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 a 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 breath work 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 share his knowledge with you. 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. 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 of those will be accessible to you. However, I am 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 in 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 our breath collective.com slash Huberman and use the code Huberman at checkout. And if you do that, they'll offer you $10 off the first month. Again, it's our breath collective.com slash Huberman 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. And my best is you know, there's a lot that we don't understand, which still keeps me employed and engaged, but we do know a lot. When 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 a flow in, inhale, and we need to have a 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 S-a-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 CO2 that we produce. So how do we generate this airflow? Well, there comes into the lungs. We have to expand the lungs. And it's the lungs expand. Basically, it's like a balloon that you would pull apart. The pressure inside that balloon drops and air will flow into the balloon. So we expand, pull the pressure on, put pressure on the lung to pull it apart. That lowers the pressure in the air sacs called LVLI, 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 principal muscle is a 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 at rest, 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 bring in because your ventilation, your metabolism goes up like during exercise. Now the muscles themselves, skeleton 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 above the spinal cord, the region called the brains them, which go to respiratory muscles, in particular for inspiration, the diaphragm and the external intercostal muscles in the rib cage. And they contract. So these respiratory muscles, these respiratory muscles become active. And they become active for a period of time. 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 banding around for thousands of years. And when I was a beginning a system 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'm phrased 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 brain stem that's once again this region sort of above the spinal cord, which was critical for generating this rhythm. It's called the prebutts in a complex and we could talk about how that was named. This small site, which contains in humans of few thousand neurons is 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 prebutts through a complex finish their burst of activity, then inspiration stops and then you begin to exhale because of this passive recall of the long and rib cage. Could I just briefly interrupt you to ask a few quick questions before we move forward in this very informative answer. And 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 doing it. I don't think we fully have the answer to that clearly there are differences between nasal and mouth breathing at rest that tendency is to do nasal breathing because the air flows that are necessary for normal breathing is easily managed by passing through the nasal cavities. And whenever 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 than 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. If I understand correctly there's no reason to suspect that there are particular perhaps even non overlapping sets of neurons in pre-butts singer area of the brain stem that triggered nasal versus mouth inhales. No, I would say that there's it's not that the pre-butts in complex is not concerned and cannot influence that but it does not appear as if there's any modulation of whether or not where the air is coming from whether it's coming through your nasal passages or through your mouth. Thank you and then the other question I have is that these intercostal muscles between the ribs that move the ribs up and out if I understand correctly and the diaphragm are those skeletal or as the breads 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 their muscles that need noral 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 noral input in order to beat it the noral inputs modulate the strength of it and the frequency but they beat on their own the skeletal muscles involved in breathing are need noral input. Now there are smooth muscles that have an influence on breathing and these are muscles that are lining the 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 and appropriately is when you have problems breathing like an asthma as much as a condition where you get inappropriate constriction of the smooth muscles of the airways. So there's no reason to think that an asthma that the pre-butts singer or these other neuronal centers in the brain that could 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 to those questions and you provided them so thank you. Now remind you again where I was in my we were just landing in pre-butts singer and we will return to the naming of pre-butts singer because it's a wonderful and important story really that I think people should be aware of but yeah maybe you could march us through the brain centers that you've discovered and others have worked on as well if that control breathing pre-butts singer as well as related cultures. So when we discovered the pre-butts singer we thought that it was the primary source of all rhythmic respiratory movements both inspiration and exploration. The notion of a single source is like day or night. It's like they're all coming they're all of the same origin that the earth rotates and day follows night and we thought that the pre-butts singer 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 expatory movements that is the exhalation. We had made a fundamental mistake with the discovery of the pre-butts singer not taking into account that at rest expatory muscle activity or exhalation is passive. So if that's the case a group of neurons that might generate active exploration that is to contract the expatory muscles like the abdominal muscles or the internal into the castles are just silent. We just thought it wasn't there 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 exploration that is this actively like a sh yeah or when you begin to exercise you have to go and actually move that air out. This group of cells which is silent the dress 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. An oscillator is something that goes in a cycle. So you can have a pendulum is 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. And it depends how regular they are. You can have oscillators that are highly regular 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 or 7. It starts in the late end of 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 it we thought it was involved in sensing carbon dioxide. It was what we call essential chemo receptor. That is we want to keep calm dioxide levels particularly in the brain at a relatively stable level because the brain is extraordinarily sensitive to changes in pH. If there's a big shift in carbon dioxide to 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 the way to regulate something in the brain is you have a sensor in the brain. And others basically identified that the eventual surface of the brain is that is the part of the brain is that it's on this side. It was critical for that and then we identified a structure that we was near the trapezoid nucleus. It was not named in any of these nor anatomical atlases. So we just picked the name out of the hat and we called it the retro trapezoid nucleus. I actually clarify for people when we when Jack is saying trapezoid doesn't mean the trapezoid muscles trapezoid refers to the shape of this nucleus this cluster of neurons. Paraphacial 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 lips max. 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 they we call that the face sort of develop the eyes where they are the mouth is there these nuclei the motor that contain 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 sub nuclei around there that had various holes 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 that of these many different sub nuclei now seems to be in mammals to be involved in the control of expatory 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 expatory 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 a something you can find and alligators and lizards that could have turned into a muscle that was a di 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 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 alveolis is part of the lung and the blood runs through capillaries which are these the smallest tubes in the circulatory system and at that point oxygen can go from the airfield alveolis into the blood which is amazing I find that amazing even though it's just purely mechanical the idea the way these little sacks in our lungs we inhale and the air goes in and literally the oxygen can pass into the bloodstream but the rate of which it passes will depend on the characteristics of the membrane how what the distance is between the alveolis 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 its entirely a pass a process there's no magic about making oxygen go in now how do you get a pack of the large surface area in a small chest when you start out with one tube which is the trachea 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 bit a little sphere which is an alveolis and it's 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 last the 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 roll it up to their body size it's not very impressive whereas when you get the mammals the amount of branching that you have is you have four to five hundred million alveoli how if we were to take those four to five million of you four hundred million four hundred hundred million excuse me and lay those out flat what sort of surface area are we talking about about seventy square meters which is about a third the size of a tennis court 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 the value of air in your lungs is about two and a half liters do we need to convert that to quartz? no it's about two and a half liters when you take a breath you're taking another five hundred milliliters a half a liter that's the size maybe a little of my fist so you're increasing the volume by 20% but you're you're doing that by pulling on this seventy 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 your bloodstream goes from a partial pressure of oxygen which is forty millimeters of mercury to a hundred millimeters of mercury so that's a huge increase in oxygen and that's enough to sustain normal metabolism so we we have this amazing mechanical advantage by having a diaphragm do you think that the 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 and 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 we we the brain utilizes maybe twenty percent of all the oxygen that we intake and it needs it continuously you can't 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 a while which poses other issues you're born and you have to mature you have the small body you have a small long you have a very planned 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 in your body where breathing 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 breathing has been the change in breathing have been described as trying to build an airplane while it's while it's flying basically what Jack is saying is that respiration science is more complex and hardworking than vision science which is the direct jab at me that some of you might have missed but I definitely do not miss and I appreciate that you always take the opportunity like a good New Yorker to to you know 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 you know 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 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 really examine 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 etc that would be I think interesting to a number of people. 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. It certainly addressed 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 bring my belly in or I can inhale push my diaphragm and belly out 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 of breathing clearly some are going to work through different mechanisms and we can talk about that but at 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 that breathing induces in emotion and cognition I have different ideas about what the influences and I don't see that primarily as how which particular muscles you're choosing but that just could be my own prejudice. We will return to that as a general theme in a little bit I want to ask you about siging one of the many great gifts that you've given us over the years is an understanding of these things that we call physiological size. Could you tell us about physiological size what's known about them what your particular interest in them is and what they're good for. Very interesting and important question so everyone has a sense of what a sigh is we certainly when we're emotional emotional in some ways was stressed with particularly happy we'll take a will sigh. It turns out that we're sighing all the time and when I would ask people who are not particularly knowledgeable that haven't read my papers or James Nester's book or listen to your podcast they're usually off by toward as a magnitude about how frequently we sigh on the low side in other words they say once an hour you know ten 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 find that every couple of minutes you're taking a deep breath. And you can't stop it you know it just it just happens now why but we have to go back to the lung again the lung has these 500 million out of your life and they're very tiny they're. 200 microns across so they're really really tiny and you can think of them as fluid fill their fluid line and the reason they're fluid line has to do with the. As a tariff 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 that is a determining factor in the when premature infants are born if they do not do not have lungs surfactant that makes it much more challenging to take care of them. And after they have lungs effect and which is sometime remember correctly in the late second early third trimester which appears in 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 water. Squeeze all the water out and now. When you squeeze all the water out you notice the size 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. Then if we're dry on the inside why is that because you have to overcome that surface tension well you'll feel I have a tendency to collapse there's 500 million of them they're not collapsing at a very high rate but it's a slow rate that's not trivial and when it alveil is collapses it no longer can receive oxygen or take common dioxide out it's sort of taken out of the equation. Now if you have 500 million of them and you lose 10 no big deal but if they keep collapsing you can lose a significant part of this surface area if you're long. Now a normal breath is not enough to pop them open but if you take a deep breath through no through no no is or mouth okay. Or it's just increased that lung volume because you're just pulling on the lungs they'll pop open 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 be put in these big steel tubes and the way they would work is that the pressure outside the body would drop that would put a expansion pressure on the lungs that oxygen on the ribcage the ribcage would expand and then the lung would expand and then the pressure would go back to normal and the longer ribcage would go back to normal. And it wasn't 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 gave bigger breaths and a 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. But they needed to do is every so often they have one big breath so they have a couple of minutes in normal breaths and then one big breath just mimicking the physiological size and the mortality rate drops significantly. And if you see someone on event event the later 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 these mechanisms for these physiological size. 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 alveolar you need a bigger pressure and a normal breath is not enough so you have to take a big inhale. And when nature is 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 want to we asked is how is this happening why every five minutes what's 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 so in dipitus event where you run across a paper and something clicks and you just you know you follow it up sometimes you go down blind ends but this time that 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 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 release a call bombus and related peptides. And you also realize because he was a breathing guy so when you stress you sign more so we said all right maybe that related bomb is in is relatively cheap to buy we said let's buy some bomb is in throw it in the brains then let's see what happens. And you know the 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 bomb is in and if bomb is in did nothing nothing lost maybe $50 to buy the bomb is in but if it did something it might be of some interest so we want to have the noon he did the experiment and he comes to me says I won't quote exactly what he said because that might need to be sent. But he said look at this and it was in a rat rats say about every two minutes they're small than we are and they need to sign more often this I rate from when from 20 to 30 per hour to 500 per hour when you put bomb us into the pre butts in a complex amazing and the way did that is he took a very very fine glass needle and a number of times when you can see the bomb is in the brain and the and anesthetize a rat and inserted that needle directly into the pre but see a complex so it wasn't a generalized delivery the peptide was localized to the pre but see the sorry went through the roof and I would add that that was an important experiment to deliver the bomb is in directly to that site because one could have concluded that the injection of the bomb is an increase sign because it increased stress rather than directly increase the stress that we saw 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 originating we never could have done this experiment and so then we then we did another experiment we said okay what happens if we take the cells in the pre but singer that are responding to the peptide 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 but see a complex probably a few hundred out of thousands so we use the technique we had used before and this is a technique that we developed by Doug Lapi down in San Diego where you could take a peptide and conjugate it with a molecule called sapperin sapperin is a plant that arrived molecule which is a cousin to rice and and many of your listeners may have heard of rice and it's very nasty it's it's a single you know stab with an umbrella will kill you which is a something that's supposedly happened to a Bulgarian diplomat by a Russian operative on a bridge in London he got stabbed and the way rice and works is it goes inside to sell 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 it's extremely dangerous fact it's firstly impossible to work on in a lab in the United States they won't let you touch a price because we've worked with sapperin many times sapperin is safe because it doesn't cross cell membranes so you get an injection of sapperin 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 sapperin whether or not you are a operative or otherwise thank you angel for protecting me there so but what Doug Lappey figured out is that when a ligand binds to receptor there's when a molecule binds to its receptor in many cases that receptor ligand complex gets pulled inside the cell of course from the membrane the cell inside the cell it's like you can't go to the dance alone but if you're coupled up you get in the door that's right so when he figured out is he put sapperin to the peptide the peptide binds to its receptor it gets internalized and then when it's inside the cell sapperin does the same thing the rice and 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 oblated 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 express that receptor then you inject the sapperin conjugated to the ligand to the peptide and only those 50 cells die so we took bombison conjugated to sapperin inject and the pre-butter complex of rats and it took about a couple days for the sapperin to actually oblate cells and what happened is that the mice started sighing less and less and less and less and less and less and less and less and essentially stopped sighing so your student or postdoc was it murdered these cells and as a consequence the sighing goes away what was the consequence of eliminating sighing on the internal state or the behavior of the rats in other words if one can't sigh generate physiological size what is the consequence on state of mind do you would imagine that carbon dioxide would build up more readily or to higher levels in the blood stream and that the animals would be more stressed that's the 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 we did not determine this but the presumption was that the lung function significantly deteriorated and they're visual at 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 sacrifice them at that point now we don't know whether that is specifically related to the fact they didn't sigh or that it's there was secondary damage due to the fact that some cells died 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 then I got a phone call from a graduate student at Stanford Kevin Yackel who starts asking 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 long in Drosophila fruit flies more cross now and I said why are you asking me this and he said I was an undergraduate UCLA and you gave a lecture on 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 is something you really affected the life of a student when you birthed a 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 on my lab but then when you leave my lab you got to work on something different no one I ever trained with said that it's open field you want to work on something you hop in the mix but there are people like that you are scientists like that I never felt I hear that their breathing apparatus erupted and it causes a brain dysfunction that leads to the behavior just just described it's actually not true but in terms of the so I the before you we talk about the beautiful story with with the apple and crafts now and felt lab I want to just make sure that I understand so if physiological size don't happen basically breathing overall suffers well that that would go back to the observations in polio victims in these ion lungs where the principal deficit was there was no hyperinflation of the lungs and they many of them deteriorated and died and just to stay on this one more moment before we move to what you were about to describe we hear often that people will overdose on drugs of various kinds because they stop breathing so barbituates alcohol combined with barbituates is a common cause of death for drug users and country indications of drugs and these kinds of things you hear all the time about celebrities dying because they combined alcohol with barbituates is there any evidence that the size that occurred during sleep or during states of you know deep deep relaxation and sedation that size recover the the brain because you can imagine that if the size don't happen as a consequence of some drug impacting these brain centers that that could be one cause of basically a fixation and death if you look at the progression of any mammal to death you find that the breathing slows down a death through the quote natural causes the breathing slows down it will stop and then they'll gasp so we have the phrase dying gas super large breaths they're often described as an attempt to order or suscitrate 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 gas are really size that are particularly large and so if you suppress the ability to gasp and 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 this has not been investigated I mean one of the things that interested in is individuals who have diseases which will affect pre-butzing of complex and there's there's data in Parkinson's disease and multiple systematrophy which is another form of neurodegeneration where there's loss of neurons in pre-buttsinger and the question is and it also may happen in ALS sometimes you'll find there's no garricks disease and mychofer gladoscarosis 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 size but to an overall suppression of the whole apparatus of the pre-buttsinger complex got it, thank you so Yakko calls you out he calls me up and he's great kids 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 brain stem and he was looking in one of these databases to see what's enriched and I said that's great we'd be willing to share work together he says no I advise it doesn't want me to do that so I said okay but Kevin's a great kid and I enjoyed talking to him and he's a smart guy and you know what I found in academia and is that the smartest people only want to hire people smarter than them and only want to have the preference interact with people smarter than them the faculty who are not at the highest level and at every institution there's a distribution there's ones above the mean and those below the mean those who 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 outcompete me because whatever he did was going to help me in the field so I would I did wherever I can't help to work with Kevin so at one point I got invited to give grand rounds in neurology at Stanford turns out an undergraduate student who had worked with me was now headed a training program from the neurologist that Stanford and he invited me and at the end of my visit I go to Mark Kraus in his office and Kevin is there and a postdoc a postdoc pungly who was also working on a project was there and towards the end of the conversation the walk says to me you know we found this one molecule which is highly concentrated in an important region for breathing and he said oh that's great what is it and he says I can't tell you because we want to work on it so 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 strict and sharing the information when I came back 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 you about bombison and that was the only unusual molecule we're working so the reason I'm rushing out the doors I have a fight to catch so I stick my head in I said is this molecule related to bombison and then I run off I don't even wait for them to reply I get to pee up for it Mark calls me and he says bombison the peptide we found is related to bombison what does it do and I said I'm not telling oh my I'm so glad I wasn't involved in this collaboration no no but but that was sort of a tease yeah because I said well let's work together on this and then we work together I was a prisoner of dilemma at that point yeah so Kevin Yackel is spectacular has his own lab at UCSF 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 is 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 they 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 lived in California for 20 years at that time I never heard a 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 joke to you before I had two goals one was to see whether or not 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 you know we have a mile 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 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 focus you know they could have had you move your index finger to the same effect but I really believed that the breathing part was involved now I'm not an unbiased observer so a question is how can I demonstrate that I didn't feel competent to do experiments in humans and I didn't feel like I designed 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 you know 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 stardag rant that not 21 from NCCIH that's the national complimentary medicine is that the 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 I totally agree with you I think that it's the kind of thing that many of us including many scientists think we're doing it to woo woo and unsubstantiated but learning more and more you know we used to laugh at neuroimmunology that the nervous system didn't have anything to do with the immune system and paying itself can influence your immune system I mean there are all these things that we're learning that we used to dismiss and I think there's real nuggets to be learned here so they were not in the women they funded this particular project 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, await mice to breathe slowly I won't tell you normally they don't breathe slowly no no no whatever the normal breath is we could slow it down by a factor of ten 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 I would say a priori we haven't seen them floating to the top of that cage we haven't weighed them maybe they weigh less you know they maybe you know levitation is 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 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 to a standard fear conditioning which we did with my colleague Michael Fanzelow 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 that we see a shock and their responses 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 rate that describe the validity of the test but it's very valid the control mice had a freezing time which was just the same as what Nuri 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 how long we have now is the grant ran out of money the post-op working limit left and now we have to train peace together everything and 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 know you're talking about a rodent study but I think the the benefits of doing rodent studies 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 doing breath work far far far greater number of people are not right I mean there's a the majority of people don't take any time to do dedicated breath work 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 breath work 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 describe so I this is wonderful I do hope the work gets completed and we can talk about ways that we can ensure that that happens but let me 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 the intervention is and so it's easy to say that the meditative response is a was has a big component which is a placebo effect my mice don't believe in the placebo effect and so if we could show this a bona fide effect and 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 it mice it's it's a non-issue so I think that that in of itself would be a 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 right so it's breath practice so there because we don't they're 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 sign during that 30 minutes? I don't know yet well no we have the data we just we're analyzing the data to be determined or to be announced at some point so so the fear centers are altered in some way that creates a shorter fear response to a foot shock 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 gets back to our prior conversation I sort of went off in that tangent we need 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 brains that are breathing like when you stressed is a effect 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 I think of those two things as different than they ultimately be 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 you possibly imagine they found a site in the amygdala which could produce that so this 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 control muscles are transmitted so the fibers coming from your motor cortex go down to this part of the brainstem which is called eventual ponds 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 are rostral 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 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 in the butterfly about a young man who had this happens to and he describes his life and it's a real testament to human condition that he does this it's a remarkable book it's a short book he write the book by blinking he wrote it by blinking to his caretaker it's pretty amazing and there was a movie which I've never seen with Javier Bardin is the protagonist but the book I highly recommend is anyone to read so I colleagues studying an individual I'd locked in syndrome and they this patient breathed very robotically totally consistent very regular they gave the patient the low oxygen mixture the 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 the breath faster nothing happened just the patient recognized the command but couldn't change it and all of a sudden the patient's breathing changed considerably and they said that the patient would happen they said you told the joke and I left and they went back whenever they told the joke that the patient found funny the patient's breathing pattern changed and you know you're breathing pattern when you left is you know inhale you go ha ha ha ha but it's also very distinctive we have some neuroscience colleagues who will go unnamed who if you heard them left 50 yards away you know exactly who they are I'll name them Eric Gandell for one has an inspiratory laugh he's famous for a as opposed to a ha ha exactly yeah exactly so it's very stereotyped but it's maintained and these people lose volitional control of breathing so there's an automotive component controlling your breathing which has nothing to do with your initial volitional control and it goes down to a different pathway because it's not disrupted by the slugd in syndrome if you look at motor control of the face we have the volitional control of the face but we also have a motor control emotional control of the face which most of us can't control so when we look at another person we tend to 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 use car salesmen poker players or now poker players you know have tells but many of them now where you know dark glasses because a lot of the tells you blink or whatnot pupil size is a pupil size pupil sizes of tell which is an autonomic function not as a scalpel muscle function but we have these all these scalpel muscles which were controlling which give us away I have the I've tried to get my imaging friends to image some of the great actors that we have in Los Angeles brain images brain images I'm sorry no that's right I mean I get brain images because I think when when I tell you ask you to smile I could tell that you're not happy that you're smiling because I ask you to smile I think I hear about the crack of joke but we're we're old friends so no I'm not that that you know when when you see a picture like at a birthday or whatnot and say say cheese you could tell that at least half of the people are not happy that saying cheese whereas a great actor when when they're able to disemble in the fact that they're sad or they're happy you believe it 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 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 image so I would like to get one of these great actors in a image 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 there's a lot of control of the facial muscles I think it's in large part similar to the emotive control of breathing so there's that emotive control and there's that volitional control and they're different they're different now you asked me about the yakle stuff the apple paper had to do with a sending that the motion what Kevin found was that there was a population of neurons in the pre-buttzing a complex that we're always looking to things that are projecting ultimately a motor neurons he found the population of cells that projected to locus serious. So one of those places in the brain that seem to go everywhere to get sprinkler system exactly and influence mood and you know you've had podcasts about this I mean there's a lot of stuff going on with the amoeba so I'm assuming the locus really is so you get into the serious you can now spray information out throughout the entire brain he found specific cells that projected from pre-buttsinger to locus serious and that these cells are inspiratory modulator. Now it's been known for a long time since the sixties that if you look in the locus serious of cats when they're awake you find many neurons that have respiratory modulation. No one paid much attention to him why why bother not why bother paying attention but why would the brain bother to have these inputs so what Kevin did with Lindsay Schwartz and Lee Lee Shun Lowslayer is they killed or bladed those cells going to locus serious from pre-buttsinger and the animals became calmer and their EEG levels changed in ways they're indicative that they became calmer and as I recall they didn't just become calmer but they weren't really capable of higher rousal states they were kind of flat. I don't think we really pursue that in the paper and so we'd have to ask Johnny Hogan on about that but I don't know the other side of my lab so we'll ask him but but nonetheless that beautifully illustrates how there is a bi-directional control right of emotion emotion well no the two the two stories of the locked in syndrome plus the yackel paper shows that emotional states influence breathing and breathing influences emotional states which but you mentioned inspiration which I was called inhalation but people will follow no that's fine people those are interchangeable people can follow that. There's some interesting papers from nobles group and from a number of other groups that as we inhale or right after we inhale the brain is actually more alert and capable of storing information than during exhales which I find incredible but it also make sense I'm able to see things far better when my eyes are open than when my eyelids are closed for that matter. I don't know if it's great let me backtrack a bit because I want people to understand that when we talk about breathing affecting emotional cognitive state, it's not simply coming from prebutzinger there are at least while there are several other sites and let me sort of this guy I need to sort of go to that one is old faction so when you're breathing normal normal breathing you're inhaling and exhaling this is creating signals coming from the nasal mucosa that is going back into the of factory bulb that's respiratory modulated and the of factory bulb has profound influence and projections to 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 a respiratory modulation. So that signal is there the brain doesn't have to be using it but when it's the you know discriminating over and what not that's riding on a oscillation which is respiratory related. Another potential source is the vagus nerve the vagus there is a major nerve which is containing afference from all of the viscera afference just being a signal signals to signals from the viscera it also has signals coming from the brain from the brain stem down which are called efference 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 lung stretch their barrel. Sorry that well you we have another like the piezo receptors of this years noble price. Yeah. Yeah. So they're responding to the expansion and relaxation 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. Electro 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 let me continue. Come to oxide 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. Have a colleague Alicia Morette who has working with patients who have who anxious and many of them hyperventilate and as a result of that hyperventilation there come dioxide levels of low. And she has developed a therapeutic treatment where she trains these people to breed slower and the bridge to restore the 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 by breath by breath but it's a 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 grief that gets exacerbated by people who get who have a panic attack. So the grief to which their ambiance CO2 levels are affecting their degree of discomfort. What about people who are tend to be too calm meaning they're feeling sleepy they 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 of unaware but that's blissfully unaware I've not looked at that literature so I don't know. I mean most people excuse me most of the scientific literature around breathing in humans and 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. Well CO2 is easy to measure. But in terms of the sort of the measures for feeling fatigue you know they're somewhat indirect stress we can we can get it pulse rates and HRV and things that sort of. Well I imagine that these devices that we're all wearing will soon be able to measure well not like a measure oxygen levels oxygen saturation. It's amazing. Yeah but oxen you know pretty much stay about 90% unless there's some pathology where you go out to let CO2 levels very quite a bit and sealed in fact because they vary your body is so sensitive the control of breathing that 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 now changes your ventilation but affects your brain state now another thing that could affect breathing how breathing practice can affect your emotional state is simply the descending command because breathing practice involves volitional control of your breathing and therefore this is signal it's originating somewhere in your motor cortex that is not of course that's going to go down to prebuttsinger 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 are exclusive does an interesting paper which shows that if you block nasal breathing you still see breathing really 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 it should I talk a little bit about the role that oscillations maybe playing in signal processing definitely but before you do I just want to ask you a intermediate question we talked a lot about inhalation inspiration and exhalation what about breath holds you know 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 it 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 to mo style windmoss style or we call it in the laboratory because frankly before two more and before whim there it was referred to as cyclic hyperventilation. So it's basically followed by a breath hold and that breath hold could be done with lungs full or lungs empty. So I had a long talk with some colleagues about what they might think the underlying mechanisms are particularly for the breath hold and there's certainly I certainly envision that there's a component with respect to the presence or absence of that with an intensity in your cortex which is having effect but the other thing with the hyperventilation hypoventilation or the apnea is your CO2 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 the University of Florida is doing some extraordinary work on episodic hypoxia. So in the 80s David Milhorn did some really intriguing work if I ask you to hold your breath to excuse me if I gave you a low oxygen mixture for a couple of minutes your breathing level would go up because you're going to have more oxygen. No, you're still in for oxidite. Okay and for a couple of minutes you 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 normal oxygen three minutes of hypoxia five minutes of normal oxygen normal air. You 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 rises again and stays up for hours. This is well validated now this was originally done in Amazon humans all the time it seems to have profound benefit on more function and cognitive function in what direction positive positive I've often toyed with the idea getting a 5% 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 you know going through the the episodic hypoxia to improve my cognitive function. Because 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 breath work presumably it's hard to lower your oxygen enough. Okay we're going 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 CO2 levels when you hold your breath your oxygen levels are dropping your CO2 levels are going up when you're doing episodic hypoxia your CO2 levels are going to stay pretty normal. Of course you're still breathing it's just the oxygen levels are going so unlike normal conditions which you described before where oxygen is relatively constant and CO2 is fluctuating depending on emotional state and activity and things that sort in episodic hypoxia. CO2 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 CO2 is relatively constant but you're 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 hypercaptic at the same time. We should explain to people what hypoxic and hypoxic are because we have it. Hypoxic is just a technical term for low levels of oxygen hyper or you could say hypoxic low hyper is high so hyperoxia or hypocapia low CO2 or hypercaptia or high levels of CO2. So when you're in episodic hypoxia if anything you're going to become hypoxic not hypercaptic and that could play an influence on this. One example that I remember in 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 flexion. That is, it's just me ankle extension to extend the ankle and so they had the patient in the seat with a 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 one 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 at athletic performance we have a project which we haven't been able to push to the next level to do golf. Because 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 their placebo control so they don't know whether they're breathing a gas mixture which is just normal air or hypoxic gas mixture, although they may be able to figure it out based on their response. So we do it on the control circumstances that do it into a net measure their blanket the drives at dispersion 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. I'm not serious about selling it, but I know you're joking. I think 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. 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, the sports part of it is a tiny, tiny miniscule 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 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 patterned 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 tumor, 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 Tuma 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. 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 about self experimentation, but I applaud that curiosity and going after it. Hyperbaric chambers here a lot nowadays about hyperbaric chambers. People are buying them and using them. And what are your thoughts on hyperbaric chambers as it relates to any of the hyper hyperbaric chambers? You're not talking about altitude. No, I don't really have much to say. I mean, your auction levels will probably go up a little bit. And that could have a beneficial effect, but that's way outside my area of comfort. I think 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, of increasing blood volume, et cetera, and hyperbaric chambers seem to be catching on much in the same way that ice baths were in and saw us seem to be right now. But anyway, a prediction we can return to it some 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 improved memory. These are a couple 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, you know, 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 and 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 are 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 four brain 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. 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 possible 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 because we know that there's a strong central component in this. In fact, there's a strong central projection to the olfactory ball. So regardless of whether or not there's any in and out of the nose, there's a respiratory input into the olfactory ball, 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. Different in terms of the levels of alertness or calmness they produce. I'm not aware of any mechanistic data on that, but there's anything worthwhile. Right nostril versus left nostril breathing that you're aware of. I'd love to know. Well, it's certainly plausible. I don't know of any data demonstrating it except the anecdotal reports. As you know, the brain is highly lateralized and we have speech on one side and a dominant hand is on one side. And so the notion that if you have this huge signal coming from the olfactory system and the some degree it's lateralized is not perfectly symmetrical. And once one side is not going evenly to both sides, then you can imagine and 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 in which either the signal still remains where the signal is removed from. 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 because there's an increase in heart rate and sympathetic tone, I would think of constriction. And I'm guessing as you relax, the people will get and you exhale the people. I think you're right, but I always get, you know, I always get the valence. Well, it's counterintuitive because people one think that when the pupils get, I mean, it depends. I mean, you can get very alert and aroused in that for stress or for good reasons. And the pupils 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 your visual window is changing in coordination with breathing. Your fear response changes with the respiratory cycle. Tell us more about that. The paper by Zolano, which I think showed rather clearly that if you show individuals. Fearful faces that they're. Measured response of fearfulness changes between inspiration, expiration. Why, but it does your reaction time changes. So you talk about blinking the reaction time changes between inspiration and expression. And 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 know, 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 they can punch faster. I have to say I don't keep a table of which is which direction things moving because I'm out of the martial arts field. My vague understanding is that exhales on strikes is the more typical way to to do that. And so as people strike, they exhale in many as you exhale, but there are other components to strike and because you want to stiffen your your rib cage, you want to make a Valsalva maneuver. So that's, you know, both an inspiration and an expiration is at the same time. I don't I don't know enough about when you say during expiration, I would assume that we make you strike. You actually sort of want to stiffen here, which is a Valsalva maneuver. And oftentimes they'll clinch their fist at the last moment because anyway, there's a whole set of motor things that we should we can talk to some fighters. We know people who know fighters. So we can ask them. Interesting. What are some other things that are modulated by breathing? You know, 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 the big this. I opening thing for me, probably a decade ago was digging into literature and and seeing how much of core collectivity and sub core activity had a respiratory modulated component to it. I think a lot of my colleagues who are studying cortex are oblivious to this. And they find I heard it talk the other day, the person who go on name, who find a lot of things correlated with a particular movement. I think it all when I looked at it, gee, that's the things that are respiratory modulated. And rather than it being correlated to the movement they were 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 a behavior 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 foundation. It's in the background. It's in the brain and oscillations playing important part in brain function. And they vary in frequency from maybe a hundred hertz down to what we can get to circadian and you know sort of monthly cycles. But breathing occupies a rather unusual place and all that because so let me talk about what the people think the oscillations are doing, particularly faster ones. They're important in coordinating signals across neurons. Just like in a computer, a computer steps. So computer knows when information is coming from another part of a computer that it was originated at a particular time. And so that the screen step by step thing is important and computer control. Now the brain is not a digital device. It's an analog device. But when I have a signal that I that coming in my ear and my eye, which is Andrew you've been 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 how do I assure that those signals coming in represent the same signal? Well, if I have to write my brain in an oscillation and the signals right 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 a high I see you as when unified thing spouting, you know, 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 this. The range when you think about milliseconds, but we have important things that I 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 point two cycles per second every five seconds, although in roads. So we'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 that the greed to which the brain is using that slow signal for anything. And it becomes part of its normal signal processing. You now change it that signal processing has to change. And as the signal processing changes acutely is a change. So you know, you asked about breath practice. How long do you have to do it? Well, a single breath will change your state. And it seems to help relax or even say. Call it what you will call it what you will. It seems to work. Now, it's not it doesn't have a permanent change. But you know, when I'm getting up to bat or getting up to the first he or getting to give a big block or coming to do a podcast. So a little bit anxious a deep breath of 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 activity 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 then get so strong you can't break them. So you can imagine depression being something going on and on and on. And you can't break it. And so we have trouble when we get to 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 shot the whole brain. That's disrupting activity and whole brain. And the 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 its end in the circuit involved in depression. We may get some relief. An electroconvulsive shock does work for relieving many kinds of depression. And so, if you're a 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. And then it's 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. And the 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 weigh that circuit down. I sort of likeness. I tell people it's like walking around on a dirt path. You build a rot to rot get so deep you can't get out of it. And what breathing is doing is sort of filling in the rut bit by bit to the point that you can climb out of that rut. And that is because breathing, the breathing signal is playing some role in the way the circuit works. And then when you disrupt it, the circuit gets a little thrown off kilter. And when, 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 happens, then it seems to improve our emotional function or our cognitive function. And, you know, 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 breath, breath, breath, word practices, which is 30 minutes of breath work is a pretty serious commitment. I think, but it's doable. Certainly is zero cost except for the time for, in most cases. What do you see out there in the landscape of breath work that's being done that you like? And why do you like it? What do you think, or what would you like to see more of in terms of exploration of breath work? And what do you do? Well, I'm a well of the new convert to breath work through my own investigation of it that 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's told they got to begin to exercise. You don't go out and run a marathon. So, you know, couch potato, you say, okay, get up and walk for five minutes, 10 minutes. And then, okay, now you're walking for a longer period, you begin to run. And then you reach a point and 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 what you have 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 relax and I have another one who's named my I don't remember. It's so it's very simple and it works for me now trying this to mo 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 styles like Wim Hof are a little intimidating to newbies. And so I would like to see something very simple that people would I tell my friends is look just try it five or 10 minutes. If you feel better, do for a few days. If you don't like it, stop it. It doesn't cost anything. And invariably they find it it's helpful. I will often interrupt my day. To take five or 10 minutes. Like if I find that I'm lagging, you know, there's 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 or 10 minutes. 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 inhales, five second hold, five second exhale, five. And sometimes I'll do doubles. I'll do 10 seconds. Just because I get bored, you know, it's just I feel like doing it. And it's it's. It's very it's very helpful. I mean, it. Now that's not the only thing I do with respect to trying to maintain my sanity and my health. I can imagine a number of things. Although you seem because you seem very sane and very healthy. I in fact know that you are both those things where you suspect. I suspect. But there's data. Well, back we had a conversation, casual conversation, but you said something that really stuck in my mind, which is that it might be that the specific pattern of breath work that one does is not as important as experiencing transitions between states based on deliberate breath work or something to that extent, which I interpreted to mean that if I were to do box breathing with five second in five second hold, five second exhale, five second hold for a second. Or maybe even a couple of minutes and then switch to 10 seconds or then switch to two more that there's something powerful perhaps in the in the transitions and realizing the relationship between different patterns of breathing in those transitions much in the same way that you can get on to into one of these cars and 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't 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 breath work practice that at least to my awareness nobody has really formalized, which is that you introduce some variability within the practice that 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 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 please. You know I was asked in this BBC interview once white and I name it the Feldman complex so the pre-butts in a complex that I already have a Feldman complex well it sounds like a psychiatric disorder but but I think the primary effect is this disruptive effect which I described and but the particular responses may clearly vary. Depending on what that disruption is. I don't know of any particular data which are some 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 cryama sort of similar but the amount of time you spend going around the boxes 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 and 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 is the signal processing disrupted which is still hypothesis but how is the disrupted could tell us a lot about you know 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 you know the fact that different breathing practices could be affecting the outcomes through different pathways. You know 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. You can get serious. You're a scientist and psychologist to do the right experiments to get it 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 is 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 apple lab UCSF and a number of I'm starting to see some papers out there 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. I think there is power in compounds both prescription non prescription natural synthesized I don't use these have hazardly but I think there's certainly power in them and one of the places where you and I converge is in terms of very interesting the nervous system and supplementation is these of the magnesium. Now I've talked at 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 this because it's the human lab podcast and we often talk about supplementation what what you do with that information. So I need to disclose that I am a scientific advisor to a company called North Centrier which my graduate student goes on Louis CEO. So that said I give you some background go song although he was in my lab work done breathing had a deep interest in learning and memory and we left my layup he went to work for it with a renowned learning and memory guy at Stanford Diction. And when he finished there is hired by Susumu Tonogawa and MIT also knows a thing or two about memory I'm teasing Susumu has a no bell for his work on immunoglobulins but then it's. World class memory researcher yeah and more he's many things and and go song had very curious very bright guy and he was interested in how signals between neurons get strengthened which is called long term potential transition 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 of 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 and all neurons and that part of it is regulated by the degree of magnesium in the exercise of bath and you mean ex you mean electrical noise electrical noise some so that's what's called the physiological range which is between point eight and one point to millimolar which don't worry about the memory of the millimolar of the magnesium. I'm always frightened that I get you know I say micro or phantom or something I go off by several or some magnitude but so in that physiological range there's a big difference in the amount of noise in the neuron between point eight and one point to millimolar. So he played around with the magnesium and he found out that when the magnesium was elevated there was more LTP right that's an observation in a tissue culture and I should just mention that more LTP essentially translates to more neuroplasticity more rewiring of connections in in essence. So he tested this in mice and basically offered them a he had control mice which kind of normal diet and one that had one that reached the magnesium and the ones that lived in rich with magnesium had higher cognitive function lived longer everything you'd want in some magic pill those mice did that. 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 blood stream into the brain they pass via a what's called a transporter transporter something in a membrane that grabs a magnesium molecule or atom. And pulls it into the other side so if you imagine you have magnesium in your got you have transporters that pull the magnesium into the blood stream well if you had taken normal magnesium supplement that you can buy it the pharmacy it doesn't cross the gut very easily and if you would take enough of it to get it in your blood stream you start getting diarrhea. So it's not a good way to go what is a good way to go. Well said so he worked with this brilliant chemist female and. They looked at a whole range of magnesium compounds and he found the magnesium 3 and 8 was much more effective in crossing the gut blood barrier. Now they didn't realize at the time but 3 and 8 is a metabolite of vitamin C and there's lots of 3 and 8 in your body so magnesium 3 and 8 would appear to be safe and maybe part of the role or the now they believe it's part of the role of the 3 and 8 is that it super charges 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 3 and 8 to mice who had no let me backtrack a bit they did a study in humans they hired a company to do a test was a hands off test it's one of these companies that gets hired by the big format to do their test for them and they got. Patients who had what diagnosis my cognitive decline is a people had cognitive this order which was age inappropriate and the the method that they use for determining how far off they were is spearman's g factor which is a. Generalize measure of intelligence that most psychologists accept and the biological age of the subjects was I think 51 and the cognitive age was 61 based on the spearman g test 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 and not these people are about 10 years older according to that metric. And. Long story short if the three months this is a placebo control double blind study the people who are in the placebo arm improved two years which is common for human studies because of the 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 of what caused the malacovina but it was pretty it was extraordinarily impressive so it moved their cognition closer to their biological age. Do you call it the doses of magnesium three and 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 new just so that they're all wholesale or who sells it to the retailers and they make whatever formulation they want. But it's it's a dosage which is minus the news rarely tolerable I take half a dose. I take half a dose is that I had my magnesium blood magnesium measured and it was low normal for my age I took half a dose became high normal and I felt comfortable staying in the normal range. You know a lot of people taking the full dose and and for at my age I'm not looking to get smarter I'm looking to decline more slowly and it's hard is you know it's hard for me to tell you whether or not it's effective or not well you remember the millimolar of the magnesium and solution and I'm the high and low and so I would say it's not a well controlled study when it's an end of one but. It seems to be working when I when I've recommended to my friends academics who are not by nature skeptical if not cynical and insist that they try it they usually don't report a major change in their cognitive function although sometimes they do report while I feel a little bit more alert and my new my physical movements are better but many of them report they sleep better and and that makes sense I think. There's good evidence that three and eight can accelerate the transition into sleep and maybe even access to deeper modes of sleep for some people there for many people actually a small percentage of people who take three and eight including one of our podcast staff here. Have stomach issues with it they can't tolerate I would say I'm just anecdotally about five percent of people don't tolerate three and eight well stop taking in their fine it caused them die or something 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 they're more on the way. But this that's very interesting because I until you and I had the discussion about three and eight I wasn't aware of the cognitive enhancing effects but the story makes sense from a mechanistic perspective 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 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 know you really are a pioneer in this field of studying respiration and the mechanisms underlying respiration with modern tools for now for many decades you know and the field of neuroscience was one that. What's perfectly content to address issues like memory and vision and you know sensation perception and setter but the the respiratory system was largely overlooked for a long time and you've just been steadily clipping away and clipping away and much because of the events of. Related to covid and a number of other things and this huge interest in breathwork and brain states and wellness I did feel the respiration and interest in respiration is 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 that 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 my silo for a long time and it's been a wonderful experience to communicate to people outside the silo have an interest in. And I think that there's a lot that remains to be done and I enjoy speaking to people have interest in this I find the interest to be quite mind boggling and it's quite wonderful that people are willing to. To listen to things that can be quite a certain 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 thanks again Jack by 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 slash Andrew Huberman 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 every day life during today's podcast and on many previous podcast episodes we talk about supplements while supplements aren't necessary for everybody many people derived 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 Thor and THORN 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 slash the letter you slash 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 slash you slash 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 as 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 our breath collective.com slash 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.