Welcome to the Huberman Lab podcast where we discuss science and science-based tools for everyday life. I'm Andrew Huberman, an upper professor of neurobiology and ophthalmology at Stanford School of Medicine. Today my guest is Dr. Charles Zucker. Dr. Zucker is a professor of biochemistry and molecular biophysics and of neuroscience at Columbia University School of Medicine. Dr. Zucker is one of the world's leading experts in perception, that is how the nervous system converts physical stimuli in the world into events within the nervous system that we come to understand as our sense of smell, our sense of taste, our sense of vision, our sense of touch, and our sense of hearing. Dr. Zucker's lab is responsible for a tremendous amount of pioneering and groundbreaking work in the area of perception. For a long time his laboratory worked on vision, defining the very receptors that allow for the conversion of light into signals that the rest of the eye in the brain can understand. In recent years his laboratory has focused mainly on the perception of taste and indeed his laboratory is responsible for discovering many of the taste receptors leading to our perception of things like sweetness, sourness, bitterness, saltiness, and umami, that is savouriness in food. Dr. Zucker's laboratory is also responsible for doing groundbreaking work on the sense of thirst, that is how the nervous system determines whether or not we should ingest more fluid or reject fluids that are offered to us. A key feature of the work from Dr. Zucker's laboratory is that it bridges the brain and body. As you'll soon learn from today's discussion, his laboratory has discovered a unique set of sugar sensing neurons that exist not just within the brain, but a separate set of neurons that sense sweetness and sugar within the body. And that much of the communication between the brain and body leading to our seeking of sugar is below our conscious detection. Dr. Zucker has received a large number of prestigious awards and appointments as a consequence of his discoveries in neuroscience. He is a member of the National Academy of Sciences, the National Academy of Medicine, and the American Association for the Advancement of Science. He is also an investigator with the Howard Hughes Medical Institute. For those of you that are not familiar with the so-called HHMI, the Howard Hughes Medical Institute, Howard Hughes Medical Institute investigators are selected on an extremely competitive basis. And indeed they have to come back every five years and prove themselves worthy of being reappointed as Howard Hughes investigators. Dr. Zucker has been a Howard Hughes investigator since 1989. What all that means for you as a viewer and or listener of today's podcast is that you are about to learn about the nervous system and its ability to create perceptions, in particular the perception of taste and sugar sensing from the world's expert on perception and taste. I'm certain that by the end of today's podcast, you're not just going to come away with a deeper understanding of our perceptions and our perception of taste in particular, but indeed you will come away with an understanding of how we create internal representations of the entire world around us. And in doing so, how we come to understand our life experience. I'm pleased to announce that the Hubertman Lab podcast is now partnered with momentous supplements. We often talk about supplements on the Hubertman Lab podcast and while supplements aren't necessary for everybody, many people derive tremendous benefit from them. For things like enhancing the quality and speed with which you get into sleep or for enhancing focus or for hormone support. The reason we partnered with momentous supplements is several fold. First of all, their supplements are of the absolute highest quality. Second of all, they ship internationally, which is important because many of our podcast listeners reside outside the US. Third, many of the supplements that momentous makes and most all of the supplements that we partnered with them directly on are single ingredient formulations. This is important for a number of reasons. First of all, if you're going to create a supplement protocol that's customized for your needs, you want to be able to figure out which supplement ingredients are most essential and only use those. And supplements that combine lots of ingredients simply won't allow you to do that. So in trying to put together a supplement protocol for yourself that's the most biologically effective and cost effective, single ingredient formulations are going to be the most useful. If you'd like to see the supplements that we partnered with momentous on, you can go to livemomentus.com slash Hubertman. And there you'll see many of the supplements that we've talked repeatedly about on the Hubertman Lab podcast episodes. I should mention that the catalog of supplements that are available at livemomentus.com slash Hubertman is constantly being expanded. So you can check back there livemomentus.com slash Hubertman to see what's currently available and from time to time you'll notice new supplements being added to the inventory. 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. And now for my discussion with Dr. Charles Zucker. Charles, thank you so much for joining me today. My pleasure. I want to ask you about many things related to taste and gustatory perception, but maybe to start off and because you've worked on a number of different topics and neuroscience, not just taste. How do you think about perception? Or rather, I should say, how should the world and people think about perception? How it's different from sensation? And what leads to our experience of life in terms of vision, hearing, taste, etc. So, you know, the brain is an extraordinary organ that weights maybe 2% of your body mass. Yet it consumes anywhere between 25 to 30% of all of your energy and oxygen. And it gets transformed into a mind. And this mind changes the human condition. It changes, it transforms, you know, fear into courage. Conformity into creativity. Sadness into happiness. How the hell does that happen? Now, the challenge that the brain faces is that the world is made of real things. You know, this here is a glass. And this is a cord, and this is a microphone. But the brain is only made of neurons that only understand electrical signals. So, how do you transform that reality into nothing that electrical signals that now need to represent the world? And that process is what we can operationally define as perception. In the senses, let's say, of factory, other taste, vision, you know, we can very straightforwardly separate detection from perception. Detection is what happens when you take a sugar molecule, you put it in your tongue, and then a set of specific cells now sends that sugar molecule. That's detection. You haven't perceived anything yet. That is, yes, your cells in your tongue interacting with this chemical. But now that cell gets activated and sends a signal to the brain, and now detection gets transformed into perception. And he's trying to understand how that happens, that's been the maniacal drive of my entire career in neuroscience. How does the brain ultimately transform detection into perception so that it can guide actions and behaviors? Does that make sense? Absolutely. And is a very clear and beautiful description. That sort of high level question related to that. And then I think we can get into some of the intermediate steps. Yes. I think many people would like to know whether or not my perception of the color of your shirt is the same as your perception of the color of your shirt. What an excellent question. Am I okay to interrupt you as you're guessing what you're going? All right, very. Interruption is welcome on this podcast. The audience will always penalize me for interrupting you and will never penalize you for interrupting. I like the one way penalize. Now, given what they told you before, that the brain is trying to represent the world based in nothing but the transformation of these signals into electrical languages that now neurons had to encode and decode. It follows that your brain is different than my brain. And therefore it follows that the way that you're perceiving the world must be different than mine, even when receiving the same sensory cues. Okay. And I'll tell you about an experiment. It's a simple experiment yet brilliant that demonstrates why we perceive the world how we perceive the world different. So in the world of vision, as you know, well, well, now we have three classes of photo receptor neurons that sense three basic colors red, blue and green. Blue, green and red if we go, you know, from sure too long wavelength. And these three are sufficient to accommodate the full visible spectra. I want to take three light projectors. And I'm going to project with one into a white screen. Red light and the other one green light. I'm going to overlap the two beams and on the screen to be yellow. Okay, this is super position when you have two beams of red and green. And then I'm going to take a third projector. And I'm going to put a filter that projects right next to that mixed beam. A spectrally pure yellow. And I'm going to ask you to come to the red and green projectors and play with intensity knobs. So that you can match that yellow that you are projecting to the spectrally pure next to it. Is this making sense? Perfect. And I'm going to write down the numbers in those two volume intensity knobs. And then I'm going to ask the next person to do the same. And then I'm going to ask every person around this area of battery park in New York to do the same. And guess what? We're going to end up with thousands of different number combinations. Amazing. So for all of us is yellow enough that we can use a common language. But for every one of us, that yellow is going to be every so slightly differently. And so I think that simple psychological experiment beautifully illustrates how we truly perceive the world differently. I love that example. And yet in that example, we know the basic elements from which color is created. If we migrate into a slightly different sense, let me pick a hard one. Like sound, sound or or faction. Very hard then to do an experiment that will allow us to get that degree of granularity and beautiful causality. Where we can show that a produces and leads to be if I give you the smell of a rose, you can describe it to me. If I smell the same rose, I can describe it also. But I have no way whether the two of us are experiencing the same. But it's close enough that we can both pretty much say that it has the following, you know, features. Or other determinants, but no question that your experience is different than mine. The fact that it's good enough for us to both survive, that your perception of yellow and my perception of yellow, at least up until now is good enough for us both to survive. Raises a thought about a statement made by a colleague of ours, Marcus Meister at Caltech. It's never been on this podcast, but in the review that I read by Marcus at one point, he said that the basic function of perception is to divide our behavioral responses into the outcomes downstream of three basic emotional responses. Yum. I like it. Yuck. I hate it. Or meh. Whatever. What do you think about, I'm not looking to establish a debate between your markets without Marcus here. I understand. But what I like about that is that it seems like the, we know the brain is a very economical organ in some sense, despite its high metabolic demands. And this variation in perception from one individual to the next, at once seems like a problem, because we're all literally seeing different things. And yet we function. We function well enough for most of us to avoid death and cliffs and eating poisons and so forth, and to enjoy some aspects of life, one hopes. So is there a general statement that we can make about the brain not just as a organ to generate perception, not just as an organ to keep us alive, but also an organ that is trying to batch our behaviors into general categories of that. I think so, but, but again, I think the role of Marcus to and I think he's right that, you know, broadly speaking, you could categorize a lot of behaviors falling into the true categories. And that's 100% likely to be the case for animals in the wild. Where, you know, the choices are not necessarily binary, but they're very unique and distinct. Do I want to eat this? Do I want to kill that? Do I want to go there or do I want to go here? We humans deviated from that world long ago and, you know, learn to experience life where we do things that we should not be doing. Some of us more than others, exactly. You know, in my own world of taste, yeah. The likelihood that an animal in the wild will enjoy eating something bitter. It's inconceivable. Yet we, you know, love Tonic water. We enjoy, we like living on the edge. We love enjoying experiences that makes us human. And that goes beyond that simple set of categories, which is Yamie, Yaki, who cares? And so I think it's not about palette, but I think it's overly reductionist for certainly what we humans do. I agree. And since we're here in New York, I can say that the many options, the extensive variety of food, flora, and fauna in New York, explains a lot of the more nuanced behaviors that we observe. Let's talk about taste. Because, well, you've done extensive work in the field of vision, and it's a topic that I love. You could spend all day on taste is fascinating. First of all, I'd like to know why you migrated from studying vision to studying taste. And perhaps in that description, you could highlight to us why we should think about and how we should think about this sense of taste. My goal is always been to understand, as I highlighted before, how the brain does its magic. What part do you wonder? Ideally, I'd like to help contribute to understand all of it. How do you encode and decode emotions? How do you encode and decode memories and actions? How do you make decisions? How do you transform the textual inter perception? And the list goes on and on. But one of the key things in science, as you know, is ensuring that you always ask the right question so that you have a possibility of answering it. Because if the question cannot be tractable or reduced to an experimental path that helps you resolve it, then we end up doing some really fun science, but not necessarily answering the important problem that we want to study. Make sense? From a first person perspective, yes. The hardest question, the most important question is, what question are you going to try and answer? And so, for example, I would have to understand the neural basis of empathy. It's a big market for that. 100%. But I wouldn't even know, I mean, at the molecular level, that's what we do. How do the circuits in your brain create that sense? I have not clue how to do it. I can come up with ways to think about it, but I like to understand what in your brain makes someone a great philanthropist. What is the neural basis of love? I wouldn't even know where to begin. So, if I want to begin to study these questions about brain function that can cover so many aspects of the brain, I need to choose a problem that affords me that window. But in a way that can ask questions that get me answers. And among the senses that have the capacity of transforming the attention into perception of being stories, memories of creating emotions of giving you different actions and perceptions as a function of the internal state, you know, when your angry things taste very differently, that when you're sated, how? Why? When you taste something, you now remember this amazing meal you had with your first date. How does that happen? All right. So, if I want to begin to explore all of these things that the brain does, I have to choose a sensory system that affords some degree of simplicity in the way that the input output relationships are put together. And in a way that still can be used to ask everyone of these problems that the brain has to ultimately compute and code and decode. And what's remarkable about the taste system at the time that I began working on this is that nothing was known about the molecular basis of taste. And we knew that we could taste what has been usually defined as the basic taste qualities sweet sour bitter salty and umami. Umami is a Japanese word that means yummy delicious. Nearly every animal species the taste of amino acids and in humans is mostly associated with the taste of MSG monosodium glutamate one amino acid in particular. Just by way of example some foods that are rich in the umami evoking stimulation seaweed tomato cheese and it's a great great flavor enhancer it enriches our sensory experience. And so the beautiful thing of the system is that the lines of input are limited to five. You know, sweets are a bit of salty and umami and each of them has a predetermined meaning. You are born like in sugar and dislike in bitter you have no choice. These are hard wire systems. But of course you can learn to dislike sugar and to like beaters. But in the wild let's take humans out of the equation. These are 100% predetermined you're born with that specific valence value for each taste of sweet umami and low salt are attractive taste qualities. They evoke a pettity responses I want to consume them. And bitter and sour are innately predetermined to be a very safe. Could I interrupt you just briefly and ask a question about that exact point for something to be a petitive to and some mother taste to be aversive. And for those to be hardwired can we assume that the sensation of very bitter or of activation of bitter receptors in the mouth. Activates a neural circuit that causes closing of the mouth, retraction of the tongue and retraction of the body and that the taste of something sweet might actually induce more licking. 100% you got it the activation of the receptors in the tongue that recognize sweet versus the ones that recognize bitter activate an entire behavioral program. And that program that we can refer as a petitiveness or a version it's composed of many different subroutines. In the case of bitter is very easy to actually look at see them happening in animals because the first thing you do is you stop licking then you put unhappy face then you squint your eyes and then you start guiding. And that entire thing happens by the activation of a bitter molecule in a bitter sense in selling your talk. It's again the magic of the brain you know how how it's able to encode and decode this extraordinary actions and behaviors in response of nothing but a simple very you know a unique sensory stimuli. Now let me say that this palette of five basic tastes accommodate all the dietary needs of the organism sweet to ensure that we get the right amount of energy. Umami to ensure that we get proteins and at a central nutrient. Salt the three repetitive ones ensure that we maintain our electrolyte balance. But for you and sour most likely to prevent ingestion of spoil acid fermented foods and that's it that is the palette that we deal with now of course is a difference between basic taste and flavor. The whole experience flavor is the combination of multiple tastes coming together together with smell with texture with temperature with the look of it that gives you what you and I would call the false sense or experience it but we scientists need to reduce the problem into its basic elements so we can begin to break it apart before we put it back together. So when we think about the sense of taste and we try to figure out how these lines of information go from your tongue to your brain and how they signal and how they can integrate it and how they trigger all these different behaviors. We look at them as individual qualities so we give the animal sweet or we give them a bit or we give them sour we avoid mixes. The first stage of discovery is to have that clarity as to what you're trying to extract so that you can hopefully meaningfully make a difference by being able to figure out how easy that a goes to be to see and today. The primary colors to create the full array of the color spectrum exactly before I ask you about the first and second and third stages of taste and flavor perception is there any idea that there may be more than five degrees for example what about fat. I love that I love that and I love the texture of that especially if it's slightly burnt like the in South America when I visit Buenos Aires I found that at the end of a meal they would take a stake the trimming off the edge of the stake burn it slightly and then serve it back to me and I thought that's disgusting and then I tasted it and it's delightful it is there's nothing quite like it. This goes back to this notion before that we like to live on the edge and we like to do things that we should not be doing and driven but on the other hand look at those muscles. I don't suggest anyone eat pure fat the listeners of this podcast will meet with I'm sure there'll be a YouTube video soon that I like eating pure fat I'm not in on a ketogenic diet etc but but fat is tasty. I'm not even influenced by the obesity problem that exists. We'll talk about that in a little bit about the you know the God brain access I think it will be important to cover it because it's the other side of the taste system. So missing taste one is fat although you clearly highlighted a lot of fat taste in quotation marks is really the feeling of fat rolling on your tongue and so there is a compelling argument that a lot of what we call fat taste. It's really mechanosensory is so much of sensory cells cells they're not responding to taste but they're responding to mechanical stimulation of fat molecules rolling on the tongue that gives you that perception of fat. I love the idea that there is a perception of fat regardless of whether or not there's a dedicated receptor for fat it mostly because it's making evoking sensations and imagery of the taste of slightly burnt fat for for example you and another one you could argue is metallic taste you know I know exactly what it tastes like. You know you ask me to explain it I will have a hard time you know what whether the palettes of that color that can allow me to define it I wouldn't be easy but I know precisely what it tastes like you know take a penny put in your mouth and you know what it tastes like yeah or blood that's another very good example. And is there really you know a receptor for metallic taste or it's nothing but this magical combination of the activation of the existing lines think of it as lines of information just separate lines by the keys of a piano yeah. Sweet sour beat is all too mommy you played a key and you activate a one chord and that one chord in the case of a piano leads to a note you know tune and in the case of taste leads to an action and a behavior. But you play many of them together and something emerges that it's different than any one of the pieces. And it's possible that metallic for example represents the combination of the activity just in the right ratio. Make sure these other lines make sense and it actually provides a perfect the your example the piano provides a perfect segue for what I'd like to touch on next which is. If you would describe the sequence of neural events leading to a perceptual event of taste and I'm certain that somewhere in there you will embed an answer to the question of whether or not we indeed have different taste receptors distributed in different locations on our tongue or elsewhere in the mouth yes. So let's start by by the banking that that all tail and meat who came up with that. There are many views but the most prevalent is that there was an original drawing describing the sensitivity of the tongue to different tastes. So imagine I can take a Q tip this is a thought experiment and I'm going to dip that Q tip in salt and in quainine as something bitter and glucose as something sweet. And I'm going to take that Q tip as you to stick your tongue out and start moving around your tongue and ask you what do you feel. And then I'm going to change the concentration of the amount of salt or the amount of bitter and ask can I get some sort of a map of sensitivity to the different taste. And the argument has emerged is that there is a good likelihood that the data was simply mistranslated as it was being drawn. And of course that led to an entire industry. This is the way you maximize your wine experience because now we're going to form the vessel that you're going to train from so that it acts maximally on the receptors which happened. Now there is no tongue map. All right. We have taste bats distributed in various parts of the tongue so there is a map on the distribution of taste bats. But each taste bat has around a hundred taste receptor cells. And those taste receptor cells can be of five types, sweet sour, bittersalted or umami. And for the most part, all taste bats have the representation of all five taste qualities. Now there's no question that there is a slight bias for some taste like bitter is particularly in reach at the very back of your tongue. And there is a teleological basis for that actually a biological basis for that. That's the last line of defense before you swallow something bad. So let's make sure that the very back of your tongue has plenty of these bad news receptors so that if they get activated, you can trigger a gagging reflex and get rid of this that otherwise may kill you. But the notion that you know all sweeties in the front and soldies on this side, it's not real. And go ahead. Oh, I was just going to ask are there. It's first of all, thank you for disveling that myth. Yes. And we will propagate that information as far and wide as we can. Because I think that's the number one myth related to taste. The other one is, are there taste receptors anywhere else in the mouth? For instance, on the palate, the palate, not the lips. So it's in the far range at the very back of the oral cavity, the tongue and the palate. And the palate is very rich in sweet receptors. I have to pay attention to this the next time I eat something sweet. Yeah, whether whether you pull it up. Yeah. Now, the important thing is that, you know, after the receptors for this fight, the detectors, the molecules that sense sweets, our beets, all too many. These are receptors proteins found on the surface of taste receptor cells that interact with these chemicals. And once they interact, then they trigger the cascade of events biochemical events inside the cell that now sense an electrical signal that says. There is sweet here or there is salt here. Now, having these receptors and my laboratory identify the receptors for all five basic taste classes, sweet bit result to mommy and most recently sour. Now, completing the palate, you can now use these receptors to really map where are they found in the tongue in a very rigorous way. This is no longer about using a q tip and trying to figure out what you're feeling, but rather what you have in your tongue. This is not a guest. This is now a physical map that says the sweet receptors are found here. The bitter are found here. And when you do that, you find that in fact every taste bad. Throughout your oral cavity has receptors for all of the basic taste classes. Amazing. And as it turns out, and I'm sure you'll tell us important in terms of thinking about how the brain computes and codes of decodes. This thing we call taste. I'm going to inject a quick question that I'm sure is on many people's minds before we get back into the biological circuit, which is many people including myself are familiar with the experience of drinking a sip of tea or coffee that is too hot. And burning my tongue is the way I would describe it. Horrible. And then disrupting my sense of taste for some period of time afterward. Yes. When I experience that phenomenon, that unfortunate phenomenon, have I destroyed taste receptors that regenerate or have I somehow used temperature to distort the function of the circuit so that I no longer taste the way I did before. Excellent question. And the answer is both. It turns out that your taste receptors only leave for around two weeks. And this by the way makes sense because here you have an organ, the tongue, that is continuously exposed to everything you could range from the nicest to the most horrible possible things. Yes, you're imagination. And so you need to make sure that these cells are always coming back in a way that I can re-experience the world in the right way. And there are other organs that have the same underlying logic. You're got your intestines are the same way. Amazing. Again, they're receiving everything that you ingest. God forbid what's there. From the spiciest to the most horrible tastings for the most delicious. And again, those intestinal cells whose role is to ultimately take all these nutrients and bring them into the body also renewal in a very, very fast cycle. All factory neurons in your nose is there the example. So then a yes, you're burning a lot of yourselves and it's over for those. The good news is that they're going to come back. But we know that when you burned yourself with tea, they come back within 20 minutes, 30 minutes an hour. And these cells are not renewing that in that timeframe. They're not listening to your needs. They have their own internal clock. And so you are really affecting your damage in them in a way that they can recover. And then they come back and you also damage your somatosensory cells. These are the cells that feel things, not taste things. And then you wait half an hour or so and then my goodness, thank God, it's back to normal. Most of the time, I don't even notice the transition realizing as you tell me. And later I'll ask you about the relationship between odor and taste. But as a next step along the circuit, let's assume I ingest some, let's keep it simple, a sweet taste. Let's make it even simpler. But at the same time, perhaps more informative. Let's compare and contrast sweet and bitter as we follow their lines from the tongue to the brain. So the first thing is that the two of us, they're not two colors that represent polar opposites because they're black and white. They're a polar opposite to one that takes only one thing. They're not one that takes everything. But they don't evoke different behaviors, even the political parties have some over now. Sweet and bitter are the two opposite ends of the sensory spectra. Now a taste can be defined by two features. Again, I'm a reductionist, I'm reducing it in a way that I think it's easier to follow the signal. The two features are its quality and its valence and valence with a little V. That's what we say in Spanish with a V. Means the value of that experience. Or in this case of that stimuli and you take sweet, sweet has a quality and identity and that's what you and I will refer to as the taste of sweet. We know exactly what it tastes like, but sweet also has a positive valence, which makes it incredibly attractive and repetitive. But it's attractive and repetitive as I'll tell you in a second, independent of its identity and quality. In fact, we have been able to engineer animals where we completely remove the valence from the stimuli. So these animals can taste sweet, can recognize it as sweet, but it's no longer attractive. It's just one more chemical stimuli. And that's because the identity and the valence are encoded in two separate parts of the brain. In case of bitter, I can't eat has on the one hand its identity, its quality and you know exactly what bitter taste like. I can taste it now even as you describe it, but it also has a valence and that's a negative valence because it evokes averse behaviors. Are we on? Absolutely. When it comes to mind, I remember telling some kids recently that we're going to go get ice cream and it was interesting, they looked up and they started smacking their lips. They'll actually vote anticipatory response. Absolutely. When we talk about the gut brain, maybe we'll get there. So then the signals, if we follow now these two lines, they're really like two separate keys at the two ends of this keyboard. You press one key and you activate this chord so you activate the sweet cells throughout your oral cavity and they all converge into a group of sweet neurons in the next station, which is still outside the brain is one of the taste ganglia. These are the neurons that innervate your tongue and the oral cavity. Where did they sit approximately? Around there, yeah, right here around there. The lymph nodes more or less. You got it. And there are two main ganglia that innervate the vast majority of all taste buds in the oral cavity. And then from there, that sweet signal goes onto the brain stem. The brain stem is the entry of the body into the brain. And there are different areas of the brain stem and there are different groups of neurons in the brain stem. And there's this unique area in a unique topographically defined location in the rostral side of the brain stem that receives all of the taste input. And there's this dense area of the brain, a very rich area of the brain exactly. And from there, the sweet signal goes to this other area higher up on the brain stem. And then he goes through a number of stations where that sweet signal goes from sweet neuron to sweet neuron to sweet neuron to eventually get to your cortex. And then it gets to your taste cortex. That's where meaning is imposed into that signal. It's then, and only then, this is what the data suggests, that now you can identify this as a sweet stimuli. And how quickly does that all happen? The time scale of the nervous system eats fast. And within less than a second. I rarely mistake bitter for sweet. Maybe with respect to people and my own poor judgment. But not with respect to taste. And in fact, we can demonstrate this because we can stick electrodes at each of these stations conceptually. And then we can stimulate the tongue and then we can record the signals pretty much time log to stimulus delivery. You deliver the stimuli and within a fraction of a second. You see now their response in this following stations. Now it gets to the cortex here. And now in there, you impose meaning to that taste. And area of your brain that represents the taste of sweet in taste cortex. And a different area that represents the taste of bitter. In this instance, there is a topographic map of this taste quality that is inside your brain. Now we're going to do a thought experiment. Now if this group of neurons in your cortex really represents the sense of sweet. And this added different group of neurons in your brain represents the taste, the perception of bitter. Then we should be able to do two things. First, I should be able to go into your brain. Somehow silence those neurons, find a way to prevent them from being activated. And I can give you all the sweet you want. And you'll never know that your taste in sweet. And conversely, I should be able to go into your brain, come up with a way to activate those neurons. Well, I'm giving you absolutely nothing. And you're going to think that you're getting that full person. And that's precisely what we have done and that's precisely what you get. This of course is in the brain of my see. But presumably in humans it would work. Absolutely the same. Zero doubt. I have no question. So this attest to two important things. The first to the predetermined nature of the sense of taste. Because it means I can go to this part of your brain in the absence of any stimuli. And have you throw the full behavioral experience. In fact, when we activate in your cortex these bitter neurons, the animal can start gagging. But it's drinking only water. But the animal thinks that it's getting a bit stimuli. It's amazing. And so, and the second, you have to finish the line so that it doesn't sound like it teaches two things. And then I only give you one lesson. Is that, you know, it substances this capacity of the brain to segregate, to separate in these nodes of action. The representation of these two diametrically opposed bursts, which is sweet, for example, versus bitter. The reason I say amazing, and that is also amazing, is the following. You told us earlier, and you're absolutely correct, of course, that the end of the day, whether or not it's one group of neurons over here and another group of neurons over there. Which is the way it turns out to be. Electrical activity is the generic common language of both sets of neurons. So that raises the question for me of whether or not those separate sets of neurons are connected to areas of the brain that create this sense of valence. Or whether or not they're simply connected, excuse me, to sets of neurons that evoke distinct behaviors of moving towards and inhaling more and licking or aversive. Are we essentially interpreting our behavior and our micro responses or our micro responses and our behaviors, the consequence of the person. Excellent, excellent question. So first the answer is they go into an area of the brain where valence is imposed. And that area is known as the amygdala. And the sweet neurons go to a different area than the bitter neurons. Now, I want to do a thought experiment because I think your audience might appreciate this. Let's say I activate this group of neurons and the animal increases licking and I'm activating the sweet neurons. And so that's expected because now it's tasting this water as it was sugar. Now this is Moses transforming water into wine. In this case, we're going to and today's Passover. So then it's an appropriate example. We're transforming it into sweet. But how do I know? How do I know that activate them is evoking a positive feeling inside a goodness, a satisfaction. I love it. Versus I'm just increasing licking, which is the other option because all we're seeing is that the animal is licking more and we're trying to infer that that means that is feeling something really good versus you know what? That piano line is going back straight into the tongue and all is doing is forcing it to move faster. Well, we can actually separate this by doing experiments that allows to fundamentally distinguish them. And imagine the following experiment. I'm going to take the animal and I'm going to put them inside a box that has two sides. The two sides have features that make them different. One has yellow little toys. The other one has green toys. One has little black stripes. The other one has blue stripes. So the animal can tell the two halves. I take the mouse, put them inside this arena, this play arena, and it will explore and pots around both sides with equal frequency. And now what I'm going to do is I'm going to activate this neurons, the sweet neurons, every time the animal is on the side with the yellow stripes. And if that is creating a positive internal state, what would the animal now want to do? It will want to stay on the side with the yellow stripes. There is no licking here. The animal is not extending its tongue every time I'm activating this neuron. This is known as a place preference test. And it's generally used in just one form of many different tests to demonstrate that the activation of a group of neurons in the brain is imposing, for example, a positive versus a negative valence. Whereas if I do the same thing by activating the bitter neurons, the animal will actively want now to stay away from the side where these neurons are being activated. And that's precisely what you see. And that's precisely what we see. Many people, including myself, are familiar with the experience of going to a restaurant, eating a variety of foods. And then, fortunately, it doesn't happen that often, but then feeling very sick. I learned coming up in neuroscience that this is one strong example of one trial learning that from that point on, it's not the restaurant or the waitress or the waiter or the date. But it's my notion of it had to have been the shrimp. That leads me to then want to avoid shrimp in every context, maybe even shrimp powder. You got it for a very long time. I can imagine all the adapt evolutionarily adaptive reasons why this such a phenomenon would exist. Do we have any concept of where in this pathway that exists? We do. We know actually a significant amount at a general level. In fact, more than shrimp oysters are even a more dramatic example, one bad oyster. It's all you need to be driven away for the next six months. I think because the texture alone is something that one learns to overcome. I actually really enjoy the oysters. I despise muscles. I despise shrimp, not the animal, but the taste. And yet oysters for some reason I've yet to have a bad experience. It's like, it's like, Ooni, by the way, you know, texture is hard to get over. But once you get over, it's delicious. That's what they tell me. We were both in San Diego at one point and I'll give a club just sushi Oda is kind of the famous good old. And they have amazing Ooni and I've tried it twice and it's an over two. It's somehow the texture outweighs any kind of the deliciousness that people require. It's a very acquired taste. It's like beer. You know, if you I grew up in Chile, that's where the accent comes from in case anyone wondered. And you know, by the time I came here to graduate school, I was 19, too old to, you know, overcame my heavy Chilean accent. So here I am for the years, 50 years late, not quite. We are the class. And I still sound like I just came off the boat. So in Chile, you don't drink beer when you're young. You drink wine. You know, Chile is a huge wine producer. So when I came to the US, all of my classmates, you know, were drinking beer because they, you know, they had finished college where they were all, you know, you're drinking and you know, graduate school. You're working 18 hours a day every day the way they, you know, relax. Let's go and have some beers and beer is cheaper and beer is cheap and we were being clearly underpaid. Yeah. I couldn't do it. It's an acquired taste. It was too late by then. And here I am, you know, 60 plus. And if you take all the beer I've drunk in my entire life, I would say they add to less than an eight ounce glass of water. Impressive. Well, your health is probably better for it. I'm not sure. Your physical health. So, you know, it goes back to, you know, acquire taste. This is the connection to uni and to oysters. Now going back to the one trial learning. You know, this is the great thing about our brains. Certain things we need to repeat a hundred times to learn them. Hello operator. Can I have the phone number for sushi otta please and then she'll give it to you over the phone, at least in the old days. And then you need to repeat it to yourself over and over and over over the next minute so you can dial sushi otta. And five minutes later, it's gone. That's what we call working memory. Yeah, then there is the short term memory. Yeah, we park our car. And if we're lucky by the end of the day, we remember where it is. And then there is the long term memory. We remember the bird days of every one of our children for the rest of our lives. Well, there are events that a single event is so traumatic. Yeah, that it activates the circuits in a way that it's a one trial learning and the taste system is literally at the top of that food chain. And there is a phenomenon known as condition taste a version. You can pair an attractive stimuli with a really bad one. And you can make an animal begin to vehemently dislike, for example, sugar. And that's because you've conditioned the animals to now be averse to this otherwise nice days because it's been associated with malaise. And when you do that, now you can begin to ask why does change in the signal as it travels from the tongue to the brain in a normal animal versus an animal where you have now transformed sweet from being attractive to be never is. And this is the way now you begin to explore how the brain changes the nature, the quality, the meaning of a stimuli as a function of its state. But a number of questions related to that all of which relate to this idea of context because you mentioned before that flavor is distinct from taste because flavor involves smell texture, temperature, some other features. And I can only see it's an example of I can sense the texture. It actually now I won't describe what it reminds me of for various reasons. The ability to place context into to insert context into a perception or rather to insert a perception into context is so powerful. And there's an element of kind of mystery about it. But if we start to think about some of the more nuance that we like to live at the edge as you say. How many different tastes some taste dial to go back to your analogy earlier the color dial do you think that there could be for something as fixed as bitter. So for instance, I don't think I like bitter taste but I like some fermented foods that seem to have a little bit of sour and have a little bit of that briny flavor. How much plasticity do you think there is there and in particular across the lifespan because I think one of the most salient examples of this is that kids don't seem to like certain vegetables but they all are hardwired to like sweet taste. And yet you could also imagine that one of the reasons why they may eventually grow to incorporate vegetables is because of some knowledge that vegetables might be better for them. So is there a change in the receptors, the distribution, the number of the sensitivity, et cetera, they can explain the transition from wanting to avoid vegetables to being willing to eat vegetables. Simply in childhood to early development. I want to take the question slightly differently but I think it would illustrate the point. And I want to just use the difference between the olfactory system and the taste system to make the point. Taste system, five basic palettes, sweets, our beer sold at mommy, each of them has a predetermined identity. We know exactly what the and valence these are attractive. These are aversive. In the olfactory system, it's claimed that we can smell millions of different others. Yet for the most part, none of them have an innate predetermined meaning. In the olfactory system, meaning is imposed by learning and experience, even the smell of smoke. So I'm going to give you, I'm going to make it differently. They are a handful of the millions of others that were claimed that you could immediately tell me these are aversive and these are attractive. So vomit, it's not correct because I can assure you that their cultures and societies were things which are far less appealing than vomit, do not evoke an aversive reaction. So, sulfur would be maybe a universal. I'm not talking pheromones. Pheromones are in a different category that trigger innate responses. But nearly every other is afforded meaning by learning and experience. And that's why you like broccoli and I despise broccoli because I remember my mother forcing me to eat broccoli. Same sensory experience. This accommodates two important things. In the case of taste, you have neurons at every station that are for sweet, for sour, for bitter, for salty, and umami. It's only five classes. So it's not going to take a lot of your brain. If we can infect smell a million others and everyone else of others had to have predetermined meaning, there's not going to be enough brain just to accommodate that one sense. And so evolution in its infinite wisdom, evolve a system where you put together a pathway and a cortex of factory cortex where you have the capacity to associate every other. In a specific context that now gives it the meaning. Now, let's go back to the original question then. So, other than clearly plastic, mega plastic because it's it's fundamental basis and neural organization. But taste we just told you that's you know predetermined hard wire but predetermined hard wire doesn't mean that's not modulated by learning or experience. It only means that you're born like in sweet and this like in bitter. And we have many examples of plasticity beer being one example. So why do we learn to love beer is in a coffee is because it has an associated gain to the system. And that gain to the system that positive valence that emerges out of that negative signal is sufficient to create that positive association. And in the case of beer of course is alcohol. The feeling good that we get after is more than sufficient to say I want to have more of this. And in the case of coffee of course is cafe in activating a whole group of neurotransmitter systems that give you that that high associated with coffee. So yes, this is changeable it's malleable and is subjected to learning and experience. I like the factory system is restricted in what you could do with it because it's goal is to allow you to get nutrients and survive. The goal of the factory system is very different is being used not in our case but in every admiral species to you know identify friend versus foe to identify mate. To identify ecological niches they want to be in so it plays a very broad role that then requires that it be set up organized and function in a very different type of context. So this is about can we get the nutrients we need to survive and can we ensure that we are attracted to the ones we need and we are versed to the ones that are going to kill us. And being over this implicit and reductionist but I think it illustrates a huge difference between these two key more sensoresist. I don't think it would be overly simplistic I think it illustrates that the key and tractable nature of this system and the way you've approached it and I think it's important for people to hear that because everybody as we are mystified with empathy and love etc. So in fairness to that I'm going to ask a sort of high level question or abstract question so it's based on a conversation I had with a former girlfriend where we're talking about chemistry between individuals. Very complicated topic on the one hand but on the other hand quite simple in that certain people for whatever reason evoke a tremendous sense of arousal for lack of a better word between two people one would hope. At least for some period of time. I didn't know this was that kind of a podcast. No well the reason I go but this has to do with taste because she said something I think in part to maybe irritate me a bit but we were commenting not about our own experience of each other but of someone that she was now very excited about we're on good terms. And she said what do you think it is this thing of chemistry so maybe she was trying to you know warn you what's coming warn me what's coming and she said I have a feeling something about it is in smell. And something about it is actually in taste literally the taste of somebody's breath that's the way she described it and I thought that it was a very interesting example for a number of reasons but in particular because it gets to the merging of odor and taste but also to the idea that of course the context of a new relationship I'm assuming that in fact they're both attractive people et cetera there's a whole context there but I've had the experience of the odor of somebody's breath being aversive not because I could identify it as aversive because you like it because it just didn't like it but that's because you also see it with others that trigger that negative you know a very steep reaction by the way absolutely there are certain particular to me that are aversive you got it and there are there are other sense in can recall sense of skin of foods et cetera that are immensely repetitive so I could I've experienced both sides of this equation myself and she was describing this and to me more than tasting wine which is the typical example where people inhale it and then they drink it to me this seems like something that more people might be able to relate to that certain things and people smell delicious even mothers describing the smell of their babies mother of course I mean you know our own babies when they're next that's the magic out place the back of their neck there you go oh my goodness I have a grand child now so I know exactly what Rio that's his name smells like okay so more beautiful examples always more fun to think about the beautiful positive the repetitive examples the smell of the back of your grandson's neck yes I mean you couldn't you could get more specific but not a lot more so what is going on in terms of the combination of odor and taste given that these two systems are so different yes and and they come together ultimately there is a place in the brain where they come together to integrate the two into what we would call you know that sensory experience and I'll tell you an experiment that you could do that demonstrates this I think in I think it's good for the you know for for your audience you have to get a sense of how we approach these problems so that we can get in a meaningful scientific answer so we know where the olfactory cortex is in the brain we know where the taste cortex is in the brain there in two different places we can go to each of these two cortices put color traces we put green in one we put red in the area and we see where the colors go to that's a reflection of where those neurons are projection a projecting tool into their next targets once they get the signal where do they send the signal tool and then we reason that if other and taste come together somewhere in the brain we should find an area that now it's getting red and green color and we found such an area and next we anticipate it we hypothesize that maybe this is the area in the brain of the mouse corresponding area in the brain of humans that integrates other and taste it's known this the term normally uses multi sensory integration and if this is true we could do the following experiment we can train a mouse to click sweet and if they guess correctly that that is supposed to be sweet they should go now to the right port to the right side to get a water reward if they go to the lift when he was sweet then they're incorrect and they get no reward and they actually get a time out now the mice are thirsty so they're very motivated to perform and if you repeat this task a hundred times a hundred trials incredibly now this animal learn to recognize the sweet and execute the right action and by their action we now are being told what that animal is tasting we can make it more interesting and we can give him sweet and bitter and say if he's sweet go to the right and he's bitter go to the left and after you train him this mice with 90% accuracy will tell you when you randomize now the stimuli what was sweet and what was bitter we can now do the same experiment but now mix taste with order and say if you got order alone go to the right or push this lever in mice if you get taste alone go to this other part or push this other lever and if you get it to together do this something else and if you train the mice the mice are able now to report back to you when he's sensing taste alone order alone or the mix make sense now we can go to the brain of this mice and go to this area that we now uncover discover as being the site of multi-sensory integration between taste and order and silence it prevent it from being activated experimentally and if that area really represented the integration of these two the animals should still be able to recognize the taste alone they still should be able to recognize the order alone but should be incapable now to recognize the mix and exactly as predicted that's exactly what you get the brain is basically a series of engineering circuits complex you got it and our task is to figure out how can we extract this amazing architecture of these circuits in a way that we can begin to uncover the mysteries of the brain and why certain people's breath tastes so good and other people's not so good so I never answer that by the I told you how we can figure out where in the brain is happening as we've been having this discussion I thought a few times about similarities to the visual system or differences to the visual system the visual system there are a couple of phenomenon that I wonder if they also exist in the taste system and the visual system we know for instance that if you look at something long enough and activate the given receptors long enough that object will actually disappear we offset this with little micro-imew and so on but the principle is a fundamental one this habituation or desensization everyone seems to call it something different but you get the idea of course in the taste system I'm certainly familiar with eating something very very sweet for the first time in a long time and it tastes very sweet but a few more licks a few more bites and now it tastes not as sweet with old faction I'm familiar with the odor in a room I don't like or I like and then it disappearing so similar phenomenon where does that occur and can you imagine a sort of system by which people could leverage that because I do think that most people are interested in eating not more sugar but less sugar and then we have better ways to approach that and we can transition from taste into these other circuits that makes sugar so extraordinarily impossible not to consume impossible exactly so where does this this the sensitize in happens that's the term that we use it and it's I think it happening at multiple stations it's happening at the receptor level i.e. the cells in your tongue that are sensing that sugar as you activate this receptor and it's triggering activity after activity after activity eventually you exhaust the receptor again I'm using terms which are extraordinarily loose for the sake of the discussion the receptor gets to a point where he undergoes a set of changes chemical changes where it now signals far less efficiently or it even gets removed from the surface of the cell and now what will happen is that the same amount of sugar will trigger far less of a response and that is a huge side of this modulation and then the next I believe is the integrated again loss of signaling that happens by continuous activation of the circuit at each of these different neural stations you know there is from the tongue to the ganglia from the ganglia to the first station in the brainstem a second station in the brainstem to the thalamus then to the cortex so there are multiple steps that this signal is traveling now you might say why this is a label line why do you need to have so many stations and that's because the taste system is so important to ensure that you get what you need to survive that it has to be subjected to modulation by the internal state and each of these nodes provides a new side to give it plasticity and modulation not necessarily to change the way that something tastes but to ensure that you consume more or less or different or differently of what you need I'm going to give you one example of of how the internal state changes the way the taste system works Salt is very appetitive at low concentrations and that's because we need it it's our electrolyte balance requires salt every one of the neurons uses salt as the most important of the ions you know with potassium to ensure that you can transfer these electrical signals within and between neurons but at high concentrations let's say ocean water is incredibly aversive and we all know this because we go into the ocean and then when you get in your mouth it's not that great however if I sold the prime view and we can do this in experimental models by readily now this incredibly high concentration of salt one molar sodium chloride becomes amazingly appetitive and attractive what's going on in here your tongue is telling you this is horrible but your brain is telling you I don't care you need it and this is what we call the modulation of the taste system by the internal state presumably if one is hungry enough even une will taste good just get right on the money no no this is exactly correct or if you're thirsty and hungry you suppress hunger so that you don't waste water molecules in digestion food why because if you're thirsty and you have no water you will die within a week or so but you can go on a hunger strike as long as you have water for months because you're going to eat up all your energy reserves water is a different story so you could see or that there are multiple layers at which the taste system that guides you know our drive and our motivation to consume the nutrients we need has to be modulated in response to the internal state and of course internal state itself has to be modulated by the external world and so that I think is a reason why what could otherwise would have been an incredibly simple system from the tongue to the cortex in one yes wire it's not because you have to ensure that you know each step you give the system that level of flexibility or what we call neuroscience plasticity I think we're headed into the gut but I have a question that has just been on my mind for a bit now because I was drinking this water and it has essentially no taste yes is there any kind of signal for the absence of taste despite having something in the mouth and here is why I ask what I'm thinking about is saliva and while it's true that if I eat a lot of very highly palatable foods that does change how I experience more bland foods I must confess when I eat a lot of these highly processed foods I don't particularly like them I tend to crave healthier foods but that's probably for contextual reasons about nutrients etc but I could imagine an experiment where you see a taste of no taste right is there a taste of no taste because in the visual system there is you close the eyes and you start getting increases in activity in the visual system as opposed to decreases which often surprises people but there are reasons for that because everything is about signal to noise signal to background and it's a good question I can tell you that most of our work is trying to focus on how the taste system works not how it doesn't work well but you know yes I know you're being playful and I knew when inviting you here to now setting myself up for actually on a different we're trying to learn things I know however all right listen I was weaned in this system of and I'll say it here for the second actually I recorded a podcast recently with a very prominent podcast at Lex Friedman podcast and I made reference to the so called New York neuroscience mafia I won't say whether or not we are sitting in the presence of the New York neuroscience mafia member but in any event I know the sorts of a ribbing that they provide for those listening this is the kind of hazing that happens benevolent hazing in academia I'm the target of course it's it's the it's a sign of love exactly it's going to tell me that and it's always about this science in the right but it's an interesting question look I am I don't know the answer and and I don't even know how I would explore it in a way that you will rigorously teach me it but in here let me tell you why I'm asking and then I'll offer an experiment yes that I'd love to see someone here to do I'm thinking about saliva yes which it's no no but that we know that we can figure it out but the question is whether or not the saliva in a fed state is distinct from the saliva in an unfed state such that it modulates it's not the sensitive that experiment has been done no it has been done yeah and so the answer is no it's not yeah and you and the way you could do the experiment is because we use artificial saliva there's such a thing I know there's a lot of different things but no no we I don't mean that you go to Walgreens that you get I mean we my laboratory we know the composition of saliva and so you can make such a thing and and and you can take you know taste cells in culture or in a tongue where you wash it out of and then you can apply artificial saliva and what happens is that the system is being engineered to decensitize to become a agnostic for saliva to become invisible and there is no difference on the state of the animal this is the reason to do experiments yeah absolutely so it doesn't defeat any grand hypothesis it's just a pure curiosity so you know that curiously killed the cat I do but saves the career of a scientist every single time that drives us absolutely every single story of our lives exactly okay so if it's not saliva and apparently it is not what about internal state and what aspects of this internal milieu are relevant because there's autonomic there's a sleep and awake there's stress one of the questions that I got from hundreds of people when I saw the questions in advance of this episode was why do I crave sugar when I'm stressed for instance and that could be contextual but what are the basic it makes us feel good by the way we'll get to that so that's the answer so that it activates what I'm going to generically refer to as reward for centers in a way that it dramatically changes our internal state this is in a why do we eat a gallon of ice cream when we're very depressed yeah in fact this is a good way to go into the into into this an entire different world yeah of the body telling your brain what you need in in in in important things like sugar and fat yeah okay by anyways go ahead you are going to ask something well no I I would like to discuss the most basic elements of internal state in particular the ones that are below our conscious detection and this is a of course is a segue into this incredible landscape which is the gut brain axis which I think 15 years ago was almost a maybe it was a closer to the meeting and then now I believe you you and others there companies there have companies there are active research programs there's and beautiful work maybe you could describe some of that work that you and others have been involved in and a lot of the listeners of this podcast will have heard of the gut brain axis and there are a lot of misconceptions about the gut brain axis many people think that this means that we think with our stomach because of the quote unquote gut feeling yes aspect but I'd love for you to talk about the aspects of gut brain signaling that drive our per change our perceptions and behaviors that are completely beneath our awareness yes excellent so let me begin maybe by by stating that you know the brain needs to monitor the state of every one of our organs organs it has to do it this is the only way that the brain can ensure that every one of those organs are working together in a way that we have healthy physiology now this monitoring of the brain has been known for a long time but I think what hadn't been fully appreciated that this is a two way highway where the brain is not only monitoring but is now modulating back what the body needs to do and that includes all the way from monitoring the frequency of heartbeats and the way that inspiration and aspirations in the breathing cycle operate to what happens when you ingest sugar and fat now let me give you an example again of of aim of how the brain can take what we would refer to contextual associations and transform into incredible changes in physiology and metabolism remember Pavlov so Pavlov in his classical experiments in conditioning you know associated conditioning he would take a bell it will ring the bell every time he was going to feed the dog and eventually the dog learned to associate the ringing of the bell with food coming now the first incredible finding in maybe is the fact that the dog now in the presence of the bell alone will start to celebrate and we will call that you know neurologically speaking an anticipatory response okay I could understand it I get it you know news in the brain that form that association now represent food is coming and they're sending a signal to more neurons to go into your salivary glands to squeeze them so you release you know in our saliva because you know food is coming but what's even more remarkable is that those animals are also releasing insulin in response to a bell okay this illustrates one part of this two way highway the highway going down somehow the brain created these associations and their neurons in your brain now that no food is coming and send a signal somehow all the way down to your pancreas then now it says release insulin because sugar is coming down all right this goes back to the magic of the brain it's a never ending source of both joy and intrigue how the hell do they do this okay I mean the neurons I share it I share your delight in fascination there's not a day or a lecture or some talks are better than others or talk where I don't sit back and just think it's absolutely how do you know over the past I know dozen years it and with great force over the last five years now the main highway that is communicating the state of the body with the brain it has been and cover as being what we now refer to as the gut brain axis and the highway is a specific bundle of nerves you know which emerge from the Vega ganglia the nodos ganglia and so is the Vega snare that it's innovating the majority of the organs in your body it's monitoring their function sending a signal to the brain and now the brain going back down and saying this is going all right do this or this is not going to well do that and I should point out as you well know every organ spleen pancreas long mass they all must be monitor other in fact you know I now I have no doubt that the thesis that we have normally associated with metabolism physiology and even immunity are likely to emerge as the thesis conditions state of the brain I don't think obesity is a disease of metabolism I believe obesity is a disease of brain circuits I do as well yeah and and so and so this this this is view that we have you know been working on for the longest time because you know the molecules that were dealing with are in the body not in the head you know led us to you know to view of course this issues and problems has been one of metabolism physiology and so forth they remain to be the carriers of the ultimate signal but the brain ultimately appears to be the conductor of this orchestra of physiology and metabolism all right now let's go to the get brain and sugar may please please I mean the the Vegas nerve has in popular culture has been kind of converted into this single meaning of calming pathways mostly because I actually have to tip my hat to the yogic community was among the first to talk about Vegas on and on and on it there are calming pathways of you know so-called parasympathetic pathways within the Vegas but I think that the more we learn about the Vegas the more it seems like an entire set of neural connections as opposed to one nerve just wanted to just mention that because I think a lot of people have heard about the Vegas turns out experimentally in the laboratory many neuroscientists will stimulate the Vegas to create states of alertness and arousal when animals or even people believe it or not are close to dying or going into coma stimulation of the Vegas is one of the ways to wake up the brain and counter to the idea that it's just a site way of calming oneself down and also of course I mean what one has to be cautious there in that so the the the Vegas nerve is made out of many thousands of fibers you know individual fibers that make this gigantic bundle and it's likely as we're speaking that each of these fibers carries a slightly different meaning they're not necessarily one by one maybe five five or 10 five or 20 to the all right but they carry meaning that's associated with their specific task this group of fibers is telling the brain about the state of your heart this group of fiber is telling the brain about the state of your gut this is telling your brain about its nutritional state this your pancreas this your langies and they are again to make the same simple example the keys of this piano yes you're right there is a lot of data showing that activating the entire Vegas bundle has very meaningful effects in a wide range of conditions in fact it's being used to treat untractable depression those stimulator api-laptic seizures but again there are thousands of fibers carrying different functions so to some degree in a this is like turning the lights on the stadium because you need to illuminate where you lost your keys under your seat yet 10,000 balls of a thousand watts each of just come on only one of this is pointing to where and so I'm lucky enough that one of them happened to point to my side so here you activate the bundle thousands of fibers I'm lucky enough that some of those happen to do something to make a meaningful difference in depression or to make a meaningful difference in api-laptives but it should not be missed on the school as arguing that this broad activation has any type of selectivity or specificity where yes lucky enough that among all the things are being done some of those happen to change the biology of this process now the reason this is relevant because the magic of this God brain access is the fact that you have these thousands of fibers really doing different functions and our goal and along with many other great scientists including Steve Libertless that started a lot of this molecular dissection on this vague Al-Gad brain communication line at Harvard is trying to uncover why there are each of those lines doing what are each of those keys of this piano playing what's the latest there just as a brief update I know see been really some I think I was there when he got his Howard Hughes and I did not so that was fun always great is to get beat by excellent people first of all I'm happy you did and because that way you can focus on these amazing both of us that's very gracious of you it's always feels better it's not good to get beat out by excellent people Steven Steven is in his second to none and he is defining as you said the molecular constituents of different elements of these many many fibers is there an update there are they finding multiple parallel pathways they are they are some set control hard beat some that control the respiratory cycle some of my being involved in a gastric movement you know this notion that you are full and you feel full in part because your God gets distended your stomach for example and then there are little sensors that are reading that and telling the brain your full yeah yeah so the text will soon change on the basis of the leverlies and other work in essence I think we are learning enough about this this lines that could really help put together this this holistic view of you know how the brain it's truly changing body physiology metabolism and immunity the part that hasn't been yet developed and that it needs a fair amount of work but it's an exciting thrilling you know during your discovery is how the signal comes back to now change that biology you know the example I gave you before with Pablo's dog I figure out you know how the association created this link between the bell but then how does the brain tell the pancreas to release in the right amount of insulin okay so tell me tell me let me tell you about the God brain axis and our insatiable appetite for sugar and fat insatiable for sugar and quenchable for fat and this is a story about the fundamental difference between liking and wanting liking sugar is the function of the taste system and it's not really liking sugar is liking sweet wanting sugar our never ending appetite for sugar is the story of the God brain axis liking versus wanting and this work is work of my own laboratory you know that began long ago when we discovered the sweet receptors and you can now engineer mice that lack these receptors so in essence this animals will be unable to taste sweet alive without sweetness or or and if you give a normal mouse a bottle containing sweet and we're going to put either sugar or an artificial sweetener alive they bother sweet they have slightly different tastes but that simply because artificial sweeteners have some of tastes but as far as the sweet receptor is concerned they both activate the same receptor trigger the same signal and if you give an animal an option of a bottle containing sugar or a sweetener versus water this animal will drink 10 to 1 from the bottle containing sweet that's the taste system animal goes samples each one leaks a couple of leaks and then say that's the one I want because it's a petitive and because I love it to it prefers sugar to artificial sweetener no no no no no no no no this experiment this experiment this experiment I'm going to put only sweet in one bottle and it could be either sugar or artificial sweetener that's a matter of which one okay we're going to do the next experiment where we separate us to for now is sweet versus water versus water. Okay. And sweet means sweet, not sugar. Sweet means anything that tastes sweet. All right. And sugar is one example and splendor is another example. Aspartane, monk, free. All right. Yeah. It doesn't matter. Yeah. I mean, there's some that only humans can taste. Mice can not taste because their receptors between humans and mice are different. But we have put the human receptor into mice, we engineer mice, and we completely humanize this mouse's taste world. All right. But for the purpose of this conversation, we're only comparing sweet versus water. An option, my goodness, they will leak to no end up from the sweet side. Okay. 10 to 1 at least versus the water. Make sense? All right. Now we're going to take the mice and we're going to genetically engineer it to remove the sweet receptors. So this mice no longer have in their oral cavity any sensors that can detect sweetness, be that sugar molecule, be the artificial sweetener, be it anything else that tastes sweet. I need you give this mice an option between sweet versus water, sugar versus water, artificial sweet versus water. It will drink equally well from both because it cannot tell them apart, because it doesn't have the receptors for sweet so that sweet bottle tastes just like water. Make sense? Make sense. Very good. Now we're going to do the experiment with sugar. From now on, let's focus on sugar. So I'm going to give a mouse a sugar versus water. Normal mouse will drink from the sugar, sugar, sugar, sugar, very little from the water. Know how the sweet receptors eliminate them. Mouse can no longer tell them apart and they will drink from both. But if I keep the mouse in that cage for the next 48 hours, something extra ordinary happens when I come 48 hours later and I see what the mouse is leaking or drinking from. The mouse is drinking almost exclusively from the sugar bottle. How could this be? He cannot taste it. Doesn't have sweet receptors. During those 48 hours, the mouse learn that there is something in that bottle that makes me feel good. And that is the bottle I want to consume. Now how does the mouse identify that bottle? It does so by using other sensory features. The smell of the bottle, the texture of the solution inside, sugar, the high concentrations is kind of goopy. The sadness in which the bottle is in the cage. It doesn't matter what. But the mouse realized there is something there that makes me feel good and that's what I want. And that is the fundamental basis of our unquenchable desire and our craving for sugar and is mediated by the gut brain access. The first clue is that it takes a long time to develop. Immediately suggesting a post-injustive effect. So we reason if this is true and it's the gut brain access that's driving sugar preference, then there should be a group of neurons in the brain that are responding to post-injustive sugar. And lo and behold, we identify a group of neurons in the brain that does this and these neurons receive their input directly from the gut brain access from other neurons. You got it. And so what's happening is that sugar is recognized normally by the tongue, activates an repetitive response. Now you ingest it. And now it activates a selective group of cells in your intestines that now send a signal to the brain via the vagal ganglia. That says, I got what I need. The tongue does it know that you get what you need. It only knows that you tasted it. This knows that you get to the point that it's going to be used, which is the gut. And now it sends the signal to now reinforce the consumption of this thing because this is the one that I needed. Sugar, source of energy. And are these neurons in the gut? So these are not neurons in the gut. So these are gut cells that recognize the sugar molecule. See send the signal and that signal is received by the vagal neuron directly. Got it. And this sends a signal through the gut brain access to the cell bodies of these neurons in the vagal ganglia. And from there to the brain stem to now trigger the preference for sugar. Two questions. One, you mentioned that these cells that detect sugar within the gut are actually within the intestine. You didn't say stomach, which surprised me. I always think gut as stomach, but of course, intestine because that's where all the absorption happens. So you want the signal. You see, you want the brain to know that you had successful ingestion and breakdown of whatever you consume into the building blocks of life. And glucose, amino acids, fat. And so you want to make sure that once they are in the form that intestines can now absorb them, is where you get the signal back saying this what I want. Okay. Now let me just take it one step further. And this now sugar molecules activates this unique gut brain circuit that now drives the development of our preference for sugar. Now a key element of this circuit is that the sensors in the gut that recognize the sugar do not recognize artificial sweeteners at all. Well, because their nutrient value is uncoupled from the taste. Generically speaking, one can make that by this because it's a very different type of receptor. I see turns out that it's not the tongue receptors being used in the gut. It's a completely different molecule that only recognizes the glucose molecule, not artificial sweeteners. This has a profound impact on the effect of ultimately artificial sweeteners in curving our appetite, our craving, our insatiable desire for sugar. Since they don't activate the gut brain axis, they'll never satisfy the craving for sugar like sugar does. And the reason I believe that artificial sweeteners have failed in the market to curve our appetite, our need, our desire for sugar is because they beautifully work on the tongue, they like to recognize sweet versus non-sweet, but they fail to activate the key sensors in the gut that now inform the brain. You got sugar, no need to crave anymore. So the issue of wanting, can we relate that to a particular set of neurochemicals upstream of... So the pathway is... So glucose is activating these cells in the gut through the vagus that's communicated through the presumably the nodos ganglion and up into the brainstem. Very good. And from there where does it go? Yeah, where is it going? What is the substrate of wanting? Of course, I think molecules like dopamine, craving, there's a boat even called the molecule of more, et cetera, et cetera. Dopamine is a very diabolical molecule, as you know, because it evokes both a sense of pleasure-ish, but also a sense of desiring more of craving. So if I understand you correctly, artificial sweeteners and I agree are failing as a means to satisfy sugar craving at the level of nutrient sensing. And yet, if we trigger this true sugar evoked wanting pathway too much, and we've all experienced this, then we eat sugar and we find ourselves wanting more and more sugar. Now that could also be insulin dysregulation, but can we uncopple those? Yeah, I mean, look, if we have a mega problem with over-consumption of sugar and fat, in we're facing a unique time in our evolution where the diseases of malnutrition are due to over-nutrition. I mean, how nuts is that? I mean, historically, the diseases of malnutrition have always been linked to under-nutrition. And so we need to come up with strategies that can meaningfully change the activation of these circuits that control our wanting, certainly in the populations at risk. And this gut brain circuit that ultimately, you know, it's the lines of communication that are informing the brain, the presence of intestinal sugar in this example. It's a very important target in the way we think about. Is there a way that we can minimally modulate these circuits? So I make your brain think that you got satisfied with sugar, even though I'm not giving you sugar. So that immediately raises the question, are the receptors for glucose in these gut cells susceptible to other things that are healthier for us? That's very good. Excellent idea. And I think an important goal will be to come up with a strategy and identify those very means that allow us to modulate the circuits in a way that, certainly for all of those, where this is a big issue, it can really have a dramatic impact in improving a human health. I could be wrong about this and I'm happy to be wrong. I'm off and wrong. And told I'm wrong that we have cells within our gut that don't just sense sugar glucose, which to be specific, but also cells within our gut that sense amino acids and fatty acids. I could imagine a scenario where one could train themselves to feel immense amounts of satiety from the consumption of foods that are rich in essential fatty acids, amino acids, perhaps less caloric or less insulin dysregulating than sugar. I'll use myself as an example. I've always enjoyed sweets, but in the last few years, for some reason, I've started to lose my appetite for them probably because I just don't eat them anymore. At first, that took some restriction. Now, I just don't even think about it. Yeah, and you're not reinforcing the circuits. And so your innocence are moving yourself, but you tend to be the exception. We have a huge, a huge, incredible large number of people there being continuously exposed to highly processed foods. And hidden, so-called hidden sugars. They don't even have to be hidden. It's right there. Hiding in plain sight. Yeah, I agree so much is made of hidden sugars that we often overlooked that they are. They're also the overt. We can have a long discussion on the importance of coming up with strategies that could meaningfully change public health when it comes to nutrition. But I want to go back to the notion of this brain centers that are ultimately the ones that are being activated by this essential nutrients. So sugar, fat and amino acids are building blocks of our diets. And this is across all animal species. So it's not unreasonable then to assume that dedicated brain circuits would have evolved to ensure their recognition, their ingestion, and the reinforcement that that is what I need. And indeed, animals evolve these two systems. One is the TAE system that allows you to recognize them and trigger these predetermined, hard wire immediate responses. Oh my goodness, this is so good, it's so sweet. I personally have a sweet tooth, my eye out. And oh my god, this is so delicious, it's fatty or umami recognizing the amino acids. So that's the liking part, well, yeah. But in the wisdom of evolution, that's good but doesn't quite do it. You want to make sure that these things get to the place where they're needed. And they're not needed in your tongue. They're needed in your intestines where they're going to be absorbed as the nutrients that will support life. And the brain wants to know this. And he wants to know it in a way that he can now form the association between that that I just tasted is what got where it needs to be. And he makes me feel good. And so now next time that I have to choose, what should I eat? That association now guides me to that's the one I want. I want that fruit, not that fruit. I want those leaves, not those leaves. Because these are the ones that activate the right circuits that ensure that the right nutrients got to the right place until the brain. This is what I want and need. Are we on? We're on. One thing that intrigues me and puzzles me is that this effect took a couple of days at least in mice. Yes. And the sensation, sorry, the perception of taste is immediate. It's immediate. And yet this is a slow system. And so it's a beautiful way, but in a kind of mysterious way, the brain is able to couple the taste of a sweet drink with the experience of nutrient extraction in the gut. Under a context where the mouse and the human is presumably ingesting other things, smelling other mice, smelling other people, that's incredible. Yeah, but you have to think of it, not as as humans. Remember, we inherited the circuits of our ancestors and they threw evolutionary from their ancestors. And we haven't had that many years to have fundamentally changed in many of these hard wire circuits. So forget as humans. Let's look at animals in the wild, okay? Which is easier now to comprehend the logic. You know, why should this take a long time of continuous reinforcement, given that I can taste it in a second? You want to make sure that this source of sugar, for example, in the wild, is the best. Is the riches. Is the one where I get the most energy for the least amount of extraction. The least amount of work. I want to identify which sources of sugar. And if the system simply responds immediately to the first sugar that gets to your gut, you're going to form the association with those sources of food, which are not the ones that you should be eaten from. Don't fall in love with the first person you encounter. Oh my goodness, exactly. And so evolutionarily, by having the taste system given you the immediate recognition, but then by forcing this gut brain access to reinforce it only when sustained in a repeated exposure as in form the brain. This is the one you don't want to form the association before. And so when we remove it from the context of we know we just go to the supermarket. We're not hunting there in the wild where I need to form. And so what's happening is that highly processed foods are hijacking, co-opt in the circuits in a way that we would have never happened in nature. And then we not only find these things repetitive and palatable, but in addition, we are continuously reinforcing the wanting in a way that, oh my god, this is so great. What do I feel like eating? Let me have more of these. You've just forever changed the way that I think about supermarkets and restaurants. There are understanding this fast signaling and this slower signaling and the utility of having both makes me realize that supermarkets and restaurants are about the most unnatural thing for our system ever. Almost the equivalent of living in small villages with very few suitable mates versus online dating for instance. I'm not going to make a judgment call there because they do serve an important purpose. I like restaurants too. And so do supermarkets than God. I think they're not the culprits. I think the culprits of course are reliance on foods that are not necessarily healthy. Now going back to the supermarket, the food. Don't fall in love with the first. You take a tangerine and you take an extract of tangerine that you used to cook that spike, let's say with sugar. And you equalize in both where they both provide the same amount of calories. If you eat them both, they're going to have a very different effect in your gut brain access and your system. Once you make the extract and you process it and you add it process sugar, you know, to use it now to cook, to add, to make it really sweet tangerine thing. Now you're providing now a fully ready to use broken-down source of sugar. In the tangerine, that sugar is mixed in the complexity of a whole set of other chemical components. Fiverr, long chains of sugar molecules that need a huge amount of work by your stomach, your gut system to break it down. So you're using a huge amount of energy to extract energy. And the balance, it's very different that when I take this process, highly extracted tangerine, by the way I used tangerines because I had a tangerine yesterday before it came in delicious. They are delicious. And so, and so this goes back to the issue of supermarkets. And so to some degree, you know, a, giving a choice, you don't want to eat processed, highly processed foods because everything is already been broken down for you. And so your system has no work. And so you are co-opting hijacking these circuits in a way that they're being activated at a time scale that normally wouldn't happen. Well, this is why I often feel that, and I think a lot of data are now starting to support the idea that while indeed the laws of thermodynamics apply, calories ingested versus calories burn is a very real thing, right? That the appetite for certain foods and the wanting and the liking are phenomena of the nervous system, brain and gut, as you've beautifully described, and that that changes over time depending on how we are receiving these nutrients. Absolutely. Look, in we have a lot of work to do. I'm talking to society. I'm not talking about you and I. We also have a lot of work to do. Now, I think understanding the circuits is given as important insights. And how ultimately, hopefully, we can improve human health and make a meaningful difference. Now, it's very easy to try to, you know, connect the dots, A to B, B to C, C to D. And I think there's a lot more complexity to it. But I do think that the lessons that are emerging out of understanding how these circuits operate can ultimately inform how we deal with our diets in a way that we avoid what we're facing now, you know, as a society. I mean, it's not that the overnutrition happens to be such a prevalent problem. And I also think the training of people who are thinking about metabolic science and metabolic diseases, largely divorced from the training of the neuroscientist and vice versa. No one field is to blame. But I fully agree that the brain is the key or the nervous system to be more accurate is the one of the key overlooked features. Is the RV tour ultimately is the RV tour of many of these pathways? As a final question and one which is simply to entertain my curiosity and the curiosity of the listeners, what is your absolute favorite food? Oh my goodness. Taste, I should say. Yes. Taste to distinguish between taste and the nutritive value or lack that is. Look, we, unlike every animal species, eat for the enjoyment of it. It doesn't happen in the wild. Most animals eat when they need to eat. That's the mean they don't enjoy it, but it's a completely different story. Yeah. I have too many favorite foods because I enjoy the sensory experience. Rather than that food itself, to me is the whole thing. It's from the present look. There have been experiments done in psychophysics. I'm going to take a salad made out of 11 components. And I'm going to mix them all up in a potpourri of greens and other things here. And in the other one, I'm going to present it in a beautiful arrangement. And I'm going to put it behind a glass cabinet. And I'm going to sell them. And I'm going to sell one for two dollars and one for eight dollars. Precisely the same ingredients, exactly the same amount of each. Ultimately, you're going to mix them. They're all going to be the same. And people will pay the eight dollars because you know what? It evokes a different person. It gives you the feel that, oh my goodness, I'm going to enjoy that salad. So going back to what is my favorite food? To me, eating is really a sensory journey. I don't mean the everyday. Let me have some chicken wings because I'm hungry. But every piece, I think, has an important evoking sensory role. And so, you know, in terms of categories of food, you know, I grew up in Chile. Yes, so meat is always been. But I eat it so seldom now. Is that right? Yeah, because you know, I know that's not necessarily the whole thing. Read me them talking about it. And so I grew up eating it every day. I'm talking seven days a week. Chile and Argentina, you know, that's the main stay of our diet. Now maybe I have read meat. I know once every four weeks. And you enjoy it. Oh, I love it. Part of it is because I haven't had it in four weeks. But you know, I love sushi. But I love the the art of sushi. You know, the whole thing, you know, the way it's presented, it changes the way you taste it. I love ethnic food. In particular, you're in the right place. You got it. That was the main reason I wanted to come to New York. No, I'm just kidding. There's also that Columbia University that's and I came here because I wanted to be with, you know, people that are thinking about the brain the same way that I like to think, we know can we solve this big problem? This big question. And certainly you're making amazing strides in that direction. And I love your answer because it really brings together the many features of the circuitries and the phenomena we've been talking about today, which is that while it begins with sensation and perception, ultimately, it's the context and that context is highly individual to person, place, and time and many, many other things. On behalf of myself and certainly on behalf of all the listeners, I want to thank you. First of all, for the incredible work that you've been doing now for decades in vision, in taste, and in this bigger issue of how we perceive and experience life. It's truly pioneering and incredible work. And I feel quite lucky to have been on the sideline, seeing this over the years and hearing the talks and reading the countless beautiful papers. But also for your time today, did come down here and talk to us about what drives you and the discoveries you've made. Thank you ever so much. It was great fun. Thank you for having me. We'll do it again. We shall. Thank you for joining me today for my discussion about perception. And in particular, the perception of taste with Dr. Charles Zucker. If you're learning from and are enjoying this podcast, please subscribe to our YouTube channel. That's a terrific zero-cost way to support us. In addition, please subscribe to the podcast on Spotify and Apple. And on Spotify and Apple, you can leave us up to a five-star review. If you have feedback for us in terms of comments related to topics we've covered or questions or topics or guests that you'd like us to cover on future episodes of the Uramin Lab podcast, please put those in the comment section on YouTube. We do read all the comments. On today's episode of the Uramin Lab podcast, we didn't talk about supplements, but on many previous episodes of the Uramin Lab podcast, we talk about supplements that are useful for sleep, for focus, for hormone support, and other aspects of mental health, physical health, and performance. If you're interested in some of those supplements, you can go to livemomentus.com slash Huberman to see the catalog of supplements that we've helped them formulate and that map directly onto specific protocols described on the Huberman Lab podcast. Again, that's livemomentus.com slash Huberman. If you're not already following us on social media, we are Huberman Lab on Twitter and Huberman Lab on Instagram and at both Twitter and Instagram, I cover science and science-related tools, some of which overlap with the content of the Uramin Lab podcast, but much of which is distinct from the information contained in the Huberman Lab podcast. We also have a newsletter in which we spell out protocols and some summaries from previous podcast episodes. If you'd like to check those out, you can go to HubermanLab.com, go to the menu, and you'll find the neural network newsletter. You can sign up for that newsletter simply by providing an email. It's completely zero cost. We have a very strict privacy policy. We do not share your email with anybody. Again, that's HubermanLab.com. Go to the menu and look for the neural network newsletter. If you'd like examples of previous newsletters, you'll also find those at HubermanLab.com. Once again, thank you for joining me today in my discussion with Dr. Charles Zucker about the biology of perception and the biology of the perception of taste in particular. I hope you found that discussion to be as enriching as I did. And last but certainly not least, thank you for your interest in science.