at other times of blinking to seldom.
To my knowledge, I don't have ADHD.
I've never been prescribed ADHD meds.
I've never been tested for ADHD.
I don't think I have ADHD.
And yet taking our modafinals certainly increased my levels of attention.
But at least by that one experience, it's not something that I would want to repeat again.
I certainly would not want to be in that state for learning new material.
When I sit down to research a podcast or research papers in my lab or forage for information or learn from people or books or lectures or podcasts,
I want to be in a state of alertness but calm where I can really consider the ideas, where I can script things out by hand.
I'm a big believer in writing things out by hand to remember them later, drawing little diagrams.
I would not want to be in the state that even that very low dose of our modafinals put me in in order to learn.
And I should mention that both modafinals and our modafinals are associated with a good number of

side effects.
If they don't agree with you or if the dosage is too high, things like decreased appetite, people can get a runny nose, headache.
There's this instance of skin rashes.
In fact, one of the reasons why modafinals and our modafinals aren't more broadly prescribed is that there's a very rare skin condition in which people who have taken certain drugs,
not just modafinals or our modafinals, have developed these very severe burn type blisters.
And in some cases, this can be fatal.
This is, again, very rare.
And it was observed in at least one patient who took modafinals as part of a trial for modafinals treatment for ADHD.
It's called Stevens-Johnson syndrome.
Please, if you are squeamish to images of skin abrasions and lesions and things of that sort, please don't look it up on the internet unless you're able to handle that and maybe not at all.
The point here is that one of the reasons that modafinals and our modafinals are not more widely prescribed for ADHD and that it's still only prescribed off-label is that Stevens-Johnson syndrome was flagged as kind of a potential risk,
although the ADHD specialists that I spoke to are somewhat frustrated with that because they insist that the frequency of this syndrome that causes this skin rash that's sometimes fatal is no more frequent in those that took modafinals in this trial than with other drugs that have been approved.
So this gets into all sorts of issues around what drugs make it to approval and which ones don't.
And as we know, modafinals and our modafinals are already being prescribed in the general population for other things.
This was dealing specifically with the question of whether or not it should be prescribed in kids with ADHD and certainly I am a proponent of exerting extreme caution when thinking about which drugs should be approved for the treatment of anybody, but especially kids.
And to round out our discussion of drugs used for the treatment of ADHD that fall into let's call it the atypical category, right?
The typical category being Adderall, Vivants, methylphenidate and things of that variety.
The less typical would be modafinil, armodafinil, propyrin, well butrin and so forth.
The last in this category of atypical is Guanfacine.
Guanfacine is an interesting compound.
It's a compound that was developed to lower blood pressure and indeed it does lower blood pressure and it is an alpha 2a agonist, alpha 2a being a receptor for norepinephrine.
So Guanfacine is a non-stimulant medication to treat ADHD and it's also used to treat some other conditions as well that is only working on the noradrenergic system.
It is not tapping into the dopamine system.
But all the other stuff that we talked about is really ramping up dopamine and norepinephrine.
Guanfacine is only increasing norepinephrine and it's doing so by what we say agonizing or stimulating one particular aspect of the noradrenergic system and that's the alpha 2a system.
What's interesting about Guanfacine is that it has a bunch of pathways that it activates that feed back onto the autonomic nervous system to dampen down the activation of the sympathetic nervous system.

So whereas most of what we talked about today are sympathomimetics.
They tend to make us more ramped up, more aroused in alert.
Guanfacine is doing the opposite.
And as a consequence, it's not prescribed that often because a lot of times when people take Guanfacine, it either has no effect on ADHD symptoms or it tends to make people feel very sleepy.
However, there's a small subset of individuals, probably about 5 to 10% of people that try it, including kids, that do get some significant relief from their ADHD symptoms and they seem to tolerate Guanfacine better than they're tolerating some of the other drugs that we've talked about up until now.
The way Guanfacine works is also really interesting.
You're now familiar with the locus ceruleus, this packet where we call it a nucleus of neurons in the back of the brain that release norepinephrine at other sites in the brain.
And they're going to be those alpha 2a receptors that Guanfacine works on and stimulates lots of different places in the brain related to increasing salience and relevance of particular stimuli that we see and that we need to attend to.
It appears that Guanfacine can activate the prefrontal cortical networks in ways that are above their normal baseline, so that's good.
So improvements in executive function, that orchestra or teacher like function we talked about before, and can increase the efficacy of that output from locus ceruleus.
And what that seems to do is increase the coordinated firing of locus ceruleus neurons with prefrontal cortex.
So in many ways it's acting like a fine tuning of that orchestra conductor operation that is so valuable in teaching these brain circuits during childhood of how to attend to one thing and ignore everything else.
So this is one reason why Guanfacine is now approved not just for adults with ADHD, but is primarily used in kids aged six to 17 years old for the treatment of ADHD.
Again, with the hope that these kids can take the drug and these circuits can learn how to focus and how to attend to certain things and limit impulsivity and hyperactivity and then perhaps come off the drugs, although sometimes, again, people have to stay on them indefinitely.
The other thing about Guanfacine is that because it lowers blood pressure and it has this effect of kind of dampening down overall sympathetic arousal, sometimes it is prescribed in conjunction with other ADHD meds.
So yes, there are kids out there and adults out there who are taking Adderall and Guanfacine or they're taking Vyvance and Guanfacine.
And this is where it starts to get into drug cocktails and a bunch of other things that gets everybody a little bit uncomfortable, I think, because the idea of taking one drug to dampen down the side effects of another drug and to offset things and compensate is getting towards what's called polypharmacology.
And, you know, I think it's understandable that people be concerned about that.
And yet, again, in viewing this with some of the experts on ADHD, there do seem to be a certain category of children out there and adults who really struggle with the standard ADHD meds.
And in that case, Guanfacine has provided a certain number of these individuals tremendous relief.
One note about Guanfacine, in no way, shape or form, am I encouraging anyone who's not

prescribed Guanfacine to take it?
But should you know someone who's taking Guanfacine off label in order to improve their focus or enhance any aspect of their biology or psychology?
Please let them know that it has a profound effect on lowering the tolerance for alcohol such that even small amounts of alcohol can lead to really serious problems and even potentially death.
So that's a very serious warning with Guanfacine.
So today we discussed a lot of different compounds for the treatment of ADHD, and it now should become clear what the general themes of those compounds is.
The general theme is that they tend to increase overall levels of arousal and wakefulness, which leads to decreased levels of hyperactivity, impulsivity and focus.
And on the face of it, that might seem counterintuitive, raise arousal to reduce hyperactivity and impulsivity.
Indeed, that's the case because these compounds, because they act on neuromodulator systems like dopamine and norepinephrine, are effective in creating neuroplasticity.
They change the strength of the connections in the neural circuits of the brain that lead to states of heightened focus and reduced impulsivity and reduced hyperactivity.
So we talked about the different mechanisms by which the different medications for ADHD accomplish this.
Both the typical sort like methylphenidate and adarol and vivants and some of the atypical compounds that are now being used in addition, such as modafinil or modafinil, guanfacine and wellbutrin.
And where possible, I tried to highlight both the short and long-term effects of these various compounds.
And I tried to address some of the major concerns about these compounds, most notably the question of why are we putting so many kids on amphetamine and what is the long-term consequence of that.
And throughout today's episode, I tried to highlight both the immediate and long-term benefits, but also the immediate and long-term risks that can exist with these compounds, certainly when taken without a prescription.
Recreationally, there is a real risk for abuse and addiction, as well as even a risk for psychotic episodes, but also the risks that accompany long-term use of these drugs in people with ADHD.
And yet it is also clear that not treating the symptoms of ADHD carries significant risk as well.
And what's very clear from the scientific and clinical literature and is covered in a significant amount of detail in the episode that I did about ADHD, which you can find at hubermanlab.com, is that combinations of drug treatments and behavioral protocols seem to surpass either drug treatments or behavioral protocols alone.
Speaking to the tremendous importance of combining multiple methodologies when treating ADHD and working with a board-certified psychiatrist who really understands ADHD and is really up to date on all the latest scientific and clinical literature.
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If you have questions for me or comments about the podcast or suggestions about guests you'd like me to include on the hubermanlab podcast, please put those in the comment section on YouTube. I do read all the comments. Not so much on today's episode, but on many previous episodes of the hubermanlab podcast, we discussed supplements.
While supplements aren't necessary for everybody, many people derive tremendous benefit from them for things like improving sleep, hormone support, as well as focus.
The hubermanlab podcast is proud to have partnered with Momentus supplements. If you'd like to see the supplements discussed on the hubermanlab podcast, you can go to livemomentus spelled OUS, so it's livemomentus.com slash huberman.
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Thank you for joining me for today's discussion all about pharmaceutical interventions for the treatment of ADHD.
And last but certainly not least, thank you for your interest in science.