

## How to Control Your Sense of Pain & Pleasure | Huberman Lab Podcast #32

This episode I discuss our sense of pain and pleasure: where and how they each arise in our mind and body and various ways to control their intensity. I discuss the science of behavioral tools like acupuncture and hypnosis and directed pressure, including the neural circuits they each activate to modulate our experience of pain or pleasure. I also discuss whole body pain, pain "syndromes" and novel pain relief compounds such as Acetyl-L-Carnitine, SAMe and Agmatine. I discuss neuroplasticity of the pain system and the key role that visual perception plays in pain modulation. Finally, I address the link between dopamine, serotonin, and oxytocin, with arousal, pleasure and pain. As always, both basic science and various protocols are described.

Note: The description of the dorsal root ganglia (DRGs) was intentionally simplified and does not include mention of dorsal horn spinal relay neurons, etc.. For an excellent full text review of this anatomy and circuits for touch sensing, please see:

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3811145/>

#hubermanlab #pain #pleasure #dopamine #motivation

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- [Andrew Huberman] Welcome to the Huberman Lab Podcast, where we discuss science and science-based tools for everyday life. [bright upbeat music] - I'm Andrew Huberman, and I'm a Professor of Neurobiology and Ophthalmology at Stanford School of Medicine. Today, we continue our discussion of the senses. And the senses we are going to discuss are pain and pleasure. Pain and pleasure reflect two opposite ends of a continuum, a continuum that involves detection of things in our skin and the perception, the understanding of what those events are. Our skin is our largest sensory organ and our largest organ indeed. It is much larger than any of the other organs in our body. And it's an odd organ if you think about it, it has so many functions. It acts as a barrier between our organs and the outside world, it harbors neurons nerve cells that allow us to detect things like light touch, or temperature or pressure of various kinds. And it's an organ that we hang ornaments on. People put earrings in their ears. People decorate their skin with tattoos and inks and other things. And it's an organ that allows us to experience either great pain or great pleasure. So it's a multifaceted organ and it's one that our brain needs to make sense of in a multifaceted way. So today we're going to discuss all that. And most importantly, how you can experience more pleasure and less pain by understanding these pathways. We will also discuss things you can do, and if

you wish things you can take that will allow you to experience more pleasure

00:01:50 Protocol 1: Maximizing Motivation (with Dopamine & Pleasure)

and less pain in response to a variety of different experiences. Before I go any further, I want to highlight a particularly exciting area of science that relates to the skin and to sensing of pleasure and pain, but has everything to do with motivation. Motivation is something that many people struggle with, not everybody, but most people experience dips and peaks in their motivation even if they really want something. How should we think about these changes in motivation? What do they reflect? Well at a very basic level, they reflect fluctuations changes in the levels of a chemical called dopamine. Most of us have heard of dopamine. Dopamine is a neuromodulator meaning it modulates or changes the way that neurons nerve cells work. Most of us have heard that dopamine is the molecule of pleasure. However, that is incorrect. Dopamine is a molecule of motivation and anticipation. To illustrate how dopamine works, I want to highlight some very important work largely carried out by the laboratory of a guy named Wolfram Schultz. The Schultz Laboratory has done dozens of excellent experiments on the dopamine system and have identified something called reward prediction error. Although in some sense you can think about it as reward prediction variance. Changes in the levels of dopamine depending on whether or not you expect a reward and whether or not you get the reward. So I'm going to make this very simple. Dopamine is released into the brain and body and generally makes us feel activated and motivated, as if we have energy to pursue a goal. And it is released into the brain and body in anticipation of a reward. Measurements of dopamine have been made in animals and humans. And what you find is that when we anticipate a reward, dopamine is released, we will put in the work to achieve that reward. That work could be mental work or physical work, but when the reward arrives, dopamine levels drop back down to baseline. That's right. When we receive a reward, dopamine levels go back down to baseline. So the way to envision this as you can just imagine a sort of increase in dopamine as we anticipate something we're working towards it, we're working towards a goal. We're excited about seeing somebody or meeting somebody or receiving some reward and then the reward comes and dopamine goes down. Now that's all fine and good, but there is a way to get much more dopamine out of that process and therefore a way to have much more motivation, energy, and focus because those are the consequences of elevated dopamine. The way

to do that is to not deliver the reward on an expected schedule. So experiments have been done where there's an anticipation of a reward, there's work, and then the reward only arrives every other or every third about of work, okay? So this would be like getting a pat on the head. If you're a dog or a, perhaps a child or an adult, or getting a monetary reward only for every third project or every third race that you win. Pick any kind of goal. It doesn't matter. These molecules don't care about what you're pursuing. They are a common currency of different types of activities. That's a regular reward schedule, and it will not alter the pattern of dopamine release that I described before. However, if the reward arrives intermittently almost randomly, so you anticipate a reward as a maybe it might come, it might come. Then you work, work, work, work, work, no reward. You repeat the work, work, work, work, work, work, and then you get a reward. So some trials, you do some trials, you don't, and it's completely random. Under those conditions, the amplitude, the amount of dopamine that's released into your system and the motivation to continue working hard or playing whatever kind of game you're playing, doubles or triples. And this is the basis of things like slot machines and gambling. And this is why so many people will give so much of their money up to casinos and the casinos always win. Sometimes people walk away with more money than they came to the casino with, but the vast majority of the time, the house wins as they say. And it's because they understand intermittent reward schedules. And you can apply this to stay motivated in your own pursuits. Rather than thinking about the pleasure of a reward, understand that dopamine is released in response to anticipation reward, and that is the fuel for work. And every once in awhile at random remove the reward. That's the way to continue to stay motivated. Not to reward every action or every goal. And this is also true, if you're trying to train up children or train up players on a team, you should not celebrate every win. I know that's a little counter-intuitive, we're going to go more into the biology of dopamine and how it relates to the pleasure system later on in the podcast, but for now understand intermittent reward schedules

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harness the biology of dopamine in ways that can allow you essentially infinite motivation over time. Before I go any further, I want to acknowledge that this podcast is separate from my teaching and research roles at Stanford. It is however, part of my desire and effort to bring zero cost to consumer information about science and science-

related tools to the general public. In keeping with that theme, I'd like to thank the sponsors of today's podcast. Our first sponsor is InsideTracker. InsideTracker is a personalized nutrition platform that analyzes data from your blood and DNA to help you better understand your body and help you reach your health goals. I've long been a believer in getting regular blood work done for the simple reason that many, if not all of the factors that impact your immediate and long-term health can only be analyzed from a quality blood test. And nowadays with the advent of DNA tests, you can get further knowledge into the mechanisms that are going on in your body and how those mechanisms are changing as they relate to metabolism and hormones and other aspects that profoundly impact your wellbeing. The problem with most blood tests, however, is that you get information back and it will tell you whether or not your levels of something are higher, low, or within range, but it doesn't give you any directives. It doesn't tell you what to do with that information. With InsideTracker has this wonderful feature. It's a very easy to use dashboard that has suggestions about lifestyle factors, exercise, nutrition, supplementation, et cetera, that one could take in order to adjust those numbers according to your personal goals. So the whole thing is made very easy. In fact, they can come to your home to do the blood test and DNA test if you like. If you'd like to try InsideTracker, you can go to [insidetracker.com/huberman](https://insidetracker.com/huberman). And if you do that you'll get 25% off any of InsideTracker's plans. Just use the code `huberman@checkout`. And I should also mention that through August 15th, 2021, you can get a free inner age test. That's a measure of your biological age according to your DNA and other factors with any purchase from InsideTracker store. So go to [insidetracker.com/huberman](https://insidetracker.com/huberman) to get 25% off any of InsideTracker's plans and up to up and through August 15th, you can get a free inner age test. Today's episode is also brought to us by Helix Sleep. Helix makes mattresses and pillows that are ideally suited to your sleep needs. Everybody's different. Some people sleep on their sides, some people sleep on their stomach, some people sleep on their back, some people run warm during the night, some people run cold. If you go to the Helix's website, [helixsleep.com](https://helixsleep.com), you can take a quick two-minute quiz, and then it will tell you what your ideal mattress is. It will match you to your ideal mattress. I did this and I matched to the so-called Dusk mattress. I like a mattress that's not too firm nor too soft. I tend to run hot during the night and I tend to sleep on my side or on my stomach. I started sleeping on a Helix mattress about nine months ago, and I'm sleeping better than I ever have before. So if you're interested in upgrading your mattress to one that's ideally suited to your sleep needs, go to [helixsleep.com/huberman](https://helixsleep.com/huberman), take their two-

minutes sleep quiz, and they'll match you to a customized mattress. And you'll get up to \$200 off that mattress order, and two free pillows. They have a 10-year warranty and you get to try out the mattress for a 100 nights risk-free, they'll even pick it up for you if you don't love it, but I think you really will love it. So again, if you're interested, go to [helixsleep.com/huberman](https://helixsleep.com/huberman) for up to \$200 off and two free pillows. Today's episode is also brought to us by Athletic Greens. Athletic Greens is an all-in-one vitamin mineral probiotic drink. I started drinking Athletic Greens way back in 2012. And so I'm delighted that they're sponsoring the podcast. The reason I started drinking Athletic Greens and the reason why I still drink it once or even twice a day is because it takes care of all my foundational nutritional needs. It includes vitamins, minerals, and probiotics which are important for the gut microbiome, this colony of bacteria, healthy bacteria that we all have living in our guts. And when that bacteria is healthy, our brain functions better, our immune system functions better. There is now a lot of research to support that. Athletic Greens taste delicious. I mix mine with water and a little bit of lemon juice. And as I mentioned, I drink it once or twice a day, usually in the morning and again in the afternoon. If you'd like to try Athletic Greens, you can go to [athleticgreens.com/huberman](https://athleticgreens.com/huberman) and claim a special offer. That special offer is a year supply of vitamin D3K2. There's now a robust literature showing that vitamin D3 is critical for various aspects of our health, metabolic health, endocrine health, et cetera. And you'll also get five free travel packs. When you travel mixing up Athletic Greens is made really easy by these little travel packs. You just put them in a jar or other a water bottle, mix it with water. It's very easy to do on a plane or in the et cetera. Again, go to [athleticgreens.com/huberman](https://athleticgreens.com/huberman) to get the Athletic Greens, the five free travel packs

00:12:04 Pleasure & Pain, & Skin Sensors

and the year supply of vitamin D3K2. So let's talk about pleasure and pain. I think we all intuitively understand what pleasure and pain are. Pleasure generally is a sensation in the body and in the mind that leads us to pursue more of whatever is bringing about that sensation. And pain is also a sensation in the body and in the mind that in general leads us to want to withdraw or move away from some activity or interaction. That's not always the case. Some people actively seek out pain. Some people somehow can't seem to engage with or experience pleasure, but most people operate on this basis of pleasure and pain. Scientists would call this appetitive behaviors, meaning behaviors that lead us

to create an appetite for more of those behaviors and aversive behaviors, behaviors that make us want to move away from something. The simplest example of that would be putting your hand near a hot flame, at some point, there would be a reflex or a deep desire to withdraw your hand. Tasting something delicious in general makes us want to eat more of that thing. Interactions with other people that we find delicious, also make us want to interact with those people more. None of this is complicated or sophisticated. This is simply to illustrate the fact that pleasure and pain tend to evoke opposite responses, opposite behavioral responses and opposite emotional responses. So how does that come about? Well, it really comes about by an interaction that starts at one end of our body, meaning our skin and the other end of the organs of our body, which is deep within the brain. So let's consider these two ends of the spectrum of pleasure and pain and what they contribute to those experiences of pleasure and pain. The organ that we call the skin, as I mentioned earlier, is the largest organ in our body. And throughout that organ, we have neurons, little nerve cells. Now to be really technical about it, and the way I'd like you to understand it is that the so-called cell body meaning the location of a cell in which the DNA and other goodies the kind of central factory of the cell, that actually sits right outside your spinal cord. So all up and down your spinal cord on either side are these little blobs of neurons, little collections of neurons. They have a name if you'd like to know for you aficionado or those who are curious, they're called DRGs dorsal root ganglia. A ganglion is just a collection or clump of cells. And those DRGs are really interesting because they send one branch that we call an axon, a little wire out to our skin, also to our muscles into our organs, but here we're talking about the skin. They send a wire out to our skin and that wire literally reaches up into the skin. It's actually in our skin and they have another wire from that same cell body that goes in the opposite direction, which is up to our brain and creates connections within our brain in the so-called brainstem. What this means is that the neuron in your body that we call the DRG that sends a wire an axon to sense what's going on in your big toe and then sends another axon in the opposite direction into the base of your brain, that is the largest cell in your entire body of any kind. Fat cell, muscle cell, nerve cell, et cetera. Is extremely long cells. It can be a meter or more depending on how tall you happen to be. So we have these cells that have wires they go off in two different directions and the wire that's within our skin will respond to any number of different categories of stimuli. These wires are positioned within the skin to respond to mechanical forces. So maybe light touch, some will only send electrical activity up toward the brain in response to light touch.



Meaning if you press on the skin really hard, they don't respond. You stroke the skin lightly with your fingertips or a feather and they respond very robustly. Others respond to course pressure, the hard pressure, but they won't respond to a light feather, for instance. Others respond to temperature. So they will respond to the presence of heat or the presence of cold or changes in heat and cold. And still others respond to other types of stimuli, like certain chemicals on our skin. Many of you have probably experienced the sensation of eating a hot pepper. Well, I don't recommend doing this, but were you to take a little slice of jalapeno or other hot pepper, habanero pepper or something like that and rub it on your skin, you would actually feel something at that location. And that's because that pepper doesn't just create a sensation within your mouth, it will create a similar sensation on your skin. So these neurons are amazing. They're collecting information of particular kinds from the skin throughout the entire body and sending that information up toward the brain. And what's really incredible, I just want you to ponder this for a second. What's really incredible is that the language that those neurons use is exactly the same. The neuron that responds to light touch sends electrical signals up toward the brain, the neurons that respond to cold or to heat or to habanero pepper, they only respond to the particular thing that evokes the electrical response. I should say that they only respond to the particular stimulus, the pepper, the cold, the heat, et cetera, that will evoke an electrical signal, but the electrical signals are a common language that all neurons use. And yet, if something cold is presented to your skin, like an ice cube, even if you don't see that ice cube, if your eyes are closed, or someone comes up behind you and puts an ice cube against your bare skin back, you know that that sensation, that thing is cold.

00:18:13 Sensing Touch with Your Brain: Magnification of Feet, Hands, Lips, Face, Genitals

You don't misperceive it as heat or as a habanero pepper. So that's amazing. What that means is that there must be another element in the equation of what creates pleasure or pain. And that element is your brain. Your brain takes these electrical signals and interprets them. Partially based on experience, but also there are some innate meaning some hard wired aspects of pain and pleasure sensing that require no experience whatsoever. A child doesn't have to fall down but once to know on that first fall, that hurt. They don't have to touch a flame, but once and the very first time they will withdraw their

hand from the flame. So no prior experiences required. Other things prior experience is required. For instance, if you're somebody that has an intense, intense aversion to spicy foods, that's probably because you've tasted spicy foods before. Likewise, if you really like sweet foods, it's probably because you've tasted them before. So you can start to make predictions based on prior experience, but the pain and pleasure system don't need prior experience. What they need is a brain that can interpret these electrical signals that can take these electrical signals and somehow create what we call pleasure and pain out of them. So what parts of the brain? Well, mainly it's the so-called somatosensory cortex. The portion of our neocortex, which is on the outside of our brain, that kind of bumpy part, not kind of if you have a normally formed brain, it will be bumpy. If you have a smooth brain that's not good. Some animals just have a smooth brain. Humans have a bumpy brain, which means it has a very large surface area. And those bumps are 'cause you squeezed it like a pizza and clump and you bunched it all up and put inside the skull. That's good. That means you have a lot of neurons. And in your somatosensory cortex, you have a map of your entire body surface. That map is called a homunculus. And if we were to take your cortex and lay it out on a table, I've actually done this with the cortices of various animals and humans included. What you would find is that there's literally a map of your entire body surface. But it wouldn't look exactly like you, this map would be very distorted. Why would it be distorted? Well, certain areas of your body have a much denser innervation as we call it, or put simply many more of these sensory wires from these DRGs within your skin. So this map of you that exists in your brain, and you do have one of these on each side of your brain, so you have two of these maps to homunculi, that is you, it's your representation of touch including pleasure and pain. And in that map, your lips are enormous. And your back is very, very small. And the area around your eyes and the area representing your face is absolutely enormous. So you would look like some sort of odd, weird clay doll from some sort of bizarre late night animation thing. And just imagine the psychedelic experience of that character of you and that's what it would look like. But it's not randomly organized. To the contrary, it's highly organized in a very particular way, which is that the areas of your skin that have the highest density of the sensory receptors are magnified in your brain. So it's sort of like having more pixels in a certain part of a camera than others, and in doing that allowing higher resolution in this case of touch, not a vision, but of touch sensation in certain parts of your body. What are the areas that are magnified? Well, the lips, the face, the tips of the fingers, the feet, and the genitals. And so this map of you

has very large lips, face, tips of fingers, bottoms of feet, and genitals. And that's because the innervation, the number of wires that go into those regions of your body far exceeds the number of wires for sensation of touch

00:22:16 Two-Point Discrimination, Dermatomes

that go to other areas of your body. You can actually experience this in real time right now by doing a simple experiment that we call two-point discrimination. Two-point discrimination is your ability to know whether or not two points of pressure are far apart, near each other, or you actually could perceive incorrectly as one point of pressure. You might want a second person to do this experiment. Here's how you would do it. You will close your eyes, that person would take two fine points. Don't make them too sharp, please. So it could be two pencils or pens or the backs of pens. Two pens I'm holding in my hands. If you're just listening to this, I'm just holding two pens. My favorite pens, these pilot, V5 or V7, which I love. If you were to close your eyes and I were to take these two pens and put their points close together about a centimeter apart and present them to the top of your hand, I'm going to just going to do that now to myself. You, even though your eyes were closed, you would be able to perceive that that was two points of pressure presented simultaneously to the top of your hand. However, if I were to do this to the middle of your back, you would not experience them as two points of pressure. You would experience them as one single point of pressure. In other words, your two point discrimination is better, is higher on areas of your body which have many, many more sensory receptors. You are more sensitive at those locations. Now this makes perfect sense once you experience it or you hear about it. However, most of us don't really appreciate how important and what a profound influence this change in density of receptors across our body surface has. And we can go a step further and describe another feature of the way that you're built and the way that you experience pleasure and pain, which is called the dermatome. The dermatome is literally the way in which your body surface is carved up into different territories. Much like a map of the United States is carved up into different territories of states and counties, et cetera. The dermatome is the way in which neurons connect to different parts of your body. Now, you've actually experienced the dermatome before. The dermatome is when you have a neuron that connects to a particular area of the body and that neuron doesn't just send one little wire out like one little line and go up into the skin to detect mechanical, or

thermal, or chemical stimuli. It actually sends many branches out like a tree. But remember those branches of the tree come from one single neuron. Now, occasionally what will happen is you will experience something like cold, or heat, or pain, or tingling on a patch of your body. And occasionally that patch of body will actually have a very cleanly demarcated boundary, a very stark boundary with the areas around it. A good example of this would be the herpes simplex 1 virus, which if one has this virus, and I should mention that somewhere between 80 and 90% of people have this virus, this is not a sexually transmitted virus. This is a virus is transmitted very easily between people through various forms of contact non-sexual contact, it's present in children, it's present in adults and most people get it, some get symptoms and some don't some get recurring symptoms, some don't. We can talk about that at the end, if you like, but this virus lives on what's called the fifth cranial nerve also called the trigeminal nerve. The trigeminal nerve sends branches out to the lips, to the eyes, and to certain portions of the face. So for those of you listening, I've just kind of put my right hand across my face and to sort of simulate the three branches, the trigeminal aspect of this nerve. So tri three. Now, when the herpes virus flares up, as they say, in response to stress or other factors, the virus inflames that nerve and people experience tingling and pain on the nerve. Sometimes they'll get a cold sore or a blister on their lip or near their mouth, sometimes they'll get a collection of those. And that's because that dermatome is actually inflamed. Now other people will experience something like shingles. It's a fairly common viral infection. And what they'll notice is they'll get a rash that has a boundary. It's like, they'll get a bunch of bumps, sometimes blisters, and it'll have a sharp boundary. That boundary exists because the virus exists on the nerve. And so it actually is boundaried with the neighboring area of the body that's receiving input from another nerve and that one doesn't have the virus living on it. So anytime you see a rash or a pattern on the body surface on the skin that has a pretty stark boundary, chances are that's an event that's impacting the dermatome. I've experienced this before then not through herpes simplex, but through the experience of having a lot of blood sort of aggregating in a kind of a segment across the front of my face, it was really bizarre. I looked in the mirror and I thought, what is going on here? I was having an allergic reaction to something I'd eaten. And that allergic reaction clearly was affecting one of the nerves and therefore the dermatome and what it showed up was, it was almost like someone had drawn lines on my face that said, okay, this rash or this reaction rather can happen here, but not in a region right next to it. Whenever you see that chances are it's a reaction of the nerves of

the dermatome. So you'll start to see these things more and more when you start to look for them. You don't always have to have a viral infection to experience this. Sometimes you'll just experience tingling or even a pleasant sensation, and it will be restricted in kind of a strict boundary on one location on your body surface and not another. Not corresponding to an organ like, okay, this arm or just your feet or something like that. But just a segment. It's almost like someone outlined a particular area of her body surface.

#### 00:28:11 Thoughts & Genes That Make Physical Pain Worse

That's the dermatome. So you've got sensors in the skin and you've got a brain that's going to interpret what's going on with those sensors. In fact, we can take an example of a sudden rash or inflammation at one location, the dermatome, and we can ask what would make it hurt? What would make it worse? What would make it go away? And believe it or not, your subjective interpretation of what's happening has a profound influence on your experience of pleasure or pain. There are several things that can impact these experiences, but the main categories are expectation. So sort of whether or not you thought or could expect that this thing was going to happen, right? If someone tells you this is going to hurt, I'm going to give you an injection right here, it might hurt for a second. That's very different and your experience of that pain will be very different than if it happened suddenly out of the blue. There's also anxiety, how anxious, or how high or low your level of arousal, autonomic arousal, that's going to impact your experience of pleasure or pain. How well you slept and where you are in the so-called circadian or 24-hour cycle. Our ability to tolerate pain changes dramatically across the 24-hour cycle. And as you can imagine is during the daylight waking hours that we are better able to tolerate, we are more resilient to pain, and we are better able to experience pleasure. At night our threshold for pain is much lower. In other words, the amount of mechanical or chemical or thermal meaning temperature stimulated that can evoke a pain response and how we rate that response is much lower at night. And in particular, in the hours between 2:00 AM and 5:00 AM, if you're on a kind of standard circadian schedule. And then the last one is our genes. Pain threshold and how long a pain response lasts is in part dictated by our genes. And later I'm going to discuss this myth or whether or not it's really a myth as to whether or not certain people in particular red heads, people who have red pigmented hair and fair skin, whether or not their pain thresholds differ. And to just give you a little sneak peek into that, indeed they do and it's because of a genetic

difference in a particular gene, in a particular pattern of receptors in the skin that are related to the pigmentation of hair and skin. So we have expectation, anxiety, how well we've slept, where we are in the so-called 24-hour circadian time and our genes. So let's talk about expectation and anxiety because those two factors can powerfully modulate our experience of both pleasure and pain in ways that will allow us to dial up pleasure if we like and to dial down pain, if indeed that's what we want to do. So let's talk about expectation and anxiety because those two things are somewhat tethered. There are now a number of solid experiments, both in animal models and in humans that point to the fact that if we know a painful stimulus is coming, that we can better prepare for it mentally and therefore buffer or reduce the pain response. However, the timing in which that anticipation occurs is vital for this to happen. And if that timing isn't quite right, it actually can make the experience of pain far worse. So here I'm summarizing a large amount of literature, but essentially if subjects are warned that a painful stimulus is coming, their subjective experience of that pain is vastly reduced. However, if they are warned just two seconds before that pain arrives, it does not help. It actually makes it worse. And the reason is they can't do anything mentally to prepare for it in that brief two second window. Similarly, if they are warned about pain that's coming two minutes before a painful stimulus is coming electric shock or a poke or cold stimulus or heat stimulus that's pretty extreme, that also makes it worse because their expectation ramps up the autonomic arousal. The level of alertness is all funneled toward that negative experience that's coming. So how soon before a painful stimulus should we know about it if the goal is to reduce our level of pain? And the answer is somewhere between 20 seconds and 40 seconds is about right. Now, I'm averaging across a number of different studies, but if you have about 20 seconds or 40 seconds advance warning that something bad is coming, you can prepare yourself for that, but the preparation itself and the arousal that comes with it, the kind of leaning in, okay, I'm either going to relax myself or I'm going to really kind of dig my heels in and kind of meet the pain head on. That seems to be the optimal window. This can come and useful in a variety of contexts, but I think it's important because what it illustrates is that it absolutely cannot be just the pattern of signals that are arriving from the skin, from these DRGs, these neurons that connect to skin that dictates our experience of pain or pleasure. There has to be a subjective interpretation component,

00:33:45 Expectations, Anxiety, & Pain Threshold

and indeed that's the case. So let's talk about the range of pain experiences. And from that, we will understand better what the range of pleasure experiences are that different people have because we are all different in terms of our pain threshold. First of all, what is pain threshold? Pain threshold has two dimensions. The first dimension is the amount of mechanical or chemical or thermal stimulation that it takes for you or me or somebody else to say, I can't take that anymore. I'm done. But there's another element as well which is how long the pain persists. I'll just describe myself for example, I don't consider myself somebody who has a particularly high pain threshold. I don't think it's particularly low either, but I wouldn't consider myself somebody that has a particularly high pain threshold. When I stubbed my toe against the corner of the bed, it absolutely hurts. But one thing that I've noticed is that I have very sharp inflections, very high inflections in my perception of pain, and then they go away quickly. I don't know if that's adaptive or not. It's probably not, but my experience of pain is very intense, but very brief. Other people experience pain in a much kind of slower rising, but longer-lasting manner. And to just really point out how varied we all are in terms of our experience of pain, let's look to an experiment. There been experiments done at Stanford School of Medicine and elsewhere, which involved having subjects put their hand into a very cold vat of water and measuring the amount of time that they kept their hand in that water. And then they would tell the experimenter very quietly, how painful that particular stimulus was on a scale of one to 10 so-called Likert scale for your aficionados. That simple experiment revealed that people experience the same thermal in this case, cold stimulus, vastly different. Some people would rate it as a 10 out of 10 extreme pain. Other people would rate it as barely painful at all, like a one. Other people, a three other people, a five, et cetera. Now what's interesting is that the same thing is true for experience of a hot, painful stimulus 120 degree hot plate, where you have to put your hand on it, and then at some point you remove your hand. Some people are able to keep their hand on there the whole time, but people rate that experience as very painful, a little bit painful or moderately painful depending on who they are. Now, that's interesting, probably not that surprising, however, but what is very interesting is that when the same experiment was done on medical doctors or medical doctors in training, they too of course experienced pain through a range of subjective experiences. Some of them just like any other person off the street said a particular stimulus of a particular temperature was very painful, other said it wasn't painful at all and some said it was moderately painful. And that turns out to

be vitally important for the treatment of pain because pain is not an event in the skin. Pain is a subjective, emotional experience. You may have heard that we have a particular category of these DRGs that innervate the skin, which are called nociceptors. Nociceptor comes from the word *noci, nocere* I believe it is, which means to harm. However, nociceptors don't carry information about pain, they carry information about particular types of stimuli impacting the skin. And then the brain assigns a value of valence to it, a label and says that's painful. And where people draw the line between not painful and painful varies. Now, because physicians are people and because physicians treat pain, what we know from a lot of data now is that if someone comes into the clinic and says they're experiencing chronic pain or whole body pain or acute pain after an injury or one location, it doesn't really matter what the cause is or even if there's a cause at all, how the doctor reacts to that report of the patient's pain will dictate in many cases the course of treatment. And of course doctors, their goal is to treat the patient to going to the patient's needs, not their own. And that's what good doctors do. However, it's been found and I think now there is work being done to try and change this, but if a doctor has a very high threshold for pain, their interpretation of somebody else's report of pain is going to be different. They might not discount the patient, right? This doesn't necessarily mean that they think, oh, this person their pain is irrelevant, probably not. In fact, from having a high threshold for pain, if someone comes in and says, I'm in extreme pain, that doctor probably thinks, wow, this has to be really, really extreme, but they can be talking about two different experiences. Similarly, if a physician has a very low threshold for pain, and someone comes in and says, yeah, I'm experiencing some pain in my back. I've got the sciatica thing, but yeah, it's a little bit uncomfortable. It's like a, I don't know like a four out of 10. Well, that physician might interpret that four out of 10 as a pretty extreme sense of pain or pretty extreme experience of pain. And so you can start to see how the subjective nature of pain can start to have real impact on the treatment of pain because treatment of pain is carried out by physicians. In fact, there is no objective measure of pain. We can ask how long somebody can keep their hand on a hot plate or in a cold bath. You can do various experiments. They even have some extreme experiments where they'll shave a portion of the leg and they'll put on a very painful chemical compound and see how long people can tolerate that. These are very uncomfortable experiments as you can imagine, but in general, we don't have a way of measuring somebody else's subjective experience of pain. There is no blood pressure measure. There's no heart rate beats per minute measure of pain. So one of the great



efforts of neuroscience and of medicine is to try and come up with more objective measures of pain. Similarly, pleasure is something that we all talk about. Ooh, that feels so good, or I love that or more of that please or less of that, but we have no way of gauging what other people are experiencing except what they report through language. And so this is really just to illustrate that this whole thing around pain isn't a black box. We do have an understanding of the elements. There are elements in the skin, there's elements of the brain, there's expectation, anxiety, sleep, and genes, but that it is very complicated. And yet there are certain principles that fall out of that complicated picture

00:40:27 Protocol 2: Cold Sensing Is Relative; Getting Into Cold Water

that can allow us to better understand and navigate this axis that we call the pleasure-pain axis. So rather than focus on just the subjective nature of pain, let's talk about the absolute qualities of pain and the absolute qualities of pleasure so that we can learn how to navigate those two experiences in ways that serve us each better. First of all, I want to talk about heat and cold. We do indeed have sensors in our skin that respond to heat and cold. And for any of you that have entered a cold shower or a cold body of water of any kind or ice bath, et cetera, you will realize that getting into cold is much harder if you do it slowly. Now, despite that people tend to do it very slowly. I have noticed an enormous variation with which people can embrace the experience of cold. I noticed it because I do some work with athletes and I do some work with military and I do some work with the general public. And one of the best tests of how somebody can handle pain is to ask them to just get into an ice bath. It's not a very sophisticated experience, but it really gets into the core of the kind of circuitry that we're talking about, both in the skin and in the brain. Some people regardless of sex, regardless of age, and regardless of physical ability can just get into the cold. They're somehow able to do it. Now, I don't know what their experience of the cold is. And neither do you. You only know your experience, but they're able to do that. Some do it quickly, some do it slowly. Others find the experience of cold to be so aversive that they somehow cannot get themselves in. They start quaking, they start complaining and many of them just simply get out. They can't do it. Some don't even get in past their knees. This isn't necessarily about pain threshold, but it's related to that. I think it can be helpful to everyone to know that even though it feels better at a mental level to get into the cold slowly and people ask, oh, I just want to get in slowly, I want to take my time. It is actually much worse from a neuro-

biological perspective. The neurons that sense cold respond to what are called relative drops in temperature. So it's not about the absolute temperature of the water. It's about the relative change in temperature. So as you move from a particular temperature, whether or not it's in the air next to an ice bath or cold shower, or from a body of water that's warm to a body of water that's colder, or sometimes in the ocean, you'll notice it's warm. And then as you swim out further, you'll get into a pocket of water where it's much colder. That's when the cold receptors in your skin start firing and sending signals up to your brain. Therefore, you can bypass these signals going up to the brain with each relative change one degree change, two degrees change, et cetera, by simply getting in all at once. In fact it is true and maybe you've been told this before, and it is true that if you get into cold water up to your neck, it's actually much more comfortable than if you're halfway in and halfway out. And that's because of the difference in the signals that are being sent from the cold receptors on your upper torso, which is out of the water in your lower torso. Now, I wouldn't want anyone to take this to mean that they should just jump into an unknown body of water. There are all sorts of factors like currents, and if it's very, very cold, yes, indeed. You can stop the heart. People can have heart attacks from getting into extremely cold water, like a melted mountain stream that's been frozen all winter, or has been very, very cold or as a snow pack going into it. If very cold, you can indeed have a heart attack. So please be smart about how cold and what bodies of cold water you happen to put yourself into. But it is absolutely true that provided it safe, getting into a cold water is always going to be easier to do quickly and is going to be easier to do up to your neck. In fact, you actually want to get your shoulders submerged. There are a number of other things you can do if you really want and it's safe to do. You can put your face under and activate the so-called dive reflex, which also makes the tolerance of cold easier believe it or not. So it's very counterintuitive. It's like getting into water faster and more completely you will experience as less uncomfortable, less cold. And indeed that's the case. And that's because these cold receptors are measuring every relative drop in temperature. So every single one is graded as we say in biology, it's not absolute. As an additional point, if you're sitting in a body of cold water and it's not circulating, you'll notice that you start to warm up a little bit. Or even if you feel like you're freezing cold, if you move and that water around you moves, of course, then you'll notice it's got even colder. And that's because there's a thermal layer. You're actually heating up the water that surrounds your body like a halo around every aspect of your body. A sort of silhouette of you of heat where you're heating that water.

### 00:45:22 Protocol 3: Heat Is Absolute

When you move, you disrupt that thermal layer. Now heat is the opposite. Heat and the heat receptors in your skin respond to absolute changes in temperature. And this is probably because our body and our brain can tolerate drops in temperature much better than it can tolerate increases in temperature safely. So when you move from say a standard outdoor environment, I mean, here in the States we measure in terms of Fahrenheit. So maybe it's a 75 or an 80 degree, or even 90 degree day, and you get into a 100 degrees sauna, or if you're in a cool air conditioned building and you go outside and it's very warm outside, you sort of feel like the heat hits you all at once, boom. Hits you all at once, kind of like a slap in the face, but then it will just stay at that level. Your body will acclimate to that particular temperature. However, if that temperature is very, very high, you'll notice that your experience of that heat and your experience of kind of pain and discomfort and your desire to get out of that heat will tend to persist. You don't really adapt in the same way. And certain people who are really good at handling very hot sauna, get better at this. You learned to calm your breathing, et cetera, lower your autonomic arousal. Obviously you don't want to let your body temperature go too high because neurons cook, they die. If neurons die, they don't come back and that's bad. Many people unfortunately harm themselves with hyperthermia. Everyone has a different threshold for this, but in general, you don't want your body temperature to go up too high. That's why a fever of like 103 starts to become worrisome 104. You really get concerned if and it goes up into that range or higher, that's when you need to really cool down the body or get to hospital so they can cool you down. Heat is measured in absolute terms by the neurons. So gradually moving into heat makes sense, and finding that threshold, which is safe and comfortable for you, or if it's uncomfortable, at least resides within that realm of safety. So that's heat and cold, and those are sort of non-negotiables. You can try and lower your level of arousal. In fact, many people who get into a cold shower and ice bath I think the recommendation that I always give is that you have two possible approaches to that. You can either try and relax yourself, kind of just stay calm within the cold, or you can lean into it. You can actually take mental steps to generate more adrenaline to kind of meet the demands of that cold. And at some point we'll do a whole episode on how to use cold and heat to certain advantages we've done a little bit of this in past episodes using the cold to supercharge human performance and

things of that sort. But in general, cold is measured in relative terms. And therefore getting in all at once is a good idea provided you can do it safely. And heat is measured in absolute levels by your brain and body and therefore

#### 00:48:10 Injury & Pain

you want to actually move into it gradually. So it's the kind of the inverse of what you might think. One of the most important things to understand about the experience of pain and to really illustrate just how subjective pain really is, is that our experience of pain and the degree of damage to our body are not always correlated. And in fact, sometimes can be in opposite directions. A good example of this would be x-rays. We all occasionally get x-rays at least in the US we get x-rays when we go to the dentist from time to time, and the occasional x-ray might be safe depending on who you are provide you're not pregnant, et cetera. I've gone to the dentist. They put you in the chair, they cover you with the lead blanket, and then they run behind the screen to protect themselves. And they beam me with the x-rays to get a picture of your teeth and your jaws and your skull, et cetera. Well, if you were to get too many x-rays, you could severely damage the tissues of your body, but you don't experience any pain during the x-ray itself. In contrast, you can think that your body is damaged and experienced extreme pain and yet your body can have no damage. A classic example of this was published in the British Journal of Medicine, in which a construction worker fell from I think it was a second story, which he was working and a nail went up and through his boot and he looked down and he saw the nail going through his boot and he was in absolute excruciating pain. They took him to the hospital and because the nail was so long and because of where it had entered, it exited the boot, they had to cut away the boot in order to get to the nail. And when they did that, they revealed that the nail had passed between two of his toes. It had actually failed to impale his body in any way. And yet the view, the perception of that nail entering his boot at one end and exiting the boot at the other was sufficient to create the experience of a nail that had gone through his foot. And the moment he realized that that nail had not gone through his foot, the pain completely evaporated. And this has been demonstrated numerous times. People that work in emergency rooms actually see variations on this. Not always that extreme, but many times what we see and how we perceive that wound or that event has a profound influence on how we experience pain. And I mentioned this, not just because it's a kind

of sensational and fantastic example of this extreme, subjective nature of pain, but also because it brings us back to this element which is, we don't know how other people feel. Not just about pain, but about pleasure. We think we do, we have some general sense of whether or not an event ought to be painful or pleasurable, but actually we barely understand how we feel let alone how other people feel, and we can be badly wrong about how we feel meaning we can misinterpret our own sense of pain or our own sense of pleasure depending on what we see with our eyes and what we hear with our ears. So we hear a scream like a shrill scream, and we think it must be pain. And if we look at something that's happening to somebody and it fits a prior category or a prior representation of what we would consider painful stimulus, well, then we think that they're an extreme pain, but actually they might not be in pain at all. Now this highly subjective nature of pain and the way in which we use our visual system to interpret other people's pain and our own pain has actually been leveraged to treat a very extreme form of chronic pain. And it's an absolutely fascinating area of biology and neuroscience. And it's one that we can actually all leverage toward reducing our own levels of pain

#### 00:52:04 Protocol 4: Plasticity of Pain: Key Role of Vision

whenever we are injured. Or believe it or not, even in chronic pain. To describe this area of science requires a kind of extreme example, but I want to be clear that even if you don't suffer from this extreme example, there's relevance and a tool to extract for you. The extreme example is that of an amputated digit, meaning one of your fingers or your toes, or of an amputated limb. So people that have digits or limbs that are gone missing from an injury or surgical removal, will often have the experience that it's still there. The so-called phantom limb phenomenon. Now, why would that be? Well, when you remove a particular finger or limb, obviously that finger and limb is gone and the dorsal root ganglion neuron that would normally send a wire out to that particular region of the body, that wire is no longer there because that portion of the body is no longer there. And in some cases, those neurons die almost always, but not always. However, the map your so-called homunculus, your representation of yourself in the brain is still there. And this map, the so-called homunculus map that you have in that I have is very plastic. It can change. And so as a consequence areas of the map that adjacent to one another can actually start to invade other areas of the map. So for instance, there are neuroimaging

studies that have documented that somebody that has say a complete removal of their left arm, the representation of their left arm still exists in the cortex. And experimentally if one is to stimulate that area of the cortex, that person, and if that person were you, would experience having that arm that it were being stimulated, even though it's not there. Now, someone who has an amputated arm doesn't need to have their brain stimulated in order to have the experience of that phantom limb being present. In fact, many people who have limbs that were amputated feel as if that limb is still present even though obviously it's not. And no matter how many times they look to the stump and just see a stump, somehow it doesn't reorganize that homunculus so-called central brain map. Now, that would be fine. You might even think that would be better, better to think you have the arm there than to feel as if it's missing, and yet many people who have amputated limbs report phantom limb pain. They don't feel that the arm is just casually draped next to them. They feel as if it's bunched up and it's an extreme pain. In fact, this kind of contorted stance that I'm taking right here in my chair is not unlike the way that these patients described this. They feel as if it's kind of cramped up, it's very uncomfortable for them. Now, and absolutely creative and you could even say genius scientists by the name of Ramachandra. That's actually his last name, his complete name is a little bit more complicated. So you all almost always hear Ramachandran referred to as Ramachandran or V.S Ramachandran because his full name is Vilayanur Subramanian Ramachandran. So a lot of letters in there, a lot of vowels, but Ramachandran is a neuroscientist. He was actually a colleague of mine when my lab was formerly at the University of California, San Diego. Has done a lot of work on this phantom limb phenomenon. And Ramachandra actually started off as a vision scientist. And he understood the power of the visual system in dictating our experience of things like pain and pleasure. And so what he developed was a very low technology yet neuroscientifically sophisticated treatment for phantom limb. It consisted of a box, literally a box that had mirrors inside of it. And the patient would put the intact hand or limb into one side, and obviously they couldn't put the amputated limb into the other side, but because of the configuration of the mirrors, it appeared as though they had two symmetric limbs inside the box. And then he would have them look at that limb and move it around. And as they would do this, they would report real time movement, or I should say real time perception of movement in the phantom limb. Now this is absolutely incredible but makes total sense when you think about the so-called top down or contextual modulation of our sensory experience, remember it's anticipation, it's anxiety,

it's interpretation of what's happening that drives our perception of what's happening. And so, as he would have these patients move their intact limb to a more relaxed position, the patients would feel as if the phantom limb were relaxing. And this was used successfully to treat phantom limb pain in a number of different people. It didn't always work. And you can imagine sometimes it might be a little trickier like for a leg although there have been leg boxes that have been developed and arranged for this purpose. And what was remarkable is that they could finish these experiments and have the patient, the person enter a state of relaxation, reduced the pain in the phantom limb, and it would stay there even though, of course, as they exited the mirror box, they would go about their life and use their intact limb for its various purposes. I love this experiment because it really speaks to the subjective nature of pain and pleasure. It speaks to the power of the visual system, like what we see just like the nail through the boot experiment. What we see profoundly impacts our experience of pleasure and pain in this case pain. Now, there's another aspect to the phantom limb experience and of these maps, the so-called homunculus maps in the cortex that Ramachandran worked on, which has very interesting and reveals the degree

00:58:08 Sensing Disparate Body Parts As Merged

to which these maps are plastic or can change in response to experience. Turns out that because of the locations of different body part representations within these maps, certain parts of our body that normally we don't think of as related can start to create merged experiences. What do I mean by that? Well, Ramchandran described a patient who had a somewhat odd experience of having lost their foot. So they actually had their foot amputated about midway up the Achilles. So lower portion of the calf and foot. I don't recall what the reason was for having it removed. And fortunately for this patient, they did not experience pain in that portion of their body, but rather they confided in him that whenever they would have sex, they would experience their orgasm in their phantom foot in addition to in their genitals, of course. And Ramachandra understood the homunculus map. And he understood that this was because the representation of the foot within the homunculus actually lies adjacent to, and is somewhat interdigitated with it actually kind of merges with the representation of the genitalia. Now that's a weird situation. And yet you now know that the density of innervation of the feet and the genitalia, as well as the lips and the face are actually the highest sensory innervation

that you have in your entire body. And this speaks to, I think, a more important general principle for all people of the experience of pleasure or pain, which is that an aspect of our pain or pleasure can be highly localized. It can be because of a cut to a particular location on the body or it can be because of a fall injury or a kind of bruise on one side of our body. And yet our experience of pleasure and pain can also be an almost a body-wide experience. And yet it's always most rich. It's always most heightened in these regions of our body that have dense sensory innervation. So we experience pain and pleasure according to local phenomenon receptors in the skin, and this homunculus map that has all these different territories, but because of the way that those territories are related, this kind of wild example of somebody experiencing orgasm in their phantom foot speaks to the larger experience. The more typical rather experience that I should say that all people have, which is that pleasure can be body-wide or we can experience it in our face or the bottoms of our feet and other areas of the body that we experience pleasure and similarly with pain.

01:01:00 Pain "Syndromes", Psychogenic Fever, "Psychosomatics"

And that brings us to the topic of whole body pain, not just localized pain, as well as whole body pleasure not just localized pleasure. There are a number of examples of whole body pain that people suffer from. And one common one is called fibromyalgia. I want to just first share with you a little bit of medical insight. A few months back, I did an Instagram live with Dr. Sean Mackey who's an MD medical doctor and a PhD at Stanford School of Medicine that was recorded and placed on my Instagram. If you want to check it out, we can provide a link to that in the show notes. Dr. Mackey is the Chief of the Division of Pain at Stanford School of Medicine. So he's a scientist. He studies pain and he treats patients dealing with various forms of pain, whole body pain, like fibromyalgia, acute pain, et cetera. And he shared with me something very interesting, which is that anytime you hear or see the word syndrome, that means the medical establishment does not understand what's going on. A syndrome is a constellation of symptoms that point in a particular direction or some general set of directions about what could be going on, but it doesn't reveal a true underlying disease necessarily. It could be aggregative diseases or it could be something else entirely. And I want to make sure that I emphasize the so-called psychosomatic phenomenon. I think sometimes we hear psychosomatic and we interpret that as meaning all in one's head. But I think it's



important to remember that everything is neural, whether that's pain in your body 'cause you have a gaping wound and you're hemorrhaging out of that wound or whether or not it's pain for which you cannot explain it on the basis of any kind of injury. It's all neural. So saying body, brain, or psychosomatic it's kind of irrelevant. And I hope someday we move past that language. Psychosomatic is interesting. There was a paper that was published in 2015, and then again in 2020 a different paper focused on the so-called psychogenic fevers or psychosomatic effects. I just briefly want to mention this because it relates back to pain. These studies have shown that there are areas of the so-called thalamus, which integrates and filter sensory information of different kinds. And within the brainstem, an area called the DMH and I can also provide a link to this study if you like, that shows that there is a true neurological basis. There are brain areas and circuits that are related to what's called psychogenic fever when we are stressed. And in particular, if we think that we were injured or that we were infected by something, we can actually generate a true fever. It is not an imagined fever. It is our thinking generating an increase in body temperature. And so this has been called psychosomatic. It's been called psychogenic, but it has a neural basis. So when we hear syndrome and a patient comes into a clinic and says that they suffer for instance, from something which is very controversial frankly like chronic fatigue syndrome, some physicians believe that it reflects a real underlying medical condition, others don't. However, syndrome means we don't understand. And that doesn't mean something doesn't exist. Fibromyalgia or whole body pain for a long time was written off or kind of explained away by physicians and scientists frankly, my community as one of these syndromes.

01:04:40 Fibromyalgia, Naltrexone, Protocol 5: Acetyl-L-Carnitine

It couldn't be explained. However, now there is what I would consider and I think others would and should consider from understanding of at least one of the bases for this whole body pain. And that's activation of a particular cell type called glial. And there's a receptor on these glial for those of you that want to know called the toll 4 receptor and activation of the toll 4 receptor is related to certain forms of whole body pain and fibromyalgia. Now, what treatments exist for fibromyalgia. And even if you don't suffer from fibromyalgia, and even if you don't know anyone who does this is important information because what I'm about to tell you relate to how you and your body, which is you of course can deal with pain of any kind. And there are actually things that one can

do and take that can encourage nerve health in general. In other conditions like diabetic neuropathy, but in all individuals. So there are clinical data using a prescription drug. This is work that actually was done by Dr. Mackey and colleagues. The drug is called naltrexone. Naltrexone is actually used for the treatment of various opioid addictions and things of that sort, but it turns out that a very low dose, I believe it was a one 10th the size of the typical dose of naltrexone has been shown to have some success in dealing with and treating certain forms of fibromyalgia. And it has that success because of its ability to bind to and block these toll four receptors on glial. So this so-called syndrome or this thing that previously was called a syndrome, fibromyalgia actually has a biological basis. It was not just in patients heads. And I really tip my hat to the medical establishment including Dr. Mackey and others who explored the potential underlying biologies of things like fibromyalgia and are starting to arrive at treatments. Now, I'm not a physician, I'm a professor, so I'm not prescribing anything. You should talk to your doctor of course, if you have fibromyalgia or other forms of chronic or whole body pain to explore whether or not these low dose naltrexone treatments are right for you. But I think it's a beautiful case study if you will, not a case study of an individual patient, but a case in study of linking up the patient's self-report of these experiences and using science to try to establish clinical treatments. There's another treatment, or I should say there's another approach that one could take. And again, I'm not recommending people do this necessarily. You have to determine what's right and say for you, I cannot do that. There's no way your situation's very far too much, and it would be outside of my wheelhouse to prescribe anything, but there's a particular compound which in the United States is sold over the counter and in Europe is prescription. It's one that I've talked about on this podcast before for other purposes. And that compound is acetylcarnitine. Acetylcarnitine as I mentioned is by prescription in most countries in Europe and the US you can buy this over the counter. There is evidence that acetylcarnitine can reduce the symptoms of chronic whole body pain and other certain forms of acute pain at dosages of somewhere between one to three and sometimes four grams per day. Now acetylcarnitine can be taken orally. It's found in 500 milligram capsules, as well as by injection. By injection in the States in the United States that is also requires a prescription or requires a prescription I should say. The over-the-counter forms are generally capsules or powders. Those apparently do not require a prescription. There are several studies exploring acetylcarnitine in this context, as well as for diabetic neuropathy. And what's interesting about acetylcarnitine is it's one of the few compounds

that isn't just used for the treatment of pain, but has also been shown in certain contexts to improve peripheral nerve health generally. And for that reason, it's an interesting compound. I've also talked about acetylcarnitine on here previously, because it has robust effects on things like sperm motility and health, including the speeds at which sperms swim, how straight they swim turns out that swimming for sperm is more efficient if they swim straight, as opposed to like those kids in on the swim team, they're like banging up against the lane lines and zigzagging all over the place. So it does turn out to be the case that the quickest route between any two places is a straight line and the good sperm know that, and the less good sperm don't seem to know that. And acetylcarnitine seems to facilitate straight swimming trajectories as well as speed of swimming and overall sperm health. And there is evidence from quality peer reviewed studies showing that acetylcarnitine supplementation can also be beneficial for women's fertility in ways that it affects perhaps we don't really know the mechanism, health and status of the egg or egg implantation. There are a large number of studies on acetylcarnitine. You can look those up on Pub Med, if you like, or on examine.com. There are some studies that I don't think are included there which are particularly interesting. One that I just would like to reference the last name of the first author is Mahdavi M-A-H-D-A-V-I. The title of the paper is Effects of L-Carnitine Supplementation on Serum Inflammatory Markers and Matrix Metalloproteinases Enzymes in Females with Knee Osteoarthritis. So this is a randomized double blind placebo controlled pilot study that showed really interesting effects of short term supplementation of acetylcarnitine. Longer term, the effects were less impressive. So it's pretty interesting that this compound has so many different effects. How could it have these effects? Well, it appears that it's having these effects through its impact on the so-called inflammatory cytokines. Inflammatory cytokines for those of you that don't know are secreted by the immune system in response to different stressors, physical stressors, mental stressors too food that you eat that isn't good for you. The so-called hidden sugars. Yes, will increase inflammation if they're ingested too often, or in amounts that are too high in quantity. Things like Interleukin 1 beta, things like C-reactive protein, things like interleukin 6. Interleukin 6 is kind of the generic inflammatory marker that all studies refer to. And yet there are other interleukins, please note that there are other interleukins like interleukin 10 that are anti-inflammatory. So immune system can secrete inflammatory molecules to deal with wounds and stress and things. And in the short term that's good, and in the longterm that's bad. And it can secrete anti-inflammatory cytokines like IL10.

And these matrix metalloproteinases, it's kind of a mouthful, but these matrix metalloproteinases are very interesting. Anytime you see A-S-E, ASE that's generally an enzyme, which means that these compounds in this case, these matrix metalloproteinases are used to break down certain elements around wounds and scarring which might sound like a bad thing, but in some cases is good because it allows certain cells like glial cells so-called microglia to come in like low ambulances, like low paramedics and clean up wounds. So scarring and inflammation is kind of a double-edged sword. It can be good, but too much scarring. If it contains a wound too much, doesn't allow the infiltration of cell types to move in and take care of that wound and heal it up. So it appears that L-carnitine is impacting a number of different processes, both to impact pain and perhaps, and I want to underscore perhaps,

01:12:24 Protocol 6: Agmatine, S-adenosyl-L-methionine (SAME), L-5-Methyltetrahydrofolate\*

but there are good studies happening now, perhaps accelerate wound healing as well. As long as we're talking about acute pain and chronic pain and supplementation and non-prescription drugs, at least in the United States that people can take to deal with pain of various kinds, I'd be remiss if I didn't mention the two that I get asked most often about, which are agmatine and S-adenosyl-L-methionine, which is sometimes called SAME. Both of those have been shown to have some impact categorized on examine as notable impact on various forms of pain, due to osteoarthritis, or due to injury of various kinds of indifferent subject population, men, women, people of different ages, et cetera. SAME in particular has been interesting because it's been shown head to head with drugs like Naproxen and other drugs of that sort, which are well established and sold over the counter in the US to work at least as well as some of those compounds at certain doses. But it's also shown that SAME and some of those things take more time in order to have those effects. In fact, head to head with things like Naproxin have been shown that they can take up to a month in order to have the pain relieving effect. Now, whether or not that makes them a better choice or a worst choice really depends on your circumstances. I'm certainly not recommending that anybody take anything, but I do think it's interesting and important to point out that things like agmatine, things like SAME have been shown under certain circumstances to be beneficial for pain and they are outside the realm of prescription drugs. I think this is a growing area of some people call

them supplements, some people call them nutraceuticals. Look, at the end of the day these are compounds that affect cellular processes. And the more that we understand how they affect those cellular processes as we now do for things like acetylcarnitine, I think the more trust that we can put into them, or the more to which we might want to avoid them because of some of the side effects or contra-indications that those compounds could have. If you're interested in those other compounds, I do invite you as I always do to check out [examine.com](http://examine.com), but also to do your research on those compounds by simply putting them into Google or putting them into PubMed, which would be even better. And if you are going to go into PubMed, if you're going to start playing scientist, which I do encourage you to do, I would encourage you to not just read abstracts, but if you can, if the studies are freely available, I realized not all of them are freely available to try and read those studies at least to the extent that you can. There's a particularly nice study that you might look at that was published in 2010 in *Pain Medicine*, which is Keynan et al K-E-Y-N-A-N, which looked at the safety and efficacy of dietary agmatine sulfate on lumbar disc associated radiculopathy not laughing at the condition. It's a painful condition that describes a, it's a kind of a range of symptoms that relate to pinching of nerves. The spinal columns, I was laughing at my pronunciation of it. That particular study is quite good. And the conclusion of that study that they drew was that there were limited side effects and that dietary agmatine sulfate is safe and efficacious for treating and alleviating pain and improving quality of life and lumbar-disc associated pain. However, there were very specific dosage regimens that were described there and duration of treatment. And so you should not take anything that I say or that study to mean that you can just take this stuff willy-nilly or at any concentration of course, or dose. You always want to pay attention to what the science says. That paper fortunately is freely available online. And we will also provide a link to that study. For those of you that are interested in SAME and its usage for the treatment of various types of pain, and perhaps other benefits, a number of companies have stopped making SAME instead what they're now focusing on is what they think is a better or more bioavailable alternative, which is 5-methyltetrahydrofolate or 5-MTHF. This molecule is necessary for converting homocysteine to methionine, which is then converted to SAME so rather than taking SAME directly, the idea is to take something that's upstream of SAME and make more SAME endogenously available. This is a different strategy. I've talked about this strategy before for increasing other things like growth hormone, et cetera. There's always this question of whether or not in trying to

increase the amount of a particular molecule in the body, whether or not taking that specific molecule was the best thing or working further upstream as it's referred to working on the precursor or increasing the levels of the precursor is the better way to go. It appears that this 5-MTHF is the strategy that people are now taking in place of taking SAME directly. So in other words, they're taking this

01:17:27 Acupuncture: Mechanism, Non-Responders, Itch & Inflammation

in order to get elevated levels of SAME. Now, I'd like to turn our attention to a completely non drug, non supplement related approach to dealing with pain. And it's one that has existed for thousands of years. And that only recently has the Western scientific community started to pay serious attention to, but they have started to pay serious attention to it. And there is terrific mechanistic science to now explain how and why acupuncture can work very well for the treatment of certain forms of pain. Now, first off, I want to tell you what was told to me by our director or Chief of the Pain Division at Stanford School of Medicine, Dr. Sean Mackey, which was that some people respond very well to acupuncture and others do not. And the challenge is identifying who'll respond well and who won't respond well. Now, when I say won't respond well, that doesn't necessarily mean that they responded in a negative way, that it was bad for them, but it does appear that a fraction of people experienced tremendous pain relief from acupuncture and others experience none at all or very little to the point where they have to seek out other forms of treatment. The science on this is still ongoing. There was actually an excellent paper published on this in the Journal of the American Medical Association, one of the premier medical clinical journals. And it basically reinforced the idea that you have responders and non-responders. A number of laboratories have started to explore how acupuncture works. And one of the premier laboratories for this is Qiufu Ma's lab at Harvard Medical School. Qiufu has spent many years studying the pain system and a system that's related to the pain system, which is the system that controls our sensation of itch. Just as a brief aside about itch, itch and pain are often co associated with one another. I was recently in Texas, and I will tell you, they have some mean mosquitoes. They're small, but whatever they're injecting into your skin. Well, here I am talking now about my subjective experience of pain, whatever they injected into my skin felt to me like the most extreme mosquito bites I've ever had, not while they were biting me, not while they were injecting the venom, but boy, those Texas mosquitoes

make me itch. How do they do it? Well, their venom creates little packets of so-called histamine that travel around those packets are called mast cells, little packets of histamine that go to that location and make me and presumably you want to scratch those mosquito bites. I scratch mine you scratch yours, but we both scratch our mosquito bites. And when we do that, the histamines are released. That gets red and inflamed and the itch even worse. The inflammation is actually caused by the histamine. Well, that experience of inflammation and pain and itch is what we call a pyrogenic experience. So we we have pain which is nociception, essentially, I know that the pain of aficionado always get a little upset because they say, oh, there's no such thing as a pain receptor, it's no susceptible receptors and pain is subjective experience. Yes, I acknowledge all that. But for fluency, let's just think about pain as a certain experience and itch as a separate experience, but they often exist together because those mosquito bites were what I would call painful, or at least not pleasant. They didn't just itch, they were also painful nuts because itch brings with it inflammation and inflammation often brings with it pain relief, but it can also bring with it the sensation of pain. So itch and pain are two separate phenomenon. It was actually discovered through a really interesting phenomenon that relates to something that is actually consumed in supplement form, which is this tropical legume. It's actually a bean called *Mucuna pruriens*. That's M-U-C-U-N-A that's one word P-R-U-I-E-N-S *Mucuna pruriens* is a bean, it's as legume that this bean is 99% L-DOPA. It's dopamine or rather it's the precursor to dopamine and people buy this stuff and take it over the counter as ways to increase their levels of dopamine. It does make you feel really dopamine doubt, meaning it makes you feel a little high and really motivated and really energetic a lot like other drugs that will do that. I don't necessarily recommend taking *Mucuna pruriens*. I personally don't like taking it. Doesn't make me feel good. I crash really hard when I take it. But on the outside of this bean is a compound that makes people itch. So they remove this when you take it in supplement form. In fact, it's usually in capsule form, but the outside of this bean, it's like a hairy bean. And those little hairs contain a compound, which was actually used to study and identify these itchy receptors in the skin. So we don't have time to go into all the details of itch, but it's pretty interesting that you have these compounds out in nature that can make us itch. Inside them they have dopamine. I mean, this is really weird, but plant compounds are really powerful. So don't let anyone tell you that because something's from a plant or an earth that it's not powerful. There are very powerful plant and herb compounds. *Mucuna pruriens* being one of them with

dopamine on the inside and itchy stuff on the outside. Now, what does this all have to do with acupuncture? Well, Qiufu Ma's lab has not just identified the itch pathway, this pruritus genes as they're called, which causes itch and the pyrogenic phenomenon of itch being separate from pain. His lab has also studied how acupuncture causes relief of, but also can exacerbate pain. Now, the form of acupuncture that they explored was one that's commonly in use called electroacupuncture. So this isn't just putting little needles into different parts of the body. These needles are able to pass an electrical current, not magically, but because they have a little wire going back to a device and you can pass electrical current. Here's what they found. This is a study published in the journal *Neuron*, excellent journal, very high stringency. So what Qiufu Ma's lab found was that if electroacupuncture is provided to the abdomen, to the stomach area, it creates activation of what are called the sympathetic ganglia. These have nothing to do with sympathy in the emotional sense has to do with the stress response. Sympa just means together. So it activated a bunch of neurons along the spinal cord. And the activation of these neurons evolves neural adrenaline and something called NPY neuropeptide Y. The long and short of it is that stimulating the abdomen with electroacupuncture was either anti-inflammatory or it could cause inflammation. It could actually exacerbate inflammation depending on whether or not it was of low or high intensity. Now that makes it a very precarious technique. And this may speak to some of the reason why some people report relief from acupuncture and others do not. However, they went a step further and stimulated other areas of the body using electroacupuncture. And what they found is that stimulation of the legs of the hind limbs, as it's called in animals, and the legs in humans caused a circuit, a neural circuit to be activated that goes from the legs up to an area of the base of the brain called the DMV not the DMH, which I mentioned earlier, but the DMV like you go to the DMV, which is a miserable experience for most people, forgive me, DMV employees, but let's be honest most people don't enjoy going to the DMV as patrons, but we have to so we go. The DMV and low intensity stimulation, this electroacupuncture of the hind limbs activated the DMV and activated the adrenal glands, which sit at top of your kidneys and cause the release of what are called catecholamines. And those were strongly anti-inflammatory. In other words, electroacupuncture of the legs and feet can, if done correctly, be anti-inflammatory and reduce symptoms of pain. And can we think accelerate wound healing because activations of these catecholaminergic pathways can accelerate wound healing as well. So the takeaway from this is that while there are



thousands of years and millions of subjects involved in explorations of electroacupuncture and acupuncture, Western medicine is starting to come into this and start to explore underlying mechanism. Now, for those of you that love acupuncture and are real proponents of it, it's worked for you, you might say, well, why does Western medicine even need to come into this? Why should they even be exploring this? But we should all be relieved that they are because what's starting to happen now is that as the mechanistic basis for this is starting to come to light, insurance coverage of things like acupuncture is starting to emerge as well. And this is in contrast to other therapies for which there's a lot of anecdotal evidence, but very little mechanistic understanding. One example of that would be laser photo biomodulation the use of lasers of different types really to treat pain and to accelerate wound healing. A lot of people claim that this can really help them. However, most places, at least in the States, won't cover this with insurance or don't perform this in standard clinics. And the reason is the underlying mechanism isn't known. I'm not going to get into the argument about whether or not mechanistic understanding should or should not be required in order to have insurance coverage of things that work. That's not what this is about. And that actually will be a boring discussion because I'm shouting at a tunnel through you. And I wouldn't be able to hear you shout back no matter what your stance on that is, but just trust me when I say that I am both relieved and delighted to hear that excellent medical institutions like Stanford are starting to think about electroacupuncture and how it can work. That places like Harvard Medical School are starting to explore this at a mechanistic level. And I do believe that there's an open-mindedness that starting to emerge for instance, the National Institutes of Health, not only has an institute for mental health and cancer research and an eye institute, but now complementary health, the so-called NCCIH. National Institutes of Complementary Health that is exploring things like electroacupuncture, meditation, various supplements and things of those sort. I do think that we're entering a new realm in which things like pain and pain management will be met with more openness

01:28:20 Laser Photobiomodulation, Protocol 7: Hypnosis (reveri.com)

by all physicians, at least that's my hope. So please take that into consideration right now. The mechanistic evidence for laser photobiomodulation is not strong. One of the major issues or the barriers to that is that most of the studies that are out there were

actually paid for by companies that build devices for laser photobiomodulation. And so we really need independent studies funded by federal institutions that have no bias or financial relationship in order to gain trust in whatever data happen to emerge. There is a technique that at one time was considered alternative, but now has a lot of mechanistic science to explain how it works, and it does indeed work for the treatment of chronic and also for acute pain. And that treatment is hypnosis in particular self-hypnosis. Now, my colleague at Stanford in fact, my collaborator, Dr. David Spiegel, our Associate Chair of Psychiatry has devoted his professional life to developing hypnosis tools that people can use to help them sleep better, focus better, stay motivated, et cetera. While most people hear hypnosis and they think, oh, this is stage hypnosis. People walking around like chickens are being forced to laugh or fall asleep on command, et cetera. This is completely different than all that. This is self hypnosis and there are now dozens, if not more quality peer reviewed studies published in excellent journals done by Dr. Spiegel and others at other universities. It really all has to do with how self-hypnosis can modulate activity of the prefrontal cortex

#### 01:30:00 Protocol 8: Pressure-Based Pain Relief, "Gate Theory of Pain (Relief)"

and related structures like the insula. The prefrontal cortex is involved in our executive function as it's called, our planning, our decision making, but also how we interpret context, what the meaning of a given sensation is. And that's extremely powerful. I just want to remind everybody that the currency of the brain and body has not changed in hundreds of thousands of years. It's always been dopamine, serotonin, glutamate, GABA, testosterone, estrogen. What's changed are the contingencies, the events in the world that drive whether or not we get an increase or decrease in testosterone or estrogen, the events in the world that dictate whether or not we get an increase or a decrease in dopamine. Believe me, the events that drove those increases and decreases were very different even a 100 years ago than they are now. And as we create new things and societies change, et cetera, they will continue to exchange information in the same currency, which is dopamine, serotonin, and all these other neuromodulators and chemicals. Hypnosis takes advantage of this by allowing an individual, you, if you like to change the way that you interpret particular events and to actually experience what would be painful as less painful or not painful. And that's just the example of pain. Hypnosis is powerful for other reasons too. It actually can help

rewire neural circuits so that you don't experience as much pain so that you can sleep faster, focus faster. If this is all sounding very fantastical well, it's supported by data. The data are that when people do self-hypnosis even brief self-hypnosis of 10 or 15 minutes, a few times a week, maybe even returned to that hypnosis by just using a one minute a day hypnosis, they can achieve significant and often very impressive degrees of pain relief in chronic pain whether or not that chronic pain arises through things like fibromyalgia or through other sources. If you want to check this out, there's a wonderful zero cost resource that's grounded in this work. It's the app [reveri.com](https://www.reveri.com). So R-E-V-E-R-I.com. There you can download a zero cost app for Apple phones or for Android phones. And there are a variety of different hypnosis scripts. These are actually self hypnosis scripts, and you'll actually hear Dr. David Spiegel talking to you. He can teach you about hypnosis and how it works. There are links to scientific studies that web address that I gave you before [reveri.com](https://www.reveri.com). You can see the various studies and the various write-ups related to those studies and how this all works. And they're simple protocols. You just click on a tab and you listen to the self-hypnosis and it will take you into hypnosis. And several of those hypnosis grips have been shown clinically to relieve certain patterns of chronic pain. So it's a powerful tool, and I encourage you not to write off the non-drug non supplement tools as less than powerful because indeed many people experience tremendous relief from them. And of course, they also can be combined with drug treatments if that's right for you or with supplements and things of that sort to treat pain, if that's right for you. So again, electroacupuncture now often supported by insurance, not always, but often. Great mechanistic data starting to emerge. Hypnosis, terrific tool. There's even the self-hypnosis tool that one can access through the zero cost app Reveri and lots of great clinical data and scientific mechanistic data. There are neuro imaging studies showing that different brain areas are activated in hypnosis the so-called default network, kind of where your brains is kind of idles and the different circuits that are active in at rest shift with hypnosis and shift long-term in ways that positively conserve you. And then these things like laser photobiomodulation still more or less in that experimental medical community. I should say, Western Medical Community, not so certain, but hopefully there will be data soon, and hopefully those data will point to mechanisms that allow the insurance companies and other sort of medical bodies to support them if indeed they have a mechanistic basis. I just want to briefly touch on a common method of pain relief that speaks to a more general principle of how things like electroacupuncture, and also some of these new emerging techniques of kind of like

active tissue release and this principle that you hear a lot about in sports medicine now that when you have pain or injury at one site, that you should provide pressure above and below that site. You may have seen this in the Olympics, which is ongoing now where people will put tape on their body at certain locations oftentimes. The logic or what they're saying is that this is designed to create relief in a joint or in a limb that's below the tape, not necessarily under the tape, but above or below. So for instance, if there's pain in one shoulder, sometimes we'll put it on the trapezius muscle or things of that sort. It turns out that there is a basis for this because of the way that these different nerves run in from the skin and from the muscles up into the spinal cord and into the brainstem providing pressure on one nerve pathway can often impact another pathway. And the simplest and most common example of this is one that we all do instinctually or intuitively even animals do this. This is something that in the textbooks is all called the Gate Theory of Pain developed by Melzack and Wall kind of classic theory. Basically we have receptors in our skin, the so-called C fibers, that's just a name for these little wires that come from a particular class of DRGs that's very thin that brings about certain kinds of nociceptive information. I want to say pain information, but then the pain people believe are not their pain people. Sometimes they're a pain because what they tell me is they're on pain receptors okay, nociceptors That information comes in C fibers and what happens when we injure something well, provided that we won't damage it worse by touching it, oftentimes what we will do is we will rub the source of pain or the location in which we were experiencing pain. And it turns out that's not an unuseful thing to do. When we rub our skin or an area, or we provide pressure nearby it, we activate the so-called A fibers, the bigger wires and neurons that innervate, meaning they jut into that area of skin. And those A fibers, the ones that respond to mechanical pressure actually are able to inhibit those C fibers, the ones that are carrying that so-called pain information. So rubbing an area or providing pressure above or below an injury actually provides real pain relief support for the location of that injury or that pain because of the way that these different patterns or these different types of neurons interact with one another. And when I say it inhibits it, I don't mean that it like shouts at it, what it does is it releases it's literally kind of like vomits up a little bit of a neurotransmitter called GABA. And GABA is a neurotransmitter that inhibits it quiets the activity of other neurons. And so it's acting as kind of an analgesic, if you will, it's acting as its own form of drug that you make with your body to quiet the activity of these pain neurons. So rubbing a wound provided it doesn't damage the wound worse or providing pressure above or below

typically it's above a particular injury can have a real effect in relieving some of the pain of that injury. And some people have speculated this as through fascia, or this is through other bodily organs and tissues. And it might be we're going to do a whole episode on fascia. It's extremely interesting tissue, but right now it seems that the main source of that pain relief is through this A fiber inhibition

01:37:53 Redheads & Pain Thresholds, Endogenous Opioids

of these C fibers so-called Melzack and Wall Gate Theory of Pain if you'd like to look it up and learn about that further. Now, let's talk about a phenomenon that has long intrigued and perplexed people for probably thousands of years. And that's redheads. You may have heard before that redheads have a higher pain threshold than other individuals. And indeed, that is true. There's now a study that looked at this mechanistically. There's a gene called the MC1R gene. And this MC1R gene encodes for a number of different proteins. Some of those proteins of course are related to the production of melanin. This is why redheads often not always, but often are very fair skinned. Sometimes have freckles, not always. And of course have red hair. Some people are really intense ginger's not psychologically or emotionally intense perhaps that too, but meaning their hair is very, very red. Others, it's a lighter red. So of course there's variation here, but this gene, this MC1R gene is associated with a pathway that relates to something that I've talked about on this podcast before during the episode on hunger and feeding and this is POMC. POMC stands for pro-opiomelanocortin and POMC is cut up. It's cleaved into different hormones, including one that enhances pain perception. This is melanocyte stimulating hormone. And another one that blocks pain beta endorphin. Now, if you listen to the episodes on testosterone and estrogen and the episodes on hunger and feeding, some of these molecules will start to ring a bell. Things like melano stimulating hormone relate to pigmentation of the skin relate to sexual arousal, et cetera, but it turns out that in red heads, because of the fact that they have this gene, this MC1R gene, the POMC Pro-opiomelanocortin, that's cut into different hormones, melanocyte-stimulating hormones and another one beta endorphin. Beta endorphin should cue you to the fact that this is in the pain pathway. The endorphins are endogenously made, meaning made within our body opioids. They actually make us feel numb in response to certain kinds of pain. Now, not completely numb, but they numb or reduce our perception of pain because of the ways in which they are released from

certain brain centers. We'll talk about those brain centers in a moment. So what's really interesting is that this study showed that the presence of these hormones is in everybody. We all have melanocortin 4, we all have beta endorphins. We all have POMC et cetera, but red heads make more of these endogenous endorphins. And that's interesting. It allows them to buffer against the pain response. I have a personal anecdote to share with you about this red head and heightened levels of pain tolerance phenomenon. Obviously I'm not a redhead. I don't dye my hair, but my partner for many years was a red head and still is a red head. She had bright red hair and had that since childhood. Well, we had the fortunate experience of becoming friends with Wim Hof and family. They actually came out to visit us and did a series of seminars in the bay area. This was in 2016, as I recall. And my partner, she had never done an ice bath. She had never done any kind of real cold water exposure experience before, but as one particular gathering as is often the case when women's around, there was an ice bath and a number of people were getting into this thing. This was actually before a dinner event. And I think for most people who have never done an ice bath getting in for 30 seconds or a minute is tolerable, but it takes some effort. It takes some willpower and take some overcoming that pain barrier 'cause it is a little bit painful. Not a lot. Some people can stay in longer three minutes, five minutes without much discomfort. What was incredible is that without any desire to compete with anybody else, my partner redhead got into the ice bath and just like sat there for 10 minutes. In fact, at one point she just kind of turned to me and said, "I don't really feel pain. I'm not really in pain." And Wim loved this. Wim thought it was great. He thought it was the most terrific thing in the world. And he got back in the ice bath and they became fast friends, and I think they're probably still fast friends. So in any event, that's an end of one. What we call an anecdote example. Anecdote is not really a term that we should use too much 'cause it's N of one anecdotes are just that. They're just anecdotes. But it's been described many times in various clinics by anesthesiologists, by observation of coaches, et cetera, that redheads men and women who are redheads seem to have this higher pain threshold. And it does seem to be because their body naturally produces ways to counter the pain response. They produce their own endogenous opioids. Now this of course should not be taken to mean that redheads can tolerate more pain and therefore should be subjected to more pain, all it means is that their threshold for pain on average, not all of them, but on average is shifted higher than that of other individuals. And it remains to be determined whether or not other light skin, light haired individuals also have a heightened level of

pain threshold. And I should mention because I mentioned the ice bath that of course pain threshold is something that can be built up and provide you do that safely in ways that aren't damaging your tissues because of course, pain is a signal that is designed to help you to keep from harming yourself, but provided that you can do that in a way that's safe and doesn't damage your tissues, increasing your pain threshold through the use of things like ice baths is something that really can be done. It has a lot to do with these contextual or top-down modulations of the experience. You can tell yourself that this is good for me, or I'm doing this by choice or whatever it is. You can distract yourself.

#### 01:44:02 Protocol 8: Love & Pain, Dopamine

There are a huge number of different ways that one could do that. One of the more interesting ways for which there are actually really good scientific data come from my colleagues, Sean Mackey's Lab. And that actually looked at how love and in particular, the experience of obsessive love could actually counter the pain response, not just in redheads, but in everybody. So that study I'll just briefly describe it involved having people come into the laboratory and experience any one or a number of different painful stimuli, but they had selectively recruited subjects that were in new relationships for which there was a high degree of infatuation so much so that the people couldn't stop thinking about or communicating with that new partner up to 80% of their waking time, which is a lot. That constant obsessing about that partner was correlated with. It wasn't causal necessarily, but was correlated with the ability to sustain higher levels of pain than people who were in more typical non obsessive forms of love, longstanding relationships, where there wasn't long obsessive love rather. And of course in this study, there were a lot of good control groups. They included a distractor, they included people obsessing about other things, their pet, et cetera. They included other forms of love and attachment, but it does seem that certain patterns of thinking can allow us to buffer ourselves against the pain response. And that should not be surprising. Certain forms of thinking are associated with the release of particular neuromodulators in particular dopamine. And dopamine, it may seem is kind of the thing that underlies everything, but it's not. Dopamine is a molecule that's associated with novelty expectation, motivation, and reward. We talked about this at the beginning of the episode, that it's really the molecule of expectation and motivation and hope and excitement more than it's associated with the receipt of the reward. Well, dopamine is coursing throughout the

brain at heightened levels and coursing throughout the body at heightened levels when we fall in love. This probably has some adaptive mechanism that ensure paired bonding between people or who knows, maybe it ensured not bonding to multiple people. Nobody really knows how dopamine functions in terms of pair bonding, but it is known that when people fall in love, new relationships create very high levels of dopamine. And that's probably the mechanistic basis by which these people were able to buffer the pain response by thinking about their partner or this new relationship that they're in almost obsessively or obsessively. Now that raises a deeper question we should always be asking. Yeah, but how, how? Well, the dopamine system can have powerful effects on the inflammation system. And it doesn't do this through mysterious ways. It does this by interacting through the brainstem and some of the neurons that innervate the spleen and other areas of the body, that deploy cells to go combat infection, inflammation, and pain. And the ways in which dopamine can modulate pain, and in this case, this particular study transform our experience of pain. Maybe even to something that's pleasurable is not mysterious. It's really through the activation of brainstem neurons that communicate with areas of our body, that deploy things like immune cells. So for instance, we have neurons in our brain stem that can be modulated by the release of dopamine and those neurons in the brainstem control the release of immune cells from tissues like the spleen or organs like the spleen. And those immune cells can then go combat infection. We've heard before that when we're happy, we're better able to combat infection, deal with pain, deal with all sorts of things that essentially makes us more resilient. And that's not because dopamine is some magic molecule, it's because dopamine affects particular circuits and tells in a very neuro-biological way in a biochemical way tells those cells and circuits that conditions are good. Despite the fact that there's pain in the body conditions are good. You're in love or conditions are good. You want to be in this experience. Or conditions are good this is for a greater cause that you're fighting or suffering for some larger purpose. So all of that has existed largely in the realm of psychology and even motivational literature in this kind of thing, but there's a real mechanistic basis for it. Dopamine is a molecule that can bind to receptor sites on these brain areas. Those brain areas can then modulate the organs and tissues of the body that can allow us to lean into challenge. And those challenges can be infection, it can be physical pain, it can be long bouts of effort that are required of us. And I think many people have described the feeling of being newly in love as a heightened level of energy, a capacity do anything. I mean, the whole concept of a muse is one in which some individual or some



thing either imagined or real enters our life and we can use that as fuel. And that fuel is chemical fuel and that chemical fuel is dopamine. And it really does allow for more resilience and can even transform the experience of pain or what would otherwise be pain

01:49:23 Pleasure & Reproduction, Dopamine & Serotonin, Oxytocin

into an experience of pleasure. So, along those lines, let's talk about pleasure. With all the cells and tissues and machinery related to pain, you might think that our entire touch system is designed to allow us to detect pain and to avoid tissue damage and well, a good percentage of it is devoted to that. A good percentage of it is also devoted to this thing that we call pleasure. And that should come as no surprise. Pleasure isn't just there for our pleasure. It serves adaptive role, and that adaptive role relates to the fact that every species has a primary goal which is to make more of itself otherwise it would go extinct. That process of making more of itself sexual reproduction is closely associated with the sensation and the perception of pleasure. And it's no surprise that not only is the highest density of sensory receptors in and on and around the genitalia, but the process of reproduction evokes sensations and molecules and perceptions associated with pleasure. And the currency of pleasure exists in multiple chemical systems but the primary ones are the dopamine system, which is the anticipation of pleasure and the work required to achieve the ability to experience that pleasure, and the serotonin system which is more closely related to the immediate experience of that pleasure. And from dopamine and serotonin stem out other hormones and molecules, things like oxytocin, which are associated with pair bonding. Oxytocin is more closely associated with the serotonin system biochemically and at the circuit level meaning the areas of the brain and body that manufacture a lot of serotonin, usually not always, but usually contain neurons that also manufacturer and make use of the molecule oxytocin. Those chemicals together create sensations of warmth, of well being, of safety. The dopamine molecule is more closely associated with hormones like testosterone and other molecules involved with pursuit and further effort in order to get more of whatever could potentially cause more release of dopamine.

01:51:40 Protocol 9: PEA, L-Phenylalanine (Precursor to Tyrosine)

So this is a very broad strokes, no pun intended description of the pleasure system. There are of course, other molecules as well. One in particular that's very interesting is something called PEA. PEA, it stands for Phenethylamine sometimes also referred to as Phenethylamine depending on who you are and where you live, how you pronounce it doesn't really matter. PEA is a molecule, which is incredibly potent at augmenting or increasing the activity of certain cells and neural circuits that relate to the pleasure system. PEA has purportedly been thought to be released in response to ingestion of things like certain forms of dark chocolate. Some people take it in supplement form. It's a bit of a stimulant, but it also seems to heighten the perception of pleasure in response to a particular amount of dopamine and or serotonin. So for instance, in a kind of a arbitrary experiment and units type example, if a given experience evokes a particular amount of serotonin and dopamine and gives rise to a subjective experience of pleasure of say level three out of 10, the ingestion of PEA prior to that experience can increase the rating of that experience as more pleasurable. Maybe a four or a five, or even a six. And PEA is known to be present in or I should say it's releases stimulated by a number of different compounds, such as dark chocolate, certain things like aspartame and certain people can actually increase the amount of PEA released. Some of these glutamate related molecules like aspartame or things are in the glutamate pathway can increase PEA release. And then some people will actually take PEA in supplement form for its mild stimulant properties as well as for increasing the perception of, or the ability to experience pleasure. It's not a sledgehammer. It's not like dopamine itself. People that take things like Mucuna pruriens, L-DOPA or drugs of abuse, which I certainly don't recommend things like cocaine or amphetamine experience tremendous increases in dopamine, not so much increases in serotonin. Some people will take serotonin in precursor form like 5HTP or serotonin itself, or they'll take the amino acid precursor like tryptophan. I'm not saying these things as recommendations for increasingly one sense of pleasure, I'm describing them because of what they do generally falls into two categories. The first category is to raise the foundation, what we call the tonic level of dopamine and serotonin. So if levels of serotonin and dopamine are too low, it becomes almost impossible to experience pleasure. There's a so-called anhedonia. This is also described as depression. Although it needn't be long-term depression. So certain drugs like antidepressants like Wellbutrin Bupropion as it's commonly called or the so-called SSRI, the serotonin selective re-uptake inhibitors like Prozac, Zoloft and similar will increase dopamine and serotonin respectively. They're not increasing the peaks in those

molecules. What we call the acute release of those molecules, what they're doing is they're raising the overall levels of those molecules. They're raising the sort of foundation or the tide if you will, think about it as your mood or your pleasure rather is like a boat, and if it's on the shore and it can't get out to sea, unless that tide is high enough, that's kind of the way to think about these tonic levels of dopamine and serotonin. Now, most of us fortunately, do not have problems with our baseline or autonomic levels of dopamine and serotonin release. Things like PEA in that case will cause a slight increase

#### 01:55:40 Contextual Control of Pleasure by Autonomic Arousal, Dopamine Baselines

in that tide and make the ability of certain experiences to increase dopamine further more available. What we call this in neurosciences so-called gain control. I can kind of turn up the volume, bring us closer to the threshold to activate certain circuits. And this is really what we mean when we say a neuromodulator, okay? This is why when you are very happy about something, let's say you're out with your friends. You're really excited. Maybe depending on where you live and what's going on in your area of the world right now, like I have a niece and she's been locked up in quarantine for a long time recently because it was deemed safe. She got to go to summer camp. I have never seen that kid so happy to spend with her friends. She was so excited and it was really amazing to see how excited she was. Her baseline levels of dopamine were clearly up so much so that when she saw her friends, she literally started squealing. They were squealing, she was squealing. Everyone was squealing. I wasn't squealing. I would admit it if I was squealing. I wasn't squealing, but it was such a delight to see and I'm sure that made my dopamine levels go up, which was, she was just so excited such that anything and everything felt like an exciting stimulus. This is pleasure, right? And I don't want to write off the experience from an neuro-biological reductionist standpoint, quite the opposite. It's really beautiful to see again this principle that different experiences and the experience of pleasure from different things. Seeing your friends for the first time, summer camp for a kid, whatever it might happen to be use the same currency, dopamine use the same currency serotonin. And this is a principle that I hope in listening to this podcast and even some of it's repetitive features from one episode to the next. I'm hoping that those will start to embed in your mind that the brain and body use these common currencies for different experiences. So yes, if your dopamine and serotonin, or

I should say if your dopamine and or serotonin levels are too low, it will be very hard to achieve pleasure to experience physical pleasure or emotional pleasure of any kind. That's why treatments of the sort that I described a minute ago might be right for you. Obviously we can't determine if they're right for you. It's also why they have side effects. If you artificially increase these molecules they're associated with pleasure, oftentimes you get a lack of motivation to go seek things like food. People don't get much interest in food 'cause why should they if their serotonin levels are already up. Again, there's a ton of individual variation. I don't want to say that these antidepressants are always bad. Sometimes they've saved lives. They've saved millions of lives. Sometimes people have side effects that make them not the right choice. So it has to be determined for the individual. Things like PEA or a more subtle effect. I should mention PEA supplementation is something that a number of people use but it's very short-lived. Because of the half-life of this molecule was very brief, the effect only lasts about 20 minutes or so. Things like L-dopa, Mucuna pruriens lead to longer baseline increases in dopamine. But remember, any time you raise a baseline, you reduce the so-called signal to noise. What it means is if you're riding around at really high dopamine, at first, everything will start to seem exciting like my niece and seeing her friends for the first time. Everything's exciting. But then what will happen is when your dopamine levels return to more normal levels, it will take a much greater dopamine increase of much bigger event, more novel, more exciting in order to achieve the sense that what you're experiencing is pleasurable. And this is because of the relationship between pleasure and pain. Now, in a future episode we are going to go deep into this relationship between pleasure and pain, but just briefly as a precursor to that and because it's relevant to the conversation that we've been having, you might want to be wary of any experience, any experience, no matter how it arrives,

01:59:40 Pleasure-Pain Balance

chemical, physical, emotional, or some combination, you might want to be wary of letting your dopamine go too high and certainly you want to be wary of it going too low. Because of the way that these circuits adjust. Basically every time that the pleasure system is kicked in in high gear, an absolutely spectacular event, you cannot be more ecstatic. There is a mirror symmetric activation of the pain system. And this might seem like an evil curse of biology, but it's not. This is actually a way to protect this whole

system of reward and motivation that I talked about at the beginning of the episode. It might sound great to just ingest substances or engage in behaviors where it's just dopamine, dopamine, dopamine, and just constantly be motivated, but the system will eventually crash. And so what happens is when you have a big increase in dopamine, you also will get a big increase in the circuits that underlie our sense of disappointment and re adjusting the balance. And with repeated exposure to high levels of dopamine, not naturally occurring wonderful events, but really high chemically induced peaks in dopamine, high magnitude, chemically induced peaks in dopamine. What happens is those peaks in dopamine start to go down and down and down in response to the same, what ought to be incredible experience. We start to what's called habituate or attenuate, and yet the pain increases in size. And this has a preservative function in keeping us safe, believe it or not. But what I just described is actually the basis of most if not all, forms of addiction something that we will deal with in a future episode in depth. So what should you think about all?

#### 02:01:24 Protocol 10: Controlling Pleasure, Dopamine & Motivation Over Time

How should you think about pleasure and how should you think about pain? What is too much pleasure? Well, that's going to differ from person to person, but to the extent that one can access pleasure repeatedly over time, ideally without chemical augmentation, certainly not excessive chemical augmentation, that means that this pleasure system is tuned up well and can continue to experience pleasure. However, if you find yourself engaging in the same behavior over and over again, but achieving less and less pleasure from it, chances are you want to adjust down how often you engage in that behavior. And or adjust down your expectation of reward every time you engage in that behavior. What do I mean by that? Well, at the beginning of the episode I talked about how dopamine will allow us to get into bouts of hard work. We will work very hard to pursue a reward, and that's really what dopamine does. And then when the reward comes that doesn't increase our dopamine. In fact, our dopamine levels go down. One of the key things that we can all do to adjust our ability to experience pleasure is to engage in that intermittent reward schedule. You can either adjust down the peak in dopamine, meaning not let yourself ever get too happy, but that's no fun, right? Life is about occasionally achieving or experiencing ecstasy, but every once in a while, remove the reward. And of course, I don't mean ecstasy the drug that's a separate matter. The

MDMA trials are a separate matter. Very interesting, I want to be clear. I meant psychological and physical ecstasy of the natural sort. I've immense interest in what's going on in the MDMA trials, but just for clarity purposes, that's a separate topic that we will cover in an episode very soon. So how do you adjust this dopamine system? Well, every once in a while at random, not in a predictable way, you remove the reward and that will keep you and your dopamine system tune up in the proper ways. The gain of the dopamine system, as we say, will be adjusted so that you can continue to experience dopamine and serotonin when you actually get the reward. This can be translated into a huge number of different domains, but I want to give some examples because I'm sure that many of you are asking, wait, what does this actually mean? Okay, let's say you're a student, or this could be a student in academia, or this could be a student of a physical practice. Every once in a while when you do something really well, maybe that's even just showing up to the practice rather than pat yourself on the back, just tell yourself yeah, that's the minimum that's expected of me. When everyone's excited about something that you're doing, maybe you're excited about it, try and adjust down your excitement a little bit. I know this might seem counterintuitive, but you're preserving the ability to experience excitement in a variety of contexts. Let's say you get a big monetary award. Well, that's great. I'm happy for you. And that's wonderful. However, you should be a little bit wary if you care about your dopamine system and you care about your ability to get subsequent monetary rewards, excuse me, awards rewards doesn't matter which through effort, if you want to be able to maintain the ability to exert effort, well, then you probably wouldn't want to run out and immediately buy something with that monetary reward. In other words, you wouldn't want to layer on more dopamine release, okay? You might, but you might not. You might skip it. What you'll find then is that your motivation is essentially infinite. This is what I described at the beginning of the episode. And again, it's because dopamine is this currency. It's like these days you hear a lot about Bitcoin, and Ethereum, and Dogecoin, and USs dollars, and Euros and other stuff. But the currency that you use in your body doesn't matter what external currency those are. In fact, as you watch the value of different currencies go up whether or not it's cryptocurrency or standard currency, the value is actually reflective of the dopamine that exists inside of people. So all the excitement about a particular currency crypto or otherwise is really just dopamine. That's the currency that we all use. And there's no negotiating that. That's just the way that we're built. Now, to give yet other examples. Let's say you're teaching other people how to do something and they do something

exceptionally well. If you reward them every single time. and in particular, if you reward them with something that's even greater than the experience of what they did. So let's say kids win a soccer game and they're ecstatic. They're jumping all over the place. They're super excited and you reward them with an even bigger experience, a celebration, you are actually inhibiting their ability to perform the same set of activities that led them to the win if, and I really want to underscore if you reward them every time. Of course we should reward kids and each other and ourselves for our accomplishments, but you don't want to do it every time. And sure there will be some disappointment

02:06:40 Protocol 11: Immediate, Non-Goal-Directed Pleasure, PAG

from suddenly removing the reward that you expected, but that's exactly the point. That's what keeps these circuits tuned up properly. Now there's the other form of pleasure, which is the more immediate visceral or sensory experience of pleasure. This is distinct from goals and goal-directed behavior. I'm talking about the immediate experience. This is more of the serotonergic system. There are other systems involved too, but this is also the system that draws out those endogenous opioids from a particular structure. We have a structure in the back of our brain called PAG P-A-G, it's the periaqueductal gray area. Very interesting brain area that is associated with pain, but also with pleasure because under certain conditions, it deploys endogenous opioids and gives us a kind of blissed out feeling. This is not like the opioids of the opioid epidemic sort that people take and unfortunately have led to tremendous amounts of suffering and abuse. These are endogenously released opioids. These are the kinds of opioids that come out from long distance bouts of physical exercise and running. These are the opioids that are deployed in response to giving birth and overcoming the tremendous pain of childbirth. So PAG is very contextual and there are few types of stimuli or I should say events in life... I'm really showing my nerdy side. There are a few types of stimulate, I'm talking about experiences that evoke endogenous opioid release from PAG. One is sexual activity. Sexual activity can increase pain threshold. And here I am not suggesting or getting involved in anyone's particular proclivities or personal experiences. You're welcome to editorialize this however you like, however, what I'm talking about are animal data and yes, human data as well, that show that pain thresholds are increased anytime PAG is activated because of the release of these endogenous opioids. There's also the

immediate experience of whether or not a particular form of touch

02:08:40 Direction of Touch: Pleasure Versus Pain, Arousal & Touch "Sensitivity"

is pleasurable or not. And there there's some very interesting biology that relates to really how those little wires from those DRGs innervate our skin. Work studies I should say done by David Ginty's lab at Harvard Medical School, the Ginty lab has spent years working on the somata sensory system, the touch system has identified a particular category of neurons that innervate the skin and then those neurons of course send that information up to the brain too. And they actually respond to direction of touch. Now, some of you might be more sensitive to this than others, but it turns out that certain hairs like to be deflected one way versus another. Whether you like cats or not, you can do this experiment. You can pet a cat in the direction that they're fur lies. So it lies down in a particular direction. You'll notice that there's actually a gene that dictates that the hairs lie down in a particular direction. And if you pet them in a way that's co-operating with that direction. So not pushing the hairs up, but rather stroking the hairs on the back of the cat. Well, you'll notice as they often like that. Not all cats some cats are pretty grouchy, but if you stroke their hair, they will often per, they'll often push into you. If you were to stroke their hair in the opposite direction, pushing the hairs up against the direction that they want to lie down, cats do not like that. And it turns out that people don't like that either. Some people do like to have their hair pushed in a direction against the direction in which it wants to lay down. But there is more typically response a feeling like it's pleasurable for instance, when someone brushes or combs their hair in the direction that it wants to lay down. And that's because the way in which these neurons, they innervate these hairs sends information up to the brain bifurcates actually, it splits into brain centers that evoke a sense of pleasure or a sense of not pleasure. It's not necessarily pain. So you might find that certain people are very particular. They like to be touched in a certain way, but not others. You might be one of those people. And areas of our skin that have high density of receptors are very, very sensitive in a real way, in a real sense of the word to patterns of touch and whether or not a touch is too firm or too light. And that will be modulated by overall levels of arousal. And when I talk about arousal, what I'm talking about is how alert or how sleep we are. It is impossible to experience pain when we are deep in sleep. I don't mean sleeping like of the typical night's sort. I mean, of the anesthesia sort. That's the purpose of anesthesia to bring the



brain and body into a deep plane of rest, very deep in fact, and it's very hard if not impossible to achieve or experience pleasure when we are in a very low state of arousal as well. When we are in heightened states of arousal, we can achieve pain, we can experience pain and we can experience pleasure. And under those heightened states of arousal, we are more sensitive. Literally the passage of electrical signals from those locations on the body that have heightened degrees or higher degrees, I should say of receptors, use your imagination. They include the lips, the face, the feet, and the genitals and nearby areas, literally nearby areas. Under conditions of higher arousal two things happen, the ability to achieve or experience pleasure at those locations goes up and our tolerance and our threshold for pain also goes up. So the principle here is that as our levels of arousal, that foundation of arousal goes up or down, so too goes up and down our ability to achieve pleasure and pain. And so these two extremes of being deep within anesthesia or another extreme as asleep or an heightened levels of arousal, our ability to achieve pleasure and pain are going to scale according to those. And this is why, and I'm certainly not suggesting this, but this is why some people will take stimulants or drugs of abuse that increase arousal in order to achieve pleasure of other kinds. The problem is is that those drugs in particular are things like cocaine and methamphetamine and amphetamine become their own form of reinforcement

02:13:00 Synthesis & How to Conceptualize Pain and Pleasure, Support

so much so that the person doesn't seek out any other form of excitement or arousal. So today we weren't talking about addiction. We weren't necessarily talking about motivation, but we touched on those topics as sort of a precursor of what's to come. We talked about the pathways in the skin and in the brain and elsewhere in the body that control our sense of pleasure and pain. We described a number of different tools ranging from hypnosis to different supplements, to electroacupuncture and various other tools that one could use to modulate your sense of pleasure or pain. And of course, in thinking about pleasure, we have to think about the dopamine system and the serotonin system and some of the related chemical systems. I realized that today's podcast had a lot of scientific details. We've timestamped everything for you so that you don't have to digest it all at once of course I don't expect that everyone would be able to understand all these details all at once. What's more important really is to understand the general principles of how something like pleasure and pain work. How they interact, and the very seldom

systems within the brain and body that allow them to occur and that modulator or change their ability to occur. And of course your subjective experience of pleasure or pain. So I do hope that this was on hole more pleasurable than painful for you. If you're enjoying this podcast and you're learning from it, and you'd like to support us, you can do that in a number of different ways. Some of which are totally cost-free. The first one is please subscribe to the YouTube channel. That really helps us. In addition, you can leave us comments and suggestions for future podcast episodes on the YouTube channel. You can also subscribe on Apple and or Spotify or all three that would really help us. And on Apple, you can leave us up to a five star review and leave us feedback. There are other ways to support the podcast as well. We have a Patreon that's [patreon.com/andrewhuberman](https://patreon.com/andrewhuberman). And there you can support the podcast at any level that you like. In addition, please check out our sponsors that we mentioned at the beginning of the podcast. We only work with sponsors and brands that we absolutely love their products and that we wholeheartedly endorse, and that we use ourselves. In addition, we've partnered with Thorne. Thorne as a supplement company, and we've partnered with them because they have the highest levels of stringency in terms of the quality of the ingredients they use and the quantity of the ingredients they use. By quantity I mean that unlike a lot of supplement companies out there, the amounts that are listed on the bottle are absolutely what you find in those capsules and tablets in the bottle. If you go to Thorne that's T-H-O-R-N-E/U/Huberman, you can see the supplements that I take and you can get 20% off any of those supplements as well as any of the other supplements that Thorne makes. Just go into the Thorne site through that portal, [thorne.com/u/huberman](https://thorne.com/u/huberman) and even if you navigate off from that location in the site, you'll get 20% off any of the items that you might select from other locations within the Thorne site. If you're not already following us on Instagram, it's Huberman Lab at Instagram, and there I do various tutorials about neuroscience, offer neuroscience related tools all backed by science. And last but not least, I thank you for your time and attention and thank you for your interest in science. [bright upbeat music]