

Understanding & Controlling Aggression | Huberman Lab Podcast #71

This episode I describe the neural mechanisms that activate and control aggressive states and behaviors and the role of hormones—estrogen and testosterone—in mediating violent and/or competitive aggression. I also describe tools that can be used to modulate the factors that have been shown to ‘prime’ an individual for aggression, including sunlight, estrogen sensitivity, competition within social settings, and overall stress levels, and the hormone cortisol. I discuss how substances such as caffeine and alcohol can impact impulsive behaviors and how nutrition and supplementation can be used to regulate mood and aggression.

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Other Links

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VMH stimulation causes mouse to display aggressive behaviors toward an inanimate object (e.g., glove): <https://youtu.be/AlIp69kfjw?t=689>

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- Welcome to the Huberman Lab Podcast, where we discuss science and science based tools for everyday life. [cheerful music] I'm Andrew Huberman, and I'm a professor of neurobiology and ophthalmology at Stanford School of Medicine. Today, we are discussing aggression. I'm going to explain to you that there are several different types of aggression, for instance, reactive aggression versus proactive aggression. Meaning sometimes people will be aggressive because they feel threatened or they are protecting those that they love, who also feel threatened. There's also proactive aggression where people go out of their way to deliberately try and harm others. And there is indirect aggression, which is aggression, not involving physical violence, for instance, shaming people and things of that sort. It turns out that there are different biological mechanisms underlying each of the different types of aggression. And today I will define those for you. I'll talk about the neural circuits in the brain and body that mediate each of the different kinds of aggression. Talk about some of the hormones and peptides and neurotransmitters involved. I promise to make it all accessible to you, even if you do not have any biology or science background, I will also discuss tools, psychological tools and biological tools that one can use to better control aggression. Now, right here at the outset, I want to acknowledge that any discussion about aggression has to have an element of context within it. To be fair, human beings invest a lot of money, a lot of time, and a lot of energy, and indeed can even derive pleasure from aggression. Later I'll talk about neural circuits in the brain and body that reinforce, in other words, reward through the release of chemicals that make people feel good. Acts of aggression. However, what I'm mainly referring to is the context in which human beings will pay money in order to derive what we call vicarious aggression, put it simply people spend an enormous amount of money and time and energy watching other people engage in, for instance, aggressive sports. And we know that observing your team winning over another team causes the release of neurochemicals in your brain and body that make you feel good. And yes, that can make you feel more aggressive. We also know of course that most governments invest many billions if not trillions of dollars in infrastructure, technologies and human beings in order to engage in aggression if needed, so-called military warfare, et cetera. So today's discussion will include a description of aggression in the pathological sense. We'll actually talk about an explosive aggressive disorder that most of you probably haven't heard of, but is actually far more common than perhaps, you know, we'll talk about the role of things like attention deficit, hyperactivity disorder, and how that can relate to aggression through the relationship between impulsivity and

aggression. And we'll talk about verbal aggression, physical aggression, proactive aggression, as mentioned before, and reactive aggression. I'm certain that by the end of the episode, you will come away with a much more thorough understanding of what this thing that we call aggression really is. And when you see it in other people, I think it will make more sense to you. And when you observe it in yourself or the impulse to engage in aggression, verbal, or physical or otherwise, I hope that you'll understand it better as well. And of course, the tools that I will describe should allow you to modulate and control

00:03:33 AG1 (Athletic Greens), ROKA, Helix Sleep

aggressive tendencies or predispositions to aggressiveness and just generally to be able to engage with people in a more adaptive way overall. 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 Athletic Greens. Athletic Greens is an all-in-one vitamin mineral probiotic drink that's designed to meet all your foundational health needs. I started taking Athletic Greens way back in 2012. So I'm delighted that they're sponsoring this podcast. The reason I started taking Athletic Greens and the reason I still take Athletic Greens once or twice a day is that it covers all of my basic vitamin mineral and probiotic needs. The probiotics are especially important to me. There are now abundant data showing that the gut microbiome, which is basically a community of trillions of little bacteria that live in our guts are beneficial for our immune system, for brain function, for mood and many other aspects of our health. The gut microbiome thrives on probiotics and Athletic Greens contains the proper array of probiotics to optimize the gut microbiome. Athletic Greens also has adaptogens for recovery from physical and mental exertion, digestive enzymes for gut health, vitamin C, zinc, as I mentioned before, all the other vitamins and minerals that you need in order to cover your basic needs each day. If you'd like to try Athletic Greens, you can go to athleticgreens.com/huberman and claim a special offer. That'll give you five free travel packs that make it easy to mix up Athletic Greens while you're on the road and a year supply of Vitamin D3K2. There's now a wealth of data showing that vitamin D3 is important for many aspects of our immediate and long term health. Many people, even if

they get out in the sunlight are not getting enough Vitamin D3, and the K2 is thought to be beneficial for calcium regulation and a number of other things important to our health. So again, if you go to athleticgreens.com/huberman, you can claim the special offer of the five free travel packs and the year's supply of vitamin D3K2. Today's episode is also brought to us by ROKA. ROKA makes sunglasses and eyeglasses that are the absolute highest quality. The company was founded by two All-American swimmers from Stanford and everything about their eyeglasses and sunglasses were designed with performance in mind, I've spent a lifetime working on the biology of the visual system, I can tell you that your visual system has to contend with some pretty tough challenges as you move throughout the day. For instance, if you go from a brightly lit region to a dimmer region, your visual system has to adjust. ROKA eyeglasses and sunglasses were designed with those sorts of adjustments in mind. So for instance, if you're outside in the shade, you move into the sun and then back into the shade, you don't have to take your sunglasses on and off. Their glasses were initially designed for sports performance and the great thing is they could be used for that, but also they have a terrific aesthetic, so you can wear them to work or out to dinner. I wear readers at night and when I drive at night and I wear sunglasses, if I'm out a lot on really bright days. The terrific thing about ROKA glasses is that even if you get sweaty, they won't fall off. So you can run with them, you can cycle with them. Or as I mentioned before, you can just wear them out and about. If you'd like to try ROKA, you can go to roka.com, that's R-O-K-A.com and enter the code "Huberman" to save 20% off your first order. Again, that's ROKA roka.com and enter the code "Huberman" at checkout. Today's episode is also brought to us by Helix Sleep. Helix Sleep makes mattresses and pillows that in my opinion are the very best you'll find. I started sleeping on a Helix mattress a little over a year ago, and it's the best sleep I've had ever since. If you go to the Helix site, they have a terrific sleep quiz that just takes a few minutes, ask you questions like, "Do you tend to sleep on your side, your back or your stomach?" Maybe you don't know because you're asleep, but many people do know. And even if you don't know that's okay, it will also ask you questions like, "Do you tend to run hot or cold?" Do you tend to wake up in the middle of the night or not? And by taking that brief quiz, they will match you to the specific mattress that's ideal for you and your sleep needs. And that's really what sets Helix Sleep mattresses apart. Everybody's unique, and they know that. So if you take this quiz, you'll get matched to a particular mattress. For me, it was the "Dusk" mattress D-U-S-K, but again, that's just me, and you may match to that one, or you may match to a different one. If you're

interested in upgrading your mattress and sleeping much better, go to helixsleep.com/huberman. Take that two minute sleep quiz and they'll match you to a customized mattress and you'll get up to \$200 off any mattress order and two free pillows. I also love their pillows. I've always had this issue with pillows that they heat up too much. I'm always looking for the pillow that can cool itself. Somehow the pillows stay nice and cool. They're also not too big, so I'm not propped up, not getting the Text Neck in the middle of the night, where I'm letting my chin push my chest, nor am I falling back and having trouble breathing in the middle of the night. They're designed just right. They also have a 10 years warranty and you get to try it out for a hundred nights, risk free. They'll even pick it up for you if you don't love it. But I think that you will.

00:08:29 Neural Circuits for Aggression, "Hydraulic Pressure Model"

Again, if you're interested, you can go to helixsleep.com/huberman for up to \$200 off and two free pillows. Let's talk about aggression. I think that many people out there are put off by aggression, although others are drawn to aggression both in themselves and when observing it in others. The reason to talk about aggression is, that as mentioned before, the context of aggression really matters. So there are instances where aggression is adaptive. For instance, a mother protecting her children if she's being attacked, or if her children are being threatened. I think most people would agree that so-called maternal aggression of that sort, provided the context is right, is a great thing. Protecting our young is after all one of the primary adaptive drives of our species, and thank goodness it is. Of course, other forms of aggression like unprovoked, proactive aggression, somebody simply being violent to somebody else, even when unprovoked, most of us cringe when we see that kind of behavior, it can even evoke aggression in people when they observe that kind of behavior. So again, context really matters, but a more general and perhaps an even more important reason to think about and understand aggression is that by understanding the biology and psychology of aggression, you will be in a much better position to understand how all emotional states come to be, both in yourself and in others. For instance, many of you have probably heard the statement that I believe arises from pop psychology, not from formal academic psychology, that aggression is just sadness. It's a form of sadness that's amplified and it shows up as aggression. But when we look at the underlying biology and the peer reviewed literature on this, nothing could be further from the truth. We have distinct

circuits in the brain for aggression versus grief and mourning, those are non-overlapping. Now that doesn't mean that you can't be sad and aggressive or in a state of mourning and aggressive at the same time, but the idea that sadness and aggression are one in the same thing is simply not true. And by understanding that, or perhaps by understanding that irritability and aggression are not the same thing, you'll be in a much better position to apply some of the tools that we will talk about in this episode in order to be able to reduce or eliminate, or if it's adaptive to you to modulate aggression. And yes, there are cases where modulating your aggression in some cases, even amplifying aggression can be adaptive. Now this of course is not the first discussion about the biology of aggression or the psychology of aggression. And we really can look to the beginning of the last century as the time in which the formal study of aggression really began. One of the names that's most associated with the formal study of aggression is none other than Konrad Lorenz. Some of you may be familiar with that name, others of you may not be familiar with that name. Konrad Lorenz studied so-called imprinting behaviors and fixed action pattern behaviors. He's most famous, at least in scientific circles, for getting geese to believe that he was their parent. And if you were to put into Google Conrad with a K, Lorenz, just as it sounds, Konrad Lorenz, geese, you're going to see a lot of photos of Conrad walking down roads with a lot of geese following him or swimming in lakes with a lot of geese following him. He had a habit of geese adopting him because of the behaviors that he partook in. So he would swim out on a lake in front of a bunch of little geese and then they would think that he was the parent and they would imprint on him. He even lived with these animals and they lived with him, sort of a strange character from what I hear. But nonetheless, all this work was deserving of a Nobel prize because what he discovered were fixed action patterns. That is patterns of behavior that could be evoked by a single stimulus. Okay. This is really important. The idea that you can get a whole category of behaviors, like swimming behind a parent, or looking to somebody for comfort, and only them, the idea that you could get a huge category of different behaviors in a bunch of different contexts triggered by just the presence of that person is remarkable, because what it suggested and what turns out to be true is that there are neural circuits, not just individual brain areas, but collections of brain areas that work together to engage a pattern of behaviors. And that's the first fundamental principle that we need to define today, that when we talk about aggression, we are talking about activation of neural circuits, not individual brain areas, but neural circuits that get played out in sequence like keys on a piano, but that playing out in

sequence means that aggression is a verb. It has a beginning, a middle and an end, and it's a process. It's not an event. And as you'll see, that turns out to be very important in terms of thinking about how one can halt aggression, prevent it from happening before it's initiated, or maybe even prolonging aggression, if that's what's needed. Now, Konrad Lorenz had no real knowledge of neural circuits. I mean, obviously he knew there was this thing that we call a brain and a nervous system, and he knew that there were chemicals in the brain and hormones and things of that sort that were likely to play a role, but he really didn't take any measures to define what the neural circuits were, frankly, he didn't need to. He had his Nobel prize and he did all this beautiful work. He's known for an abundance of work, but he did think about what sorts of underlying processes could drive something like aggression. And he talked about one particular feature that's especially important, and that's this notion of a pressure. The idea that yes, certain hormones will bias somebody or an animal to be aggressive, certain neural transmitter states, and you'll learn what those are today will bias somebody to be more or less aggressive, maybe even submissive and passive, maybe outright proactively aggressive towards anyone or anything in front of them. And yes, of course there will be historical features based on their childhood, et cetera, et cetera. He understood that there will be a constellation of things that would drive people to be aggressive. And he described a so-called pressure, almost like a hydraulic pressure. Just think about fluid pressure in a small container being pushed, pushed, pushed until the can, or the container is ready to explode and how multiple features, multiple variables could impinge on that and create that pressure. It turns out that's exactly the way the system works. There is no single brain area that flips the switch for aggression. Although we'll soon talk about a brain structure that generally houses the propensity and the output of aggression. This notion of a hydraulic pressure that can drive us toward aggressive behavior or conversely can be very low pressure and keep us in a state of non-reactivity, maybe even passivity or submissiveness is a very important feature because it really captures the essence of how neural circuits work when we're talking about primitive behaviors generally. And you can start to notice this in yourself and in others, you can start to notice when you are veering toward aggression or when someone is veering toward aggression, verbal or physical. Now that veering is the buildup of this hydraulic pressure

00:15:50 Brain Regions Controlling Aggression, Ventromedial Hypothalamus (VMH)

that Lorenz was referring to, and it really does have an underlying biological basis. Now it was some years later that the first experiments came along, which really started to identify the brain areas and the biological so-called pressures that can induce aggressive behavior. And the person that really gets credit for this is a guy by the name of Walter Hess, who at that time was working on cats. And I know that when you say working on cats, a lot of people will cringe. A lot of people have cats as pets, and certainly cats can be delightful. Some people like them more, some people like them less. Most people cringe at the idea of doing experiments on cats. I should say that these days, very few laboratories work on cats. Most laboratories that work on animal models will work on flies, *Drosophila* fruit flies for their capacity to do genetics, on laboratory mice, sometimes rats, but usually mice. And occasionally you'll find a lab that still works on cats. Back in the time of Hess, very few laboratories worked on mice, most laboratories worked on cats or rats. And the reason for that is nowadays most laboratories use mice if they use animal models because of the genetic tools that exist in mice to knock out this gene or knock in this gene, et cetera, which can't be done in humans or non-human primates, at least not very easily at this point in history. So when I say he was working on cats, I realized that probably evokes some negative emotions in some of you, maybe even aggression in some of you, what we can do, however, is look at the data and make use of the data in terms of our understanding. What Hess did was he had cats that were awake and he was able to lower a stimulating electrode into their brain. Now keep in mind that the brain does not have any pain sensors. So after a small hole is made in the skull, electrodes are lowered into the brain. This is what's done commonly in human neurosurgery. And he was able to stimulate different brain areas and he was sort of poking around. And when I say sort of, he was doing this with some logical intent and purpose, he wasn't just poking around in there for fun. He was trying to identify brain regions that could generate entire categories of behavior, ALA Lorenz, right? These fixed action pattern behaviors. Eventually his electrode landed in a site and he provided electrical stimulation to the cat that caused this otherwise passive purring relaxing cat to suddenly go into an absolute rage. So arched back, hissing hair up. So called piloerection, where the hairs go up, animals try to make themselves as big as possible often when they're aggressive. Drooling, maybe even spitting, believe it or not, cats and other animals can do this. And the cat tried to attack him or anyone else, and anything else, even inanimate objects when he stimulated this particular brain area. So Hess

obviously took notice of this incredible transformation in behavior. And the fact that when he turned off the stimulation of this particular brain area, the cat very quickly within seconds, went back to being passive calm kitty. Now, of course, he repeated this experiment in other animals because he had to confirm that it wasn't just happenstance, that there wasn't something unique about this one cat that perhaps he had stimulated an area that had been built up during the kittenhood of this cat and had been reactivated. Maybe this kitten had been traumatized early in life or scared and reactivation of a particular circuit, unique to that cat created this aggressive behavior. That wasn't the case, every cat that he looked at and stimulated this particular brain area, the cat would immediately go into an aggressive, almost rage type behavior. Now, of course we can't anthropomorphize. We don't know what the cat was feeling. For all we know the cat could be happy, although that seems pretty unlikely and later experiments done in mice, but also in humans confirm that indeed, stimulation of this brain area evoked not just behavioral aggression, but also subjective feelings of aggression and anger. So what was this incredible brain area, or rather, I should say, what is the brain area that harbored this incredible capacity to generate aggressive behavior in Hess's experiments? Well, for those of you that are regular listeners of this podcast, you'll probably be relieved to know that today we're going to talk about some new neural circuits, oftentimes we'll center back on the amygdala or the prefrontal cortex, and those names will come up. And for those of you that haven't heard them before, don't worry, I'll make it clear as to what those brain areas are and what they do. But today we're going to talk a lot about the so-called VMH or ventromedial hypothalamus. The ventromedial hypothalamus is a nucleus, meaning a small collection of neurons... What are neurons? Nerve cells, and that small collection of neurons that we call the ventromedial hypothalamus is truly small. It's only about 1,500 neurons on one side of your brain and a matching 1,500 neurons on the other side of your brain and that combined 3000 neurons or so, it's not exactly 3000, but 3000 neurons or so is sufficient to generate aggressive behavior of the sort that Hess observed in the cat, and believe it or not, when you see somebody who's in an act of rage or in an act of verbal aggression or in an act of defensive aggression, protecting their family or loved ones or country, et cetera, almost certainly those neurons are engaged in that behavior. Those neurons are perhaps even generating that behavior. And next I'll describe some experiments that were done just recently within the last 10 years or so, but leading right up until this year and even last month that keep confirming again and again and again, that it is the

activity of neurons in the ventromedial hypothalamus that are both necessary and sufficient to generate the full catalog of aggressive behaviors. Now, before I go further to describe the beautiful recent studies on the VMH, the ventromedial hypothalamus, and the important role of testosterone, and more importantly, estrogen, in the activation of aggressive behavior, that's right.

00:22:14 Psychiatric Disorders & Aggression

That's soon to be clear to you why that's the case. I want to emphasize that the ventromedial hypothalamus is something that we should all care about. Why? Well, it turns out that many categories of psychiatric disorders, developmental disorders, and psychological challenges, things like schizophrenia, PTSD, post-traumatic stress disorder, depression, borderline personality disorder, and even certain forms of autism can include elements of aggression and even violence. Now it's certainly not the case that aggression and violence are present in all people who suffer from schizophrenia or PTSD or depression or autism or borderline personality disorder. I'm absolutely not saying that. However, it can be a feature of those. And it's a well described feature in terms of trying to understand the constellation of challenges that people suffer from when they have those. So thinking about the VMH goes way beyond just understanding basic aggression in the context of adaptive aggression. So, you know, when earlier I use the example, maternal aggression, that's one adaptive form of aggression. It also can be pathologic aggression, meaning it can harm ourselves or others. So keep this in mind as we go forward, because later we're going to talk about specific tools designed to modulate or prevent aggression in, for instance,

00:23:36 Stimulation of the VMH, Estrogen Receptors & Aggression

people with attention deficit hyperactivity disorder, and especially kids with ADHD. In the meantime, let's return to the VMH, this relatively small collection of neurons. And the reason I say relatively small is, well, your brain has many hundreds of billions of neurons, maybe even trillions of neurons, the exact number of neurons isn't really clear, but it's a lot. And it certainly is a lot relative to the number of neurons this 3000 or so neurons living in your hypothalamus that can evoke this aggressive response. Experiments done by David Anderson's lab at Caltech were really the first to parse the

fine circuitry and to really show that the ventromedial hypothalamus is both necessary and sufficient for aggressive behavior. These are important experiments and they're worth knowing about. What they did was they identified, first of all, where the ventromedial hypothalamus was in the mouse, that was pretty straightforward to do was sort of known before they started these experiments. And then they analyzed which genes, meaning which DNA, which of course becomes RNA and RNA becomes protein, which DNA and therefore which proteins are expressed in particular cells of the ventromedial hypothalamus. And it turns out that there's a particular category of neurons in the ventromedial hypothalamus that make an estrogen receptor. And it is those neurons in particular that are responsible for generating aggressive behavior. How did they know this? Well, they used a tool that's actually been described by a previous guest of this podcast. We had an episode with the psychiatrist and bioengineer and my colleague at Stanford School of Medicine, Karl Deisseroth, he and others have developed tools that allow people to control the activity of neurons essentially by remote control, by shining light on those neurons. So in the context of an experiment on a mouse, which is what David's lab did, and these were the beautiful experiments of Dayu Lin who's now in her own laboratory at New York University, put a little fiber optic cable down into the brain into the hypothalamus that is of the mouse. The mouse is able to move around in its cage freely moving, even though it has a little tether, this little wire, it's a very thin wire. And that little thin wire is actually a little what we call optrode. And the experimentalist in this case, Dayu, was able to stimulate the turning on of a little bit of blue light and that blue light activated only those estrogen receptor neurons in only the ventromedial hypothalamus and the way she was able to do that, is she had introduced a gene that had been developed by our friend, Karl Deisseroth that allows light to trigger electrical activity in those neurons. So if any of that is confusing, or if all of that is confusing, here's the experiment. There's a mouse in a cage. It has a little wire coming out of its head. It doesn't notice, believe it or not. We know this 'cause it's still eating and mating and doing all the things that mice like to do on a daily basis and sleeping, et cetera. And the mere pressing of a button will activate a little bit of light released at the end of that wire, that light activates particular neurons in this case, it's the estrogen receptor containing neurons in only the ventromedial hypothalamus. When that mouse is in a cage with another mouse, a couple of things happen depending on what the other mouse is, or we could say who the other mouse is. If it's a male mouse and you put in there with a female mouse, the male mouse will attempt to mate with a female mouse

provided that the male mouse has gone through puberty. He will try to mount and mate with the female mouse. Now female mice are either in a receptive phase or a non-receptive phase of their so-called estrous cycle. They don't have a menstrual 28 day cycle. They have an estrous cycle. And on particular days of the estrous cycle, they are not happy to mate. They will basically keep their hindquarters away from the male mouse at all costs. They'll even attack the male mouse. On certain days of the estrous cycle, however, the female mouse will undergo what's called lordosis, which is an arching of her back and she'll allow the male to mount and mate with her. So a large number of experiments were done, but the first experiment really was to put the male mouse in with a female mouse who's in the so-called receptive phase of estrus. That is, she will allow mating and he starts mating with her and they go through the standard repertoire of mating behaviors that you observe in mice: mounting, thrusting, intromission as it's called in the mouse sex world. Well, I guess I don't know what the mice call it, but that's what the experimenters call it. And then afterwards that he will dismount, okay. So they observe this kind of mounting and sex behavior is very typical, but about halfway through the behavior, Dayu turned on the light to stimulate these estrogen receptor containing neurons only in the male mouse and what she observed was incredibly dramatic. The male mouse ceases from trying to mate with the female mouse and immediately tries to kill the female mouse. He starts attacking her. Then she turns off the light, the male stops and goes back to trying to mate with the female mouse. So I'm sure all of this was very confusing and disturbing to the female mouse. Nonetheless, that was the repertoire. They would mate. She would stimulate these ventromedial hypothalamus neurons. The male mouse would immediately try and attack and kill the female mouse. And then she would stop the stimulation and he would stop trying to attack and kill the female mouse, return to the attempt, at least, to mate with the female mouse. These are such dramatic shifts in behavior triggered only by the activation of only the small set of neurons within the ventromedial hypothalamus. And for those of you that think that you can watch this sort of thing without being disturbed, I encourage you to go to YouTube. We will provide a link where you can see a video of this type of behavior. It's incredibly dramatic. The shift in behavior is almost instantaneous, occurs within seconds, if not milliseconds, thousandths of a second. The next experiment that she did was to put a male mouse with this stimulation with light capability in its ventromedial hypothalamus into a cage alone, but with a rubber glove filled with air or water. Mouse, walking around sniffing, peeing, which is what male mice

seem to do. They seem to urinate everywhere, that's actually an interesting, perhaps interesting feature of male mice and actually many male animals, perhaps even humans. We don't know, or maybe we do know, basically this has been an observed time and time again in experiments, mainly by Lisa Stowers's lab at the Scripps Institute, that's characterized this. If you put female mice into an arena or a cage, they always urinate in a very small corner of that cage. Whereas if you put male mice into an arena or a cage, they urinate everywhere, they have this obsession with spraying their urine everywhere, you can transpose that to human behavior if you like. In any event, Dayu put the mouse in the cage alone, but with this rubber glove, the mouse is walking around urinating, et cetera, doing whatever is that mice do, then she stimulates the activation of these ventromedial hypothalamus neurons, and the mouse immediately tries to kill the glove. It goes into a rage, attacking the glove as if it were another mouse or some other animate object. But of course it's an inanimate object. It's just a rubber glove. She stops the stimulation and the mouse immediately goes back to being completely calm or at least not attacking. Again, we don't know what the mouse was feeling. So these are very dramatic videos. Again, you can see them by following the link that we'll provide in the caption. If that sort of thing is going to disturb you, by to see, for instance, the attack, one mouse attacking another, please just don't watch them. I'm not interested in traumatizing anybody or you traumatizing yourself, that is. A number of different variations were done on this experiment. For instance, stimulating the VMH in female mice, as opposed to male mice, putting the female mice in with other female mice or with other male mice, no matter what variation one carries out, so it doesn't matter if it's male with female, male with male, female with female, et cetera, stimulation of the ventromedial hypothalamus

00:31:57 Neural Circuits Mediating Physical Acts of Aggression, Biting

in a male mouse or a female mouse evokes this very dramatic, almost instantaneous aggressive behavior, physically aggressive behavior. Subsequent experiments done by Dayu Lin in her own laboratory and other laboratories have shown that the ventromedial hypothalamus connected with a bunch of other brain areas that are interesting, And I'll talk about some of those in a little bit, but one of them that I want to call out now is the so-called PAG, the periaqueductal gray nucleus. This is a large structure in the back of the brain that houses things like neurons that can create opioids. We all know of the opioid crisis, but these are neurons that can produce endogenous, means made by the

body, chemicals that can cause pain relief. You could understand why that might occur in a circuit for aggression, right? Even if one is the aggressor, it's likely that they may incur some physical damage and they'd want some pain relief. The PAG also is connected to a number of neural circuits that eventually, through several processing stations, excuse me, arrive at things like the jaws. And in fact, stimulation of the ventromedial hypothalamus can evoke biting and aggressive biting behavior. Now aggressive biting behavior is particularly interesting because in humans and especially in human children, biting is something that, while young children might do as a form of aggression, tends to disappear pretty early in childhood. And if it doesn't, it's often seen as a mark of pathology. I have a story about this, actually, when I was a kid, I went to a summer sports camp and I'll never forget this, so we're playing soccer and in a rare stroke of luck or accident, I happened to score a goal. I wasn't a particularly good soccer player, especially not at that stage of my life. They later figured out that it was just better to make me a fullback, 'cause I could just wait there and do what fullbacks do. I was better at taking the ball or the person out than I was putting the ball in the goal. Nonetheless, I, again, by chance, scored a goal and I was trotting back to my side of the field, and all of a sudden I felt this sting in my back, a kid, not to be named, although I do remember your name, I'm not going to tell you what his name was. A kid jumped on my back and bit me on the top of my back. And this of course resulted in a discussion and a timeout and all the usual things and parents I think got involved. I don't recall, I didn't think much else of it, but I recall that this was considered especially troubling behavior because he bit me as opposed to hit me or shoved me down or something that sort, and it does seem as if the tendency to use biting as an aggressive behavior is associated with a more primitive circuitry. Now here I'm truly anthropomorphizing. I don't know what this other kid happened to be thinking or feeling at the time, how could I? And I certainly am not going to say that biting in every case reflects a pathology, although I think there is general agreement in the psychology community, in the psychiatric community that past a certain age, the using of one's teeth to impart aggression and damage on others is a particularly primitive and troubling or at least for the observer or the person experiencing is a pretty disturbing event. Dayu's lab has shown that activation of the ventromedial hypothalamus triggers a downstream circuit in the periaqueductal gray which then triggers a whole other set of circuits of fixed action patterns. Here we are back to Lorenz with fixed action patterns, including swinging of the limbs, right punching. And this wouldn't necessarily be controlled punching, but also biting behavior. So it's

remarkable to me, at least that we have circuits in our brain that can evoke violent use of things like our mouth or violent use of things like our limbs. That of course could be used for things like singing or kissing or eating or, you know, gesticulating in any kind of polite or impolite way. The point here is that neural circuits,

00:35:56 Testosterone & Competitiveness/Estrogen & Aggression

not individual brain areas evoke the constellation of behaviors that we call aggression. Now, many of you are probably puzzled or at least should be because I've been talking about this highly specialized brain area, the ventromedial hypothalamus and this highly specialized subcategory of neurons in the ventromedial hypothalamus, these neurons that make estrogen receptors. And yet the activation of those cells triggers dramatic and immediate aggression, both in males and in females and both against males and against females. So what's going on here? Most of us think about estrogen and we don't immediately think of aggression. Most of us hear testosterone and we might think about aggression, although other things as well. In order to understand this, I just want to briefly refer back to a conversation that I had on a previous episode of the Huberman Lab Podcast. And that was with my colleague, the great Robert Sapolsky of course, is a professor at Stanford who studied testosterone and its impacts on behavior as well as estrogen and other hormones and their impacts on behavior. To make a long story short and to dispel a still unfortunately very common myth. Testosterone does not increase aggressiveness, testosterone increases proactivity and the willingness to lean into effort in competitive scenarios. Sometimes this is referred to as the challenge hypothesis, but to make a long story short, if people are given testosterone, or if you look at people who have different levels, excuse me, of testosterone, endogenously that they naturally make. What you'll find is that testosterone tends to increase competitiveness, but not just in aggressive scenarios. So if somebody is already aggressive, giving them testosterone will have the tendency to make them more aggressive. If somebody however is very benevolent and altruistic, giving them testosterone will make them more benevolent and altruistic, at least up to a point. Now, of course there are certain forms of synthetic testosterone that are known in sports circles and in other circles to increase aggressiveness because of the way those particular forms of synthetic testosterone work. But in general, most of the experiments that I'm referring to have not been done using those, they've been done using the let's call them the more traditional biological

forms of testosterone or that resemble the biological forms of testosterone. In fact, Robert Sapolsky described a really interesting experiment in which, if you look at testosterone levels or you administer additional testosterone to people who are doing philanthropy, giving money to organizations and so they're essentially doing good because these are organizations doing good. What you find is that increased testosterone or further increasing testosterone makes people more willing to compete, to give more money than the other person in the room in order, you know, to put it in air quotes, "To Alpha out the other person," by giving more money. So this is an act of altruistic or benevolent philanthropy. It is not an act of aggression. Of course, we don't know what the people are feeling underneath all that. Again, we can't anthropomorphize or project onto other people what they're feeling. But the point is that testosterone itself does not make people more aggressive. And in the experiments that we've been talking about up until now, it's actually the activation of estrogen receptor containing neurons that makes these animals more aggressive. And it turns out there's evidence that in certain context, estrogen can make people more aggressive. So what's going on here? Well, what's going on is that testosterone can be converted into estrogen through a process called aromatization. There's an enzyme called aromatase. Anytime you have word that ends in A-S-E, at least if it's in the context of biology, it's almost always not always, but almost always an enzyme. So the aromatase enzyme converts testosterone into estrogen, and it is actually testosterone, aromatized, converted into estrogen and then binding to these estrogen containing neurons in the ventromedial hypothalamus that triggers aggression. I want to repeat that, it is not testosterone itself, that triggers aggression. It is testosterone aromatized into estrogen within the brain and binding to these estrogen receptor containing neurons in the ventromedial hypothalamus that evokes aggression and dramatic aggression at that. Now this effect of estrogen causing aggression in the brain is very robust, so much so that if you take a mouse that lacks the aromatase enzyme or a human that lacks the aromatase enzyme, and they do exist, then there is a reduction in overall aggression, despite high levels of testosterone. And if people who or mice who have the aromatase enzyme have that enzyme blocked, well, then it doesn't matter how much you increase testosterone or any of its other derivatives. You do not observe this aggression. So this runs counter to everything that we know and think about the role of testosterone. Again, testosterone increases competitiveness. It can increase the desire to work under challenge. I've said it before, and I ran this or pressure tested this against Robert Sapolsky who's been working on testosterone and

it's role in the brain and behavior for many decades now. It is fair to say that testosterone has the net effect of making effort feel good, or at least increasing the threshold at which effort feels bad or unsustainable. And it does that by way of changing the activity or the threshold for activation of brain structures, like the amygdala and other brain structures associated with anxiety. So the next time somebody says, testosterone makes people aggressive. You can say, "Ah, no, actually it's estrogen that makes people aggressive, and animals aggressive for that matter. Now of course it is the case that because males have relatively less estrogen circulating in their brain and body than females, right? Because they have testes, not ovaries, that testosterone is required in the first place in order to be converted into estrogen, to activate this aggressive circuit involving these estrogen receptor containing neurons in the ventromedial hypothalamus. But nonetheless, it is estrogen that is the final step. It is the hormone on which aggression hinges. And I think for most people, that's a quite surprising finding. And yet this is perhaps one of the more robust findings in both the animal and human literature, as it relates to hormones and psychological states and behavior. Now, of course it is the case that if testosterone is low, that a person or an animal will exhibit less aggressive behavior, but that's not because of reduced testosterone per se. It's because of the subsequent reduction in testosterone,

00:43:00 Sunlight, Melatonin & Aggression

meaning if there's no testosterone to aromatize into estrogen, estrogen will also be lower. So we've established that it's not testosterone, but testosterone converted into estrogen that activates these circuits for aggression. But nonetheless, it's still surprising, right? I mean, most of us don't think about estrogen as the hormone that stimulates aggression, but it turns out it's all contextual. There are beautiful data showing that whether or not estrogen stimulates aggression, can be powerfully modulated by whether or not days are short or days are long. In other words, whether or not there's a lot of sunshine or not. Now, obviously brain is encased in skull. So it doesn't really know if there's a lot of sunshine out there even though you can see the sun with your eyes, you can feel it on your skin. Day length is converted into hormonal signals and chemical signals and the primary hormonal and chemical signals involve melatonin and dopamine and also the stress hormones. So to make a very long story short, in the long days where we get a lot of sunlight, both in our eyes and on our skin, melatonin levels are

reduced. Melatonin is a hormone that tends to produce states of sleepiness and quiescence. It also tends to activate pathways that tend to reduce things like breeding and sexual behavior. In long days, dopamine is increased. Dopamine is a molecule associated with feelings of wellbeing and motivation and the desire to seek out all sorts of things, all sorts of motivated behaviors. And in long days provided we're getting enough sunlight on our skin and to our eyes, the stress hormones, especially cortisol, and some of the other stress hormones are reduced in levels. If estrogen levels are increased experimentally under long day conditions, it does not evoke aggression. However, in short days, if estrogen is increased, there's a heightened predisposition for aggression. And that makes perfect sense. If you think about what short days do to the biology of your brain and body. In short days, the melatonin signal goes up. There's more melatonin circulating for more of each 24 hour cycle. Stress hormones are circulating more. Why? Short days tend to be associated with winter. In winter, we are bombarded with more bacterial viruses because bacterial viruses actually survive better in cold than they do in heat. In fact, in my laboratory, we work with a lot of viruses and bacteria and when we want to keep them alive, we put them in the freezer. If we want to kill them, if we want to inoculate them, we put them under UV light. Like you would see from the sunlight. So shorter days are conducive to aggression. Not because days are short per se,

00:45:46 Cortisol, Serotonin & Aggressive Behaviors

but because stress hormone levels are higher and because dopamine levels are lower. Now, here's where all of this starts to converge on a very clear biological picture, a very clear psychological picture, and indeed a very clear set of tools that we can think about and use. Under conditions where cortisol is high, where this stress hormone is elevated and under conditions where the neuromodulator serotonin is reduced there is a greater propensity for estrogen to trigger aggression. Now, again, I know I've said it before, but for males who make a lot of testosterone relative to estrogen, you have to swap in your mind this idea that if testosterone is high, that means that estrogen is low because while that can be true in the periphery in the body, if testosterone is high, there is going to be some aromatization, that conversion of testosterone to estrogen. So anytime you hear that testosterone is high, you should think testosterone is high in the body and perhaps estrogen is low in the body. But that means that there's going to be heightened levels of

estrogen in the brain and therefore increased propensity for aggression. In females who generally make less testosterone relative to estrogen, there is sufficient estrogen already present to trigger aggression. So both males and females are primed for aggression, but that's riding on a context and that context of whether or not you get a tendency for aggression or not. depends on whether or not cortisol is high or low, and I'm telling you that if cortisol is relatively higher in any individual, there's going to be a tilt, an increase in that hydraulic pressure that Lorenz talked about toward aggression. And if serotonin, the neuromodulator that is associated with feelings of wellbeing and sometimes even of slight passivity, but certainly of wellbeing, if serotonin is low, there's also going to be a further shift towards an aggressive tendency. So if we return to Lorenz's hydraulic pressure model of aggression in other internal states, we realize that external stimuli, things that we hear, things that we see, for instance, someone saying something upsetting or us, seeing somebody do something that we don't like to others or to us, as well as our internal state, our subjective feelings of wellbeing, but also our stress level, our feelings of whether or not we have enough resources and are content with what we have. All of that is converging on this thing that we call internal state and creating this pressure of either to be more aggressive or less aggressive. And now we have some major players feeding into that final pathway. That question of whether or not will we hit the other, person, will we say the thing that is considered aggressive? Will we not say it? If somebody says something or does something aggressive to us, will we respond or will we be submissive or even passive? Again, there are many things funneling into that question and dictating whether or not the answer is, "Absolutely I'll fight back," or, "I'm going to attack them even unprovoked." Or if they say this, I'm going to do that, or no matter what they do, I'm not going to respond. These kinds of things are very complex. And yet we really can boil them down to just a few common elements. And I'm telling you that those elements are whether or not cortisol levels are relatively lower or relatively higher. Again, relatively higher is going to tend to make people more reactive. Why? Because reactivity is really a function of the autonomic nervous system, which is sort of like a seesaw that oscillates between the so-called sympathetic arm of the autonomic nervous system, which tends to put us into a state of readiness through the release of adrenaline. Cortisol and adrenaline when they're circulating the brain and body, make us more likely to move and to react and to speak. It's actually what will induce a kind of low level tremor, which is an anticipatory tremor to be able to move more quickly, right? A body in motion is more easily set into further motion, that is, and the neuromodulator

serotonin is a neuromodulator that in general is associated with feelings of wellbeing in response to what we already have. So when we are well fed, serotonin tends to be released in our brain and body, in particular, well fed with carbohydrates, the precursor to serotonin is tryptophan. And indeed there are nice studies exploring the types of diets, nutritional programs that can reduce aggressive behavior, both in children and in adults and tryptophan-rich diets or supplementation with tryptophan. So for tryptophan rich diets, things like white turkey meat, but then there are also a number of carbohydrates you can look up. It's very easy to find foods that contain lots of tryptophan. Those foods contain the precursor to serotonin. Now it isn't simply the case that eating more foods with tryptophan will tend to reduce your aggression. I suppose it could do that, if you ate it in abundance, it could make you tired and then you're less likely to be aggressive, I don't recommend that strategy, but the idea here is that when it's been explored, increasing levels of tryptophan either by supplementation or by food or drugs, prescription drugs that increase serotonin. So for instance, fluoxetine sometimes called Prozac or Zoloft or any number of the other SSRIs tend to reduce aggressive behavior. Now, not always, but in general, that's the case. Similarly, because elevated cortisol tends to shift the whole system, again, create more of a hydraulic pressure towards aggressive states. If cortisol levels are reduced, well then the tendency for aggressive behavior is reduced. This is supported by a number of peer reviewed studies. We'll provide links to some of those in the caption show notes. And we're going to return to these a bit later in the context of specific studies that have looked at genetic variants in different individuals that cause them to make more or less serotonin, or at least to metabolize serotonin differently. This is also the case for so-called intermittent explosive disorder that can often be associated with gene variants that control how much serotonin is made

00:51:56 Tool: Omega-3 Supplementation & Mood

or how it's metabolized or how much cortisol is made and how much it's metabolized. In thinking about tools that are a number of things that one could consider. First of all, there are a number of decent studies exploring how supplementation with the Omega-3 fatty acids, which are precursors of some of the transmitter systems, including serotonin that can modulate not directly mediate, but modulate mood and emotional tone supplementation with the omega 3 S has been shown to reduce impulsivity and

aggressiveness in certain contexts in things like ADHD or in individuals who have a predisposition for aggressive type behavior or aggressive thinking. Now that doesn't necessarily mean that the omega 3 fatty acids are going directly to the ventromedial hypothalamus and changing the activity of neurons there more likely they are causing or modulating an overall shift in mood through the immune system, through hormone systems that are changing the overall tone or the propensity for neurons in the ventromedial hypothalamus to be activated. How much omega 3 fatty acid, what source? Well, we've talked about this on the podcast before. You can, of course get omega 3 fatty acids from a number of different foods. Getting them from whole foods is probably the best way to do it, but many people, including people with depression will often supplement with one gram or more of omega 3 fatty acid per day. Some people including myself will take them every day as just a general mood enhancer. I don't suffer from depression, but I've found it be beneficial for my health. And so some people do that, and I've talked about before, how in double blind placebo controlled studies, people taking one to three grams of omega 3 fatty acids per day, typically in the form of a high quality fish oil, although there are other sources as well, algae and so forth, can experience improvements in mood that are on par with some of the SSRIs, the selective serotonin reuptake inhibitors. And of course, if you're prescribed an SSRI by your psychiatrist or other doctor, please do take that and don't cease to take it just simply to take omega 3s. However you might mention to them, and you can find links to the studies in our previous episodes on depression that supplementation with omega 3 fatty acids of at this one gram or more of EPA specifically, so getting above that one gram threshold, as high as three grams per day of the EPA has allowed people

00:54:18 Tool: Sunlight, Sauna & Cortisol Reduction

to take lower doses of SSRIs and still keep their mood in a place that's beneficial for them. And in terms of keeping cortisol in a range that's healthy and doesn't bias someone toward high levels of aggression and irritability, that's again, going to be set by a number of larger modulators or contextual cues. And I've talked about some of those on the podcast, but I'll just briefly recap them now, obviously getting sunlight in your eyes early in the day, and as much sunlight as you safely can in your eyes throughout the day is going to be important. Again, because of this effect of estrogen in long days, not increasing aggression, however, in shorter days, estrogen increases aggression

because of the increase in cortisol observed in short days. Another way to reduce cortisol was discussed in our episode on heat and the use of sauna and heat, but also hot baths. It turns out that hot baths and sauna can be very beneficial for reducing cortisol. All the details on that are included in the episode on heat and it's timestamped, so you can go directly to that if you want to learn about the temperatures and the various durations, but to just give a synopsis of that, a 20 minute sauna at anywhere from 80 to a hundred degrees Celsius is going to be beneficial for reducing cortisol. If you don't have access to a sauna, you could do a hot bath, adjust the temperature so you don't burn yourself. I think 80 to a hundred degrees Celsius is going to be too hot for many people if it's a hot bath, whereas many people who can't tolerate that hot bath can tolerate the sauna. So safety first always, and of course,

00:55:54 Tool: Ashwagandha & Cortisol Reduction

but hot baths reduce cortisol, hot saunas, reduce cortisol of a duration about 20 or 30 minutes is going to be beneficial. And of course, some of you may be interested in exploring the supplementation route and for reductions in cortisol, really the chief player there is ashwagandha, which is known to decrease cortisol, fairly potently. I should just warn you that if you're going to use ashwagandha in order to reduce cortisol, first of all, check with your doctor or healthcare provider before adding or subtracting anything from your supplementation or health regimen. Of course, I don't just say that to protect us. I say that to protect you, you are responsible for your health, what you take and what you don't take. Chronic supplementation with ashwagandha can have some not so great effects of disruption of other hormone pathways and neurotransmitter pathways. So the limit seems to be about two weeks of regular use before you'd want to take a break of about two weeks. So ashwagandha again, a very potent inhibitor of cortisol, but with some other effects as well, don't use it chronically for longer than two weeks. But if your goal is to reduce cortisol, let's say you're going through a period of increased irritability and aggressive tendency, maybe you're also not getting as much light as you would like, and perhaps also, if there are other circumstantial things leading you towards

00:57:06 Tool: Seasonality/Sunlight, Genetic Variation in Estrogen Sensitivity

more aggressiveness and your goal is to reduce aggressiveness, that can be potentially

helpful. And in light of all this stuff about cortisol and estrogen and day length, I should mention that there are in fact, some people who have a genetic predisposition to be more irritable and aggressive, and there are a couple of different gene pathways associated with this. We never like to think about just one gene causing a specific behavior. The way to think about genes is that genes generally code for things within our biology. In the context of today's discussion, things like neural circuits or the amounts of neurotransmitters that are made, or the amounts of hormones that are made, or the amount of neurotransmitter hormone receptors or enzymes, et cetera, that shift the activity of our biology in a particular direction. They bias our biology. And in fact, there is a genetic variant present in certain people that adjusts their estrogen receptor sensitivity, and that estrogen receptor sensitivity can result in increased levels of aggression, sometimes dramatic increases, however, and also very interestingly, photo period, meaning day length, is a strong modulator of whether or not that aggressiveness turns up or not. Whether or not that person with the particular gene variant is more aggressive or not, depends on how long the day is and how long the night is. One particular study that I like that references this is Trainer, et al, the title of the study is "Photo period reverses the effects of estrogens on male aggression, via genomic and non-genomic pathways." This was a paper published in the proceedings of the National Academy of Sciences. We'll put a reference to this in the show notes, if you'd like to explore it further, but it really points to the fact that rarely, sometimes, but rarely, is it the case that just one gene will cause somebody to be hyper aggressive. Almost always there's going to be an interplay between genetics and environment and as environment changes such as day length changes and the length of night changes, so too, will the tendency for people with a given genetic variant to be more aggressive or not. Now, of course, in the absence of detailed genetic testing for this particular estrogen receptor variant, most people, I'm guessing you, are probably not walking around knowing that you have this gene or not. Regardless, I think it's important to pay attention to how you feel at different times of year, depending on whether or not summer, whether or not it's winter, whether or not you're getting sufficient sunlight, meaning viewing sufficient sunlight or not, whether or not you're getting sufficient sunlight exposure to your skin or not, whether or not you're indoors all the time. Generally those things correlate with season, but not always. You can go through long bouts of hard work in the summer months when days are long, but you're indoors a lot and getting a lot of fluorescent light exposure late in the evening. And perhaps that's when you're feeling more aggressive. So we have to be careful about

drawing a one-to-one relationship between any biological feature and certainly psychological or behavioral feature like aggressiveness, but it's, I believe, helpful to know that these genetic biases exist, how they play out again, they shift our biology in a general thematic direction. They don't change one thing. They change a variety of things that bias us toward or away from certain psychological and behavioral outcomes and the various things that we can do in order to offset them. And we described those earlier in terms of trying to keep cortisol low by getting sufficient sunlight

01:00:37 Testosterone & Aggression, Competitive Work Environments

regardless of time of year, and regardless of whether or not you happen to have this particular genetic variant. So earlier I talked about how it is testosterone converted into estrogen that's activating aggression in the ventromedial hypothalamus, not testosterone itself. However, there are some studies carried out in humans that have evaluated the effects of testosterone and how levels of testosterone correlate with aggressiveness in the short term. I'm just going to detail a few of those studies because I think they are interesting and important. First of all, there is a study that has explored levels of testosterone in men of different professions. Now, before I tell you the data, I want to be very clear here, with a study such as this, one never knows whether or not these men went into a particular profession because they had a testosterone level of a given value or whether or not the work itself altered their testosterone levels or both. And I think it's fair to assume that it's probably both. So be very careful in assuming that a given testosterone level is causal for choosing a particular career or that a particular career is causal for creating a particular testosterone level. This study used salivary testosterone levels as the measure, which to be fair is not the best way to measure testosterone. Typically blood draw would be the best way to measure testosterone, but nonetheless, provided the appropriate methods are used, salivary testosterone can be a reasonable measure of testosterone. The different occupations that were looked at were, and here they just looked at men in this particular study were ministers, salesmen, they didn't say what particular types of salesmen, firemen, professors, of all things, physicians and NFL players. And what they discovered was that the testosterone levels were essentially in that order from low to highest. So minister, salesman, fireman, professor, physician, NFL player. Now we could micro dissect all the different stereotypes and all the different features of each of these jobs. For instance, we don't know whether or not the fact that

the firemen happened, at least in this study to have lower testosterone levels on average than the professors or the physicians was because firemen have lower testosterone levels or because they have a much more stressful job and their cortisol levels are higher than the professor or the physician and cortisol and testosterone, not always, but generally are in somewhat antagonistic push-pull mode because they derive from the same precursor, et cetera. Typically, when cortisol is high, testosterone tends to be lower and vice versa. So we don't know what's causing these effects. And again, this is just one study and just six occupations, but I think it's relatively interesting given the fact that each of these professions involves different levels of competitiveness, right? So we don't necessarily just want to think about the level of physical exertion that's required, but also the level of competitiveness because it's known that competitive interactions can cause increases in testosterone, in particular, in the winners of competitive interactions, a topic for a future podcast. Meanwhile, studies that have analyzed also again, salivary testosterone in prisoners, in this case, female prisoners, so these are incarcerated individuals, have looked at levels of testosterone according to whether or not the person committed a non-violent or a violent crime in order to arrive in prison. And higher levels of salivary testosterone were related to those that had arrived in prison because of conviction of a violent crime, as opposed to a nonviolent crime. Likewise, when they analyzed prison rule violations, so an indirect measure of aggressiveness, but in this case, it was strongly associated with aggressiveness because they knew what the violations were, they found were for prisoners that had none, no prison violations, prison rule violations I should say, their testosterone levels tended to be lower than the testosterone levels of women that had some, even one, or more aggressive violations of prison rules. We'll provide links to these studies in the show notes if you'd like to go into them further, obviously studies like this need to be taken with a grain of salt because there are so many different factors, different prisons have different degrees

01:05:07 Testosterone, Amygdala, Challenge & Effort

of violence to begin with and competitiveness to begin with. But just as a final pass at examining the role between testosterone and aggressiveness, there was a very interesting study from Goetz, et al, G-O-E-T-Z published in 2014, that looked at serum, so in this case, blood levels of testosterone. 30 minutes after application of a gel-based testosterone that goes transdermal so that the testosterone can go very quickly into the

bloodstream, and then did brain imaging to evaluate the activity of neurons in the so-called corticomedial amygdala, the cortico, the medial amygdala is one of the areas of the amygdala complex as we call it because it's complex, it's got a lot of different nuclei, you know, know what nuclei are, low clusters of neurons. It's got a lot of different ones, but that medial and that cortico medial amygdala in particular, is known to be associated with aggressive type behaviors. It's linked up with as part of the larger circuit that includes the ventromedial hypothalamus and other brain areas that we referred to earlier, such as the PAG. What is remarkable about this study is that it showed that just 30 minutes after application of this so-called AndroGel, this testosterone that seeps into the bloodstream, there was a significant increase in of course, testosterone and corticomedial amygdala activation. So testosterone can have acute effects, immediate effects on the pathways related to aggression. And I think this is something that's not often discussed because many of the effects of steroid hormones like testosterone, and estrogen are very slow acting. In fact, steroid hormones, because they have a certain biochemical composition can actually pass through the membranes of cells, so the outside of a cell and into the nucleus of the cell and change gene expression in the cell, you think about puberty, the kid that goes home for the summer and then comes back looking completely different. Well that's because of a lot of genes got turned on by steroid hormones like testosterone and estrogen, but the steroid hormones can also have very fast acting effects and with testosterone in particular, those can be remarkably fast acting and one of the most apparent and well documented fast acting effects is this effect: the ability to activate cells within the amygdala, so you might say, "Well, I thought the amygdala was associated with fear?" Wouldn't testosterone then cause fear? No. Turns out that the amygdala harbors, both cortisol, corticosteroid receptors and testosterone receptors, and they each adjust the activity in the amygdala differently, such that testosterone tends to activate amygdala circuitry for inducing states of mind and body that are more action based and indeed in animals and in humans, testosterone application and activation of this corticomedial amygdala pathway will make animals and humans lean into effort. This is why I say testosterone makes effort feel good, or at least biases the organism toward leaning into challenge. So if you recall, there's not just one type of aggression, there's reactive aggression, which is triggered when one is confronted with something that sometimes is inevitable, right? One needs to fight for their life or for somebody else's life, but also proactive aggression and proactive aggression involves activation of those go-pathways in the basal ganglia and a leaning

into effort to overcome whatever state one happens to be in to begin with. And so this is very important because it points to the fact that yes, estrogen is activating aggression pathways that are in the ventromedial hypothalamus, but it's very likely the case that testosterone is acting to accelerate or to bias states of mind and body toward those that will lead to aggression. Again, aggression is not like a switch, on and off. It's a process. It has a beginning, a middle and an end. Remember that hydraulic pressure that Conrad Lorenz hypothesized? Well, think of testosterone as increasing the pressure toward an aggressive episode and then estrogen actually triggering that aggressive episode in the ventromedial hypothalamus. So if somebody tells you that testosterone, endogenous or exogenous makes people aggressive, tell them no, testosterone tends to make people lean into effort. And if that effort involves being aggressive, either reactively aggressive or proactively aggressive,

01:09:27 Caffeine, Alcohol & Impulsivity

well then it will indeed lead to aggression. But the actual aggression itself is triggered by estrogen, not testosterone. Now, thus far, we really haven't talked too much about the social context in which aggression occurs. And that's because there is a near infinite, if not infinite number of variables that will determine that. So for instance, violent aggression is entirely appropriate at a professional boxing match provided it's occurring inside the ring and only between the competitors and within the bounds of the rules of the sport, et cetera. However, there are some things that tend to bias certain social context toward being more aggressive or less aggressive and not always physical aggression. And those generally come in two forms that many of you are familiar with, which are alcohol and caffeine. Let's discuss caffeine first. Why would caffeine increase aggressive impulsivity? Well, the general effects of caffeine are to increase autonomic arousal. The activity of the so-called sympathetic arm of the autonomic nervous system, which is to put it very much in plain language it's the alertness arm of your nervous system. That is, it creates a sense of readiness in your brain and body and it does so by activating the so-called sympathetic chain ganglia. Again, as I always remind people, simpans and sympathetic does not mean sympathy. Simpa means together, we're all at ones. And caffeine tends to bias our brain and body to activate the sympathetic chain ganglia, which run from about the base of your neck until the top of your pelvis and deploy a bunch of chemicals that jut out into the rest of your body, activate adrenaline

release. There's a parallel increase in of adrenaline in your brain, creating the state of alertness and readiness. That state of alertness and readiness can be for all sorts of things, not just aggression. However when we are in a state of increased sympathetic tone, meaning more alert, such as after drinking caffeine, we will bias all those brain and body systems, the hormones, the chemicals, et cetera that exist, toward action as opposed to inaction. So put simply, caffeine can increase impulsivity, no surprise there. On the opposite end of things, alcohol tends to decrease activity in the sympathetic arm of the autonomic nervous system, tends to make us feel less alert. Now, initially it can create a state of alertness because of its effects in inhibiting the forebrain, our forebrain prefrontal cortex in particular has what's called top-down inhibition. It exerts a inhibitory or a quieting effect on some of the circuits of the hypothalamus, such as the ventromedial hypothalamus. The way to conceptualize this is that your forebrain is able to rationalize and think clearly and to suppress behavior and to engage the no-go pathways telling you, "Don't say that mean thing." "Don't do that violent thing," et cetera. Alcohol initially tends to increase our level of overall activity by reducing inhibition, not just in that forebrain circuit, but in other circuits. Tends to make us more active. We tend to talk more than we normally would, move more than we normally would, but very shortly thereafter starts acting as a sedative by way of reducing activity in the forebrain, releasing some of the deeper brain circuits that are involved in impulsivity, but also causing a somewhat sedative effect. And then of course, as alcohol levels increase even further, people eventually will pass out, blackout, et cetera. So what we've got with alcohol and caffeine is we've got two opposite ends of the spectrum, caffeine increasing arousal and readiness,

01:13:15 Tool: Caffeinated Alcohol Beverages, Impulsivity & Aggression

and the tendency for impulsivity and alcohol also increasing impulsivity, but through a different mechanism. A really interesting study, and I should just mention that the title of the study is, "Caffeinated and non-caffeinated alcohol use and indirect aggression at the impact of self-regulation." So the title is almost self-explanatory. This was a paper published in the Journal of Addictive Behavior in 2016, examining how ingestion of alcohol that's either caffeinated or non-decaffeinated alcohol drinks impacted what they call indirect aggression. And just to remind you what indirect aggression is, these are not physical acts of aggression. These are verbal acts of aggression, so embarrassing

others or otherwise, somehow trying to reduce the wellbeing of others by saying certain things in particular in groups, this study examined both males and females. This was done on by way of a college campus study, subjects were 18 to 47 years old. I guess there's some older students on that campus, or maybe they use some non-students, but you know, these days you've also got some students that are in their thirties and forties. So they have a fairly broad swath of subjects included, fairly broad racial background as well, included, not at equal numbers, but at least they included a pretty broad spectrum of people with different backgrounds. They looked in particular people that ingested non-caffeinated alcohol drinks at a frequency of 9.18 drinks per week, okay. Again, there's a college campus, not that I encourage that. I'm one of these people that I don't, I've never really liked drugs or alcohol and sort fortunate in that way I can drink or not drink and tend to not drink. But so to me, 9.18, drinks per week sounds like a lot, but I know for some people that might actually be typical. And then others who are drinking at least one caffeinated alcoholic beverage per week. And those individuals end as high, I should say as 7.87 caffeinated alcohol beverages per week. So this would be energy drinks combined, typically with hard alcohol, that's fairly commonly available in bars and so forth. And some individuals drank as much as goodness, 20.36 alcoholic drinks per week, total, some that were caffeinated, some that were not caffeinated. The basic outcome of this study was that the more alcohol someone tended to consume, the more likely it was that they would engage in these indirect aggressive type behaviors. And in terms of the caffeinated alcoholic beverages, there, the effect was especially interesting. Here I'm just going to paraphrase or I'll actually read from the study, quote, "With regard to caffeinated alcoholic beverage use, our findings indicated that heavier caffeinated alcohol beverage use was associated positively with indirect aggression, even after considering one's typical alcohol use and dispositional aggression." What this means is that even though alcohol can bias certain individuals to be more aggressive, and even though certain individuals already have a disposition toward being more aggressive, there was an effect that was independent, meaning above and beyond both alcohol and a predisposition, meaning if someone was consuming caffeinated alcoholic beverages, they had a particularly high likelihood of engaging in indirect aggressive behavior. Now this makes perfect sense in light of the model they propose, which is this self-regulation model, that basically self-regulation involves several things. It involves engaging in certain behaviors and suppressing other behaviors. So as described before, because alcohol tends to have a sedative suppressive effect on the autonomic nervous system, at

least after the initial period, it's going to tend to reduce the likelihood that people will engage in any type of behavior. Whereas caffeine will increase autonomic arousal and increase the likelihood that someone will engage in a particular type of behavior, aggressive or otherwise. So the combination of caffeine and alcohol is really acting as a two prong system to bias people towards more impulsivity that is less self-regulation. So it's really yanking your volitional control, your ability to engage in prefrontal top down inhibition

01:17:18 Tool: ADHD, Acetyl-L Carnitine & Aggressive Behavior

over your hypothalamus from two distinct and specific circuits. By now, you should be getting the impression that self-regulation is a key feature of whether or not somebody, maybe even you, is going to engage in aggressive speech or aggressive behavior. And we've talked about a number of tools that one can use to reduce the probability that that will happen. I suppose, if the context were appropriate, you could even take those tool recommendations and just invert them and increase the likelihood that aggressiveness would happen. But regardless, self-regulation is key. And in light of that, I want to share with you a study that's focused on kids, but that has important ramifications for adults as well. As you probably are already aware there are many kids out there that suffer from so-called attention deficit hyperactivity, disorder, ADHD. There are also many adults we are finding that are suffering from ADHD. And there's also an epidemic I would say of people that are concerned about whether or not they have ADHD. Now whether or not they have true, clinical ADHD or not, is not clear. We did an episode all about ADHD and tools for ADHD. I would encourage you to check out that episode and some of the diagnostic criteria. If you have the opportunity you can find at hubermanlab.com, as this study I'm about to share with you aptly points out, there is no objective diagnostic marker of ADHD. There's no biomarker or blood draw or blood test for ADHD, whether or not one has ADHD depends on their performance on a number of different cognitive tests and behavioral tests and self report. In any event, the study I'm about to share with you explored how a particular pattern of supplementation in kids with ADHD was able to reduce aggressive episodes and impulsivity and increased self-regulation. And the title of the study is, "Efficacy of carnitine in the treatment of children with attention deficit, hyperactivity disorder." Even though they put carnitine in the title, that what they focused on was whether or not acetyl-L-carnitine supplementation could somehow adjust the

behavioral tendency of these kids with ADHD and to make a long story short, indeed it did. There was a very significant effect of acetyl L-carnitine supplementation on improving some of the symptomology, excuse me, of ADHD. A few details about this study that might be relevant to you. This was a randomized double blind placebo controlled double crossover study, this was done as an outpatient study. So the kids weren't in a hospital, they were living out in the world. This again was done on younger kids. So this was six to six to 13 year old kids that were diagnosed with ADHD. They received either acetyl L-carnitine or placebo, and they did all the good practice stuff that good researchers do of making sure that the placebo and the acetyl L-carnitine had similar look and taste. It was consumed twice daily after meals. I should just mentioned that acetyl L-carnitine typically is taken in capsule form or occasionally an injectable form. Here, they they were using this as a drink, which essentially the same as capsule form, but the powders just going directly into liquid and the carnitine dosage was 100 milligrams per kilogram. So they're doing this according to the body weight of these kids with a maximum dosage of four grams per day, the quantity of the medication was supplied here. I'm reading for a period of eight weeks and every eight weeks a new quantity of medication was supplied. So basically this is a fairly long term study, exploring behavioral outcomes and psychological outcomes in week eight, 16 and 24. They also looked at blood things that you could only get through a blood draw, so things like hemoglobin, hematocrit, red blood cell count, white blood cell count, et cetera, they, these are kids and even if it were adults, they were quite appropriately examining a lot of the physiological measures that one would want to carry out to make sure, first of all, that blood levels of carnitine are increasing. And indeed they confirmed that, but also that no negative effects are showing up in the physiology as well as the psychology of these kids. So, first I'll just tell you the basic outcome of the study, which was, here I'm paraphrasing, "Here, given twice daily, carnitine appeared to be effective and well tolerated treatment for a group of children with ADHD." "They showed significant, the abnormal behavior compared to these other boys." And now I'm moving to the table of results. They showed significant reductions in their so-called "Total Problem Score." The total problem score is a well-established measure of behavioral problems in kids with ADHD. And I should say adults with ADHD, has to do with challenges in social and learning environments and how well or poorly an individual tends to perform. Reductions in intentional problems, overall reductions in delinquency, and most important for sake of today's discussion, significant reductions in aggressive behavior. Now what's especially

nice about this study, I think, is that even though it's a relatively small number of subjects and certainly needs to be repeated in other studies and other laboratories, that they were able to confirm the shifts in L-carnitine within the bloodstream of these kids, that is they were able to correlate the physiology with the psychological changes, in studies like this. And frankly in all studies of human pharmacology, you have to worry about effects that show up, not just because of placebo effects, but because of so-called off target effects or related things, totally independent of the drug or the particular supplement that you happen to be looking at, to put in the words of a great neuroscientist. Unfortunately, he passed away some years ago, but he was a member of the national academy, extremely accomplished neuroscientist once turned to me and said, "Never forget a drug is a substance that when injected into an animal or a human being creates a paper," meaning you can see effects of pretty much any drug or any supplement in most all conditions. However, it is in cases such as this study, where you can quite convincingly see that the particular feature of physiology that you expected to change, actually changed. And you see a psychological outcome that you can gain much greater confidence that the changes in delinquency, in this case reduced delinquency, improved attention, reduced aggressiveness and so forth was at least somehow related to the shift in blood physiology and levels of L-carnitine or acetyl L-carnitine and carnitine in the bloodstream of these children, as opposed to something else like L-carnitine going and affecting some downstream target that you have no knowledge of. Now, of course that's still entirely possible, but I think studies such as these increase our confidence that things like L-carnitine can be used perhaps in concert with things like omega 3 supplementation, diets that are biased towards increasing more tryptophan and therefore more serotonin,

01:24:10 Factors Affecting the "Hydraulic Pressure Model" of Aggression

obviously avoiding things like alcohol and as it appears from the study I just described, reducing one's intake or not consuming any caffeinated alcoholic beverages seems like it would be a good idea if your goal is to reduce aggressiveness, to think about the hormone context and whether or not you tend to have higher testosterone, an estrogen or lower testosterone, an estrogen, maybe even think about the work environment, whether or not you are existing in a particularly competitive work environment and even day life, time of year and whether or not you're getting sufficient sunlight, whether or not

you're avoiding light in the evening and so on. So studies such as this I think are useful because they point to the fact that very seldom, if ever, will there be one supplement or one nutritional change or even one behavioral change, that's going to completely shift in individual from being aggressive and impulsive, but rather that by combining different behavioral regimens, by paying attention to things like time of year and work conditions and school conditions and overall levels of stress and likely therefore levels of cortisol, et cetera, that you can use behaviors, diet, and supplementation as a way to shift that overall internal milieu from one of providing a lot of internal hydraulic pressure as it's been called throughout the episode toward aggressive impulsivity and relax some of that hydraulic pressure and reduce aggressive tendencies. So once again, and frankly, as always, we've done a deep dive into the neurobiology

01:25:44 Book by Dr. David Anderson, Aggression & Social Relationships

and the psychology of what I believe to be an important feature of our lives, in this case aggression. I want to point out that in a episode in the not too distant future, I'm going to be hosting Dr. Professor David Anderson from Caltech University, who is the world expert on the neurobiology of aggression. In fact, he is the senior author on many of the studies related to the ventromedial hypothalamus that I discussed today. Our discussion will touch on aggression, of course. So hearing today's episode will help you digest that information, but we are also going to talk about other emotional states. He is an expert, not just in aggression, but in motivated states related to sex and mating behavior, social relationships of all kinds and how those relate, not just to biology and psychology, but also certain forms of pathology, things like PTSD and the relationship for instance, between anger, fear, anxiety, and depression, and many other important topics that I know many of you, if not all of you will be interested in. In the meantime, I want to point you to his recently released and wonderful book entitled, "The Nature of the Beast, How Emotions Guide Us." And again, the author is David Anderson from Caltech. This is a wonderful book. It serves as a tremendous introduction to the history of the study of these areas, the current science and discoveries being made in these areas, all made accessible to the scientist and non-scientist alike. It's a very engaging read and so much so that even though he was gracious in sending me a copy, I also purchased myself a copy to give to somebody who is a therapist, and I've purchased another copy to give to a high school kid that I mentor because he's very interested in the neuroscience of

emotions. And I think we are all interested in emotions, not just fear and some of these negative states, not just aggression, but also the positive emotions of our lives.

01:27:35 Zero-Cost Support, YouTube Feedback, Spotify & Apple Reviews, Sponsors, Patreon, Momentous Supplements, Neural Network Newsletter, Instagram, Twitter

And so, "The Nature of the Beast, How Emotions Guide Us," by David Anderson is a wonderful read. I can't recommend it highly enough. If you're learning from and or enjoying this podcast, please subscribe to our YouTube channel. That's a terrific zero cost way to support us. In addition, please subscribe to our podcast on Apple and Spotify. And on Apple, you have the opportunity to leave us up to a five star review. Also, if there are any episodes of the podcast that you particularly like, please share them with others. And if you have suggestions about particular guests or topics that you'd like us to cover on the podcast, please put that in the comment section on YouTube, we do read all those comments. Please also check out the sponsors mentioned at the beginning of today's episode, that is the best way to support this podcast. We also have a Patreon it's patreon.com/andrewhuberman and there you can support the podcast at any level that you like. During today's episode and on many previous episodes of the Huberman Lab Podcast, we discussed supplements. While supplements aren't necessary for everybody, many people derive tremendous benefit from them, for things like improving the transition time and the quality of your sleep and improving alertness and focus. And so on. Anytime you're considering taking supplements, there are several key considerations. First of all, those supplements should be of the very highest quality. And you want to make sure that what's listed on the bottle is actually what's in the bottle, which is a problem for any supplement companies out there. The Huberman Lab Podcast is pleased to announce that we are now partnered with Momentous supplements because we believe Momentous supplements to be of the very highest quality of any supplements out there. And we've been working very closely with them in order to direct them, to create supplements that are individual ingredient supplements of the particular quality and sources that we would like to see, and that relate to the science and studies covered on the Huberman Lab Podcast. If you'd like to see some of those supplements, you can go to livemomentous.com/huberman, and there you'll see some of the supplements that we've talked about on this podcast before such as magnesium threonate for augmenting sleep,

things like L-tyrosine for augmenting dopamine and things like L-carnitine, which we've discussed on today's podcast. Right now, the list of supplements and the products that are there is only partial to what will soon be included in the future. So that's an ever expanding catalog of, again, what we believe to be the very highest quality supplements available to you. For those of you that are interested in behavioral, nutritional and supplementation based tools for neuroscience and other aspects of your biology, the impact, your health and performance, we have a newsletter. It is a zero cost newsletter. It's called "The Neural Network Newsletter." You can go to hubermanlab.com and there in the menu, you'll find "The Neural Network Newsletter" sign-up. You can just put your email. We do not share your email with anybody else. You will also find examples of the newsletter that you can download right away without having to sign up and decide if signing up is right for you. And if you're not already following us on Twitter an Instagram, we are Huberman Lab on both Instagram and Twitter. And at both places, I describe science and science based tools, some of which overlaps with the content of the Huberman Lab Podcast, but much of which is distinct from the content of the Huberman Lab Podcast. Once again, thank you for joining me for our discussion about the biology, psychology and actionable tools around aggression, and as always, thank you for your interest in science. [inspirational music]