Dr. David Anderson: The Biology of Aggression, Mating, & Arousal | Huberman Lab Podcast #89

My guest is David Anderson, PhD, a world expert in the science of sexual behavior, violent aggression, fear and other motivated states. Dr. Anderson is a Professor of Biology at the California Institute of Technology (Caltech), a member of the National Academy of Sciences and an investigator with the Howard Hughes Medical Institute (HHMI). We discuss how states of mind (and body) arise and persist and how they probably better explain human behavior than emotions per se. We also discuss the many kinds of arousal that create varying levels of pressure for certain behaviors to emerge. We discuss different types of violent aggression and how they are impacted by biological sex, gender, context, prior experience, and hormones, and the neural interconnectedness of fear, aggression and sexual behavior. We also discuss peptides and their role in social isolation-induced anxiety and aggression. Dr. Anderson also describes novel, potentially powerful therapeutics for mental health. This episode should interest anyone wanting to learn more about mental health, human emotions, sexual and/or violent behavior.

Newsletter: https://hubermanlab.com/neural-network

Dr. David Anderson
Dr. David Anderson: https://davidandersonlab.caltech.edu/davidanderson
The Nature of the Beast: https://amzn.to/3qsrdOH
Dr. David Anderson's Lab: https://davidandersonlab.caltech.edu
Dr. Anderson's publications: https://bit.ly/3L5uGMl

Articles
Two Different Forms of Arousal in Drosophila Are Oppositely Regulated by the Dopamine D1 Receptor Ortholog DopR via Distinct Neural Circuits: https://bit.ly/3Dmyh7b

Resources
Mouse switching from mating behavior to aggressive behaviors upon stimulation of VMH: https://youtu.be/AIlp69kfqjw?t=882
VMH stimulation causes mouse to display aggressive behaviors toward an inanimate object (e.g., glove): https://youtu.be/AIlp69kfqjw?t=689
Picture of Periaqueductal Gray (PAG): https://neuroscientificallychallenged.com/posts/know-your-brain-periaqueductal-gray

Timestamps

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- Welcome to the Huberman Lab Podcast, where we discuss science and science-based tools for everyday life. I'm Andrew Huberman, and I'm a professor of neurobiology and ophthalmology at Stanford School of Medicine. Today, my guest is Dr. David Anderson, Dr. Anderson is a professor of biology at the California Institute of Technology, often commonly referred to as Caltech University. Dr. Anderson's research focuses on emotions and states of mind and body, and indeed he emphasizes how emotions, like happiness, sadness, anger and so on, are actually subcategories of what are generally governed by states, that is, things that are occurring in the nervous system in our brain

and in the connections between brain and body that dictate whether or not we feel good about how we are feeling, and that drive our behaviors, that is, bias us to be in action or inaction and strongly influence the way we interpret our experience and our surroundings. Today, Dr. Anderson teaches us, for instance, why people become aggressive and why that aggression can sometimes take the form of rage. We also talk about sexual behavior, and the boundaries and overlap between aggression and sexual behavior. And that discussion about aggression and sexual behavior also starts to focus on particular aspects of neural circuits and states of mind and body that govern things like, for instance, male-male aggression, versus male-female aggression, versus female-female aggression. So today, you will learn a lot about the biological mechanisms that govern why we feel the way we feel. Indeed, Dr. Anderson is an author of a terrific new popular book, entitled "The Nature of the Beast: How Emotions Guide Us". I've read this book several times now, I can tell you it contains so many gems that are firmly grounded in the scientific research. In fact, a lot of what's in the book contrasts with many of the common myths about emotions and biology. So whether or not you're a therapist, or you're a biologist, or you're simply just somebody interested in why we feel the way we feel and why we act the way we act, I cannot recommend the book highly enough. Again, the title is "The Nature of the Beast: How Emotions Guide Us". Today's discussion also ventures into topics such as mental health and mental illness, and some of the exciting discoveries that have been made by Dr. Anderson's laboratory and other laboratories identifying specific peptides, that is, small proteins that can govern whether or not people feel anxious or less anxious, aggressive or less aggressive. This is an important area of research that has direct implications for much of what we read about in the news, both unfortunate and fortunate events, and that will no doubt drive the future of mental health treatments. Dr. Anderson is considered one of the most pioneering and important researchers in neurobiology of our time. Indeed, he is a member of the National Academy of Sciences and a Howard Hughes Medical Institute investigator. I've mentioned the HHMI once or twice before when we've had other HHMI guests on this podcast, but for those of you that are not familiar, the Howard Hughes Medical Institute funds a small number of investigators doing particularly high-risk, high-benefit work, and it is an extremely competitive process to identify those Howard Hughes investigators. They are essentially appointed, and then every five years, they have to compete against one another and against a new incoming flock of would-be HHMI investigators to get another five years of funding. They are literally given a grade every five years as to

whether or not they can continue, not continue, or whether or not they should worry about being funded for an extended period of time.

00:03:33 Momentous Supplements

Dr. Anderson has been an investigator with the Howard Hughes Medical Institute since 1989. I'm pleased to announce that the Huberman Lab Podcast is now partnered with Momentous supplements. We partnered with Momentous for several important reasons. First of all, they ship internationally, because we know that many of you are located outside of the United States. Second of all, and perhaps most important, the quality of their supplements is second to none, both in terms of purity and precision of the amounts of the ingredients. Third, we've really emphasized supplements that are single-ingredient supplements, and that are supplied in dosages that allow you to build a supplementation protocol that's optimized for cost, that's optimized for effectiveness, and that you can add things and remove things from your protocol in a way that's really systematic and scientific. If you'd like to see the supplements that we partner with Momentous on, you can go to livemomentous.com/huberman. There, you'll see those supplements, and just keep in mind that we are constantly expanding the library of supplements available through Momentous

00:04:27 Levels, Helix Sleep, LMNT

on a regular basis. Again, that's livemomentous.com/huberman. 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 Levels, Levels is a program that lets you see how different foods affect your health by giving you real-time feedback on your diet using a continuous glucose monitor. One of the most important factors governing our immediate and long-term health and indeed our ability to think and focus clearly is our blood glucose levels, also referred to as blood sugar. To maintain healthy energy and focus throughout the day, you want to keep your blood glucose levels steady and avoid peaks and crashes. I first started using Levels about a year ago as a way to better understand how specific foods, food combinations,

exercise and supplements impact my blood glucose levels, and it's been tremendously informative. In fact, it's changed and shaped the way that I organize my entire day. Levels even provides a simple score after you eat a meal so you can see how different foods affect you and develop a personalized nutrition program that's ideal for you. So if you're interested in learning more about Levels and trying a continuous glucose monitor yourself, you can go to levels.link/huberman, that's levels.link/huberman. Today's episode is also brought to us by Helix Sleep. Helix Sleep makes mattresses and pillows that are of the absolute highest quality. They also have some really unique features, because they are customized to your unique sleep needs. I've talked over and over again on this podcast and on other podcasts about the fact that sleep is the foundation of mental health, physical health and performance, there's just simply no other substitute for a quality night's sleep on a regular basis. I've been sleeping on a Helix mattress for well over a year now and it's the best sleep that I've ever had, and that's in large part because the mattress was designed for me. What you need to know, however, is what's the ideal mattress for you, and you can do that by going to Helix's site, you can take their brief quiz, which will ask you, "Do you sleep on your side, your back, your stomach? Or maybe you don't know, or maybe all three. Do you tend to run hot or cold in the night? Maybe you know, maybe you don't." At the end of that short quiz, they will match you to the ideal mattress for you. I matched to the Dusk, the D-U-S-K mattress, but again, that's what I need, that's not necessarily what you need in order to get your best night's sleep. But if you're interested in upgrading your mattress, go to helixsleep.com/huberman, take their two-minute sleep quiz and they'll match you to a customized mattress for you and you'll get up to $200 off any mattress order and two free pillows, they have terrific pillows. And you get to try out that mattress for 100 nights risk free. They'll even pick it up for you if you don't love it, but I'm certain you will. Again, if you're interested in it, you go to helixsleep.com/huberman for up to $200 off your mattress order and two free pillows. Today's episode is also brought to us by LMNT. LMNT is an electrolyte drink that has everything you need and nothing you don't, meaning no sugar, but it has sodium, magnesium and potassium in the proper ratios. Sodium, magnesium and potassium are critical for the functioning of all your cells, but of your neurons, your nerve cells in particular. Many people out there, believe it or not, need to ingest more sodium and more potassium, and magnesium in the proper ratios to sodium and potassium. For those of you that are prehypertensive or hypertensive, you definitely don't want to crank up your sodium intake, but many people out there, especially people following low-carb

diets or eating exceptionally clean very well may need more sodium. And by drinking LMNT mixed with water, which is what I do once or twice a day, and certainly also during workouts and after workouts, you can optimize mental functioning and physical performance by increasing your electrolyte balance in the proper ratios. If you'd like to try LMNT, you can go to drinklmnt, that's L-M-N-T, .com/huberman, and you'll get a free sample pack with your order. Again, that's drinklmnt.com/huberman

00:08:10 Emotions vs. States

to get a free sample pack with your order. And now for my discussion with Dr. David Anderson. David, great to be here and great to finally sit down and chat with you. - Great to be here too, thank you so much. - Yeah, I have a ton of questions, but I want to start with something fairly basic, but that I'm aware is a pretty vast landscape, and that's the difference between emotions and states, if indeed there is a difference, and how we should think about emotions. What are they? They have all these names, happiness, sadness, depression, anger, rage, how should we think about them and why might states be at least as useful a thing to think about, if not more useful? - That's great. First, the short answer to your question is that I see emotions as a type of internal state, in the sense that arousal's also a type of internal state, motivation's a type of internal state, sleep is a type of internal state. And the sort of simplest way I think of internal states is that, as you've shown in your own work, they change the input-to-output transformation of the brain. When you're asleep, you don't hear something that you would hear if you were awake, unless it's a really, really loud noise. So from that broad perspective, I see emotion as a class of state that controls behavior. The reason I think it's useful to think about it as a state is it puts the focus on it as a neurobiological process rather than as a psychological process. And this gets around all of the definitional problems that people have with the word emotion, where many people equate emotion with feeling, which is a subjective sense that we can only study in humans, because to find out what someone's feeling, you have to ask them, and people are the only animals that can talk, that we can understand. So that's how I think about emotion, if you think of an iceberg, it's the part of the iceberg that's below the surface of the water, the feeling part is the tip that's sort of floating above the surface of your consciousness. Not that that isn't important, it is, but you have to understand consciousness if you want to understand feelings,

00:10:36 Dimensions of States: Persistence, Intensity & Generalization

and we're not ready to study that in animals yet, and so that's how I think about it. - What are the different components of a state? You mentioned arousal as a key component, what are some of the other features of states that represent this, as you so beautifully put in your book, that represent below the tip of the iceberg? - Right, right. So you can break states up into different facets, or people would call them dimensions, and so there have been people who have thought of emotions as having just really two dimensions, an arousal dimension, how intense is it? And also a valence dimension, which is, is it positive or negative, good or bad? Ralph Adolphs and I have tried to expand that a little bit to think about components of emotion, particularly those that distinguish emotion states from motivational states, because they are very closely related. One of those important properties is persistence, and this is something that distinguishes state-driven behaviors from simple reflexes. Reflexes tend to terminate when the stimulus turns off, like the doctor hitting your knee with a hammer, it initiates with the stimulus onset and it terminates with the stimulus offset, emotions tend to outlast, often, the stimulus that evoke them. If you're walking along a trail here in Southern California, you hear a rattlesnake rattling, you're going to jump in the air, but your heart is going to continue to beat and your palms sweat and your mouth is going to be dry for a while after it's slithered off in the bush, and you're going to be hypervigilant, if you see something that even remotely looks snake-like, a stick, you're going to stop and jump. So persistence is an important feature of emotion states, not all states have persistence. So for example, you think about hunger. Once you've eaten, the state is gone, you're not hungry anymore, but if you are really angry and you get into a fight with somebody, even after the fight is over, you may remain riled up for a long time and it takes you a while to calm down, and that may have to do with the arousal dimension or some other part of it. And then generalization is an important component of emotion states that make them, if they have been triggered in one situation, they can apply to another situation. And my favorite example of that is, you come home from work and your kid is screaming, if you had a good day at work, you might pick it up and sooth it, and if you had a bad day at work, you might react very differently to it and scream at it. And so that's a generalization of the state that was triggered at work, by something your boss said to you, to a completely different interaction. And again, that's something that distinguishes emotion states from motivation states, motivation states are really specific, find and eat food, obtain and

consume water, and they're involved in homeostatic maintenance. So states are very multifaceted, and just asking questions about how these components of states are encoded, like what makes a state persist? What gives a state a positive or a negative valance? How do you crank up or crank down the intensity of the state? It just opens up a whole bunch of questions

00:14:38 Arousal & Valence

that you can ask in the brain with the kinds of tools we have now. - You mentioned arousal a few times, and you mentioned valence, realizing that there are these other aspects of states, I'd like to just talk about arousal a little bit more, and valence, because at a very basic level, it seems to me that arousal, we can be very alert and pissed off, stressed, worried, we can have insomnia, we can also be very alert and be quite happy. So the valence flips, people can be sexually aroused, people can be aroused in all sorts of ways. Is there any simple or simple-ish neurochemical signature that can flip valence? So for instance, is there any way that we can safely say that arousal with some additional dopamine release is going to be of positive valence, and arousal with very low dopamine is going to be of negative valence? - I would be reluctant to say that it's a chemical flip, I would say it's more likely to be a circuit flip. - Mm-hmm. - Different circuits being engaged. And it might be that a given neurochemical, even dopamine, is involved in both positively valanced arousal and negatively valanced arousal, that's why people think about these as different axes. So I think the interesting question that you touch on is, is arousal something that is just completely generic in the brain, or are there actually different kinds of arousal that are specific to different behaviors? And you raise the question, sexual arousal feels different from aggressive arousal, for example, and we actually published a paper on this, back in 2009, in fruit flies, where we found some evidence for two types of arousal states. One of which is sleep-wake arousal, you're more aroused when you wake up than when you're asleep, and flies show that, and the other is a startle response, an arousal response to a mechanical stimulus, and not just mechanical stimulus. If you puff air on flies, kind of like trying to swat the wasp away from your burger at a picnic table, they come back more and more and more vigorously. And we were able to dissect this and show that although both of those forms of arousal required dopamine, they were exerted through completely separable neural circuits in the fly. And so that really put, number one, the emphasis on it's the circuit that

determines the type of arousal, but also that arousal isn't unitary, that there are behavior-specific forms of arousal. And I think the jury is still out as to whether there is such a thing as completely generalized arousal or not. And I think some people would argue there is, but I think more attention needs to be paid to this question of domain-specific or behavior-specific forms of arousal. - Yeah, it's a super-interesting idea, 'cause I always thought of arousal as along a continuum, like you can either be in a panic attack at the one end of the extreme, or you can be in a coma, and then somewhere in the middle, you're alert and calm, but then this issue of valence really, as you say, presents this opportunity that really there might be multiple circuits for arousal. - Yeah. - Or multiple mechanisms

00:18:11 Aggression, Optogenetics & Stimulating Aggression in Mice, VMH

that would include neurochemicals, as well as different neural pathways. - Yeah. - So like to talk a bit about a state, if it is indeed a state, which is aggression, your labs worked extensively on this. And if you would, could you highlight some of the key findings there, which brain areas that are involved? The beautiful work of Dayu Lin and others in your lab that point to the idea that indeed there are kind of switches in the brain, but that thinking of switches for aggression might be too simple, how should we think about aggression? And I'll just sort of skew the question a bit more by saying, we see lots of different kinds of aggression, this terrible school shooting down in Texas recently, clearly an act that included aggression, and yet, you could imagine that's a very different type of aggression than an all-out rage or a controlled aggression, there's a lot of variation there. So what are your thoughts on aggression, how it's generated, the neural circuit mechanisms and some of the variation in what we call aggression? - Yeah, this is a great question, and it's a large area. I would say that, first of all, the word aggression, in my mind, refers more to a description of behavior than it does to an internal state. Aggression could reflect an internal state that we would call anger in humans, or could reflect fear, or it could reflect hunger if it's predatory aggression. And so this gets at the issue that you raised of the different types of aggression that exist. The work that Dayu did when she was in my lab that really broke open the field to the application of modern genetic tools for studying circuits in mice is that she found a way to evoke aggression in mice using optogenetics to activate specific neurons in a region of the hypothalamus, the ventromedial hypothalamus, VMH, which people had been

studying and looking at for decades, following, first, the work of, in cats, the famous Nobel Prize-winning work of Walter Hess, and then followed by work done by Menno Kruk, in the Netherlands, in rats, where they would stick electrical wires into the brain and send electric currents into the brain, and they could trigger a placid cat to suddenly bare its teeth, hiss and almost strike out at the experimenter, and they could trigger rats to fight with each other. And even in Hess's original experiments, he describes two types of aggression that he evokes from cats depending on where in the hypothalamus he puts his electrode, one of which he calls defensive rage, that's the ears laid back, teeth bared and hissing. And the other one is predatory aggression, where the cat has its ears forward, and it's batting with its paw at a mouse-like object, like it wants to catch it and eat it. So he already had, at that stage, some information about segregation in the brain of different forms of aggression. So fast forward to 2008, 2009, when Dayu came to the lab and we had started working on aggression in fruit flies, and I wanted to bring it into mice so that we could apply genetic tools. And we started by having Dayu, who was an electrophysiologist, just repeat the electrical stimulation of the ventromedial hypothalamus in the mouse, just like people had done in rats, in cats, in hamsters, even in monkeys. And she could not get that experiment to work over 40 different trials, it just didn't work. What she got instead was fear behaviors, she got freezing, cornering and crouching. And finally, in desperation, and we got a lot of input from Menno Kruk on this, he really was mystified, "Why doesn't it work in mice?" We realized why there had been no paper on brain-stimulated aggression in mice in 50 years, 'cause the experiment doesn't work. And the one bit of credit I can claim there is I convinced Dayu to try optogenetics, because it just had sort of come into use deep in the brain, from Karl Deisseroth and others' work. And I thought maybe because it could be directed more specifically to a region of the brain and types of cells than electrical stimulation, it might work. And Dayu said, "Never, never going to work. If it doesn't work with electricity, why should it work with optogenetics?" And the fact is that it did work, and we were able to trigger aggression in this region using optogenetic stimulation of ventromedial hypothalamus. And in retrospect, I think the reason that we were seeing all these fear behaviors is because right at the upper part, if you think of ventromedial hypothalamus like a pear sitting on the ground, the fat part of the pear near the ground is where the aggression neurons are, but the upper part of the pear has fear neurons. And it could be because it's so small in a mouse, when you inject electrical current anywhere in the pear, it flows up through the entire pear and it activates the fear circuits, and those totally

dominate aggression. And so that's why we were never able to see any fighting with electrical stimulation, whereas when you use optogenetics, you confine the stimulation just to the region

00:24:42 Aggression Types: Offensive, Defensive & Predatory

where you've implanted the channelrhodopsin gene into those neurons. And so fast forward from that, from a lot of work from Dayu now on her own at NYU, and with her postdoc, Annegret Falkner, as well as work of other people, there's evidence that the type of fighting that we elicit when we stimulate VMH is offensive aggression that is actually rewarding to male mice. - They like it. - They like it, male mice will learn to poke their nose or press a bar to get the opportunity to beat up a subordinate male mouse. And in more recent experiments, if you activate those neurons and the mouse has a chance to be in one of two compartments in a box, they will gravitate towards the compartment where those neurons are activated, it has a positive valance. And when I went into this field and I was thinking, "Well, what goes on in my brain and my body when I'm furious?" it certainly doesn't feel like a rewarding experience, it's not something that I would want to repeat because it feels good when I'm in that state, it doesn't feel good at all when I'm in that state. And it is still, I think, a mystery as to where that type of aggression, which is more defensive aggression, the kind of aggression you feel if you're being attacked or if you've been cheated by somebody, where that is encoded in the brain and how that works, still, I think, is a very important mystery that we haven't solved. And predatory aggression there has been some progress on, so mice show predatory aggression, they use that to catch crickets that they eat, and that involves different circuits than the ventromedial hypothalamic circuits. So it's become clear that, if you want to call it the state of aggressiveness, is multifaceted, it depends on the type of aggression and it involves different sorts of circuits. There's a paper suggesting that there might be a final common pathway for all aggression in a region, which is one of my favorites, it's called the substantia innominata, the substance with no name, I like. - Anatomists are so creative. - Yes. [Andrew laughing] Or the nucleus ambiguous, or the zona incerta, these are places that no one can think of what they are. Anyhow, that might be a final common pathway for predatory aggression, and offensive and defensive aggression, but it can be really hard to tell just from looking at a mouse fight whether it's engaged in offensive or defensive aggression. We've tried to take that apart using

machine learning analysis of behavior, but in rats, for example, it's much clearer when the animal is engaged in offensive versus defensive aggression. They direct their bites at different parts of the opponent's body. - [Andrew] In particular. - Offensive aggression is flank directed, defensive aggression goes for the neck, goes for the throat. - Mm, I've seen some nature specials where in a very barbaric way, [laughing] at least to me, it seems, like hyenas will try and go after the reproductive axis, they'll go after testicles and penis and they basically want to, it seems they want to limit future breeding potential. - Yes, or create pain. [David laughing] - Right, or create pain, or both. - Yeah. - Yeah, I mean, in terms of offensive aggression and your reflection that it doesn't feel good, I mean, I can say, I know some people who really enjoy fighting. - [David] Hmm. - I have a relative who's a lawyer, he loves to argue and fight. - [David] Huh. - I don't think of him as physically aggressive, in fact, he's not, but loves to fight and loves to prosecute and go after people. - Hmm. - And he's pretty effective at it. - Right. - I have a friend, former military special operations, and very calm guy, had a great career in military special operations, and he'll quite plainly say, "I love to fight." - Mm-hmm. - "It's one my great joys." He really enjoyed his work. - [David] Yep. - And also respected the other side because they offered the opportunity to test that and to experience that joy. So in a kind of bizarre way to somebody like me, who I'll certainly defend my stance if I need to. - Yeah. - But I certainly don't consider myself somebody who offensively goes after people just to go after them, there's no, quote-unquote, dopamine hit here.

00:29:20 Evolution & Development of Defensive vs. Offensive Behaviors, Fear

- Right. - Acknowledging that dopamine does many things, of course. - Yeah. - I have couple of questions about the way you describe the circuitry, I should say, the way the circuitry is arranged. - [David] Mm-hmm. - And of course, we don't know, because we weren't consulted at the design phase. [David laughing] But why do you think there would be such a close positioning of neurons that can elicit such divergent states and behaviors? I mean, you're talking about this pear-shaped structure, where the neurons that generate fear are cheek to jowl with the neurons that generate offensive aggression of all things. It's like putting the neurons that control swallowing next to the neurons that control vomiting, [laughing] it just seems to me that, on the one hand, this is the way that neural circuits are often arranged, and yet, to me, it's always been perplexing as to why this would be the case. - Yeah, I think that is a very profound question, and I've

wondered about that a lot. If you think from an evolutionary perspective, it might have been the case that defensive behaviors and fear arose before offensive aggression, because animals, first and foremost, have to defend themselves from predation by other animals. And maybe it's only when they're comfortable with having warded off predation and made themselves safe, that they can start to think about, "Who's going to be the alpha male in my group here?" And so it could be that if you think that brain regions and cell populations evolve by duplication and modification of preexisting cell populations, that might be the way that those regions wound up next to each other. And developmentally, they start out from a common pool of precursors that expresses the same gene, the fear neurons and the aggression neurons, and then with development, it gets shut off in the aggression neurons and maintained in the fear neurons. Now, that view says, "Oh, it's an accident of evolution and development," but I think there must be a functional part as well. So one thing we know about offensive aggression is that strong fear shuts it down, whereas defensive aggression, at least in rats, is actually enhanced by fear. It's one of the big differences between defensive aggression and offensive aggression. And if you think about it, if offensive aggression is rewarding and pleasurable, if you start to get really scared, that tends to take the fun out of it, and maybe these two regions are close to each other to facilitate inhibition of aggression by the fear neurons. We know for a fact that if we deliberately stimulate those fear neurons at the top of the pear, when two animals are involved in a fight, it just stops the fight dead in its tracks and they go off into the corner and freeze. So at least hierarchically, it seems like fear is the dominant behavior over offensive aggression, and how that inhibition would work is not clear, 'cause all these neurons are pretty much excitatory, they're almost all glutamatergic. And so one of the interesting questions for the future is, how exactly does fear dominate over and shut down offensive aggression in the brain? How does that work, is it all circuitry, are there chemicals involved? What's the mechanism and when is it called into play? But I think that's the way I tend to think about why these neurons are all mixed up together. And it's not just fight and freezing, or fight and flight, there are also metabolic neurons that are mixed together in VMH as well. - Mm-hmm. Controlling body-wide metabolism? - Yeah. - Very interesting. - There are neurons there that respond to glucose, when glucose goes up in your bloodstream, they're activated, and VMH has a whole history in the field of obesity, because if you destroy it in a rat, you get a fat rat. So the way most of the world thinks about VMH is they think about, "Oh, that's the thing that keeps you from getting fat." It's the anti-

obesity area, but in the area of social behavior, we see it as a center for control of aggression and fear behaviors. And again, why these neurons and these functions, I like to call them the four Fs, feeding, freezing, fighting and mating. - Mm-hmm. - That they all seem to be closely intermingled with each other, maybe because crosstalk between them is very important to help the animal's brain decide what behavior to prioritize and what behavior to shut down at any given moment. - One of the things that we will do is link to the incredible videos of these mice that have selective stimulation of neurons in the VMH, Dayu's and the other studies that you've done. Whenever I teach, I show those videos at some point, with the caveats and warnings that are required when one is about to see a video of a mouse trying to mate with another mouse, or mating with another mouse, and they seem both to be quite happy about the mating experience, at least as far as we know, as observers of mice. And then upon stimulation of those VMH neurons, one of the mice essentially tries to kill the other mouse. And then when that stimulation is stopped, they basically go back to hanging out. They don't go right back to mating. - Right. - There's some reconciliation clearly that needs to [laughing] happen first, we assume. - Yes. - But it's just so striking, and I think equally striking is the video where the mouse is alone in there with the glove, the VMH neurons are stimulated and the mouse goes into a rage, it looks like it wants to kill the glove, basically. - Yep. - So striking, I encourage people to go watch those, because it really puts a tremendous amount of color on what we're describing,

00:35:38 Hydraulic Pressures for States & Homeostasis

and it's just the idea that there are switches in the brain, to me, really became clear upon seeing that. One of the, excuse me, one of the concepts that you've raised in your lectures before and that I think was Hess's idea is this idea of a sort of hydraulic pressure. - Mm-hmm. - Or maybe it was Konrad, I can't speak now. [David laughing] Excuse me, Konrad Lorenz, pardon. - Mm-hmm. - Who talked about a kind of hydraulic pressure towards behavior. I'm fascinated by this idea of hydraulic pressure, because I don't consider myself a hot-tempered person, but I am familiar with the fact that when I lose my temper, it takes quite a while for me to simmer down. I can't think about anything else, I don't want to think about anything else. In fact, trying to think about anything else becomes aversive to me, which, to me, underscores this notion of prioritization of the different states. - Mm-hmm. - And potentially conflicting states. What do you think

funnels into this idea of hydraulic pressure toward a state? And why is it, perhaps, that sometimes we can be very angry, and if we succeed in winning an argument, all of a sudden, it will subside? Because clearly that means that there are external influences, it's a complex space here that we're creating, I realize I'm creating a bit of a cloud. - Yeah. - And I'm doing it on purpose, because, to me, the idea of a hydraulic pressure towards a state, like sleep, there's a sleep pressure. - Yeah. - There is a pressure towards aggression, that all makes sense, but what's involved? Is it too multifactorial to actually separate out the variables, but what's really driving hydraulic pressure toward a given state? - Yeah, so really important question, I think one way that is helpful, at least for me, to break this question apart and think about it is to distinguish homeostatic behaviors, that is, need-based behaviors, where the pressure is built up because of a need, like, "I'm hungry, I need to eat. I'm thirsty, I need to drink. I'm hot, I need to get to a cold place," it's basically the thermostat model of your brain. You have a set point, and then if the temperature gets too hot, you turn on the AC, and if the temperature gets too cold, you turn on the heater and you put yourself back to the set point. I don't think that's how aggression works. That is, it's not that we all go around, at least subjectively, I don't go around with an accumulating need to fight, which I then look for an excuse to release it. Now, maybe there are people that do that, and they go out and look for bar fights to get into to. - Or Twitter. - Yeah, [laughing] or Twitter, yeah. - Twitter seems to, I'm sort of half joking, because Twitter seems to draw a reasonably sized crowd of people that are there for combat of some sort, even though the total intellectual power of any of their comments is about that of a cap gun.

00:38:33 AG1 (Athletic Greens)

[David laughing] They seem to really like to fire off that cap gun. - Right, right. - But I agree. - Yeah. - Before we continue with today's discussion, I'd like to just briefly acknowledge our sponsor, Athletic Greens, now called AG1. Athletic Greens, aka AG1, is an all-in-one, vitamin-mineral probiotic drink that also has adaptogens and digestive enzymes. I've been taking Athletic Greens since way back in 2012, so I'm delighted that they're sponsoring the podcast. The reason I started taking Athletic Greens and the reason I still drink Athletic Greens twice a day is that it supplies total foundational coverage of my vitamin-mineral needs and it supplies important nutrients that I need to support my gut microbiome. The gut microbiome, as many of you know, supports the

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00:39:46 Hydraulic Pressure & Aggression

and K2 for cardiovascular health and calcium regulation. Again, you can go to athleticgreens.com/huberman to claim that special offer. - So you can think of this accumulated hydraulic pressure either being based on something that you were deprived of creating an accumulating need, or something that you want to do building up a drive or a pressure to do that, and the natural way to think about that, at least for me, is as gradual increases in neural activity in a particular region of the brain. And so for example, in the area of the hypothalamus that controls feeding, Scott Sternson and others have shown that the hungrier you get, the higher the level of activity in that region in the brain, and then when you eat, boom, the activity goes right back down again. And that state is actually negatively valenced, so it's like the animal, quote-unquote, feels increasingly uncomfortable, just like we feel increasingly uncomfortable the hungrier we are, and then when we eat, it tamps it down, but there is this increased activity. And I think in the case of aggression, our data and others show that the more strongly you drive this region of the brain optogenetically, the more of just a hair trigger you need to set the animal off to get it to fight. Now, the interesting thing is that if there is nothing for the animal to attack, it doesn't really do much when you're stimulating this region. It sort of wanders around the cage a little bit more, but it will not actually show overt attack unless you put something in front of it. And the same thing is true for the areas we've described that control mating behavior. This is what Lindsay is working on, you can stimulate those areas 'til you're blue in the face, and the mouse just sort of wanders around, but if you put another mouse in, wham, he will try to mount that mouse, if you put a kumquat in the cage. [Andrew laughing] He'll try to mount the kumquat, and so it becomes a sort of any port in the storm. So there is this idea that the drive is building up pressure that somehow needs to be released where that pressure is actually being

exerted, if you accept that it's increased activity in some circuit or circuits someplace, what is it pushing up against that needs something else to sort of unplug it in the Lorenz hydraulic model? That is, you don't see the behavior until you release a valve on this bucket and let the accumulated pressure flow out. And that's one of the things we're trying to study in the context of the mating behavior as well, how does the information that there's an object in front of you come together with this drive state that is generated by stimulating these neurons in the hypothalamus to say, "Okay, pull the trigger and go, it's time to mate, it's time to attack?" And we're just starting to get some insights into that now. - Fascinating, and I should mention to people, Dr. Anderson mentioned Lindsay, Lindsay is a former graduate student of mine that's now a postdoc in David's lab. And I haven't caught up with her recently to hear about these experiments, but they sound fascinating. I would love to spend some time on this issue of why is it that a mouse won't attack nothing, but it'll attack even a glove, and why it will only try and mate if there's another mouse to mate with? It's actually, I think, fortunately for you, you're not spending a lot of time on Twitter and Instagram or YouTube, but there's this whole online community that exists now, as far as I know, it's almost exclusively young males who are obsessed with this idea, I'll just say it, it has a name, it's called NoFap, of no masturbation as a way to maintain their motivation to go out and actually seek mates. Because of the ready availability of online pornography. - Huh. - There's probably a much larger population of young males that are never actually going out and seeking mates because they're getting porn addicted, et cetera. There's actually a serious issue that came up in our episode with Anna Lembke, who wrote the book "Dopamine Nation". - Hmm. - Because of the availability of pornography, there's a whole social context that's being created around this, and genuine addiction. So humans are not like the mice, or mice are not like the humans, humans seem to resolve the issue on their own. - Yeah. - In ways that might actually impede seeking and finding of sexual partners and/or long-term mates. - Right. - So serious issue there, I raise it as a serious issue. - Yep. - That I hear a lot about, 'cause I get asked hundreds if not thousands of questions about this, "Is there any physiological basis for what they call NoFap?" And I never actually reply 'cause there's no data. - [David] Yep. - But what you're raising here

00:44:50 Balancing Fear & Aggression

is a very interesting mechanistic scenario that can, and as you mentioned, is being

explored. So what do we know about the internal state of a mouse whose VMH is being stimulated or a mouse whose other brain region that can stimulate the desire to mate, what do we know about the internal state of that mouse if it's just alone in the cage wandering around? iI it wandering around really wanting to mate and really wanting to fight? We, of course, don't know, but is its heart rate up, is its blood pressure up? Is it wishing that there was pornography? [David and Andrew laughing] Something's going on, presumably, that's different than prior to that stimulation, and is it arousal? And what do you think it is about the visual factory perception of a conspecific that ungates this tremendous repertoire of behaviors? - Right, that is a central question. I can say, at least with respect to the fear neurons that sit on top of the aggression neurons, we know that when those neurons are activated optogenetically, in the same way we would activate the aggression neurons, that there's clearly an arousal process that's occurring, you can see the pupils dilate in the animal. There is an increase in stress hormone release into the bloodstream, we've shown that heart rate goes up. So in addition to the drive to actually freeze, which is what those animals do, there is autonomic arousal and neuroendocrine activation of stress responses. And some of that is probably shared by the aggression neurons and the mating neurons, although we haven't investigated it in as much detail, but I wouldn't be surprised because they project to many of the same regions that the fear neurons project to, which is a interesting issue in the context to discuss later maybe, in the context of why we're comfortable with mental illnesses that are based on maladaptations of fear, but not mental illnesses that are based on maladaptations of aggression if they have pretty similar circuits in the brain. But that's how I would imagine there is an arousal dimension, as you say, there are stress hormones that are activated, these regions, VMH projects to about 30 different regions in the brain, and it gets input from about 30 different regions. So I kind of see it as both an antenna and a broadcasting center, it's like a satellite dish that takes in information from different sensory modalities, smell, maybe vision, mechanosensation, and then it sort of synthesizes and integrates that into a fairly low-dimensional, as the computational people call it, representation of this pressure to attack, and it broadcasts that all over the brain to trigger all these systems that have to be brought into play if the animal is going to engage in aggression. Because aggression is a very risky thing for an animal to engage in, it could wind up losing and it could wind up getting killed, and so its brain constantly has to make a cost-benefit analysis of whether to continue on that path or to back off as well. And I think that part of this broadcasting function of this region is

engaging all these other brain domains

00:48:31 Aggression & Hormones: Estrogen, Progesterone & Testosterone

that play a role in this kind of cost-benefit analysis. - I want to talk more about mating behavior, but as a segue to that, as we're talking about aggression and mating behavior, I think, "Hormones." And whenever there's an opportunity on this podcast to shatter a common myth, I grab it. One of the common myths that's out there, and I think that persists, is that testosterone makes animals and humans aggressive, and estrogen makes animals placid and kind or emotional. And as we both know, nothing could be further from the truth, although there's some truth to the idea that these hormones are all involved. Robert Sapolsky supplied some information to me when he came on this podcast, that if you give people exogenous testosterone, it tends to make them more of the way they were before. If they were a jerk before, they'll become more of a jerk, if they were very altruistic, they'll become more altruistic. And then eventually I pointed out, "You'll aromatize that testosterone into estrogen and you'll start getting opposite effects," so it's a murky space, it's not straightforward. But if I'm not mistaken, testosterone plays a role in generating aggression, however, the specific hormones that are involved in generating aggression via VMH are things other than testosterone. Can you tell us a little bit more about that? 'Cause there's some interesting surprises in there. - Yeah, that's a really important question. So when we finally identified the neurons in VMH that control aggression with a molecular marker, we found out that that marker was the estrogen receptor. So that might strike you as a little strange, why should aggression-promoting neurons in male mice be labeled with the estrogen receptor? Other labs have shown that the estrogen receptor in adult male mice is necessary for aggression. If you knock out the gene in VMH, they don't fight. And it's been shown, and a lot of this is work from your colleague, Nirao Shah, at Stanford, who is one of my former PhD students, that if you castrate a mouse and it loses the ability to fight, not only can you rescue fighting with a testosterone implant, but you can rescue it with an estrogen implant. So you can bypass completely the requirement for testosterone to restore aggressiveness to the mice. And as you say, it's because many of the effects of testosterone, although not all, many of them are mediated by its conversion to estrogen, by a process called aromatization, it's carried out by an enzyme called aromatase. In fact, most of your listeners may have heard of aromatase 'cause aromatase inhibitors are widely used in female humans as

adjuvant chemotherapy for breast cancer. They are a way of reducing the production of estrogen by preventing testosterone from being converted into estrogen. And in fact, there are a lot of animal experiments showing if you give males aromatase inhibitors, they stop fighting, as well as also stop being sexually active. And so that's one of the counterintuitive ideas, and Nirao has shown that progesterone also seems to play a role in aggression, because these aggression neurons also express the progesterone receptor. So here are two hormones that are classically thought of as female reproductive hormones, this is what goes up and goes down during the estrous cycle, estrogen and progesterone, and yet, they're playing a very important role in controlling aggression in male mice, and presumably in male humans as well. - Fascinating, so estrogen is doing many more things than I think most people believe. - Yep. - And testosterone is doing

00:52:33 Female Aggression, Motherhood

maybe different and fewer things in some cases, and more in others. I've known some aggressive females over the time I've been alive, what's involved in female aggression that's unique from the pathways that generate male aggression? - Great question, so we and other labs have studied this in both mice and also in fruit flies. So one thing in mice that distinguishes aggression in females from males is that male mice are pretty much ready to fight at the drop of a hat, female mice only fight when they are nurturing and nursing their pups after they've delivered a litter. And there is a window there where they become hyper-aggressive, and then after their pups are weened, that aggressiveness goes away. So this is pretty remarkable that you take a virgin female mouse and expose it to a male, and her response is to become sexually receptive and to mate with him. And now you let her have her pups, and you put the same male or another male mouse in the cage with her, and instead of trying to mate with him, she attacks him. So there is some presumably hormonal and also neuronal switch that's occurring in the brain that switches the response of the female from sex to aggression when she goes from virginity to maternity. And we recently showed in a paper, this is work from one of my students, Mengyu Liu, that within VMH in females, there are two clearly divisible subsets of estrogen receptor neurons, and she showed that one of those subsets controls fighting and the other one controls mating. And in fact, if you stimulate the fighting-specific subset in a virgin, you can get the virgin to attack, which is something that we

were never able to do before, and if you stimulate the mating one, you enhance mating. The reason we could never get these results when we stimulated the whole population of estrogen receptor neurons is that these effects are opposite and they cancel out. And so it turns out that if you measure the activity of the fighting and the mating neurons going from a virgin to a maternal female, the aggression neurons are very low in their activity in the virgin, but once the female has pups, the activation ability of those neurons goes way up and the mating neurons stay the same. So if you think of the balance between them like a seesaw, in the virgin, there is more activity in the mating neurons than in the fighting neurons, whereas in the nursing mother, there's more activity or more activation the other way around, the fighting neurons in the mating. - Mm-hmm. - Did I say, "Fighting and mating," the first? Mating neurons dominate fighting in the virgin, fighting neurons dominate mating in the mother. So that's a really cool observation, and it's not something that happens in males, and we don't know what causes that or controls that. Interestingly, this gets into the whole issue of neurons that are present in females, but not in males. So the field has known for a long time that male and female fruit flies have sex-specific neurons. And most of the neurons that we've identified in fruit flies that control fighting in males are male specific, they're not found in the female brain, but recently, we discovered a set of female-specific fighting neurons in the female brain, together with a couple of other laboratories. Now, they do share one common population of neurons in both male and female flies, that in females, activates the female-specific fighting neurons, and in males, activates the male-specific fighting neurons, so it's kind of a hierarchy with this common neuron on top. And in mice, we discovered that there are male-specific neurons in VMH, and those neurons are activated during male aggression. Now, the neurons that are active in females when females fight in VMH are not sex specific, so they are also found in males. So this is already showing you some complexity, the male mouse VMH has both male-specific aggression neurons and generic aggression neurons. And then the female VMH, the mating cells are only found in females, they are female specific and not found in the male brain. And so we're trying to find out what these sex-specific populations of neurons are doing, but that indicates that that is some of the mechanism by which different sexes show different behaviors. - I'm fixated on this transition from the virgin female mouse to the maternal female mouse, and I have a couple of questions about whether or not, for instance, the transition is governed by the presence of pups. So for instance, if you take a virgin female, she'll mate with a male, once she's had pups, she'll try and fight that male, or presumably

another intruder female, right? - Yes, equally towards females and male intruders. - Does that require the presence of her pups? Meaning if you were to take those pups and give them to another mother, does she revert to the more virgin-like behavior? Is it triggered by lactation or could it actually be triggered by the mating behavior itself? 'Cause it's possible for the virgin to become a non-virgin, but not actually have a litter of pups. - Right, those are all great questions, and we don't know the answer to most of them. What I can say is that a nursing mother doesn't have to have her pups with her in the cage in order to attack an intruder male or an intruder female, she is just in a state of brain that makes her aggressive to any intruder. And those aggression neurons in that female's brain are activated by both male and female intruders equally, whereas in male mice, the aggression neurons are only ever activated by males, not by females, because males are never supposed to attack females, they're only supposed to mate with them. So that's another difference in how those neurons are tuned to signals from different conspecifics. Does it require lactation? I don't know the answer to that, I think there are some experiments where people have tried to, classical experiments, people have tried to reproduce the changes in hormones that occur during pregnancy in female rats to see if it can make them aggressive. And some of those manipulations do, to some extent, but there's a whole biology there that remains to be explored about how much of this is hormones, how much of this is circuitry and electricity,

00:59:48 Mating & Aggressive Behaviors

and how much of it is other factors that we haven't identified yet? - I don't want to anthropomorphize, but, well, I'll just ask the question. So the other day, I was watching ferrets mate, right? They're mustelids, and they're mating behavior, I guess I didn't say why I was watching this, doesn't matter. [David laughing] It simply doesn't matter, but if one observes the mating behaviors of different animals, we know that there's a tremendous range of mating behaviors in humans. There can be no aggressive component, there could be an aggressive component in humans that have all sorts of kinks and fetishes and behaviors, and most of which probably has never been documented 'cause most of this happens in private. And here, I always say on this podcast, any time we're talking about sexual behavior in humans, we're always making the presumption that it's consensual, age appropriate, context appropriate and species appropriate. Well, today, we're talking about a lot of different species. With that said, just

to set context, I was watching this video of ferrets mating, and it's quite violent actually. There's a lot of neck biting, there's a lot of squealing. If I were going to project and anthropomorphize, I'd say it's not really clear they both want to be there, one would make that assumption. And of course, we don't know, we have no idea, this could be the ritual. It seems, to me, that there is some crossover of aggression and mating behavior circuitry during the act of the mating, and do you think that reflects this sort of stew of competing neurons that are prioritizing in real time? Because, of course, as states, they have persistence, as you point out, and you can imagine that states overlapping, four different states, the motivational drive to mate, the motivational drive to get away from this experience, the motivational drive to eat at some point, to defecate at some point, all of these things are competing, and what we're really seeing is a bias in probabilities. But when you look at mating behavior of various animals, you see an aggressive component sometimes, but not always. Is it species specific, is it context specific? And more generally, do you think that there is crosstalk between these different neuronal populations and the animal itself might be kind of confused about what's going on? - Right, great questions. I can't really speak to the issue of whether this is species specific, 'cause I'm not a naturalist or a zoologist. I've seen, like you have, in the wild, for example, lions when they mate, I've seen them in Africa, there's often a biting component of that as well. One of the things that surprised us when we identified neurons in VMHvl that control aggression in males is that within that population, there is a subset of neurons that is activated by females during male-female mating encounters. Now, you don't generally think of mouse sex as rough sex, but there is a lot of what superficially looks like violent behavior sometimes, especially if the female rejects the male and runs away. And there's some evidence that those female-selective neurons in VMH are part of the mating behavior. If you shut 'em down, the animals don't mate as effectively as they otherwise would. What happens when you stimulate them we don't yet know because we don't have a way to specifically do that without activating the male aggression neurons. But I think they must be there for a reason because VMH is not traditionally the brain region to which male sexual behavior has been assigned. That's another area called the medial preoptic area, and there we have shown that there are neurons that definitely stimulate mating behavior. In fact, if we activate those mating neurons in a male while it's in the middle of attacking another male, it will stop fighting, start singing to that male and start to try to mount that male until we shut those neurons off. So those are the make-love-not-war neurons, and VMH are the make-war-not-love

neurons, and there are dense interconnections between these two nuclei, which are very close to each other in the brain. And we've shown that some of those connections are mutually inhibitory, to prevent the animal from attacking a mate that it's supposed to be mating with, or to prevent it from mating with an animal it's supposed to be attacking. But it's also possible that there are some cooperative interactions between those structures, as well as antagonistic interactions, and the balance of whether it's the cooperative or antagonistic interactions that are firing at any given moment in a mating encounter, as you suggest, may determine whether a moment of coital bliss among two lions may suddenly turn into a snap or a growl and a baring of fangs.

01:05:10 Neurobiology of Sexual Fetishes

We don't know that, but certainly the substrate, the wiring is there for that to happen. - I'm sure people's minds are running wild with all this. I'll just use this as an opportunity to raise something I've wondered about for far too long, [laughing] which is, I have a friend who's a psychiatrist who works on the treatment of fetishes. This is not a psychiatrist that I was treated by, I'll just point that out. [David laughing] But they mentioned something very interesting to me long ago, which is that when you look at true fetishes, and what meets the criteria for fetish, that there does seem to be some, what one would think would be competing circuitry that suddenly becomes aligned. For instance, avoidance of feces, dead bodies, feet, things that are very infectious, typically those states of disgust are antagonistic to the states of desire, as one would hope is present during sexual behavior. Fetishes often involve exactly those things that are aversive, feet, dead bodies, disgusting things to most people, and true fetishes, in the pathologic sense, exist when people have, basically, a requirement for thinking about or even the presence of those ordinarily disgusting things in order to become sexually aroused. - Hmm. - As if the circuitry has crossed over, and the statement that wrung in my mind was people don't develop fetishes to mailboxes, or to the color red, or to random objects and things, they develop fetishes to things that are highly infectious and counter-reproductive appetitive states. - Hmm. - So I find that interesting, I don't know if you have any reflections on that as to why that might be. I'm tempted to ask whether or not you've ever observed fetish-like behavior in mice, but I find it fascinating that you have this area of the brain that's so highly concerned with the hypothalamus, in which you have these dense populations intermixed, and that the addition of a forebrain, especially in humans, that can think and

make decisions could in some ways facilitate the expression of these primitive behaviors, but could also complicate the expression of primitive behaviors. - Right, I would agree. I think one way of looking at fetishes from a neurobiological standpoint is that they represent a kind of appetitive conditioning where something that is natively aversive or disgusting, by being repeatedly paired with a rewarding experience, changes its valence, its sign so that now it somehow produces the anticipation of reward the next time a person sees it. Now, I don't know that literature in animals, so I don't know if you could condition a mouse to eat feces, for example, although there are animals that are naturally coprophagic, and maybe mice do that occasionally, I'm not sure. But that is one way to think about it, and that could certainly involve in humans, the more recently evolved arts of the brain, the cortex that is sort of orchestrating both what behaviors are happening and whether reward states are turning on in association with those behaviors that are happening. And that's the part that I think is difficult and challenging to study in a mouse, but certainly bears thinking about, because it's a really interesting, again, sort of counterintuitive aspect. Again, like rough sex, people that want to have fighting, or violence, or aggressiveness in order to be sexually aroused, and fetishes. And in fact, when we made that discovery initially, it raised the question in my mind whether some people that are serial rapists, for example, and engage in sexual violence might, in some level, have their wires crossed in some way, that these states that are supposed to be pretty much separated and mutually antagonistic are not, and are actually more rewarding and reinforcing. I think it's going to be a long time before we have figured it out, but when you think about it, there is no treatment that we have for a violent sexual offender that eliminates the violence, but not the sexual desire and sexual urge, whether it's physical castration or chemical castration, it eliminates both. - Definitely an area that I think, well, human neuroscience in general

01:10:06 Temperature, Mating Behavior & Aggression

needs a lot of tools, right? In terms of how to probe and manipulate neural circuitry. I'd love to turn to this area that you mentioned, the medial preoptic area. I'm fascinated by it, because just as within the VMH, you have these neurons for mating and fighting, or aggression, my understanding is medial preoptic area contains neurons for mating, but also for temperature regulation. And perhaps I'm making too much of a leap here, but I've always wondered about this phrase, "In heat," as certainly the menstrual and or

estrous cycle in females is related to changes in body temperature. In fact, measuring body temperature is one way that women can fairly reliably predict ovulation, et cetera. Although this is not a show about contraception, please rely on multiple methods [laughing] as necessary, don't use this discussion as your guide for contraception based on temperature. But if you stimulate certain neurons in the medial preoptic area, you can trigger dramatic changes in body temperature and/or mating behavior. What's the relationship, if any, between temperature and mating, or do we simply not know? - I don't know what the relationship is between temperature and mating neurons in the preoptic area. I suspect that they are different populations of neurons because it's become pretty clear that the preoptic area has many different subsets of neurons that are specifically active during different behaviors, even different phases of mating behavior. So there are mounting neurons, there are intromission thrusting neurons, and ejaculation neurons and sniffing neurons. - Wait, wait, so I think I've heard this before, but I just want to make sure that people get this and I want to make sure I get this. So you're telling me within medial preoptic area, there are specific neurons that if you stimulate them, will make males thrust as if they're mating? - No, so this is not based on stimulation experiments. - Mm. - It's based on imaging experiments right now. - I see, I see. - That we see when we look in the preoptic area at what neurons are active during different phases of aggression, we see that there are different neurons that are active during sniffing, mounting, thrusting and ejaculation, and they become repeatedly activated each time the animal goes through that cycle. - During mating, yeah. - During the mating cycle. There are also some neurons there that are active during aggression, which are distinct, and we don't know whether those neurons are there to promote aggression or to inhibit mating when animals are fighting. We have some evidence that suggest it may be the latter, but we don't know for sure yet. The thermosensitive neurons are really interesting, because you mentioned the phrase, "In heat," and then in the context of aggression, you talk about hotblooded people or hotheads, there's just recently a paper showing there are thermoregulatory neurons in VMH as well. So all of these homeostatic systems for metabolic control and temperature control are intermingled in these nuclei, these zones that control these basic survival behaviors, like mating and aggression and predator defense. And I would imagine that the thermal regulation is tightly connected to energy expenditure, and that, again, these neurons are mixed together to facilitate integration of all these signals by the brain in some way that we don't understand to maintain the proper balance between energy conservation and energy consumption during this

particular behavior or that behavior. I mean, I've always been fascinated by the question, why is it that violence goes up in the summertime when the temperatures are high? Does it really have something to do with the idea that increased temperature increases violence? It seems hard to believe because we're homeothermic and we pretty much stay around 98.6 Fahrenheit. It could be other social reasons why that happens, people are outside, out on the street, bumping into each other, but I think there could well be something that ties thermoregulation to aggressiveness, as well as to mating behavior. - Fascinating, yeah. I ask in the hopes that maybe in the years to come your lab will parse some of the temperature relationships. And I realize it could be also regulated by hormones in general, so it's tapping into two systems for completely different reasons, but anyway, an area that intrigues me, because of this notion of hotheadedness. - Right. - Or cool, calm and collected. And also the fact that, and I probably should've asked about this earlier, that arousal itself is tethered to the whole mating and reproductive process. I mean, without a sort of seesawing back between the sympathetic and parasympathetic arousal, relaxed states, there is no mating that will take place.

01:15:25 Mounting: Sexual Behavior or Dominance?

So it's fascinating the way these different competing forces and seesaws operate. Several times during the discussion so far, we've hit on this idea that the same behavior can reflect different states, and different states can converge on multiple behaviors as well. You had a paper not long ago about mounting behavior, which I found fascinating. Maybe you could tell us about that result, because, to me, it really speaks to the fact that mounting behavior can, in one context, be sexual, and in another context, actually be related to, we presume, dominance. And I think that my friends who practice jujitsu, when I talk about that result, they say, "Of course, mounting the other person and dominating them, there's nothing sexual about it," it's about overtaking them physically, literally being on their neck side, as opposed to lying on their own back. - [David] Hmm. - Just fascinating, very primitive. - Hmm. - And yet, I think speaks to this idea that mounting behavior might be one of the most fundamental ways in which animals and perhaps even humans express dominance and/or sexual interactions. - Yep, and that's a fascinating question, and it was harder to figure out than you might've thought. So there's been this debate for a long time in the field, when you see two male mice mounting each other, is this homosexual behavior, is this a case of mistaken sexual

identification, or is this dominance behavior? And if you train an AI algorithm to try to distinguish male-male mounting from male-female mounting, it does not do a very good job, because motorically, those behaviors look so similar. And so how did we wind up figuring out that most male-male mounting is dominance mounting? There are two important clues, one is the context, and so male-male mounting tends to be more prominent among mice when they haven't had a lot of fighting experience. And then as they become more experienced in fighting, they will show relatively less mounting towards the other male and more attack, and they'll transition quickly from mounting to attack, and so the mounting is always seen in this context of an overall aggressive interaction. And then the second thing, which, believe it or not, was suggested by a computational, theoretical person in my lab, Ann Kennedy, who now has her own lab at Northwestern. She said, "Well, males are known to sing when they mount females, ultrasonic vocalizations, why don't you see what kinds of songs they're singing when they're mounting males? Maybe it's a different kind of song." Well, what we found out is, they don't sing at all when they're mounting a male, so you can easily distinguish whether mounting behavior by a male mouse is reproductive or agonistic, aggressive, according to whether it's accompanied by ultrasonic vocalizations or not. And it turns out that different brain regions are maximally active during these different types of mounting. So VMH, the aggression locus is actually active during dominance mounting, and you can stimulate mounting, dominance mounting, if you weakly activate VMH, whereas MPOA is most strongly activated during sexual mounting, and that's always accompanied by the ultrasonic vocalization. So this shows how difficult and dangerous it can be to try to infer an animal's state, or intent, or emotion, from the behavior that it's exhibiting because the same behavior can mean very different things depending on the context of the interaction with the animal. - And I would say, even more so with when that animal is a human or is multiple humans. - That's right, and there are many examples, animals show chasing to obtain food, a prey animal that they're going to kill and eat, and they show chasing to obtain a mate that they're going to have sex with. And so the intent of the chasing is completely different, and we don't know in all these cases whether there are separate circuits or common circuits that are being activated. - I'm obsessed with dogs and dog breeds and et cetera, et cetera, and one thing I can tell you is that female dogs will mount and thrust. We had a female pit bull mix, a very sweet dog, but in observing her, it convinced me that one can never assume that male dogs are more aggressive than female dogs. It turns out, in talking to people who are quite

skilled at dog genetics and dog breeding, that there's a dominance hierarchy within a litter and it crosses over male-female delineations. So you can get a female in the litter that's very dominant and a male that's very subordinate, and no one really knows what relates to. This is also why little dogs sometimes will get right up in the face of a big Doberman Pinscher. - Mm. - And just start barking, which is an idiotic thing for it to do, but they can be dominant over a much larger dog.

01:20:59 Females & Male-Type Mounting Behavior

- Hmm. - Very strange, to me anyway. Female-female mounting, do you observe it in mice? Are there known circuits, and what evokes female-female mounting, or female-to-male mounting if it occurs? - Good, yes, there are clear examples of females displaying male-type mounting behavior towards other females. We see this most commonly in the lab where we are housing females with their sisters, say three or four in a cage, we take one out and we have her mate with a male, where the male's doing the mounting, now we take that female and we put her back in the cage with her litter mates and she starts mounting them. Now, what the function of that is, if it has any function, or what it means, what's driving it, we don't know, but we do know that if we stimulate the neurons that control mounting in males in the medial preoptic area, if we stimulate that same population in females, it evokes male-type mounting towards either a male or a female target. In fact, we have a movie where we have a female that has just been mounted by a male, so the male's on top and she's underneath, and we stimulate that region of MPOA in the female. And she crawls out from underneath the male who has just mounted her, circles around behind him and climbs up on top of him and starts to try to mount him and thrust at him. - That has a name online, it's called a switch. [Andrew laughing] - Is that right? [laughing] - [Andrew] Don't ask me how I know that. - Okay. - But it's a pretty, yeah, it's a term that you hear. You also hear the term topping from the bottom, which it sounds like that is a literal topping from the bottom. - I see. - That's a more of a psychological phrase, from what I hear. I have friends that are educating me in this language, mostly because I find this kind of neurobiological discussion fascinating. And at some point, right? I attempt, in my mind, to superimpose observations from the online communities. - Yeah. - That I'm told about and asked about to this, but I should point out, it's always dangerous, and in fact, inappropriate to make a one-to-one link. - Yes. - Humans, they maintain all the same neural circuitry and pathways that we're

talking about today in mice, but that forebrain does allow for context, et cetera. - Yep. - Yeah. - So what the function is of female mounting, I don't know, it could be a type of dominance display. It's hard to measure that because people haven't worked on female-dominance hierarchies to the same extent that they've worked on male-dominance hierarchies, but it indicates that the circuits for male-type mounting are there in females, as early work from Catherine Dulac suggested some years ago. - Fascinating, fascinating. I love that paper because, as you pointed out for chase, for mounting behavior, we see it and we think one thing specifically, and after hearing this result, actually, I'm not a big fan of fight sports. I watch them occasionally 'cause friends are into them, but I've seen boxing matches, MMA matches, where at the end of a round, if someone felt that they dominated, they will do the unsportsmanlike thing of thrusting on the back of the other person before they get off. - Really? - Almost like, "I dominated you, and I'm," so mimicking sexual-like behavior,

01:24:40 PAG (Periaqueductal Gray) Brain Region: Pain Modulation & Fear

but there's no reason to think that it's sexual, but they're sending a message. - Yeah. - Of dominance is what it implies. I'd love to talk about something slightly off from this circuitry, but I think that's related to the circuitry, at least in some way, which is this structure that I've always been fascinated by and I can't figure out what the hell it's for, 'cause it seems to be involved in everything, which is the PAG, the periaqueductal gray, which is a little bit further back in the brain, for people that don't know. It's been studied in the context of pain, it's been studied in the context of the so-called lordosis response, the receptivity or arching of the back of the female to receive intromission and mating from the male. How should we think about PAG? Clearly, it can't be involved in everything, I'm guessing it's at least as complex as some of these other regions that we've been talking about, different types of neurons controlling different things, but how does PAG play into this? In particular, I want to know, is there some mechanism of pain modulation and control during fighting and/or mating? And the reason I ask is that, while I'm not a combat sports person, years ago, I did a little bit of martial arts, and it always was impressive to me how little it hurt to get punched during a fight and how much it hurt afterwards, [laughing] right? So there clearly is some endogenous pain control. - Yep. - That then wears off, and then you feel beat up. - [David] Yep. - Or at least, in my case, I felt beat up. What's PAG doing vis-a-vis pain, and what's pain doing vis-a-vis these other

behaviors? - Good, good. So I think of PAG like a old-fashioned telephone switchboard, where there are calls coming in, and then the cables have to be punched into the right hole to get the information, to be routed to the right recipient on the other end of it, because pretty much every type of innate behavior you can think of has had the PAG implicated. And there's a whole literature showing the involvement of the PAG in fear, different regions of the PAG, the dorsal PAG is involved in panic-like behavior, running away, the ventral PAG is involved in freezing behavior. Both the MPOA and VMH send projections to the PAG, to different regions of the PAG. So in cross-section, I hate to say this, but in cross-section, the PAG kind of looks like the water in a toilet when you're standing over an open toilet bowl. - Mm-hmm. - And if you imagine a clock face projected onto that, it's like the PAG has sectors, from one to 12, maybe even more of them, and in each of those sectors, you find different neurons from the hypothalamus are projecting. So could turn out that there is a topographic arrangement along the dorsal-ventral axis of the PAG and the medial-lateral axis of the PAG that determines the type of behavior that will be emitted when neurons in that region are stimulated. And I think sort of all of the evidence is pointing in that direction, but by no means, has it been mapped out. Now, the thing that you mentioned about it not hurting when you got beat up during martial arts, there is a well-known phenomenon called fear-induced analgesia, where when an animal is in a high state of fear, like if it's trying to defend itself, there is a suppression of pain responses, and I'm not sure completely about the mechanisms and how well that's understood, but for example, the adrenal gland has a peptide in it that is released from the adrenal medulla, which controls the fight-or-flight responses, and that peptide has analgesic activities. Now, whether. - May I ask what that peptide is? - It's called bovine adrenal medullary peptide of 22 amino acid residues. And I only know about it because it activates a receptor that we discovered many years ago that's involved in pain, and we thought it promoted pain, but it turns out that this actually inhibits pain, it's like an endogenous analgesic. Whether this is happening, this type of analgesia is happening when an animal is engaged in offensive aggression or in mating behavior, I don't know, but it certainly is possible. And I don't know whether these analgesic mechanisms are happening in the PAG, they could also be happening a little further down in the spinal cord. The PAG is really continuous with the spinal cord, if you just follow it down towards the tail of an animal, you will wind up in the spinal cord. And so it could be that there are influences acting at many levels on pain in the PAG and in the spinal cord as well. And it may well be known, I just don't know it, I want to

distinguish clearly between things that are not known, that I know are unknown, which is in a fairly small area where I have expertise, from things that may be known, but I'm ignorant of them, because I just don't have a broad enough knowledge base to know that. - Sure, we appreciate those delineations. Thank you, PAG, I think this description of it as an old-fashioned telephone switchboard, and now every time I look into the toilet, I'll think about the periaqueductal gray. - [laughing] That's right. - [Andrew] And every time I see an image of periaqueductal gray, I'll think about a toilet. - That's right. [laughing] - That is an excellent description, because, in fact, I drew a circle with a little thing at the bottom. And well, I'll put a post or link to a picture of PAG and you'll understand why David and I are chuckling here,

01:30:38 Tachykinins & Social Isolation: Anxiety, Fear & Aggression

because, indeed, it looks like a toilet, when staring into a toilet. Tell us about tachykinin, I've talked about this a couple times on different podcast episodes because of its relationship to social isolation, and in part, because the podcast was launched during a time when there was more social isolation. My understanding is that tachykinin, and you'll tell us what it is in a moment, is present in flies and mice and in humans, and may do similar things in those species. - That's right, so tachykinin refers to a family of related neuropeptides. So these are brain chemicals, they're different from dopamine and serotonin in that they're not small, organic molecules, they're actually short pieces of protein that are directly encoded by genes that are active in specific neurons and not in others. And when those neurons are active, those neuropeptides are released together with classical transmitters, like glutamate, whatever. Tachykinins have been famously implicated in pain, particularly Tachykinin-I, which is called Substance P, one of the original pain modulating, this is something that promotes inflammatory pain. But there are other tachykinin genes, in mice, there are two, in humans, I think there are three, and in Drosophila, there's one. And the way we got into tachykinins is from studying aggression in flies. We thought, since neuropeptides have this remarkable parallel evolutionary conservation of structure and function, like Neuropeptide Y controls feeding in worms, in flies and mice and in people. Oxytocin-like peptides control reproduction in worms and mice and in people. We thought we might find peptides that control aggression in flies and in people, and so we did a screen, unbiased screen of peptides, and found, indeed, that one of the tachykinins, Drosophila tachykinin, those neurons

when you activate them strongly promote aggression, and it depends on the release of tachykinin. Now, the interesting thing is that, in flies, just like in people and practically any other social animal that shows aggression, social isolation increases aggressiveness. So putting a violent prisoner in solitary confinement is absolutely the worst, most counterproductive thing you could do to them. And indeed, we found in flies that social isolation increases the level of tachykinin in the brain, and if we shut that gene down, it prevents the isolation from increasing aggression. So since my lab also works on mice, it was natural to see whether tachykinins might be upregulated in social isolation and whether they play a role in aggression. And this is work done by a former postdoc, Moriel Zelikowsky, now at University of Salt Lake City in Utah, and she found, remarkably, that when mice are socially isolated for two weeks, there is this massive upregulation of Tachykinin-II in their brain. In fact, if you tag the peptide with a green fluorescent protein from a jellyfish, genetically, the brain looks green when the mice are socially isolated 'cause there's so much of this stuff released. And she went on to show that that increase in tachykinin is responsible for the effect of social isolation to increase aggressiveness and to increase fear and to increase anxiety. And in fact, there are drugs that block the receptor for tachykinin which were tested in humans and abandoned because they had no efficacy in the tests that they were analyzed for. If you give those drugs to a socially isolated mouse, it blocks all of the effects of social isolation. It blocks the aggression, it blocks the increased fear and the increased anxiety, and Moriel described it, "The mice just look chill." It's not a sedative, which is really important, it's not that the mice are going to sleep. Most remarkably is, once you socially isolate a mouse and it becomes aggressive, you can never put it back in its cage with its brothers from its litter because it will kill them all overnight, but if you give it this drug, which is called osanetant, that blocks Tachykinin-II, that mouse can be returned to the cage with its brothers and will not attack them, and seems to be happy about that for the rest of the time. So this is an incredibly powerful effect of this drug, and I've been really interested in trying to get pharmaceutical companies to test this drug, which has a really good safety profile in humans, in testing it in people who are subjected to social isolation stress or bereavement stress. And this is one of the areas where I learned an eye-opening lesson, as a basic scientist who naively thought that if you make a discovery and it has translational applications to humans, that pharmaceutical companies are going to be falling all over themselves to try it. And they are not interested, because once burned, twice shy, these drugs were tested for efficacy in schizophrenia. I have no

idea why, there's very little preclinical data to suggest that. Not surprisingly, they failed. When a drug fails in clinical trials in Phase 3, it costs $100 million to the company that carried out that clinical trial. So there's a huge slag heap of discarded pharmaceuticals, many of them inhibitors of neuropeptide action, that could be useful in other indications, such as the one we discovered, but there's a huge economic disincentive for pharmaceutical companies to test them again, because the conclusion that they drew from all these failed tests, particularly in the 2010s and before that, is that the reason they failed is because animal experiments with drugs don't predict how humans will respond to the drugs, and therefore, we shouldn't try to extrapolate from any other data that we get from animal experiments, mouse or rat experiments to humans, because they'll lead us down the wrong track, and I think that that is probably wrong. In some cases, it may be right, but in other cases, there's good reason to think, because these brain regions and molecules are so evolutionarily conserved that they ought to be playing a similar role in humans. In fact, there is a paper showing that in humans that have borderline personality disorder, there's a strong correlation between their self-reported level of aggressiveness and serum levels of a tachykinin, in this case, Tachykinin-I, as detected by radioimmunoassay. This is work of Emil Coccaro, who's a clinical psychiatrist at the University of Chicago. So there is a smoking gun in the case of humans as well. And I was actually trying to interest a pharmaceutical company that was testing these drugs, actually, for treatment of hot flashes in females, in humans, where there is actually good animal data to think that it might be useful, but I realized that this clinical trial was going on during the COVID pandemic. And I approached him and said, "Look, nature may have actually done for you the experiment that I want you to do, 'cause some of the people who are getting drug or placebo are going to have been socially isolated and some of them will have not. Why don't you get them to fill out questionnaires and see whether the ones who were given the drug and socially isolated felt less stressed and less anxious than the ones who were not socially isolated?" And they would not touch it, because they're in the middle of a clinical trial for a different indication for this drug, and they have to report any observation that they make about that drug in their patient population. So if they were to ask these questions and get an unfavorable answer, "Oh my God, I felt even worse when I took this drug and I was isolated," they would be obliged to report that to the FDA and that could torpedo the chances for the drug being approved in the thing that it was in clinical trials for. So it's better not to ask and not to know than it is to try to find out more information that could

lead to another clinical indication. So I remain convinced that this family of drugs could have very powerful uses in treating some forms of stress-induced anxiety or aggressiveness in humans, but it's just very difficult, for economic reasons, to find a way to get somebody to test that. - Yeah, a true shame that these companies won't do this, and especially given the fact that many of these drugs exist and their safety profiles are established, 'cause that's always a serious consideration. - Yep. - When embarking on a clinical trial. Perhaps in hearing this discussion, someone out there will understand the key importance of this and will reach out to us, we'll provide ways to do that, to get such a study going in humans. Because I think if enough laboratories ran small-scale clinical trials, pharma certainly would perk up their ears, right? I mean, they're so strategic. - Yep. - Sometimes to their own. - I mean, I would like to say also, I'd like to see this tested on pets. I mean, there's a huge number of pets right now that are suffering separation anxiety because humans bought them to keep them company during the COVID pandemic, and now they're home alone. - And now they're home alone, yeah. - Okay? And if this thing works in mice, there's certainly a higher chance it's going to work in dogs or in cats than it is going to work in humans. And if it did, that would be even more encouragement to continue along those lines. People sometimes forget that although we work on animals and we ultimately want to understand humans, we care about how our results apply to the welfare of animals as well, and particularly domestic pets, which is a multi-billion-dollar industry in this country. So if there is ways that they can be made to feel better when they're separated from their owners, that would certainly be a good thing. - Absolutely, we will put out the call, we are putting out the call, and I know for sure there will be a response. Just underscoring what we've been talking about even more, every time we hear about a school shooting, like in Texas recently, or I happened to be in New York during the time when there was a subway shooting. For whatever reason, I listened to the book about Columbine, that went into a very detailed way about the origin of those boys that committed that, and every single time, the person who commits those acts is socially isolated, as far as I know. - Yeah, yeah. - There might be some exceptions there. And sometimes this crosses over with other mental health issues, but sometimes no, no apparent mental health issues. So social isolation clearly drives powerful neurochemical and neuro biological changes, I really hope that Tachykinin-I and II, those are the main ones in humans? - Yeah, yeah. - Will be explored in more detail. Also, I didn't know that Tachykinin-I is Substance P. - Yes. - And Substance P is Tachykinin-I. - Yes. Tachykinin-I is the gene name, and Tachykinin-II, in

humans, is called Neurokinin B, that's the name of the protein. I just refer to it by the gene name 'cause it makes it easier and I don't have to keep remembering two names for each thing. - And if I'm not mistaken, you put yourself in the company of geneticists because your original training was in genetics, immunology and areas related to that. - It was in cell biology, and I didn't actually have formal training in genetics as a graduate student, but I think I'm a geneticist at heart, that's just the way I like to think about things. And when I started working on flies, that sort of,

01:43:49 Brain, Body & Emotions; Somatic Marker Hypothesis & Vagus Nerve

I came out of the closet as a geneticist, as it were. [laughing] - Wonderful, as long as we're talking about humans, I'd love to get your thoughts about human studies of emotion. I know you wrote this book with Ralph Adolphs, you have this new book, which we'll provide a link to, which I've read front to back twice, it's phenomenal. - Thank you. - I've mentioned it before on the podcast, it's really, there are books that are worth reading, and then there are books that are important, and I think this book is truly important for the general population to read and understand, and neuroscientists should read and understand the contents, because we, as a culture, are way off in terms of how we think about emotions and states and behaviors. So we'll put a link to that, it's really worth the time and energy to read it, and it's written beautifully, I should say. - Thank you. - Very accessible even for non-scientists. There's a heat map diagram in that book that I think about, this is a heat map diagram of subjective reports that people gave of where they experience an emotion, or a feeling, a somatic feeling, in their body, or in their head, or both, when they are angry, sad, calm, lonely, et cetera, et cetera. And I wouldn't want people to think that those heat maps were generated by any physiological measurement, because they were not. And yet, I don't think we can have a discussion about emotions and states and the sorts of behaviors that we're talking about today without thinking about the body also. - [David] Yep. - And I'm not coming to this as a Northern California, mind-body. - Yeah. - I've been to Esalen once. [David laughing] I didn't go in the baths, I went there, I gave a talk and I left. It is very beautiful. If anyone wants to know what it looks like, I think that final scene of "Mad Men" is shot at Esalen, it's a very beautiful place. And yet, mind-body, to me, is a neurobiological construct. - Yes. - Because the nervous system extends through out of the cranial vault and into the spinal cord. - Yeah. - And body and back and forth, okay. How should we think about the

body, in terms of states? And at some point, I'd love for you to comment on that heat map experiment, because it does seem that there's some regularity as to where people experience emotions. When people are in a rage, for instance, they seem to feel it both in their gut and in their head, it seems, on average. And people love to extrapolate to gut intuition or that the chakras or anger is in the stomach, and this goes to Eastern medicine, et cetera. How should we think about mind-body in the context of states, and think about it as scientists, maybe even as neuroscientists or geneticists? - Good, so for the answer to the first question about the heat maps and people associating certain parts of their body with certain emotional feelings, this goes back to something called the somatic marker hypothesis, that was proposed by Antonio Damasio, who is a neurologist at USC, the idea that our subjective feeling of a particular emotion is, in part, associated with a sensation of something happening in a particular part of our body, the gut, the heart, I don't see the liver invoked very much in emotional characterization, but. - But gall and the gallbladder. - Yes. - Somebody having a lot of gall. - That's right. - I don't know why I make a fist when I say that. - Right. - But I'm guessing the gall bladder is shaped like a fist. [Andrew laughing] - That's right, and if there is a physiology underlying these heat maps, it could reflect increased blood flow to these different structures. And that, in turn, reflects what you were talking about, that is, emotion definitely involves communication between the brain and the body, and it's bidirectional communication, and it's mediated by the peripheral nervous system, the sympathetic and the parasympathetic nervous system, which control heart rate, for example, blood vessel, blood pressure. And those neurons receive input from the hypothalamus and other brain regions, central brain regions that control their activity. And when the brain is put in a particular state, it activates sympathetic and parasympathetic neurons, which have effects on the heart and on blood pressure, and these, in turn, feed back onto the brain through the sensory system. And a large part of this bidirectional communication is also mediated through the vagus nerve, which many of your listeners and viewers may have heard about because it's become a topic of intense activity now. People have known for a long time, so the vagus nerve is a bundle of nerve fibers that comes out basically of your skull, out of the central nervous system, and then sends fibers into your heart, your gut, all sorts of visceral organs. And that information is both, you used the words earlier in our discussion, afferent and efferent. So the vagal fibers sense things that are happening in the body, so the reason you feel your stomach tied up in knots if you're tense is that those vagal fibers are sensing the contraction of the gut muscles, and

they're also afferents, which means that information coming out of the brain can influence those peripheral organs as well. And there's work from a number of labs, just in the last six months or so, where people are starting to decode the components of the different fibers in the vagus nerve. And it's amazing how much specificity is, there are specific vagal nerves that go to the lung, that control breathing responses, that go to the gut, that go to other organs. It's almost like a set of color-coded lines, labeled lines for those things. And now how those vagal afferents play a role in the playing out of emotion states is a fascinating question that people are just beginning to scrape the surface of. But I think what's exciting now is that people are going to be developing tools that will allow us to turn on or turn off specific subsets of fibers within the vagus nerve and ask how that affects particular emotional behaviors. So you're absolutely right, this brain-body connection is critical, not just for the gut, but for the heart, for the lungs, for all kinds of other parts of your body, and Darwin recognized that as well. And I think it's a central feature of emotion state, and I think, what underlies our subjective feelings of an emotion. - Incredible, well, David, I have to say, as a true fan of the work that your lab has been doing over so many decades, and first of all, I was delighted when you stopped working on stem cells. [David laughing] Not because you weren't doing incredible work there, but because I saw a talk where you showed a movie of an octopus spitting out, or not spitting, but squirting out a bunch of ink and escaping, and you said you were going to work on things of the sort that we're talking about today, fear, aggression, mating behaviors, social behaviors. It's been incredible to see the work that your lab has done, and I know I speak on behalf of a tremendous number of people when I say thank you for taking time out of your important schedule to share with us what you've learned. My last question is a simple one, which is, will you come back and talk to us again in the future about the additional work that's sure to come? - I would be happy to do that, and I really have appreciated your questions, they've all been right on the money, you've hit all of the critical, important issues in this field. And you've uncovered what is known, the little bit is known, and how much is not known, and I think it's important to emphasize the unknown things, because that's what the next generation of neuroscientists has to solve. And so I hope this will help to attract young people into this field, because it's so important, particularly for our understanding of mental illness and mental health and psychiatry, we've got to figure out how emotion systems are controlled in a causal way if we ever want to improve on the psychiatric treatments that we have now, and that's going to require the next generation of people coming into the

field. - Absolutely, I second that.

01:52:52 Zero-Cost Support, YouTube Feedback, Spotify & Apple Reviews, Sponsors, Momentous Supplements, AG1 (Athletic Greens), Instagram, Twitter, Neural Network Newsletter, Huberman Lab Clips

Well, thank you, it's been a delight. - Thank you, great, really appreciate it. - Thank you for joining me today for my discussion with Dr. David Anderson. Please also be sure to check out his new book, "The Nature of the Beast: How Emotions Guide Us". It's a truly masterful exploration of the biology and psychology behind what we call emotions and states of mind and body. If you're learning from and/or enjoying this podcast, please subscribe to our YouTube channel, that's a simple, zero-cost way to support us. Please also subscribe to the podcast on Spotify and Apple, and on both Spotify and Apple, you have the opportunity to leave us up to a five-star review. If you have questions, or comments, or suggestions about topics you'd like us to cover, or guests you'd like us to interview on the Huberman Lab Podcast, please put those in the comment section on YouTube. We do read all those comments and we do take them to heart. Please also check out the sponsors mentioned at the beginning of today's podcast, and check out Momentous supplements, our new partners in the supplement space, and check out Athletic Greens, that's the best way to support this podcast. If you're not already following us on social media, please do so. We are hubermanlab on Twitter, and we are also hubermanlab on Instagram. And both places, I cover science and science-related tools, some of which overlap with the content of the Huberman Lab Podcast, but much of which is unique from the content covered on the Huberman Lab Podcast. Again, that's hubermanlab on Instagram and hubermanlab on Twitter. Please also check out our Neural Network monthly newsletter. This is a newsletter that has summaries of podcast episodes, it also includes a lot of actionable protocols. It's very easy to sign up for the newsletter, you go to hubermanlab.com, click on the menu, go to Newsletter. You supply your email, but we do not share your email with anybody, we have a very clear and rigorous privacy policy, which is we do not share your email with anybody. And the newsletter comes out once a month, and it is completely zero cost. Again, just go to hubermanlab.com and go to the Neural Network Newsletter. I'd also like to point out that the Huberman Lab Podcast has a clips channel. So these are brief clips, anywhere from three to 10 minutes, that encompass single concepts and actionable protocols, related to

sleep, to focus, interviews with various guests, we talk about things like caffeine, when to drink caffeine relative to sleep, alcohol, when and how and if anyone should ingest it relative to sleep, dopamine, serotonin, mental health, physical health, and on and on, all the things that relate to the topics most of interest to you. You can find that easily by going to YouTube, look for, "Huberman Lab Clips," in the search area, and it will take you there, subscribe. And we are constantly updating those with new clips. This is especially useful, I believe, for people that have missed some of the earlier episodes or you're still working through the back catalog of Huberman Lab podcasts, which admittedly can be rather long. And last but certainly not least, thank you for your interest in science.