Dr. Jack Feldman: Breathing for Mental & Physical Health & Performance | Huberman Lab Podcast #54

This episode my guest is Dr. Jack Feldman, Distinguished Professor of Neurobiology at University of California, Los Angeles and a pioneering world expert in the science of respiration (breathing). We discuss how and why humans breathe the way we do, the function of the diaphragm and how it serves to increase oxygenation of the brain and body. We discuss how breathing influences mental state, fear, memory, reaction time, and more. And we discuss specific breathing protocols such as box-breathing, cyclic hyperventilation (similar to Wim Hof breathing), nasal versus mouth breathing, unilateral breathing, and how these each effect the brain and body. We discuss physiological sighs, peptides expressed by specific neurons controlling breathing, and magnesium compounds that can improve cognitive ability and how they work. This conversation serves as a sort of \"Master Class\" on the science of breathing and breathing related tools for health and performance.

#HubermanLab #Neuroscience #Breathing



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- Welcome to the Huberman Lab Podcast, where we discuss science and science-based tools for everyday life. I'm Andrew Huberman, and I'm a Professor of Neurobiology and Ophthalmology at Stanford School of Medicine. Today, my guest is Dr. Jack Feldman. Dr. Jack Feldman is a distinguished Professor of Neurobiology at the University of California, Los Angeles. He is known for his pioneering work on the neuroscience of breathing. We are all familiar with breathing and how essential breathing is to life. We require oxygen, and it is only by breathing that we can bring oxygen to all the cells of our brain and body. However, as the work from Dr. Feldman and colleagues tells us, breathing is also fundamental to organ health and function at an enormous number of other levels. In fact, how we breathe, including how often we breathe, the depth of our breathing and the ratio of inhales to exhales actually predicts how focused we are, how easily we get into sleep, how easily we can exit from sleep. Dr. Feldman gets credit for the discovery of the two major brain centers that control the different patterns of breathing. Today, you'll learn about those brain centers and the patterns of breathing they control, and how those different patterns of breathing influence all aspects of your mental and physical life. What's especially wonderful about Dr. Feldman and his work is that it not only points to the critical role of respiration in disease, in health and in daily life, but he's also a practitioner. He understands how to leverage particular aspects of the breathing process in order to bias the brain to be in particular states that can benefit us all. Whether or not you are a person who already practices breathwork, or whether or not you're somebody who simply breathes to stay alive, by the end of today's discussion you're going to understand a tremendous amount about how the breathing system works and how you can leverage that breathing system toward particular goals in your life. Dr. Feldman shares with us his own particular breathing protocols that he uses, and he suggests different avenues for exploring respiration in ways that can allow you, for instance, to be more focused for work, to disengage from work and high stress endeavors to calm down quickly. And indeed, he explains not only how to do that, but all the underlying science in ways that will allow you to customize your own protocols for your needs. All the guests that we bring on The Huberman Lab Podcast are considered at the very top of their fields. Today's guest, Dr. Feldman, is not only at the top of his field, he founded the field. Prior to his coming into neuroscience from the field of physics, there really wasn't much information about how the brain controls breathing. There was a little bit of information, but we can really credit Dr. Feldman and his laboratory for identifying the particular brain areas that control different patterns of breathing and how that information can be leveraged towards health, high performance and for combating disease. So, today's conversation you're going to learn a tremendous amount from the top researcher in this field. It's a really wonderful and special opportunity to be able to his knowledge with you,

00:03:05 Sponsors: Thesis, Athletic Greens, Headspace, Our Breath Collective

and I know that you're not only going to enjoy it, but you are going to learn a tremendous amount. Before we begin, I'd like to emphasize that this podcast is separate from my teaching and research roles at Stanford. It is however, part of my desire and effort to bring zero cost to consumer information about science and science related tools to the general public. In keeping with that theme, I'd like to thank the sponsors of today's podcast. Our first sponsor is Thesis. Thesis as a company that makes nootropics. Now, I've talked before on the podcast and elsewhere about the fact that I don't really like the term nootropics, which means smart drugs, because smart means many different things in many different contexts. You've got creativity, you've got focus, you've got task switching. So, the idea that there will be one pill or one formula that could make us smarter and better at all those things at once, just doesn't stand up to logic. In fact, different chemicals and different brain systems underlie our ability to be creative or our ability to task switch or to be focused. And that's the basis of Thesis. Thesis as a company that makes targeted nootropics for specific outcomes. In other words, specific nootropics to get your brain into states that are ideal for what you're trying to accomplish. Thesis uses very high quality ingredients, many of which I've talked about before on the podcast, such as DHA, Gingko biloba, and phosphatidylserine. I talked about those in the ADHD podcast. Those are some of the ingredients in their so-called Logic formula. There's a lot of research showing that Gingko biloba can be very helpful for increasing levels of focus, and even for people with ADHD. However, I can't take it. When I take it, I get really bad headaches and I know some people who do and some people who don't get headaches when they take Gingko biloba. This is a great example of why nootropics need to be personalized to the individual. Thesis gives you the ability to try different blends over the course of a month and discover which nootropic formulas work best for your unique brain chemistry and genetics, and which ones are best for particular circumstances. So, they have a formulation for instance, which is Motivation. They have another formulation, which has Clarity. They've got another formulation, which is Logic. And each of these is formulated specifically to you and formulated to a specific end point or goal state of mind for your particular work. So as a consequence, the formulations that you arrive at will have a very high probability of giving you the results that you want. In addition to that detailed level of personalization, Thesis takes a step further by offering free consultations with a brain coach to help you optimize your experience, and dial in your favorite and best formulas. I've been using Thesis for close to six months now, and I can confidently say that their nootropics have been a total game changer for me. My favorite of the formulations is their Motivation formula that they've tailored to me. When I use that formula, I have very clear state of mind, I have even energy, and I use that early in the day until the early afternoon to get the bulk of my most important work done. To get your own personalized nootropic starter kit, you can go online to takethesis.com/huberman, take a three minute quiz and Thesis will send you four different formulas to try in your first month. That's takethesis.com/huberman and use the code Huberman at checkout to get 10% off your first order. Today's episode is also brought to us by Athletic Greens. Athletic Greens is an all-in-one vitamin mineral probiotic drink. I've been using Athletic Greens since 2012, and so I'm delighted that they're sponsoring the podcast. The reason I started taking Athletic Greens, and the reason I still take Athletic Greens is that it covers all of my vitamin, mineral and probiotic foundational needs. There's now a wealth of data showing that not only do we need vitamins and minerals, but we also need to have a healthy gut microbiome. The gut microbiome is a set of nerve connections that link the microbiota, literally microbacteria that live in our guts and that are healthy for us with our brain function. And our brain is also talking to our gut in a bi-directional way. And that conversation is vital for metabolism, for the endocrine system, meaning the hormonal system and for overall mood and cognition. There's just so much data now pointing to the fact that we need a healthy gut microbiome and a healthy brain gut axis as it's called. By taking Athletic Greens once or twice a day, I can get the vitamins and minerals and the probiotics needed for all those systems to function optimally. And again, it tastes great, it's great for me. In fact, if people ask me, "What's the one supplement that I should take," and they can only take one supplement, I recommend Athletic Greens for all the reasons I mentioned. If you'd like to try Athletic Greens, you can go to athleticgreens.com/huberman to claim a special offer. They're giving you five free travel packs, which are these little travel packs to make it easy to mix up Athletic Greens while you're on the road or in the car or on the plane, et cetera, and a year supply of Vitamin D3+K2. There is also a wealth of evidence showing that Vitamin D3 is vital to our overall health, and K2 is important for cardiovascular health and other systems as well. Most of us are not getting enough vitamin D3 or K2, even if we're getting some sunshine. So again, if you go to athleticgreens.com/huberman, you get the five free travel packs, a year supply of Vitamin D3+K2. Athleticgreens.com/huberman is where you go to claim that special offer. Today's episode is also brought to us by Headspace. Headspace is a meditation app that's supported by 25 published studies and benefits from over 600,000 five-star reviews. I've long been a believer in meditating. There is so much data now pointing to the fact that regular meditation leads to reduced stress levels, heightened levels of focus, better task switching, and cognitive ability. It just goes on and on. I mean, there are literally thousands of peer reviewed studies now in quality journals pointing to the benefits of having a regular meditation practice. The problem with meditation is many people, including myself, have struggled with sticking to that practice. With Headspace, it makes it very easy to start and continue a meditation protocol. The reason for that is they have meditations that are of different lengths and different styles so you don't get bored of meditation. And even if you just have five minutes, there are five minute meditations. If you've got 20 minutes, which would be even better, there are 20 minute meditations. Ever since I started using Headspace, I've been consistent about my meditation. I do meditation anywhere from five to seven times a week in my best weeks, and sometimes that's drops to three and then I find with Headspace, I can quickly get back to doing meditation every day because of the huge variety of great meditations that they have. If you want to try Headspace, you can go to headspace.com/specialoffer. And if you do that, you can get a free one month trial with Headspace's full library of meditations for every situation. That's the best deal offered by Headspace right now. So again, if you're interested, go to headspace.com/specialoffer. One quick mention before we dive into the conversation with Dr. Feldman. During today's episode, we discuss a lot of breathwork practices and by the end of the episode, all those will be accessible to you. However, I'm aware that there are a number of people out there that want to go even further into the science and practical tools of breathwork. And for that reason, I want to mention a resource to you. There is a cost associated with this resource, but it's a terrific platform for learning about breathwork practices and for building a number of different routines that you can do, or that you could teach. It's called Our Breathwork Collective. I'm not associated with the Breathwork Collective, but Dr. Feldman is an advisor to the group and they offer daily live guided breathing sessions and an on-demand library that you can practice any time free workshops on breathwork. And these are really developed by experts in the field, including Dr. Feldman. So, as I mentioned, I'm not on their advisory board, but I do know them and their work and it is of the utmost quality. So anyone wanting to learn or teach breathwork could really benefit from this course, I believe. If you'd like to learn more, you can click on the link in the show notes or visit ourbreathcollective.com/huberman, and use the code Huberman at checkout. And if you do that, they're offering you $10 off the first month. Again, it's ourbreathcollective.com/huberman

00:10:35 Why We Breathe

to access the Our Breath Collective. And now for my conversation with Dr. Jack Feldman. Thanks for joining me today. - It's a pleasure to be here, Andrew. - Yeah, it's been a long time coming. You're my go-to source for all things respiration. I mean, I breathe on my own, but when I want to understand how I breathe and how the brain and breathing interact, you're the person I call. - Well, I'll do my best. As you know, there's a lot that we don't understand, which still keeps me employed and engaged, but we do know a lot. - Why don't we start off by just talking about what's involved in generating breath. And if you would, could you comment on some of the mechanisms for rhythmic breathing versus non rhythmic breathing? - Okay, so on the mechanical side, which is obvious to everyone, we want to have air flow in, inhale, and we need to have air flow out and the reason we need to do this is because for body metabolism, we need oxygen. And when oxygen is utilized through the aerobic metabolic process, we produce carbon dioxide. And so, we have to get rid of the carbon dioxide that we produce in particular because the carbon dioxide affects the acid base balance of the blood, the pH, and all living cells are very sensitive to what the pH value is, so your body is very interested in regulating that pH. So we have to have enough oxygen for our normal metabolism, and we have to get rid of the $CO_2$ that we produce. So, how do we generate this air flow? Well, the air comes into the lungs. We have to expand the lungs and as the lungs expand, basically, it's like a balloon that you would pull apart. The pressure inside that balloon drops and the air will flow into the balloon. So we expand, put pressure on the lungs to pull it apart, that lowers the pressure in the air sacks called alveoli and air will flow in because pressure outside the body is higher than pressure inside the body when you're doing this expansion, when you're inhaling. What produces that? Well, the principle muscle is the diaphragm, which is sitting inside the body just below the lung, and when you want to inhale, you basically contract the diaphragm and it pulls it down. And as it pulls it down, it's inserting pressure forces on the lung, the lung wants to expand. At the same time, the rib cage is going to rotate up and out, and therefore expanding the cavity, the thoracic cavity. At the end of inspiration, under normal conditions when you're aggressed, you just relax and it's like pulling on a spring. You pull down a spring and you let go and relax. So, you inhale and you exhale. Inhale, relax, and exhale. - So, the exhale is passive? - At rest it's passive. We'll get into what happens when you need to increase the amount of air you're bringing in because your ventilation, your metabolism goes up like during exercise. Now the muscles themselves, skeletal muscles don't do anything unless the nervous system tells them to do something. And when the nervous system tells them to do something, they contract. So, there are specialized neurons in the spinal cord, and then above the spinal cord, the region called the brainstem, which go to respiratory muscles, in particular for inspiration in the diaphragm and the external intercostal muscles in the rib cage. And they contract. So, these respiratory muscles these inspiratory muscles become active and they become active for a period of time, 00:14:35 Neural Control of Breathing: “Pre-Botzinger Complex”

then they become silent and when they become silent, the muscles then relax back to their original resting level. Where does that activity in these neurons that innovate the muscle, which are called motor neurons, where does that originate? Well, this was a question that's been bandied around for thousands of years, and when I was a beginning assistant professor, it was fairly high priority for me to try and figure that out, because I wanted to understand where this rhythm of breathing was coming from and you couldn't know where it was coming from until you knew where it was coming from. And I didn't phrase that properly. You couldn't understand how it was being done until you know where to look. So, we did a lot of experiments, which I can go into detail and finally found, there was a region in the brainstem, that's once again this region sort of above the spinal cord, which was critical for generating this rhythm. It's called the pre-Botzinger complex. And we can talk about how that was named. This small site, which contains in humans, a few thousand neurons, it's located on either side and works in tandem and every breath begins with neurons in this region beginning to be active, and those neurons then connect ultimately to these motor neurons going to the diaphragm and to the external intercostals causing them to be active and causing this inspiratory effort. When the neurons in the pre-Botzinger complex finish their burst of activity, then inspiration stops and then you begin

00:16:20 Nose vs Mouth Breathing

to exhale because of this passive recoil of the lung and rib cage. - Could I just briefly interrupt you to ask a few quick questions - Of course. - before we move forward in this very informative answer. The two questions are, is there anything known about the activation of the diaphragm and the intercostal muscles between the ribs as it relates to nose versus mouth breathing, or are they activated in the equivalent way, regardless of whether or not someone is breathing through their nose or mouth? - I don't think we fully have the answer to that. Clearly there are differences between nasal and mouth breathing. At rest the tendency is to do nasal breathing because the air flows that are necessary for normal breathing as easily managed by passing through the nasal cavities. However, when your ventilation needs to increase like during exercise, you need to move more air, you do that through your mouth because the airways are much larger then, and therefore you can move much more air, but at the level of the intercostals and the diaphragm, their contraction is not, is almost agnostic to whether or not the nose and mouth are open. - Okay, so if I understand correctly, there's no reason to suspect that there are particular, perhaps even non overlapping sets of neurons in pre-Botzinger area of the brainstem that triggered nasal versus mouth inhales? - No, I would say that it's not that the pre-Botzinger complex is not concerned and cannot influence that, but it does not appear as if there's any modulation of whether or not it's where the air is coming from, whether it's coming through your nasal passages or through your mouth. - Great. Thank you.

00:18:18 Skeletal vs. Smooth Muscles: Diaphragm, Intracostals & Airway Muscles

And then the other question I have is that these intercostal muscles between the ribs then move the ribs up and out if I understand correctly, and the diaphragm, are those skeletal or as the Brits would say, skeletal muscles or smooth muscles? What type of muscle are we talking about here? - As I said earlier, these are skeletal, I didn't say there was skeletal muscles, but they're muscles that need neural input in order to move. You talked about smooth muscles. They are specialized muscles like we have in the gut and in the heart, and these are muscles that are capable of actually contracting and relaxing on their own. So, the heart beats, it doesn't need neural input in order to beat. The neural inputs modulate the strength of it and the frequency, but they beat on their own. The skeletal muscles involved in breathing need neural input. Now, there are smooth muscles that have an influence on breathing, and these are muscles that are lining the airways. And so, the airways have smooth muscle and when they become activated, the smooth muscle can contract or relax, and when they contract inappropriately is when you have problems breathing like in asthma. Asthma is a condition where you get inappropriate constriction of the smooth muscles of the airways. - So, there's no reason to think that in asthma that the pre-Botzinger or these other neuronal centers in the brain that activate breathing, that they are involved or causal for things like asthma? - As of now, I would say the preponderance of evidence is that it's not involved, but we've not really fully investigated that. - Thank you. Sorry to break your flow, but I was terribly interested in knowing answers

00:20:11 Two Breathing Oscillators: Pre-Botzinger Complex & Parafacial Nucleus to those questions and you provided them, so thank you. - Now, remind me again, where I was in my- - We were just landing in pre-Botzinger and we will return to the naming of pre-Botzinger because it's a wonderful and important story really, that I think people should be aware of. But maybe you could march us through the brain centers that you've discovered and others have worked on as well that control breathing, pre-Botzinger as well as related structures. - Okay. So, when we discovered the pre-Botzinger, we thought that it was the primary source of all rhythmic respiratory movements, both inspiration and expiration. Their notion of a single source is like day or night. It's like they're all coming, they all have the same origin that the Earth rotates and day follows night and we thought that the pre-Botzinger complex would be inhalation, exhalation. And then in a series of experiments we did in the early part of 2000, we discovered that there seemed to be another region which was dominant in producing expiratory movements, that is the exhalation. We had made a fundamental mistake with the discovery of the pre-Botzinger, not taking into account that at rest expiratory muscle activity or exhalation is passive. So, if that's the case, a group of neurons that might generate active expiration, that is to contract the expiratory muscles, like the abdominal muscles or the internal intercostals are just silent. We just thought it wasn't, the air was coming from one place, but we got evidence that in fact, it may have been coming from another place. And following up on these experiments, we discovered that there was a second oscillator and that oscillator is involved in generating what we call active expiration. That is this act of- - If I go [exhales]. - Yeah [exhales], or when you begin to exercise, you have to go [panting], and actually move that air out. This group of cells, which is silent at rest suddenly becomes active to drive those muscles, and it appears that it's an independent oscillator when- - Maybe you could just clarify for people what an oscillator is. - Okay, an oscillator is something that goes in a cycle. So, you can have a pendulum as an oscillator going back and forth. The Earth is an oscillator because it goes around and it's day and night. - Some people's moods are oscillating. - Oscillating. And it depends how regular they are. You can have oscillators that are highly regular or that are in a watch, or you can have those that are sporadic or episodic. Breathing is one of those oscillators that for life has to be working continuously 24/7. It starts late in the third trimester because it has to be working when you're born, and basically works throughout life and if it stops, if there's no intervention beyond a few minutes, it will likely be fatal. - What is this second oscillator called? - Well, we found that in a region around the facial nucleus, so we initially, when this region was initially identified, we thought it was involved in sensing carbon dioxide. It was what we call a central chemo receptor. That is, we want to keep carbon dioxide levels, particularly in the brain at a relatively stable level 'cause the brain is extraordinarily sensitive to changes in pH. If there's a big shift in carbon dioxide there'll be a big shift in brain pH, and that'll throw your brain, if I can use the technical term, out of whack. And so, you want to regulate that and the way to regulate something in the brain is you have a sensor in the brain. And others basically identified that the ventral surface of the brainstem, that is the part of the brainstem that's on this side, was critical for that and then we identified a structure that was near the trapezoid nucleus. It was not named in any of these noranatomical atlases, so we just picked the name out of the hat and we called it the retro trapezoid nucleus. - I should clarify for people. When Jack is saying trapezoid, it doesn't mean the trapezoid muscles. Trapezoid refers to the shape of this nucleus, this cluster of neurons. Parafacial makes me think that this general area is involved in something related to mouth or face. Is it an area rich with neurons controlling other parts of the face, eye blinks, nose twitches, lip curls, lip smacks? - If you go back in an evolutionary sense and a lot of things that are hard to figure out begin to make sense when you look at the evolution of the nervous system. When control of facial muscles, going back to more primitive creatures because they had to take things in their mouth for eating, so we call that the face sort of developed, the eyes were there, the mouth is there, these nuclei, the modem that contained the motor neurons, a lot of the control systems for them developed in the immediate vicinity. So, if you think about the face, there's a lot of sudden nuclei around there that had various roles at various different times in evolution. And at one point in evolution, the facial muscles were probably very important in moving fluid in and out of the mouth and moving air in and out of the mouth, and so part of these many different sub nuclei

00:26:20 How We Breathe Is Special (Compared to Non-Mammals)

now seems to be in mammals to be involved in the control of expiratory muscles. But we have to remember that mammals are very special when it comes to breathing, because we're the only class of vertebrates that have a diaphragm. If you look at amphibians and reptiles, they don't have a diaphragm. And the way they breathe is not by actively inspiring and passively expiring. They breathe by actively expiring and passively inspiring because they don't have a powerful inspiratory muscle. And somewhere along the line, the diaphragm developed, and there are lots of theories about how it developed. I don't think it's particularly clear. There was something that you can find in alligators and lizards that could have turned into a muscle that was the diaphragm. The amazing thing about the diaphragm is that it's mechanically extremely efficient. And what do I mean by that? Well, if you look at how oxygen gets from outside the body into the bloodstream, the critical passage is across the membrane in the lung. It's called the alveolar capillary membrane. The alveolus is part of the lung and the blood runs through capillaries, which are the smallest tubes in the circulatory system. And at that point, oxygen can go from the air filled alveolus into the blood. - Which is amazing. I find that amazing, even though it's just purely mechanical, the idea we had these little sacks in our lungs, we inhale and the air goes in and literally the oxygen can pass into the bloodstream- - Passes into the bloodstream. But the rate of which it passes will depend on the characteristics of the membrane, what the distance is between the alveolus and the blood vessel, the capillary. But the key element is the surface area. The bigger the surface area, the more oxygen that can pass through, it's entirely a passive process. There's no magic about making oxygen go in. Now, how do you get a pack, a large surface area in a small chest? Well, you start out with one tube, which is the trachea, the trachea expands. Now you have two tubes. Then you have four tubes and it keeps branching. At some point, at the end of those branches, you put a little sphere, which is an alveolus, and that determines what the surface area is going to be. Now, you then have a mechanical problem. You have the surface area, you have to be able to pull it apart. So, imagine you have a little square of elastic membrane, it doesn't take a lot of force to pull it apart, but now if you increase it by 50 times, you need a lot more force to pull it apart. So, amphibians who were breathing, not by compressing the lungs and then just passively expanding it weren't able to generate a lot of force, so they have relatively few branches. So, if you look at the surface area that they pack in their lungs relative to their body size, it's not very impressive. Whereas when you get to mammals, the amount of branching that you have is you have four to 500,000,000 alveoli. - If we were to take those four to 5,000,000- - 100,000,000, four to 500,000,000. - 100,000,000, excuse me, and lay those out flat, what sort of surface area are we talking about? - About 70 square meters, which is about a third the size of a tennis court. - Wow. - So you have a membrane inside of you a third the size of a tennis court that you actually have to expand every breath. And you do that without exerting much of a, you don't feel it, and that's because you have this amazing muscle, the diaphragm, which because of its positioning just by moving two thirds of an inch down is able to expand that membrane enough to move air into the lungs. Now, the at rest, - Wow. - the volume of air in your lungs is about two and a half liters. Do we need to convert that to quartz? - No. - Right, so about two and a half liters. When you take a breath, you're taking another 500 milliliters or half a liter. That's the size maybe of my fist. So, you're increasing the volume by 20%, but you're doing that by pulling on this 70 square meter membrane. But that's enough to bring enough fresh air into the lung to mix in with the air that's already there, that the oxygen levels in your bloodstream goes from a partial pressure of oxygen, which is 40 millimeters of mercury to 100 millimeters of mercury. So, that's a huge increase in oxygen and that's enough to sustain normal metabolism. So, we have this amazing mechanical advantage by having a diaphragm. - Do you think that our brains are larger than that of other mammals in part, because of the amount of oxygen that we have been able to bring into our system? - I would say a key step in the ability to develop a large brain that has a continuous demand for oxygen is the diaphragm. Without a diaphragm, you're an amphibian, and there's another solution to increasing oxygen uptake which is the way birds breathe, but birds have other limitations and they still can't get brains as big as mammals have. So, the brain utilizes maybe 20% of all the oxygen that we intake and it needs to continuously. The brain doesn't want to be neglected. So, this puts certain demands on breathing system. In other words, you can't shut it down for awhile, which poses other issues. You're born, and you have to mature. You have the small body, you have a small lung, you have a very pliant rib cage, and now you have to develop into an adult, which has a stiffer rib cage. And so, there are changes happening in your brain and your body, where the neural control of breathing has to change on the fly. It's not like for things like vision where you have the opportunity to sleep and while you're sleeping, the brain is capable of doing things that are not easy to doing during wakefulness, like the construction crew comes in during sleep. The change in breathing has been described as trying to build an airplane while it's flying. - Basically what Jack is saying is that respiration science is more complex and hardworking than vision science, which is a direct jab at me that some of you might've missed, but I definitely did not miss, and I appreciate that you always take the opportunity

00:33:40 Stomach & Chest Movements During Breathing like a good New Yorker to give me a good, healthy intellectual jab. A question related to diaphragmatic breathing versus non diaphragmatic breathing because the way you describe it, the diaphragm is always involved but over the years whether it be for yoga class or a breathwork thing, or you hear online that we should be breathing with our diaphragm, that rather than lifting our rib cage when we breathe [inhales] and our chest, that it is "healthier" in air quotes or better somehow to have the belly expand when we inhale. I'm not aware of any particular studies that have really examined the direct health benefits of diaphragmatic versus non diaphragmatic breathing, but if you don't mind commenting on anything you're aware of as it relates to diaphragmatic versus non diaphragmatic breathing, whether or not people tend to be diaphragmatic breathers by default, et cetera, that would be, I think interesting to a number of people. - Well, I think by default, we are obligate diaphragm breathers. There may be pathologies where the diaphragm is compromised and you have to use other muscles, and that's a challenge. Certainly at rest other muscles can take over, but if you need to increase your ventilation, the diaphragm is very important. It would be hard to increase your ventilation otherwise. - Do you pay attention to whether or not you are breathing in a manner where your belly goes out a little bit as you inhale, because I can do it both ways, right? I can inhale [inhales], bring my belly in, or I can inhale [inhales], push my diaphragm and belly out. Not the diaphragm out, but and that's interesting, right? Because it's a completely different muscle set for each version. - Well, in the context of things like breath practice, I'm a bit agnostic about the effects of some of the different patterns are breathing. Clearly, some are going to work through different mechanisms, and we can talk about that, but at a certain level for example, whether it's primarily diaphragm where you move your abdomen or not, I am agnostic about it. I think that the changes that breathing induces in emotion and cognition, I have different ideas about what the influence is and I don't see that primarily as how, which particular muscles you're choosing, but that just could be my own prejudice.

00:36:23 Physiological Sighs, Alveoli Re-Filling, Bombesin

- Okay. We will return to that as a general theme in a little bit. I want to ask you about sighing. One of the many great gifts that you've given us over the years is an understanding of these things that we call physiological sighs. Could you tell us about physiological sighs? What's known about them, what your particular interest in them is and what they're good for? - A very interesting and important question. So, everyone has a sense of what a sigh is. We certainly, when we're emotional, in some ways we're stressed, we're particularly happy, [inhales] we'll take a little sigh. It turns out that we're sighing all the time. And when I would ask people who are not particularly knowledgeable that have read my papers or James Nestor's book or listened to your podcast, they're usually off by two orders of magnitude about how frequently we sigh on the low side. In other words, they say once an hour, 10 times a day. We sigh about every five minutes, and I would encourage anyone who finds that to be a unbelievable fact, is to lie down in a quiet room and just breathe normally, just relax, just let go, and just pay attention to your breathing and you'll find that every couple of minutes, you're [inhales] taking a deep breath and you can't stop it. It just happens. Now, why? Well, we have to go back to the lung again. The lung has these 500,000,000 alveoli, and they're very tiny. They're 200 microns across. So, they're really, really tiny. And you can think of them as fluid filled. They're fluid lined. And the reason their fluid lined has to do with the esoterica of the mechanics of that. It makes it a little easier to stretch them with this fluid line, which is called surfactant. And surfactant is important during development, it is a determining factor in the, when premature infants are born. If they have not do not have lung surfactant it makes it much more challenging to take care of them than after they have lung surfactant, which is sometime, if I remember correctly, in the late second, early third trimester, which it appears. In any case it's fluid line. Now, think of a balloon that you would blow up, but now before you blow it up, fill the balloon with water, squeeze all the water out and now, when you squeeze all the water out you notice the sides of the balloon stick to each other. Why is that? Well, that's because water has what's called surface tension. And when you have two surfaces of water together, they actually tend to stick to each other. Now, when you try and blow that balloon up, you know that it, or you'll notice if you've ever done it before, that the balloon is a little harder to inflate than if we're dry on the inside. Why is that? Because you have to overcome that surface tension. Well, your alveoli have a tendency to collapse. There's 500,000,000 in them. They're not collapsing at a very high rate, but it's a slow rate that's not trivial. And when an alveolus collapses it no longer can receive oxygen or take carbon dioxide out. It's sort of taken out of the equation. Now, if you have 500,000,000 in them and you lose 10, no big deal, but if they keep collapsing, you can lose a significant part of the surface area of your lung. Now, a normal breath is not enough to pop them open, but if you take [inhales] a deep breath it pops them open. - Through nose or your mouth? -

Doesn't matter. - Okay. - Doesn't matter. - Or- - It just increased that lung volume 'cause you're just pulling on the lungs, they'll pop open every about every five minutes. And so, we're doing it every five minutes in order to maintain the health of our lung. In the early days of mechanical ventilation, which was used to treat polio victims who had weakness of their respiratory muscles, they'd be put in these big steel tubes and the way that would work is that the pressure outside the body would drop. That would put a expansion pressure on the lungs, excuse me, on the rib cage. The rib cage would expand and then the lung would expand. And then the pressure would go back to normal and the lung and rib cage would go back to normal. This was great for getting ventilation, but there was a relatively high mortality rate. It was a bit of a mystery. And one solution was to just give bigger breaths. They'd give bigger breaths and the mortality rate dropped, and it wasn't until I think it was the '50s where they realized that they didn't have to increase every breath to be big. What they needed to do was every so often they to have one big breath. So, you have a couple of minutes of normal breaths, and then one big breath just mimicking the physiological sighs, and then the mortality rate dropped significantly. And if you see someone on a ventilator in the hospital, if you watch every couple of minutes that you see the membrane move up and down, every couple of minutes there'll be a super breath and that pops it open. So, there are these mechanisms for these physiological sighs. So, just like with the collapse of the lungs, where you need a big pressure to pop it open, it's the same thing with the alveola. You need a bigger pressure and a normal breath is not enough. So, you have to take a big inhale. [Jack inhales] [Jack exhales] And what nature has done is instead of requiring us to remember to do it, it does it automatically. And it does it about every five minutes. And one of the questions we asked is how is this happening? Why every five minutes? What's doing it? And we got into it through a back door. Typical of the way a lot of science gets done. This is serendipitous event where you run across a paper and something clicks and you just, you follow it up. Sometimes you go down blind ends, but this turned out to be incredibly productive. One of the guys in my lab was reading a paper about stress, and during stress lots of things happen in the body, one of which is that the hypothalamus, which is very reactive to body state releases peptides, which are specialized molecules, which then circulate throughout the brain and body, that particular effects usually to help deal better with the stress. And one class of the peptides that are released are called Bombesin related peptides. And he also realize because he was a breathing guy, that when you're stressed you sigh more. So we said, "All right, maybe they're related."

Bombesin is relatively cheap to buy. We said, Let's buy some Bombesin and throw it in the brainstem, let's see what happens." And one of the nice things about some experiments that we try to design is to fail quickly. So here we had the idea, we throw Bombesin in and the Bombesin did nothin', nothing lost, maybe $50 to buy the Bombesin. But if it did something it might be of some interest. So, one afternoon we did the experiment and he comes to me, he says, I won't quote exactly what he said, because that might need to be censored, but he said, "Look at this." And it was in a rat. Rats sigh about every two minutes. They're smaller than we are and they need to sigh more often. Their sigh rate went from 20 to 30 per hour to 500 per hour when you put Bombesin into the pre-Botzinger complex. - [Andrew] Amazing. - And the way he did that is he took a very, very fine glass needle and anesthetized a rat, and inserted that needle directly into the pre-Botzinger complex. So, it wasn't an internalized delivery of the peptide. It was localized in the pre-Botzinger, and the sigh rate went through the roof. - And I would add that that was an important experiment to deliver the Bombesin directly to that site because one could have concluded that the injection of the Bombesin increased sighing because it increased stress rather than directly increased sighing. - Amongst hundreds of other possible interpretations. So, the precision here is very important, and that goes back to what I said at the very beginning, knowing where this is happening allows you to do the proper investigations. If we didn't know where the inspiratory rhythm was originating, we've never could have done this experiment. And so, then we did another experiment. We said, "Okay, what happens if we take the cells in the pre-Botzinger that are responding to the peptides? So, neurons will respond to a peptide because they have specialized receptors for that peptide. And not every neuron expresses those receptors. In the pre-Botzinger complex, it's probably a few hundred out of thousands. So, we used the technique we had used before, and this is a technique developed by Doug Laffey down in San Diego, where you could take a peptide and conjugate it with a molecule called saporin. Saporin is a plant derived molecule, which is a cousin to ricin. And many of your listeners may have heard of ricin and- - It's a ribosomal toxin. - It's very nasty. A single stab with an umbrella will kill you, which is something that supposedly happened to a Bulgarian diplomat by a Russian operative on a bridge in London. He got stabbed and the way ricin works is it goes inside a cell, crosses the cell membrane, goes inside the cell, kills the cell, then it goes to the next cell and then the next cell, and then the next cell. It's extremely dangerous. In fact, it's virtually impossible to work on in a lab in the United States. They won't let you touch it. -

Ricin? - Ricin 'cause- - We've worked with saporin many times. - Saporin is safe because it doesn't cross cell membranes. So, you got an injection of saporin, it won't do anything because it stays outside of cells. - Please, nobody do that, even though it doesn't cross cell membranes, please, nobody inject saporin whether or not you are a operative or otherwise. - Thank you, Andrew, for protecting me there. So, but what Doug Laffey figured out is that when a ligand binds the receptor, that's when a molecule binds to its receptor, in many cases that receptor ligand complex gets pulled inside the cell. So, it goes from the membrane of the cell inside the cell. - Sort of like you can't go to the dance alone, but if you're coupled up, you get in the door. - That's right. So, what he figured out is he put saporin to the peptide, the peptide binds to its receptor, it gets internalized and then when it's inside the cell, saporin does the same thing that ricin does. It kills the cell, but then it can't go into the next cell. So, the only cells that get killed, or the more polite term ablated, are cells that express that receptor. So, if you have a big conglomeration of cells, you have a few thousand and only 50 of them which express that receptor, then you inject the saporin conjugated to the ligand for the peptide, and only those 50 cells die. So, we took Bombesin conjugated the saporin, inject in the pre-Botzinger complex of rats, and it took about a couple of days for the saporin to actually ablate cells. And what happened is that the mice started sighing less and less, excuse me, the rats started sighing less and less and less and less, and essentially stopped signing. - So, your student or postdoc, was it? Murdered these cells, and as a consequence,

00:49:39 If We Don’t Sigh, Our Lung (& General) Health Suffers

the sighing goes away. - Right. - What was the consequence of eliminating sighing on the internal state or the behavior of the rats? Did they, in other words, if one can't sigh, generate physiological sighs, what is the consequence on state of mind? You would imagine that carbon dioxide would build up more readily or to higher levels in the bloodstream and that the animals would be more stressed. That's a kind of logical extension of the way we set it up. - It was less benign than that. When the animals got to the point where they weren't sighing then, and we did not determine this, but the presumption was that their lung function significantly deteriorated, and their whole health deteriorated significantly and we had to sacrifice them. So, I can't tell you whether they were stressed or not, but their breathing got to be significantly deteriorated that we sacrificed them at that point. Now, we don't know whether that is specifically related to the fact they didn't sigh or that there was secondary damage due to the fact that some cells die, so we never determined that. Now, after we did this study, to be candid, it wasn't a high priority for us to get this out the door and publish it. So, it stayed on the shelf. And then I got a phone call from a graduate student at Stanford, Kevin Yackle, who starts askin' me all these interesting questions about breathing, and I'm happy to answer them but at some point it concerned me because he was working for a renowned biochemist who worked on lung in drosophila, fruit flies, Mark Krasnow. - Yeah, got my next door colleague. - Right. - Yeah. - And I said, "Why are you asking me this?" And he said, "I was an undergraduate at UCLA and you gave a lecture in my undergraduate class and I was curious about breathing ever since." So, that's one of those things which as a professor, you love to hear that actually it's something you really affected the life of a student. - When you birthed the competitor, but you had only yourself to blame. - No, I don't look at that as a competitor. I think that there's enough interesting things to go on. I know some of our neuroscience colleagues say, "You can work in my lab, but then when you leave my lab, you've got to work on something different." - No one I ever trained would've said that. It's open field. You want to work on something, you hop in the mix. - And, but there are people like that, neuroscientists like that. I never felt that- - I hear that they're breathing apparati are disrupted and that causes a brain dysfunction that leads to the behavior you just described. It's actually not true, but in terms of the- - So- - So, before we talk about the beautiful story with Yackle and Krasnow and Feldman Lab, I want to just make sure that I understand. So, if physiological sighs don't happen, basically breathing overall suffers? - Well, that would go back to the observations in polio victims and these iron lungs where the principal deficit was there was no hyperinflation of the lungs and many of them deteriorated and died. - And just to stay on this one more moment before we moved to what you were about to describe, we hear often that people will overdose on drugs of various kinds because they stopped breathing. So, barbiturates, alcohol combined with barbiturates is a common cause of death for drug users and contra-indications of drugs, and these kinds of things. You hear all the time about celebrities dying because they combined alcohol with barbiturates. Is there any evidence that the sighs that occurred during sleep or during states of deep, deep relaxation and sedation that sighs recover the brain? Because you can imagine that if the sighs don't happen as a consequence of some drug impacting these brain centers, that that could be one cause of basically asphyxiation and death. - If you look at the progression of any mammal to death, you find that their breathing slows down, a death due to natural causes, their breathing slows down, it will stop, and then they'll gasp. So, we have the phrase dying gasp [inhales]. Super large breaths. They're often described as an attempt to auto resuscitate, that as you take that super deep breath and that maybe it can kickstart the engine again. We do not know the degree to such things as gasp are really sighs that are particularly large. And so, if you suppress the ability to gasp in an individual who is subject to an overdose, then whereas they might been able to re-arouse their breathing, if that's prevented, they don't get re-aroused. So, that is certainly a possibility, but this has not been investigated. I mean, one of the things that I'm interested in is in individuals who have diseases, which will affect pre-Botzinger complex. And there's data in Parkinson's disease and multiple system atrophy, which is another form of neurodegeneration where there's loss of neurons in pre-Botzinger. And the question is, and it also may happen in ALS, sometimes referred to as Lou Gehrig's disease, amyotrophic lateral sclerosis. These individuals often die during sleep. We have an idea that we have not been able to get anyone to test is that patients with Parkinson's, patients with MLS typically breathe normally during wakefulness. The disturbances that they have in breathing is during sleep. So, Parkinson's patients at the end stages of the disease often have significant disturbances in their sleep pattern, but not during wakefulness. And we think that what could be happening is that the proximate cause of death is not heart failure, is that they become apneic. They stop breathing and don't resuscitate. And that resuscitation may or may not be due to an explicit suppression of sighs, but to an overall suppression of the whole apparatus of the pre-Botzinger complex. - Got it. Thank you. So, Yackle calls you up. - So, he calls me up and he's, great kid, super smart, and he tells me about these experiments that he's doing where he's looking in a database to try and find out what molecules are enriched in regions of the brain that are critical for breathing. So, we and others have mapped out these regions in the brainstem, and he was looking at one of these databases to see what's enriched. And I said, "That's great. Will you be willing to sort of share our work together?" He says, "No, my advisor doesn't want me to do that." So I said, "Okay," but Kevin's a great kid, and I enjoy talking to him and he's a smart guy, and what I found in academia is that the smartest people only want to hire people smarter than them and have the preference to interact with people smarter than them. The faculty who are not at the highest level and at every institution, there's a distribution. One's above the mean, and those below the mean, those whom below the mean are very threatened by that.

And I saw Kevin as like a shining light, and I didn't care whether he was going to out-compete me because whatever he did was going to help me in the field, so I did whatever I can to help him, to work with Kevin. So, at one point I got invited to give grand rounds in neurology at Stanford. It turns out an undergraduate student who had worked with me was now head of the training program for neurologists at Stanford and he invited me. And at the end of my visit, I go to Mark Krasnow's office, and Kevin is there, and a post-doc punctually who was also working on a project was there. And towards the end of the conversation, Mark says to me, "We found this one molecule which is highly concentrated in an important region for breathing." I said, "Oh, that's great. What is it?" And he says, "I can't tell you because we want to work on it." So, I'm of course I'm disappointed, but I realized that the ethic in some areas of science or the custom in some areas of science is that until you get a publication, you'll be relatively restricted in sharing the information. - Mark and I are going to have a chat when I come back. - Okay, all right. - Yeah. - Well, he may remember the story differently, but I said okay, and as I'm walking out the door, I remember these experiments I described to you about Bombesin, and that was the only unusual molecule we're working. So, the reason I'm rushing out the door is I have a flight to catch. So, I stick my head in and I said, "Is this molecule related to Bombesin?" And then I run off, I don't even wait for them to reply. I can be up for it. Mark calls me and he says, "Bombesin? The peptide we found is related to Bombesin. What does it do?" And I said, "I'm not telling." [Andrew laughs] - Oh my. I'm so glad I wasn't involved in this collaboration. - No, no, but that was sort of a tease 'cause I said, "Well, let's work together on this."

01:00:42 Breathing, Brain States & Emotions

And then we worked together on this. - It was a prisoner's dilemma at that point, yeah. So, Kevin Yackle is spectacular, has his own lab at UCF, and the work that I'm familiar with from Kevin is worth mentioning now, or I'll ask you to mention it, which is this reciprocal relationship between brain state, or we could even say emotional state and breathing. And I'd love to get your thoughts on how breathing interacts with other things in the brain. You've beautifully described how breathing controls the lungs, the diaphragm, and the interactions between oxygen and carbon dioxide and so forth. But as we know, when we get stressed, our breathing changes. When we're happy and relaxed, our breathing changes. But also if we change our breathing, we, in some sense can adjust our internal state. What is the relationship between brain state and breathing? And if you would, because I know you have a particular love of one particular aspect of this, what is the relationship between brain rhythms, oscillations if you will, and breathing? - This is a topic which has really intrigued me over the past decade. I would say before that I was in my silo, just interested about how the rhythm of breathing is generated, and didn't really pay much attention to this other stuff. For some reason I got interested in it, and I think it was triggered by an article in "The New York Times" about mindfulness. Now, believe it or not, although I had lived in California for 20 years at that time, I never heard of mindfulness. It's staggering how isolated you can be from the real world. And I Googled it and there was a mindfulness institute at UCLA, and they were giving courses in meditation. So I said, "Oh, this is great because I can now see whether or not the breathing part of meditation has anything to do with the purported effects of meditation." So I signed up for the course, and as I joked to you before, I had two goals. One was to see whether or not a breathing had an effect, and the other was to levitate because I grew up with all these Kung Fu things and all the monks could levitate when they meditated, so why not? We have a motto in the lab, you can't do anything interesting if you're afraid of failing, and if I fail to levitate, well, at least I tried. And I should tell you now, I still haven't done it yet, but I haven't given up yet. - Yet. - Yet. I haven't given up. So, I took this course in mindfulness and it became apparent to me that the breathing part was actually critical. It wasn't simply a distraction or a focus. They could have had you move your index finger to the same effect. Really we believed that the breathing part was involved. Now, I'm not an unbiased observer so the question is, how can I demonstrate that? I didn't feel competent to do experiments in humans, and I didn't feel I could design the right experiments in humans, but I felt maybe I can study this in rodents. So we got this idea that we're going to teach rodents to meditate and that's laughable, but we said, but if we can, then we can actually study how this happens. So, believe it or not, I was able to get a sort of a startup grant, an R21 from NCCIH, that's the National Complementary Medicine Institute. - A wonderful institute I should mention. Our government puts major tax dollars toward studies of things like meditation, breathwork, supplements, herbs, acupuncture. This is I think not well-known, and it's an incredible thing that our government does that, and I think it deserves a nod and more funding [chuckles]. - I totally agree with you. I think that it's the kind of thing that many of us, including many scientists thinks is to woo woo and unsubstantiated, but we're learning more and more. We used to laugh at neuroimmunology, that the nervous system didn't have anything to do with the immune system and pain itself can influence your immune system. I mean, there are all these things that we're learning that we use to dismiss, and I think there's real nuggets to be learned here. So, they went out on a limb and they funded this particular project.

01:05:34 Meditating Mice, Eliminating Fear

And now I'm going to leap ahead because for three years we threw stuff up against the wall that didn't work. And recently we had a major breakthrough. We found a protocol by which we can get mice to breathe slowly, awake mice to breathe slowly. I won't tell you. - Normally they don't breathe slowly. - No, no. In other words, whatever their normal breath is, we could slow it down by a factor of 10 and they're fine doing that. So, we could do that for, we did that 30 minutes a day for four weeks, okay? Like a breath practice. - Do they levitate? - We haven't measured that yet [laughs]. I would say a priority, we haven't seen them floating to the top of that cage, but we haven't weighed them. Maybe they weigh less. Maybe levitation is graded. And so, maybe if you weigh less it's sort of partial levitation. In any case, we then tested them. And we had control animals, mice, where we did everything the same, except the manipulation we made did not slow down their breathing. So, but they went through everything else. We then put them through a standard for air conditioning, which we did with my colleague, Michael Fanselow, who's one of the real gurus of fear. And we measured a standard test is to put mice in a condition where they're concerned they'll receive a shock and their response is that they freeze, and the measure of how fearful they are is how long they freeze. This is well validated and it's way above my pay grade to describe the validity of the test, but it's very valid. The control mice had a freezing time, which was just the same as ordinary mice would have. The ones that went through our protocol froze much, much less. According to Michael, the degree to which they showed less freezing was as much as if there was a major manipulation in the amygdala, which is a part of the brain that's important in fear processing. It's a staggering change. The problem we have now is the grant ran out of money, the postdoc working on it left, and now we have to try and piece together everything, but the data is spectacular. - Well, I think it's, I'll just pause you for a moment there because I think that the, you're talking about a rodent study, but I think the benefits of doing rodent study is that you can get deep into mechanism and for people that might think, well, we've known that meditation has these benefits, why do you need to get mechanistic science? I think that one thing that's important for people to remember is that first of all, as many people as one might think are meditating out there or doing breathwork, a far, far, far, far greater number of people are not, right? I mean, the majority of people don't take any time to do dedicated breathwork nor meditate. So, whatever can incentivize people would be wonderful. But the other thing is that it's never really been clear to me just how much meditation is required for a real effect, meaning a practical effect. People say 30 minutes a day, 20 minutes a day, once a week, twice a week, same thing with breathwork. Finding minimum or effective thresholds for changing neural circuitry is what I think is the holy grail of all these practices. And that's only going to be determined by the sorts of mechanistic studies that you described. So, this is wonderful. I do hope the work gets completed and we can talk about ways that we can ensure that that happens, but- - But let me add one thing to what you're saying, Andrew. One of the issues, I think for a lot of people is that there's a placebo effect. That is in humans, they can respond to something even though the mechanism has nothing to do with what the intervention is. And so, it's easy to say that the meditative response has a big component, which is a placebo effect. My mice don't believe in the placebo effect. And so, if we could show there's a bonafide effect in mice, it is convincing in ways that no matter how many human experiments you did, the control for the placebo effect is extremely difficult in humans. In mice, it's a non-issue. So, I think that that in of itself would be an enormous message to send. - Excellent, and indeed, a better point. I think a 30 minute a day meditation in these mice, if I understand correctly, the meditation, we don't know what they're thinking about, but- - Well, it's breath practice really. - Right, so it's breath practice. So, because presumably they're not thinking about their third eye center, lotus position, levitation, whatever it is. They're not instructed as to what to do, and if they were, they probably wouldn't do it anyway. So, 30 minutes a day in which breathing is deliberately slowed or is slowed relative to their normal patterns of breathing. Got it. What was the frequency of sighing during that 30 minutes? Unclear? - We don't know yet. - Oh. - Well, no, we have the data.

01:11:00 Brain States, Amygdala, Locked-In Syndrome, Laughing

We just, we're analyzing that data. - To be determined, or to be announced at some point. So, the fear centers are altered in some way that creates a shorter fear response to a foot shock. - [Jack] Right. - What are some other examples that you are aware of from work in your laboratory or work in other laboratories for that matter about interactions between breathing and brain state or emotional state? - So, this goes back to our prior conversation. I sort of went off on a tangent. I think we need to think separately of the effect of volitional changes of breathing on emotion versus the effect of brain state on breathing. So, the effect of brain state on breathing like when you're stressed is a affect, presumably originating in higher centers if I can use that term affecting breathing. It's the reciprocal is that when you change breathing, it affects your emotional state. I think of those two things as different and they're ultimately tied together. So, there's a landmark paper published in the '50s where they stimulated in the amygdala of cats, and depending on where they stimulated, they got profound changes in breathing. There's like every pattern of breathing could possibly imagine, they found the site in the amygdala, which could produce that. So, there's clearly a powerful descending effect coming from the amygdala which is a major site for processing emotion, fear, stress and whatnot that can affect breathing. And clearly we have volitional control over breathing. So, we have profound effects there. Now, I should say about emotional control of breathing, I need to segue into talking about locked-in syndrome. Locked-in syndrome is a devastating lesion that happens in a part of the brainstem where signals that controlled muscles are transmitted. So the fibers coming from your motor cortex go down to this part of the brainstem, which is called the ventral pons. And if there's a stroke there, it can damage these pathways. What happens in individuals who have locked-in syndrome is they lose all volitional movement except lateral movement of the eyes and maybe the ability to blink. The reason they're able to still blink and move their eyes is that those control centers are rostal, closer to, are not interrupted. In other words, the interruption is below that. They continue to breathe because the centers for breathing don't require that volitional command. In any case, they're below that, so they're fine. So, these people continue to breathe. Normal intelligence, but they can't move. There's a great book called "The Diving Bell and the Butterfly" about a young man who this happens to, and he describes his life and it's a real testament to the human condition that he does this. It's a remarkable book, it's a short book. - Did he write the book by blinking? Did they translate it? - He did it by blinking to his caretaker. It's pretty amazing. And there was a movie which I've never seen with Javier Bardem as the protagonist, but the book I highly recommend this to anyone to read. So, I had colleagues studying an individual that had locked-in syndrome and they, this patient breathed very robotically, totally consistent, very regular. They gave the patient a low oxygen mixture to breathe. Ventilation went up, a CO2 mixture to breathe, ventilation went up. So, all the regulatory apparatus for breathing was there. They asked the patient to hold his breath or to breathe faster [blows raspberry]. Nothing happened. Just the patient recognized the command, but couldn't change it. Then all of a sudden, the patient's breathing changed considerably, and they said to their patient, "What happened?" They said, "You told a joke and I laughed." And they went back and whenever they told a joke that the patient found funny, the patient's breathing pattern changed. And you know your breathing pattern when you laugh is [inhales] you inhale, you go ha, ha, ha, ha. But it's also very distinctive. We have some neuroscience colleagues who will go un-named, who, if you heard them laugh 50 yards away, you know exactly who they are. - Yeah, well, I'll name him. Eric Kandel, - For one. - has an inspiratory laugh. He's famous for a [inhaling], as opposed to a ha, ha. - Exactly, exactly. - Yeah. So, it's very stereotyped, but it's maintained and these people lose volitional control of breathing. So, there's an emotive component controlling your breathing, which has nothing to do with your volitional control,

01:16:25 Facial Expressions

and it goes down to a different pathway because it's not disrupted by this locked-in syndrome. If you look at motor control of the face, we have the volitional control of the face, but we also have emotional control of the face, which most of us can't control. So, when we look at another person, we're able to read a lot about what their emotional state is, and that's a lot about how primates communicate, humans communicate and you have people who are good deceivers. Probably used car salesman, poker players. Now poker players have tells, but many of them now wear dark glasses because a lot of the tells you blink or whatnot. - Pupil sizes and stuff. - Pupil size. Pupil size is a tell, which is an autonomic function, not a skeletal muscle function, but we have all these skeletal muscles, which we're controlling, which give us away. I've tried to get my imaging friends to image some of the great actors that we have in Los Angeles. - You mean brain imagers. - Brain imagers, I'm sorry. - Yeah. No, that's all right. - I mean, yeah, no, brain imagers. Because I think when I ask you to smile, I could tell that you're not happy that you're smiling because I asked you to smile. I think that you're- - I thought you were about to crack a joke, but we're old friends, so, yeah. - No, I'm not... When you see a picture like at a birthday or whatnot, and say cheese, you could tell that at least half of the people are not happy to saying cheese, whereas a great actor when they're able to dissemble and the fact that they're sad or they're happy, you believe that they're not faking it. It's like, that's great acting. And I don't think everyone could do that. I think that the individuals who are able to do that have some connection to the parts of their motive control system that the rest of us don't have. Maybe they develop it through training and maybe not, but I think that this can be imaged so I would like to get one of these great actors in a imager and have them go through that and then get a normal person, and see whether or not they can emulate that and I think you're going to find big differences in the way they control this emotive thing. So, this emotive control of the facial muscles, I think is in large part, similar to the emotive control of breathing. So, there's that emotive control,

01:19:00 Locus Coeruleus & Alertness

and there's that volitional control and they're different. They're different. Now, you asked me about the Yackle stuff. The Yackle paper had to do with ascending, that the effect of breathing on emotion. What Kevin found was that there was a population of neurons in the pre-Botzinger complex that we're always looking at the things that are projecting ultimately on motor neurons. He found the population of cells that projected to locus coeruleus. Locus coeruleus, excuse me, is one of those places in the brain that seems to go everywhere. - It's like a sprinkler system. - Exactly, exactly. And influence mood, and you've had podcasts about this. I mean, there's a lot of stuff going on with the amygdala, so, excuse me, the locus coeruleus. So you get into the locus coeruleus, you can now spray information out throughout the entire brain. He found specific cells that projected from pre-Botzinger to locus coeruleus, and that these cells are inspiratory modulated. Now, it's been known for a long time since the '60s that if you look in the locus coeruleus of cats when they're awake, you find many neurons that have respiratory modulation. No one paid much attention. Why bother? Not why bother paying attention, but why would the brain bother to have these inputs? So, what Kevin did with Lindsey Schwarz in Liqun Luo's lab, is they killed, ablated, those cells going to locus coeruleus from pre-Botzinger and the animals became calmer, and their EEG levels changed in ways that are indicative that they became calmer. - And as I recall, they didn't just become calmer, but they weren't really capable of high arousal states. They were kind of flat. - I don't think we really pursued that in the paper. And so, we'd have to ask John Huguenard about that, but I- - He's on the other side of my lab so we'll ask him. But nonetheless, that beautifully illustrates how there is a bi-directional control, right? Of emotion- - Well, that's ascending. - Well, no, the two stories of the locked-in syndrome, plus the Yackle paper shows that emotional states influence breathing and breathing influences emotional states, which, but you mentioned inspiration, which I always call inhalation, but people will follow. No, that's fine. Those are interchangeable. People can follow that. There's some interesting papers from Noam Sobel's group and from a number of other groups that as we inhale or right after we inhale [inhales], the brain is actually more alert and capable of storing information than during exhales, which I find incredible but it also makes sense. I'm able to see things far better when my eyes are open than when my eyelids are closed, for that matter. - Maybe, right? I mean, I don't doubt, Noam's work is great. Let me backtrack a bit because I want people to understand that when we're talking about breathing affecting emotional cognitive state, it's not simply coming from pre-Botzinger. There are at least, well, there are several other sites and let me sort of describe, I need to sort of go through that. One is olfaction. So, when you're breathing, normal breathing, you're inhaling and exhaling. This is creating signals coming from the nasal mucosa that is going back into the olfactory bulb. That's respiratory modulating. And the olfactory bulb has a profound influence and projections through many parts of the brain. So, there's a signal arising from this rhythmic moving of air in and out of the nose that's going into the brain that has contained in it a respiratory modulation. So, that signal is there. The brain doesn't have to be using it, but when it's the discriminating owner and whatnot, that's riding on a oscillation, which is respiratory related. Another potential source is the vagus nerve. The vagus nerve is a major nerve, which is containing efferents from all of the viscera. - Efferents just being- - A signal. - Signals to. - Yes. Signals from the viscera. It also has signals coming from the brainstem down, which are called efferents, but it's getting major signals from the lung, from the gut. And this is going up into the brain stem. So, it's there. There are very powerful receptors in the lung that are responding to the lung volume. The lungs stretch. - So, bareovers? Oh, sorry. We have a number of, - They're pressure receptors. - Like the PA0 receptors of this year's Nobel Prize, yeah. - Yeah. So, they're responding to the expansion and relaxation in the lung. And so, if you record from the vagus nerve, you'll see that there's a huge respiratory modulation due to the mechanical changes in the lung. Now, why that is of interest is that for some forms of refractory depression, electrical stimulation of the vagus nerve can provide tremendous relief. Why this is the case still remains to be determined, but it's clear that signals in the vagus nerve, at least artificial signals in the vagus nerve can have a positive effect on reducing depression. So, it's not a leap to think that under normal circumstances, that that rhythm coming in from the vagus nerve is playing a role in normal processing. Okay, let me continue. Carbon dioxide and oxygen levels. Now, under normal circumstances, your oxygen levels are fine. And unless you go to altitude, they don't really change very much, but your CO2 levels can change quite a bit with even a relatively small change in your overall breathing. That's going to change your pH level. I have a colleague, Alicia Maurette, who has working with patients who are anxious and many of them hyperventilate. And as a result of that hyperventilation, their carbon dioxide levels are low. And she has developed a therapeutic treatment where she trains these people to breathe slower and to restore their CO2 levels back to normal, and she gets relief in their anxiety. So, CO2 levels, which are not going to affect brain function on a breath by breath level, although it does fluctuate breath by breath, but it's sort of this continuous background can change, and if it's changed chronically, we know that highly elevated levels of CO2 can produce panic attacks. And we don't know the degree to that gets exacerbated by people who have a panic attack, the agree to which their ambient CO2 levels are affecting their degree of discomfort. - What about people who are, tend to be too calm, meaning that they're feeling sleepy, they're under breathing as opposed to over-breathing? Is there any knowledge of what the status of CO2 is in their system? - I don't know which doesn't mean there's no knowledge, but I'm unaware but that's blissfully unaware. I've not looked at that literature, so I don't know. - And I have a feeling, I mean, most people, or excuse me, most of the scientific literature around breathing in humans that I'm aware of relates to these stressed states because they're a little bit easier to study in the lab, whereas people feeling under-stimulated or exhausted all the time, it's a complicated thing to measure. I mean, you can do it, but it's not as- - Well, CO2's easy to measure. - But in terms of sort of the measures for feeling fatigue, they're somewhat indirect, whereas stress we can get a pulse rates in HRV and things of that sort. - Well, I'd imagine that these devices that we're all wearing will soon be able to measure, well, now they can measure oxygen levels, oxygen saturation. - Just amazing. - Yeah, but oxygen will pretty much stay above 90% unless there's some pathology or you go to altitude. But CO2 levels vary quite a bit and in fact, because they vary, your body is so sensitive, the control of breathing, like how much you breathe per minute is determined in a very sensitive way by the CO2 level. So, even a small change in your

CO2 will have a significant effect on your ventilation. So, this is another thing that not only changes the ventilation, but affects your brain state. Now, another thing that could affect breathing, or how breathing practice can affect your emotional state is simply descending command because breathing practice involves volitional control of your breathing, and therefore there's a signal that's originating somewhere in your motor cortex. That is not, of course, that's going to go down to pre-Botzinger, but it's also going to send off collaterals to other places. Those collaterals could obviously influence your emotional state. So, we have quite a few different potential sources. None of them that are exclusive. There's an interesting paper, which shows that if you block nasal breathing, you still don't see breathing related oscillations in the brain. And this is where I think the mechanism is occurring is that these breathing related oscillations in the brain, they are playing a role in signal processing. And maybe, should I talk a little bit about the role that oscillations may be playing in signal processing?

01:29:40 Breath Holds, Apnea, Episodic Hypoxia, Hypercapnia

- Definitely, but before you do, I just want to ask you a intermediate question. We've talked a lot about inhalation, inspiration and exhalation. What about breath holds? In apnea, for instance, people are holding their breath, whether or not it's conscious or unconscious, they're holding their breath. What's known about breath holds in terms of how it might interact with brain state or oxygen CO2, and I'm particularly interested in how breath holds with lungs empty versus breath holds with lungs full might differ in terms of their impact on the brain. I'm not aware of any studies on this looking at a mechanistic level, but I find it really interesting and even if there are no studies, I'd love if you care to speculate. - Well, one of the breath practices that intrigued me is where you basically hyperventilate for a minute and then hold your breath for as long as you can. - Tummo style, - Yeah, brief shots of air. - Wim Hof style or, we call it in the laboratory, because frankly before Tummo, and before Wim, it was referred to as cyclic hyperventilation. So, it was basically [panting], right? Followed by a breath hold and that breath hold could be done with lungs full or lungs empty. - Right, yeah. So, I had a long talk with some colleagues about what they might think inline mechanisms are, particularly for the breath hold. And I certainly envisioned that there's a component with respect to the presence or absence of that rhythmicity in your cortex, which is having effect. But the other thing with the hyperventilation, hypoventilation or the apnea is your

$CO_2$ levels are going from low to high. - Anytime you're holding your breath. - Anytime you hold your breath, okay? And those are going to have a profound influence. Now, I have to talk about episodic hypoxia because there's a lot of work going on particularly with Gordon Mitchell at the University of Florida is doing some extraordinary work on episodic hypoxia. So, in the '80s, David Millhorn did some really intriguing work. If I ask you to hold your breath, excuse me. If I gave you a low oxygen mixture for a couple of minutes, your breathing level would go up 'cause you want to have more oxygen. - You're starving for air. - [Andrew and Jack] Yeah. - No, you're starving for oxygen. - All right. - Okay? And for a couple of minutes, you'd go up. You can reach some steady state level. Not so hypoxic that you can't reach an equilibrium. And then I give you room air again, the ventilation quickly relaxes back down to normal. If on the other hand, I gave you three minutes of hypoxia, five minutes of normoxia, three minutes of hypoxia, five minutes of normoxia, three minutes of hypoxia, five minutes in normoxia- - Normoxia being normal air. - Normal air. Your ventilation goes up, down, up, down, up, down, up, down. After the last episode, your breathing comes down and doesn't continue to come down, but rises again and stays up for hours, okay? This is well validated now. This was originally done in animals, but in humans all the time, it seems to have profound benefit on motor function and cognitive function. - In what direction? - Positive, positive. I've often toyed with the idea of getting an 8% oxygen, don't do this, listeners, getting an 8% oxygen tank by my desk when I'm writing a grant and doing like in "Blue Velvet" and going through the episodic hypoxia to improve my cognitive functioning, 'cause certainly could use improvement when I'm writing grants. - But you could do this without the low oxygen. I mean, you could do this through breathwork, presumably? - It's hard to lower your oxygen enough. Okay? In the experimental studies, they typically use 8% oxygen. It's hard to hold your breath long enough. And there is another difference here, that is what's happening to your $CO_2$ levels. When you hold your breath, your oxygen levels are dropping, your $CO_2$ levels are going up. When you're doing episodic hypoxia, your $CO_2$ levels are going to stay pretty normal because you're still breathing, it's just the oxygen levels are gone. - So, unlike normal conditions, which you described before, where oxygen is relatively constant and $CO_2$ is fluctuating depending on emotional state and activity and things of that sort, in episodic hypoxia, $CO_2$ is relatively constant, but you're varying the oxygen level coming into the system quite a bit. - I would say it's relatively, I would say $CO_2$ is relatively constant, but it's not going to go in a direction which is going to be significantly far from normal. Whereas when you're holding your breath, you're going to become both hypoxic and hypercapnic at the same time. - We should explain to people what hypoxic and hypercapnic are because we haven't done it. - Okay, hypoxic is just the technical term for low levels of oxygen, hyper, or you could hypoxic, low, hyper is high. So, hyperoxia or hypocapnia, low CO2 or hypercapnia, your highest levels of CO2. So, when you're, in episodic hypoxia, if anything,

01:35:22 Stroke, Muscle Strength, TBI

you're going to become hypocapnic, not hypercapnic. And that could play an influence in this. One example that I remember, and Gordon will have to forgive me if I'm misquoting this, is they had a patient who had a stroke and had weakness and ankle flection. That is, excuse me, ankle extension, to extend the ankle. And so, they had the patient in a seat where they can measure ankle extension, and then they measured it and then they exposed the patient to episodic hypoxia and they measured again, the strength of the ankle extension went way up. And so, Gordon is looking at this, they're looking at this now for spinal cord rehab. - And I imagine for all sorts of neuromuscular performance, it could be beneficial. - Gordon is looking into athletic performance. We have a project which we haven't been able to push to the next level to do golf. So, I find- - Why golf? 'Cause you love golf? - Well, it's because it's motor performance coordination. So, it's not simply running as fast as you can. It's coordination, it's concentration, it's a whole variety of things. And so, the idea would be to get a group of golfers and give them the placebo control, so they don't know whether they're breathing a gas mixture, which is just normal air or a hypoxic gas mixture, although they may be able to figure it out based on their response. Do it under controlled circumstances that do it into a net, measure their length of their drives, their dispersion and whatnot, and see what happens. Look, if we could find that this works for golfers, forget about cognitive function. We could sell this for unbelievable amounts of money. - That sounds like a terrible idea. [Jack laughs] - By the way, I'm not serious about selling it, but- - I know you're joking. I mean, maybe people should know that you are joking about that. No, I think that anything that can improve cognitive and neuromuscular performance is going to be of interest for a wide range of both pathologic states like injury, TBI, et cetera. I mean, one of the most frequent questions I get is about recovery from concussion or traumatic brain injury. A lot of people think sports, they think football, they think rugby, they think hockey. But if you look at the statistics on traumatic brain injury, most of it is construction workers, car crashes, bicycle accidents. I mean it, the sports part of it is a tiny, tiny minuscule fraction of the total amount of traumatic brain injury out there. I think these protocols tested in the context of golf would be very interesting because of the constraints of the measures as you mentioned,

01:38:08 Cyclic Hyperventilation

and it could be exported to a number of things. I want to just try and imagine whether or not there is any kind of breathing pattern or breathwork, just to be direct about it, that even partially mimics what you described in terms of episodic hypoxia. I've done a lot of Tummo, Wim Hof cyclic hyperventilation type breathing before. My lab studies this in humans, and what we find is that if people do cyclic hyperventilation, so for about a minute, then exhale, hold their breath for 15 to 60 seconds, depending on what they can do, and just keep repeating that for about five minutes, it seems to me that it at least partially mimics the state that you're talking about because afterwards people report heightened levels of alertness, lower levels of kind of triggering due to stressful events. They feel comfortable at a higher level of autonomic arousal, cognitive focus, a number of improvements that are pretty impressive that any practitioner of Wim Hof or Tummo will be familiar with. Is that pattern of breathing even, can we say that it maps to what you're describing in some general sense? - Well, the expert in this would be Gordon Mitchell. I would say it moves in that direction, but it's not as extreme because I don't think you can get down to the levels of hypoxia that they do clinically. I know that our pals at Our Breath Collective actually just bought a machine because you buy a machine that does this. - [Andrew] I see. - And they bought it and they're going to do their own self testing to see whether or not this has any effect on anything that they can measure. Of course, you have to be concerned

01:39:50 Hyperbaric Chambers

about self-experimentation, but I applaud their curiosity and going after it. - Hyperbaric chambers. I hear a lot nowadays about hyperbaric chambers. People are buying 'em and using 'em, and what are your thoughts on hyperbaric chambers as it relates to any of the- - Hyper or hypo? - Hyperbaric chambers. - Oh, so you're not talkin' about altitude? - [Andrew] No. - I don't really have much to say. I mean, your oxygen levels would probably go up a little bit and that could have a beneficial effect, but that's way outside my area of comfort. - 2022 I think is going to be the year of two things I keep hearing a lot about, which is the deliberate use of high salt intake for performance increasing blood volume, et cetera, and hyperbaric chambers seem to be catching on much in the same way that ice baths were

01:40:41 Nasal Breathing, Memory, Right vs. Left Nostril

and saunas seemed to be right now but anyway, a prediction we can return to at some point. I want to ask you about some of the studies that I've seen out there exploring how deliberately restricting one's breathing to nasal breathing can do things like improve memory. There's a couple of papers in "Journal of Neuroscience," which is a respectable journal in our field, one looking at olfactory memory. So, that kind of made sense because you can smell things better through your nose than your mouth, unless you're some sort of elk or something where they can, presumably they have some sense of smell in their mouth as well. But humans generally smell with their nose. That wasn't terribly surprising, but there was a companion study that showed that the hippocampus, an area involved in encoding memories in one form or another was more active if you will and memory and recall was better when people learned information while nasal breathing, as opposed to mouth breathing. Does that make sense from any mechanistic perspective? - Well, given that there's a major pathway going from the olfactory system into the brain and you cut that and not one from any receptors in the mouth, the degree of respiratory modulation you're going to see throughout the forebrain is going to be less with mouth breathing than nose breathing. So, it's certainly plausible. I think there are a lot of experiments that need to be done to distinguish between the two that is the nasal component and the non nasal component of these breathing related signals. But there's a tendency sometimes when you have a strong effect to be exclusive, and I think what's going on here is that there are many inputs that can have an effect. Now, whether they're parceled, that some effect this part of behavior and some effect that part of behavior remains to be investigated. There's certainly a strong olfactory component. My interest is trying to follow the central component 'cause we know that there's a strong central component in this. In fact, there's a strong central projection to the olfactory bulb. So, regardless of whether or not there's any air flowing in and out of the nose, there's a respiratory input into the olfactory bulb, which combines with the respiratory modulated signals coming from the sensory receptors. - Interesting. And as long as we are poking around, forgive the pun, the nose, what about one nostril versus the other nostril? I know it sounds a little crazy to imagine, but there have been theories in yoga traditions and others that breathing through one nostril somehow activates certain brain centers, maybe hemispherically one side of the brain versus the other or that right nostril and left nostril breathing might differ in terms of the levels of alertness or calmness they produce. I'm not aware of any mechanistic data on that, but if there's anything worthwhile about right nostril versus left nostril breathing that you're aware of, I'd love to know. - Well, it certainly plausible. I don't know of any data demonstrating it, except the anecdotal reports of the, as you know the brain is highly lateralized and we have speech on one side and a dominant hand that's on one side. And so, the notion that if you have this huge signal coming from the olfactory system and it, to some degree is lateralized, is not perfectly symmetrical. That is one side is not going evenly to both sides, then you can imagine that once the signal gets distributed in a way that's not uniform, that the effectiveness or the response is going to be particular to the cortex

01:44:50 Breathing Coordinates Everything: Reaction Time, Fear, etc.

in which either the signal still remains or the signal is removed from. - I see. What are some of the other features of our brain and body, be it blinking, or eye movements, or ability to encode sounds, or any features of the way that we function and move and perceive things that are coordinated with breathing in some interesting way? - Thank you for that question. Almost everything. So, we have, for example, on the autonomic side, we have respiratory sinus arrhythmia. That is during expiration the heart slows down. Your pupils oscillate with the respiratory cycle. I don't know what the functional basis for that is, but they do oscillate with the respiratory cycle. - When we inhale our pupils constrict, presumably 'cause you there's an increase in heart rate and sympathetic tone, I would think of constriction and I'm guessing as you relax the pupil will get, and you exhale the pupil will get bigger- - I think you're right, but I always get the valance of that- - Yeah, well, it's counterintuitive because people wouldn't think that when the pupils get, I mean, it depends. I mean, well, you can get very alert and aroused in that for stress or for good reasons, and the peoples get wider, but your visual field narrows and then the opposite is true. Anyway, I guess the idea is that the pupils are changing size and therefore the aperture of your visual window is changing in coordination with breathing. -

Okay. Your fear response changes with the respiratory cycle. - Can you tell us more about that? - Well, there's a paper by Solano, which I think showed rather clearly that if you show individuals fearful faces that their measured response of fearfulness changes between inspiration and expiration. I don't know why, but it does. Your reaction time changes. So you talk about blinking. The reaction time changes between inspiration and expiration. If I ask you to punch something that time will change between inspiration and expiration. In fact, I don't know the degree to which martial artists exploit that. You watch the breathing pattern and your opponent will actually move slower during one cycle compared to the other. - Meaning as they're, in which direction? If they're exhaling, they can punch faster? - I have to say, I don't keep a table of which is which direction things move in 'cause I'm out of the martial arts field now. - My vague understanding is that exhales on strikes is the more typical way to do that, and so as people strike, they exhale. In many- - As you exhale, but there are other components to striking because you want to stiffen your rib cage, you want to make a Valsalva maneuver. So that's both an inspiration and expiration. It's at the same time. So, I don't know enough about, when you say during expiration, I would assume that when you make your strike, you're actually sort of wanting to stiffen here, which is a Valsalva like maneuver. - And oftentimes they'll clench their fist at the last moment. Anyway, there's a whole set of motor things that we can talk to some fighters. We know people who know fighters, so what we can ask them. Interesting. What are some other things that are modulated by breathing? - I think anything anyone looks at seems to have a breathing component because it's all over your brain, and it's hard to imagine it not being effective. Now, whether it's incidental or just background and doesn't really have any behavioral advantage is possible. In other cases, it might have a behavioral advantage. I mean, the big, this eye-opening thing for me probably a decade ago, was digging into literature and seeing how much of cortical activity and subcortical activity had a respiratory modulator component to it. And I think a lot of my colleagues who were studying cortex are oblivious to this, and they find, I heard a talk the other day from a person who will go un-named, who found a lot of things correlated with a particular movement. And I think it all, when I looked, I said, gee, that's the list of things that are respiratory modulated. And rather than it being correlated to the movement they we're looking at, I think the movement they were looking at was modulated by breathing, as was everything else. So, there wasn't that the movement itself was driving that correlation. It was that they were all correlated to something else, which is the breathing movement and whether or not that is behaviorally relevant, or behaviorally something you can exploit, I don't know. - I suspect you're right, that breathing is if not the foundational driver of many, if not all of these things that it's at least one of the foundational drivers. - It's in the background, it's in the brain, and oscillations play an important part in brain function. And they vary in frequency from maybe 100 hertz down to, well, we can get to circadian and sort of monthly cycles, but breathing occupies a rather unusual place in all that because... So, let me talk about what people think the oscillation's is doing, particularly faster ones. They're important in coordinating signals across neurons. Just like in a computer, a computer steps. So, a computer knows when information is coming from another part of a computer so that it was originated at a particular time. And so, that the screen by step-by-step thing is important in computer control. Now, the brain is not a digital device, and it's an analog device, but when I have a signal that's coming in my ear and my eye, which is Andrew Huberman speaking and I'm looking at his face, I see that as a whole, but the signal is coming into different parts of my brain. How do I unify that? Well, my neurons are very sensitive to changes in signals arriving by fractions of a millisecond. So, I know we're sure that those signals coming in represent the same signal. Well, if I have throughout my brain and isolation and the signals ride on that oscillation, let's say the peak of the oscillation, I can then have a much better handle on the road of timing and say, "Those two signals came in at the same time. They may relate to the same object and ah ha, I see you as one unified thing spouting talking." And so, these oscillations come in many different frequency ranges and are important in memory formation and all sorts of things. I don't think people pay much attention to breathing because it's relatively slow to the range when you think about milliseconds, but we have important things that are thought to be important in cognitive function, which are a few cycles per second to 20, 30, 40, 50 cycles per second. Breathing in humans is maybe .2 cycles per second, every five seconds. Although in rodents they're up to four per second, which is pretty fast. So, but breathing has one thing which is special, that is you can readily change it. So, the degree to which the brain is using that slow signal for anything, if that becomes part of its normal signal processing, you now change it. That signal processing has to change. And as that signal processing changes, acutely there's a change. So, you asked about breath practice, how long do you have to do it? Well, a single breath will change your state. You're nervous, you take a deep breath and it seems to help relax, so- - Or a sigh. - Call it what you will, call it what you will. It seems to work. Now, it doesn't have a permanent change, but when I'm getting up to bat or getting up to the first tee or getting to give a big talk or coming to do a podcast, I get a little bit anxious, a deep breath, or a few deep breaths are tremendously effective in calming one down. And so, you can get a transient disruption, but on the other hand, let's take something like depression. I think it's, you can envision depression as activities sort of going around in a circuit. And because it's continuous in the nervous system, as signals keep repeating, they tend to get stronger and they can get so strong, you can't break them. So, you can imagine the depression being something going on and on and on, and you can't break it. And so, we have trouble when we get for certain levels of depression, I mean, all of us get depressed at some point, but if it's not continuous, it's not long lasting, we're able to break it. But if it's long lasting and very deep, we can't break it. So, the question is how do we break it? Well, there are extreme measures to break it. We could do electroconvulsive shock. We shock the whole brain. That's disrupting activity in the whole brain. And when this circuit starts to get back together again, it's been disruptive. And we know that the brain, when signals get disrupted a little bit, we can weaken the connections and weakening the connections of this then in this circuit involved in depression, we may get some relief and electroconvulsive shock does work for relieving many kinds of depression. That's pretty heroic. Focal deep brain stimulation does the same thing, but more localized or transcranial stimulation. You're disrupting a network. And while it's getting back together, it may weaken some of the connections. If breathing is playing some role in this circuit, and now, instead of doing like a one second shock, I do 30 minutes of disruption by doing slow breathing or other breathing practice, those circuits begin to break down a little bit, and I get some relief. And if I continue to do it before the circuit can then build back up again, I gradually can wear that circuit down. I sort of liken this, I tell people it's like walking around on a dirt path. You build a rut, the rut gets so deep you can't get out of it. And what breathing is doing is sort of filling in the right rut bit by bit to the point that you can climb out of that rut. And that is because the breathing signal is playing some role in the way the circuit works, and then when you disrupt that, the circuit gets a little thrown off kilter, and as you know when circuits get thrown off, the nervous system tries to adjust in some way or another, and it turns out at least for breathing for some evolutionary reason, or just by happenstance, it seems to improve our emotional function,

01:57:13 Dr. Feldman’s Breathwork Protocols, Post-Lunch and our cognitive function. And we're very fortunate that that's the case. - It's a terrific segue into what I want to ask you next, and this is part of a set of questions I want to make sure we touch on before we wrap up, which is what do you do with all this knowledge in terms of a breathing practice? You mentioned that one breath can shift your brain state and that itself can be powerful. I think that's absolutely true. You've also talked about 30 minute breathwork practices, which is 30 minutes of breathwork, is a pretty serious commitment I think, but it's doable. Certainly a zero cost, except for the time in most cases. What do you see out there in the landscape of breathwork that's being done that you like, and why do you like it? What do you think you, or what would you like to see more of in terms of exploration of breathwork and what do you do? - Well, I'm a relatively new convert to breathwork. Through my own investigation of it, I became convinced that it's real, and I'm basically a beginner in terms of my own practice. And I like to keep things simple, and I think I've discussed this before. I liken it to someone who's a couch potato who was told they got to begin to exercise. You don't go out and run a marathon. So, couch potato, you say, okay, get up and walk for five minutes and 10 minutes. And then, okay, now you're walking for a longer period. You'll begin to run, and then you reach a point, you say, well, gee, I'm interested in this sport. And there may be particular kinds of practices that you can use that could be helpful in optimizing performance of that sport. I'm not there yet. I find I get tremendous benefit by relatively short periods between five and maybe 20 minutes of doing box breathing. It's very simple to do. I have a simple app, which helps me keep the timing. - Do you recall which app it is? Is it the Apnea Trainer? Is that the one? - Well, I was using Calm for a long time, but I let my subscription lapse and I have another one whose name I don't remember but it's, so it's very simple and it works for me. I'm now trying this Tummo, because I'm just curious and exploring it because it may be acting for a different way and I want to see if I respond differently. So, I don't have a particular point of view. Now, I have friends and colleagues who are into particular styles like Wim Hof. And I think what he's doing is great and getting people who are interested. I think the notion is that I would like to see more people exploring this and to some degree, as you point out, 30 minutes a day, some of the breath patterns that some of these stars like Wim Hof are a little intimidating to newbies. And so, I would like to see something very simple, that what I tell my friends is, look, just try it five or 10 minutes. See if you feel better, do it for a few days. If you don't like it, stop it, it doesn't cost anything. And invariably, they find that it's helpful. I will often interrupt my day to take five or 10 minutes. Like, if I find that I'm lagging... I think there's some pretty good data that your performance after lunch declines. And so, very often what I'll do after lunch, which I didn't do today is take five or 10 minutes and just sort of breath practice. - And lately, what does that breath practice look like? - It's just box breathing for five to 10 minutes. - And the duration of your inhales and holds and exhales and holds is set by the app? Is that right? - Well, I do five seconds. - So, five seconds inhale, five second hold, five second, exhale, five second hold. - Yeah, and sometimes I'll do doubles. I'll do 10 seconds just because I get bored. It's just, I feel like doing it and it's very helpful. I mean... Now, that's not the only thing I do with respect to trying to maintain my sanity and my health. - No, I can imagine there'd be a number of things, although, because you seem very sane and very healthy, I in fact, know that you are both of those things.

02:02:05 Deliberately Variable Breathwork: The Feldman Protocol

- Right, you suspect that I am. - I suspect that there's data. Awhile back we had a conversation, a casual conversation, but you said something that really stuck in my mind, which is that it might be that the specific pattern of breathwork that one does is not as important as experiencing transitions between states based on deliberate breathwork or something to that extent, which I interpreted to mean that if I were to do box breathing with five second in, five seconds hold, five second exhale, five second hold for a couple of days, or maybe even a couple of minutes and then switch to 10 seconds or then switch to Tummo, that there's something powerful perhaps in the transitions and realizing the relationship between different patterns of breathing in those transitions, much in the same way that you can get into one of these cars at an amusement park that just goes at a constant rate and then stops. Very different than learning how to shift gears. I used to drive a manual. I still can so I'm thinking about a manual transmission, but even with an automatic transmission, you start to get a sense of how the vehicle behaves under different conditions. And I thought that was a beautiful seed for a potential breathwork practice that at least to my awareness, nobody has really formalized, which is that you introduce some variability within the practice that's somewhat random in order to be able to sense the relationship between different speeds and depths of inhales, exhales and holds and so forth. And essentially, it's like driving around the track, but with obstacles at different rates and breaking and restarting and things of that sort, that's how you learn how to drive. What do you think about that and if you like it enough, can we call it the Feldman protocol? - Oh, please [laughs]. I was asked in this BBC interview once why didn't I name it the Feldman complex, instead of pre-Botzinger complex? - You said I already have a Feldman complex. - Well, it sounds like a psychiatric disorder, but I think the primary effect is this disruptive effect, which I described, but the particular responses may clearly vary depending on what that disruption is. I don't know of any particular data, which are as in well controlled experiments, which can actually work through the different types of breathing patterns or simply with a box pattern, just varying the durations. I mean, pranayama is sort of similar, but the amount of time you spend going around the box is different. So, I don't really have much to say about this. I mean, this is why we need better controlled experiments in humans and I think this is where being able to study in rodents where you can have a wide range of perturbations while you're doing more invasive studies to really get down as to which regions are affected, how was the signal processing disrupted, which is still a hypothesis, but how it's disrupted could tell us a lot about maybe there's a resonant point at which there's an optimal effect when you take a particular breathing practice. And then when we talked about the fact that different breathing practices could be affecting the outcomes through different pathways. You have the olfactory pathway, you have a central pathway, you have a vagal pathway, you have a descending pathway, how different practices may change the summation of those things because I think all those things are probably involved, and we're just beginning to scratch the surface. And I just hope that we can get serious neuroscientists and psychologists to do the right experiments to get at this because I think there's a lot of value to human health here. - I do too, and it's one of the reasons my lab has shifted to these sorts of things in humans. I'm delighted that you're continuing to do the hardcore mechanistic work in mice and probably do work in humans already as well, if you're not already. And there are other groups, Epel Lab at UCF, and a number of, I'm starting to see some papers out there

02:06:29 Magnesium Threonate & Cognition & Memory

about respiration in humans a little bit, some more brain imaging. I can't help but ask about a somewhat unrelated topic, but it is important in light of this conversation because you're here, and one of the things that I really enjoy about conversations with you as it relates to health and neuroscience and so forth is that, you're one of the few colleagues I have who openly admits to exploring supplementation. I'm a long time supplement fan. I think there's power in compounds, both prescription, non-prescription, natural, synthesized. I don't use these haphazardly, but I think there's certainly power in them. And one of the places where you and I converge is in terms of our interest in the nervous system and supplementation is vis-a-vis magnesium. Now, I've talked endlessly on the podcast and elsewhere about magnesium for sake of sleep, and improving transit transitions to sleep and so forth. But you have a somewhat different interest in magnesium as it relates to cognitive function and durability of cognitive function. Would you mind just sharing with us a little bit about what that interest is, where it stems from, and because it's The Huberman Podcast, and we often talk about supplementation, what you do with that information. - So, I need to disclose that I am a scientific advisor to a company called Neurocentria, which my graduate student, Guosong Liu is CEO. So that said, I can give you some background. Guosong, although when he was in my lab worked on breathing, had a deep interest in learning and memory. And when he left my lab, he went to work for it with a renowned learning memory guy at Stanford, Dick Chen. And when he finished there, he was hired by Susumu Tonegawa at MIT. - Who also knows a thing or two about memory. I'm teasing. Susumu Tonegawa has a Nobel for his work on immunoglobulins, but then is a world-class memory researcher. - Yeah, and more. - He's many things. - And Guosong had very curious, very bright guy, and he was interested in how signals between neurons get strengthened, which is called long-term potentiation or LTP. And one of the questions that arose was if I have inputs to a neuron and I get LTP, is the LTP bigger if the signal is bigger or the noise is less? So, we can imagine that when we're listening to something, if it's louder, we can hear it better. Or if this less noise, we can hear it better. And he wanted to investigate this. So I did this in tissue culture of hippocampal neurons, and what he found was that if he lowered the background activity in all of the neurons, that the LTP he elicited got stronger, and the way he did that was increasing the level of magnesium in the bathing solution. This gets into some esoteric electrophysiology, but basically there's a background level of noise in all neurons, and that part of it is regulated by the degree of magnesium in the extracellular bath. - And you mean electrical noise. - Electrical noise, I'm sorry, electrical noise. And if you, in what's called the physiological range, which is between 0.8 and 1.2 millimolar, which don't worry about the number. - I can't believe you remember the millimolar of the magnesium. - Well, I'm always frightened that I get, I say micro or femto or something, I go off by several orders of magnitude, but so in that physiological range, there's a big difference in the amount of noise in a neuron between 0.8 and 1.2 millimolar. So, he played around with the magnesium, and he found out that when the magnesium was elevated, it was more LTP. All right, that's an observation in a tissue culture. - Right, and I should just mention that more LTP essentially translates to more neuro-plasticity, more rewiring of connections in essence. - So, he tested this in mice and basically, he offered them a, he had control mice, which got a normal diet and one that had, one enriched in magnesium, and the ones that lived enriched with magnesium had higher cognitive function, lived longer, everything you'd want in some magic pill, those mice did that. Excuse me, rats. The problem was that you couldn't imagine taking this into humans because most magnesium salts don't passively get from the gut into the bloodstream, into the brain. They pass via what's called a transporter. Transporter is something in a membrane that grabs a magnesium molecule or atom, and pulls it into the other side. So if you're imagining you have magnesium in your gut, you have transporters that pull the magnesium in the gut into the bloodstream. Well, if you take a normal magnesium supplement that you can buy at the pharmacy, it doesn't cross the gut very easily. And if you would take enough of it to get it in your bloodstream, you start getting diarrhea. So it's not a good way to go. - Well, it is a good way to go. I couldn't help myself. - [laughs] Well said. So, he worked with this brilliant chemist, Fay Mow, and Fay looked at a whole range of magnesium compounds and he found that magnesium threonate was much more effective in crossing the gut blood barrier. Now, they didn't realize at the time, but threonate is a metabolite of vitamin C, and there's lots of threonate in your body. So magnesium threonate would appear to be safe and maybe part of the role or now they believe it's part of the role of the threonate is that it supercharges the transporter to get the magnesium in. And remember, you need a transporter at the gut into the brain and into cells. So, they gave magnesium threonate to mice who had, no, let me backtrack a bit. They did a study in humans. They hired a company to do a test that was a hands-off test. It's one of these companies that gets hired by the big pharma to do their test for them, and they got patients who were diagnosed as mild cognitive decline. These are people who had cognitive disorder, which was age inappropriate. And the metric that they use for a determining how far off they were is Spearman's G factor, which is a generalized measure of intelligence that most psychologists except, and the biological age of the subjects was, I think 51 and the cognitive age was 61 based on the Spearman's G's test. Oh, I should say the Spearman G factor starts at a particular level in the population at age 20 and declines about 1% a year. So, sorry to say, we're not 20 year olds anymore, but when you get a number from that, you can put on the curve and see whether it's about your age or not. These people were about 10 years older according to that metric and long story short after three months this is a placebo controlled double blind study. The people who were in the placebo arm improved two years, which is common for human studies 'cause a placebo effect. The people who got the compound improved eight years on average, and some improved more than eight years. They didn't do any further diagnosis as to what caused the molecule to decline but it was pretty, it was extraordinarily impressive. - So, it moved their cognition closer to their biological age? - Biological age. Biological age. - Do you recall what the doses of magnesium threonate- - It's in the paper and it's basically what they have in the compound, which is sold commercially. So, the compound which is sold commercially is handled by a nutraceutical wholesaler who sells it to the retailers and they make whatever formulation they want. But it's a dosage which is, my understanding is rarely tolerable. I take half a dose. The reason I take half a dose is that I had my blood magnesium measured, and it was low normal for my age. I took half a dose, it became high normal, and I felt comfortable staying in the normal range, but a lot of people are taking the full dose and at my age, I'm not looking to get smarter, I'm looking to decline more slowly. And it's hard for me to tell you whether or not it's effective or not. - Well, you remembered the millimolar of the magnesium and the solution and on the high and low end, so I would say it's not a well controlled study and it's an N of one, but it seems to be working. - When I've recommended it to my friends, academics who are not by nature skeptical, if not cynical, and I insist that they try it, they usually don't report a major change in their cognitive function, although sometimes they do report, "Well, I feel a little bit more alert than my, my physical movements are better," but many of them report they sleep better. - And that makes sense. I think there's good evidence that threonate can accelerate the transition into sleep and maybe even access to deeper modes of sleep for some people. For many people actually, a small percentage of people who take threonate including one of our podcast staff here have stomach issues with it. They can't tolerate it. So, I would say just anecdotally, about 5% of people don't tolerate threonate well. Stop taking it and then they're fine. It caused them diarrhea or something of that sort, but most people tolerate it well and most people report that it vastly improves their sleep. And again, that's anecdotally. There are a few studies and there are more on the way, but that's very interesting because I, until you and I had the discussion about threonate, I wasn't aware of the cognitive enhancing effects, but the story makes sense from a mechanistic perspective.

02:18:27 Gratitude for Dr. Feldman’s Highly Impactful Work

And it brings it around to a bigger and more important statement, which is that I so appreciate your attention to mechanism. I guess this stems from your early training as a physicist and the desire to get numbers and to really parse things at a fine level. So, we've covered a lot today. I know there's much more that we could cover. I'm going to insist on a part two at some point, but I really want to speak on behalf of a huge number of people and just thank you, not just for your time and energy and attention to detail and accuracy and clarity around this topic today, but also what I should have said at the beginning, which is that you really are a pioneer in this field of studying respiration and the mechanisms underlying respiration with modern tools for now for many decades, and the field of neuroscience was one that was perfectly content to address issues like memory and vision and sensation perception, et cetera. But the respiratory system was largely overlooked for a long time and you've just been steadily clipping away and clipping away and much cause of the events of related to COVID and a number of other things, and this huge interest in breathwork and brain states and wellness, the field of respiration and interest in respiration has just exploded. So, I really want to extend a sincere thanks. It means a lot to me, and I know to the audience of this podcast as someone with your depth and rigor in this area is both a scientist and a practitioner, and that you would share this with us. So, thank you. - Well, I want to thank you. This is actually a great opportunity for me. I've been isolated in my silo for a long time, and it's been a wonderful experience to communicate to people outside the silo who have an interest in this. And I think that there's a lot that remains to be done, and I enjoy speaking to people who have interest in this. I find the interest to be quite mind-boggling and it's quite wonderful that people are willing to, and listen to things that can be quite esoteric at times, but it gets down to deep things about who we are and how we are going to live our lives. So, I appreciate the opportunity and I would be delighted to come back at any time. - Wonderful. We will absolutely do it.

02:20:53 Zero-Cost Support, Sponsors, Patreon, Instagram, Twitter, Thorne

Thanks again, Jack. - Bye now. - Thank you for joining me for my conversation with Dr.

Jack Feldman. I hope you found it as entertaining and as informative as I did. If you're learning from and/or enjoying this podcast, please subscribe to us on YouTube. That's a terrific zero cost way to support us. In addition, please subscribe to the podcast on Spotify and Apple, and on Apple you can leave us a review and you can leave us up to a five-star rating. Please also check out the sponsors mentioned at the beginning of the podcast. That's the best way to support this podcast. We also have a Patreon. It's patreon.com/andrewhuberman. And there you can support The Huberman Lab Podcast at any level that you like. In addition, if you're not already following us on Instagram and Twitter, I teach neuroscience on Instagram and Twitter. Some of that information covers information covered on the podcast, some of that information is unique information, and that includes science and science-based tools that you can apply in everyday life. During today's podcast, and on many previous podcast episodes, we talk about supplements. While supplements aren't necessary for everybody, many people derive tremendous benefit from them. One of the key issues with supplements if you're going to take them is that they be of the utmost quality. For that reason, The Huberman Lab Podcast has partnered with Thorne, T-H-O-R-N-E. Thorne Supplements are of the very highest quality, both with respect to the quality of the ingredients themselves, and the precision of the amounts of the ingredients. Why do I say that? Well, many supplement companies out there list amounts of particular substances on the bottle, and when they've been tested, they do not match up to what's actually in those products. Thorne has the highest levels of stringency for quality and the particular amounts that are in each product. They partnered with the Mayo Clinic and all the major sports teams, so there's tremendous trust in Thorne products. That's why we partnered with them. If you're interested in seeing the supplements that I take, you can go to thorne.com/ the letter U /huberman. You can see the supplements that I take from Thorne. If you purchase any of those supplements there, you can get 20% off and if you navigate further into the Thorne site to see the huge array of other products that they make, if you go in through thorne.com/u/huberman, you'll also get 20% off any of the products that Thorne makes. I also want to just mention one more time, the program that I mentioned at the beginning of the episode, which is Our Breath Collective, the Our Breath Collective has an advisory board that includes people like Dr. Jack Feldman, where you can learn detailed breathwork protocols. If you're interested in doing or teaching breathwork, I highly recommend checking it out. You can find it at ourbreathcollective.com/huberman, and that will give you $10 off your first month. So, I want to thank you once again for joining me for my conversation with Dr. Jack Feldman, and last but certainly not least, thank you for your interest in science.